

Single Technology Appraisal

**Pembrolizumab before surgery
(neoadjuvant) then with radiotherapy after
surgery (adjuvant) for newly diagnosed
resectable, locally advanced, squamous
cell head and neck cancer [ID6477]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Contents:

The following documents are made available to stakeholders:

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

- 1. Company submission** from Merck Sharp & Dohme:
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submission** from:
 - a. Swallows Head & Neck Cancer Support Group
 - b. Head and Neck Cancer UK
 - c. British Association of Otorhinolaryngologists, Head and Neck Surgeons (ENT UK)
- 4. Expert personal perspectives** from:
 - a. Professor Christopher Nutting, Professor of Radiotherapy, Consultant Clinical Oncologist – clinical expert, nominated by Merck Sharp & Dohme
 - b. Dr Will Ince, Consultant Oncologist/Affiliated Assistant Professor – clinical expert, nominated by Merck Sharp & Dohme
- 5. External Assessment Report** prepared by Sheffield Centre for Health and Related Research (SCHARR)
- 6. External Assessment Group response to factual accuracy check of EAR**

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 before surgery (neoadjuvant)
then with radiotherapy after surgery (adjuvant)
for newly diagnosed resectable, locally
advanced, squamous cell head and neck
cancer [ID6477]**

Company evidence submission



September 2025

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Abbreviations

Abbreviation/ acronym	Definition
AE	Adverse Event
AEOSI	Adverse Events of Special Interest
AJCC	American Joint Committee on Cancer
APaT	All Participants as Treated
BICR	Blinded Independent Central Review
BNF	British National Formulary
CC Score	Complications and Comorbidities Score
CI	Confidence Interval
cLDA	Constrained Longitudinal Data Analysis
CPS	Combined Positive Score
CRT	Chemoradiotherapy
DCO	Data Cutoff
DFS	Disease-Free Survival
DSA	Deterministic Sensitivity Analysis
EFS	Event-Free Survival
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
EXTREME	Cetuximab plus platinum-based chemotherapy regimen
FCE	Finished Consultant Episode
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
HR	Hazard Ratio
ICD-10	International Classification of Diseases, 10th Revision
ICER	Incremental Cost-Effectiveness Ratio
IRP	Incurable Recurrence/Progression
ITT	Intention-to-Treat
IV	Intravenous
L/SR	Local or Salvageable Recurrence
LYG	Life Years Gained
MA	Marketing Authorisation
MHRA	Medicines & Healthcare products Regulatory Agency
mPR	Major Pathological Response
NDRS	National Disease Registration Service
NHB	Net Health Benefit
NHS	National Health Service

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Abbreviation/ acronym	Definition
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PAS	Patient Access Scheme
pCR	Pathological Complete Response
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PRO	Patient-Reported Outcome
PSA	Probabilistic Sensitivity Analysis
Q3W	Every 3 Weeks
Q6W	Every 6 Weeks
QALY	Quality-Adjusted Life Year
QxM	Every x Months
QxW	Every x Weeks
R/M	Recurrent or Metastatic
RCT	Randomised Controlled Trial
RT	Radiotherapy
SAE	Serious Adverse Event
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SPC	Summary of Product Characteristics
TNM	Tumour, Node, Metastasis
UICC	Union for International Cancer Control
VAS	Visual Analogue Scale

Executive summary

Head and neck cancer is a general term that covers different cancers that start in the tissues in the head and neck area, including the oral cavity, pharynx and larynx. In England in 2022, there were 9,997 diagnoses of the cancers of the oral cavity, oropharynx, larynx, and hypopharynx. The disease, as well as the effects of treatment, have debilitating effect on patients' day-to-day general function and health-related quality of life.

The standard of care for newly diagnosed locally advanced resectable head and neck cancer has not changed for the last 20 years and consists of surgical resection of the tumour and neck lymph node dissection, followed by radiotherapy alone or in combination with cisplatin. After such treatment the rates of tumour recurrence are high (up to 56% of patients with locally advanced disease experience recurrence usually within 2 years following initial treatment) and the proportion of patients surviving after 5 and 10 years are low (69% and 10%, respectively).

This submission addresses the expected marketing authorisation for pembrolizumab [REDACTED]. This covers the technology's full expected marketing authorisation for this indication.

The clinical effectiveness of pembrolizumab in this indication is demonstrated by the phase 3, multicentre, open-label, randomised, active-controlled KEYNOTE-689 trial.

Participants with locally advanced HNSCC were randomised in a 1:1 ratio to receive 2 cycles of neoadjuvant pembrolizumab and 15 cycles of adjuvant pembrolizumab (both at a dose of 200 mg every 3 weeks) in addition to standard of care (pembrolizumab + SOC group) or standard of care alone (SOC group). Standard of care was surgery and adjuvant radiotherapy with or without concomitant cisplatin.

The latest available results from this study are from the first interim analysis (IA1) with a database cut-off date of 25th July 2024, where the median actual follow-up time was 2.25 years (range 0.04 years to 5.54 years) in patients with baseline PD-L1 CPS ≥ 1 . A total of 347 patients with baseline PD-L1 CPS of ≥ 1 were assigned to the pembrolizumab + SOC group and 335 patients to the SOC group. In these patients, a statistically significant and clinically meaningful improvement in event-free survival (EFS) was observed in the pembrolizumab + SOC group compared with the SOC group (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.55, 0.89; $p=0.00140$), reducing the risk of recurrence or progression by 30% among patients with resectable locally advanced HNSCC. The overall survival HR also favoured pembrolizumab + SOC versus SOC (HR:0.72; 95% CI: 0.56, 0.94; nominal $p=0.00666$). There was a statistically significant and clinically meaningful improvement in major pathological response (mPR) in the

pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 9.8% (95% CI: 7.0, 13.3; $p < 0.00001$), and an improvement in pathological complete response (pCR) in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 3.1% (95% CI: 1.6, 5.6; nominal $p = 0.0006$). The benefit of pembrolizumab + SOC over SOC was largely consistent across prespecified subgroups across the efficacy endpoints.

Health-related quality of life changes between the pembrolizumab + SOC and SOC groups were similar as measured by the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30 and EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L). The study showed that pembrolizumab had a manageable safety profile that was generally consistent with the well-established safety profile of pembrolizumab without any new safety concerns.

To assess the cost-effectiveness of perioperative pembrolizumab + SOC compared to SOC alone (surgery followed by adjuvant radiotherapy with or without cisplatin) in patients with resectable locally advanced HNSCC with $\text{CPS} \geq 1$, a *de novo* four-state Markov model was developed consisting of event-free (EF), local or salvageable recurrence (L/SR), incurable recurrence/progression (IRP), and death. Data from the most recent KEYNOTE-689 trial data cutoff (25 July 2024) were used to populate the model. Where model parameters were not available from KEYNOTE-689, systematic literature reviews were used to inform inputs.

The model results demonstrated perioperative pembrolizumab + SOC to be a cost-effective use of NHS resources, and extensive sensitivity and scenario analyses show the results to be robust to alternative sets of assumptions. KEYNOTE-689 is a true step-change in the management of patients with resectable locally advanced HNSCC as the first clinical study to read positive in the perioperative space, demonstrating statistically significant improvement in event free survival and a positive trend in overall survival, allowing more patients to benefit from reduced risk of recurrence in the longer term.

Pembrolizumab + SOC would be the first peri-operative treatment option available for these patients, enabling a greater proportion of patients to experience prolonged time without cancer and consequently reducing the overall burden of advanced disease treatment for the NHS. Introducing this technology to the NHS will result to significant benefits for the patients, their families, the health system and the wider society overall.

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

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

- This submission addresses the anticipated marketing authorisation for pembrolizumab [REDACTED]. This covers the technology's full expected marketing authorisation for this indication.
- 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.
- Head and neck cancer is a general term that covers a range of cancers that start in the tissues in the head and neck area, including the oral cavity, pharynx and larynx. It is a considerably burdensome disease with few treatment advances in the last 20 years, most of which were in the advanced disease stages. In England in 2020, there were a total of 7959 registrations of malignant neoplasm of the lip, oral cavity and pharynx (International classification of Diseases [ICD]-10 codes C00-C14).
- The long-term survival of patients with HNSCC depends on several factors, mainly the origin/site of the cancer and the stage of the disease at diagnosis, with the 5-year survival rate being 69% for locally advanced HNSCC. Up to 56% of LA HNSCC patients experiencing disease recurrence following treatment, contributing to poor survival outcomes, including distant metastases.
- There is considerable burden on patients living with HNSCC. The disease, as well as the effects of treatments (such as surgery and radiotherapy), can have severe impact on patients' ability to speak, swallow, breath, see, smell, and taste. These lead to a debilitating effect on patients' day-to-day general function and health-related quality of life.

- The current standard of care (SOC) treatment for patients with newly diagnosed Stage III-IV resectable LA HNSCC consists of surgical resection of the tumour and neck lymph node dissection, followed by either radiotherapy alone or in combination with cisplatin. Pembrolizumab as single agent monotherapy will be administered to patients with resectable locally advanced HNSCC with PD-L1 combined positive score (CPS) ≥ 1 as neoadjuvant treatment, then continued as adjuvant treatment in combination with radiation with or without platinum-containing chemotherapy followed by pembrolizumab as single agent.
- Use of this technology is not anticipated to raise any equity or equality considerations.

1.1 Decision problem

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

The anticipated indication in the UK is: [REDACTED].

The decision problem addressed in this submission is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated, newly diagnosed, resectable, locally advanced squamous cell head and neck cancer	Adults with newly diagnosed, nonmetastatic, resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC) [REDACTED]. Specifically, patients with: - stage III oropharyngeal p16-positive disease with tumour size T4 and node stage N0 to N2, or - stage III or IVA oropharyngeal p16-negative disease, or - stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status.	Additional details provided to align with the anticipated UK marketing authorisation and the pivotal KEYNOTE-689 trial that forms the evidence base for this submission.
Intervention	Pembrolizumab before surgery (neoadjuvant) then with radiotherapy (with or without cisplatin) after surgery (adjuvant)	Aligned with the NICE scope, specifically: <i>Neoadjuvant therapy</i>: pembrolizumab monotherapy <i>Adjuvant therapy following surgical resection</i>: pembrolizumab in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy.	Additional clarity provided to align with the anticipated UK marketing authorisation and the pivotal KEYNOTE-689 trial that forms the evidence base for this submission.
Comparator(s)	For neoadjuvant (before surgery) or adjuvant (after surgery) head and neck cancer: Established clinical management without pembrolizumab including but not limited to:	Established clinical management without pembrolizumab, consisting of: Surgical resection followed by radiotherapy with or without concomitant platinum-based chemotherapy	Management of LA HNSCC is guided first by considering whether the tumour is surgically resectable. Surgical resection is typically the recommended primary treatment for tumours of the oral cavity and larynx, whilst for oropharyngeal and hypopharyngeal tumours, surgery is usually reserved for larger (higher T stage) or more aggressive tumours. A tumour may be considered unresectable if it is too

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	○ Radiotherapy with or without chemotherapy For locally advanced head and neck cancer: • Cetuximab in combination with radiotherapy		large or if surgery would be associated with unacceptable risk of severe or irreversible functional deficits (e.g. loss of ability to speak or swallow). Patient fitness for surgery is also a consideration, as well as the patient's preference for surgical versus non-surgical management (1, 2). As the reasons affecting the choice of surgery versus organ-sparing approaches are complex and multifactorial (and result in differences in trial design and endpoint definition), it is not possible to compare the efficacy of surgical and non-surgical treatment pathways. This therefore results in <u>two distinct populations</u>: resectable (patients planned for primary/definitive surgery), and non-resectable (patients planned for primary/definitive [chemo]radiotherapy). The KEYNOTE-689 study recruited patients with <u>resectable, newly diagnosed</u>, locally advanced nonmetastatic HNSCC. Pembrolizumab was given as a perioperative intervention. To be eligible for perioperative pembrolizumab (in the trial and in clinical practice), key criteria are that patients must have a resectable tumour, be planned for surgery, and be fit enough to undergo this surgery followed by adjuvant radiotherapy (RT) ± chemotherapy. As such, any treatments which are intended for patients not

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			undergoing surgery (i.e. for the non-resectable population) are not appropriate comparators for the population under consideration in the current decision problem. Further details are provided below. Established clinical management without pembrolizumab: - Current standard of care (SOC) for patients with <u>untreated, resectable</u>, LA HNSCC is <u>surgery</u> followed by <u>adjuvant RT with or without platinum-based chemotherapy</u>. As surgery is a key component of the SOC management regimen, as well as the pembrolizumab regimen, this should be specified in the definition of the comparator. MSD considers that the final scope comparator is therefore <u>“Surgical resection followed by radiotherapy with or without concomitant platinum-based chemotherapy” and this is the only relevant comparator for the purposes of this submission.</u> - For clarity, ‘Radiotherapy (with or without chemotherapy)’ in either the neoadjuvant setting or as definitive/primary treatment would not be an appropriate comparator, as neoadjuvant RT is not used in clinical practice, and primary/definitive (i.e. with

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			curative intent) RT is not relevant to a resectable population. The wording of the comparator definition should specify that RT (with or without chemotherapy) is given following surgery (i.e. in the <u>adjuvant setting</u>) only, as specified above. MSD does not consider Cetuximab in combination with radiotherapy for locally advanced head and neck cancer to be a relevant comparator for the KEYNOTE-689 trial population: - The evidence base for cetuximab in combination with RT (for the patients specified in NICE TA145) consists of the Bonner trial, which excluded patients who had undergone surgery for HNSCC (3). The trial did not include a surgery component and cetuximab + RT was therefore used as the definitive/primary treatment option, as an alternative to RT alone, in a non-resectable population; it was not positioned in the adjuvant setting for resected patients, and therefore cetuximab + RT is intended to treat a different population than that covered by the current decision problem. - Further, the Bonner trial enrolled patients with predominantly oropharyngeal tumours (~60%), with the remainder having laryngeal (~25%) or

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			hypopharyngeal (~15%) tumours; no patients with oral cavity disease were included (3). By contrast, the KEYNOTE-689 trial was comprised primarily of patients with oral cavity (~60%) or laryngeal (~20%) tumours, with oropharyngeal tumours representing only ~10% of the trial population. This discrepancy is consistent with the different treatment guidelines for the various anatomical sites and reflects how tumour site is an important factor contributing to the choice of treatment pathway. In addition, there was a higher proportion of T4 tumours (larger, more advanced) in the KEYNOTE-689 trial (~50%) than in the Bonner trial (~30%). This, too, is consistent with treatment guidelines relating to suitability for surgical resection (i.e. larger pharyngeal tumours are more likely to be resected [and thus eligible for inclusion in the KEYNOTE-689 trial]). These observations further highlight the distinction between the resectable versus non-resectable populations. • Related to this, anatomical site and tumour T stage, along with HPV/p16 status for oropharyngeal cancer, are important prognostic factors in LA HNSCC (1, 2). Consequently, the fundamental discrepancy in the

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			composition of the two trial populations (driven by the initial clinical decision regarding whether the tumour should be surgically resected) in terms of anatomical site and T stage means that the trial results cannot be compared. • Additionally, the NICE TA145 recommendation restricts reimbursement of cetuximab + RT to patients whose Karnofsky performance-status score is 90% or greater <u>and</u> for whom all forms of platinum-based chemoradiotherapy are contraindicated (e.g. due to comorbidities) (4). This therefore corresponds to a very small subgroup of the non-resectable LA HNSCC population. • Accordingly, clinical expert feedback to MSD has indicated that cetuximab + RT is very rarely used in the locally advanced HNSCC setting and in practice is reserved only for patients who do not undergo surgical resection and who have renal impairment. They also noted that there is RCT evidence that cetuximab + RT is associated with poorer survival outcomes compared with definitive/primary platinum-based chemoradiotherapy, which contributes to the very low usage in the UK (e.g. the RTOG 1016 and De-ESCALaTE HPV trials (5, 6)).

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Therefore, given the differences in the target patient population, treatment pathway, and very low level of use in the UK clinical practice, cetuximab in combination with RT is not an appropriate comparator for this appraisal.
Outcomes	The outcome measures to be considered include: - overall survival - event-free survival - progression -free survival - disease-free survival - Major pathological response - Pathological complete response - response times - adverse effects of treatment - health-related quality of life.	- Event-free survival - Overall survival - Major pathological response - Pathological complete response - Health-related quality of life (EORTC QLQ-C30, EQ-5D-5L) - Adverse events	The KEYNOTE-689 study recruited patients with resectable newly diagnosed, locally advanced nonmetastatic HNSCC. Pembrolizumab was given as a perioperative intervention. The primary endpoint of the study was event-free survival (EFS), and overall survival (OS) was a key secondary endpoint. MSD does not consider the following outcomes to be relevant in this setting: - Progression-free survival: This was not an endpoint measured in the KEYNOTE-689 trial as it is not a relevant outcome for cancer in the early-stage (neoadjuvant/adjuvant) setting. - Disease-free survival: This was not an endpoint measured in the KEYNOTE-689 trial. In the perioperative setting, event-free survival (EFS) is the appropriate endpoint for assessing efficacy versus the comparator. - Response times: This was not an endpoint measured in the KEYNOTE-689

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			trial as it is not a relevant outcome for cancer in the early-stage (neoadjuvant/adjuvant) setting.
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 commercial schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Cost-effectiveness analysis, aligned with the NICE reference case	N/A
Subgroups to be considered	If the evidence allows subgroups will be considered based on:	• Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx) • Tumour Stage (III vs. IVA)	Other subgroup analyses pre-specified in the KEYNOTE-689 clinical trial protocol have also been included.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	PD-L1 combined positive score	- PD-L1 status (combined positive score [CPS]) - Age category (<65 vs. ≥65 years) - Sex (female vs. male) - Race (white vs. all others) - Smoking status (never vs. former vs. current) - Geographical regions (North America vs. European Union vs. Rest of the World)	
Special considerations including issues related to equity or equality	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.	N/A	N/A

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1.2 Description of the technology being evaluated

Table 2. Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAb) of the IgG4/kappa isotype designed to exert 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 yet have UK marketing authorisation for the indication under consideration in this appraisal. A submission to the Medicines & Healthcare products Regulatory Agency (MHRA) for this indication was made in [REDACTED] and marketing authorisation is expected to be granted in [REDACTED]. The indication is expected to be assessed via the MHRA International Recognition Procedure using the European Medicines Agency as the Reference Regulator.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication in the UK relevant to this appraisal is: • [REDACTED]. Current indications in the UK are: Melanoma • KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection. Non-small cell lung carcinoma (NSCLC) • KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in

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	adults whose tumours express PD-L1 with a $\geq 50\%$ 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 non-small cell lung carcinoma 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 non-small cell lung carcinoma in adults. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a $\geq 1\%$ TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. Classical Hodgkin lymphoma (cHL) • KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. Urothelial carcinoma • KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults. • 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. Head and neck squamous cell carcinoma (HNSCC) • KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

	- KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a $\geq 50\%$ TPS and progressing on or after platinum-containing chemotherapy. Renal cell carcinoma (RCC) - KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults. - KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults. - KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers: Colorectal cancer (CRC) - KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings: - first-line treatment of metastatic colorectal cancer; - treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy. Non-colorectal cancers - KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with: - advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation; - unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. Oesophageal carcinoma - KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10. Triple-negative breast cancer (TNBC)

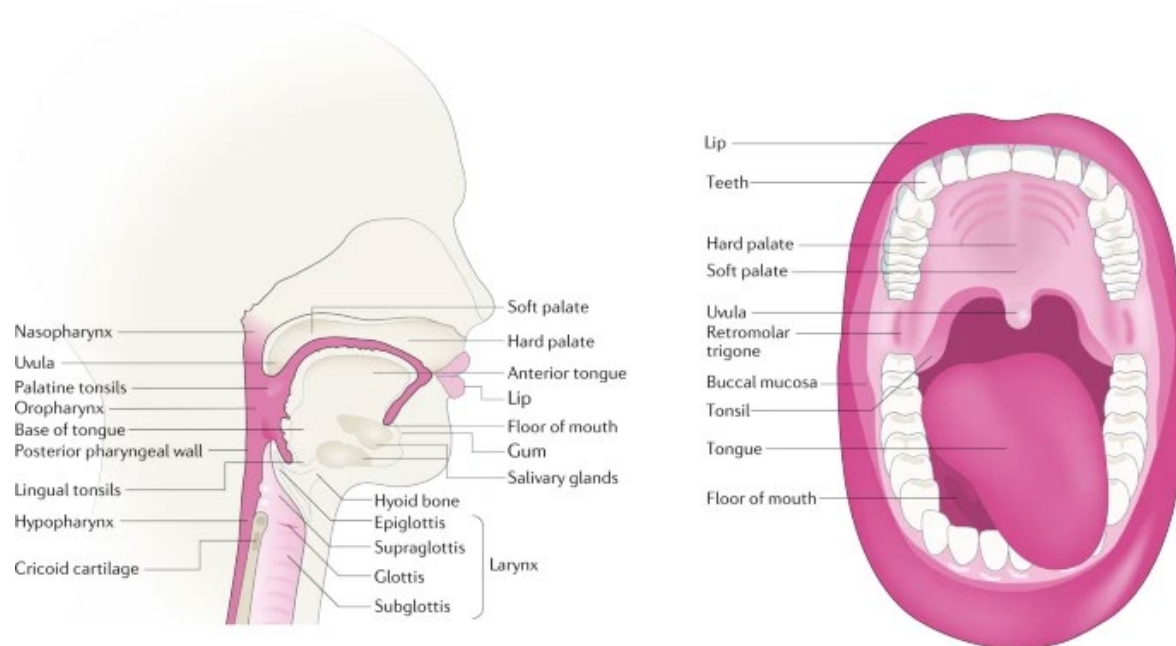
	• KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence. • KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease. Endometrial carcinoma (EC) • KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults. • KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. Cervical cancer • KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy. • KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1. Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma • KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. • KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. Biliary tract carcinoma (BTC)

	KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.
Method of administration and dosage	The recommended dosage is up to 17 cycles of intravenous pembrolizumab (200 mg) every 3 weeks (Q3W), consisting of: - Neoadjuvant: 2 cycles of intravenous pembrolizumab (200 mg) Q3W. - Post-operative: 15 cycles of intravenous pembrolizumab (200 mg) Q3W, consisting of: - Concomitant with radiotherapy with or without chemoradiotherapy: 3 cycles of intravenous pembrolizumab (200 mg) Q3W. - Adjuvant basis: 12 cycles of intravenous pembrolizumab (200 mg) Q3W. (The dosage above is as per the KEYNOTE-689 trial design, however pembrolizumab can also be administered as 400mg every 6 weeks [Q6W].)
Additional tests or investigations	
List price and average cost of a course of treatment	£2,630 per 100mg/4ml concentrate for solution for infusion vial. Two vials are required for a Q3W dose.
Patient access scheme (if applicable)	There is a patient access scheme (PAS) agreed with NHS England, which is a simple discount; see Appendix I.

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

1.3.1 Health condition

Head and neck cancer is a general term that covers different cancers that start in the tissues in the head and neck area, including the oral cavity, pharynx (throat – includes nasopharynx, oropharynx and hypopharynx) and larynx (voice box) (Figure 1) (7, 8). Squamous cells are found in the outer layer of skin and in the mucous membranes, which are the moist tissues that line body cavities such as the airways and intestines. 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. Head and neck cancers can also begin in the salivary glands, sinuses, or muscles or nerves in the head and neck, but these types of cancer are much less common than squamous cell carcinomas (9). HNSCC typically develops in the mucous membranes of the mouth, nose and throat (10). HNSCC is caused by a variety of factors that can alter the DNA in cells. The strongest risk factors for developing this form of cancer are tobacco use (including smoking or using chewing tobacco) and heavy alcohol consumption. In addition, studies have shown that infection with certain strains of human papillomavirus (HPV) is linked to the development of HNSCC. HPV infection accounts for the increasing incidence of HNSCC in younger people (10). HPV-positive and HPV-negative HNSCC represent two distinct biologies with different clinical presentations and prognosis (11). HPV infection is more specifically linked to oropharyngeal cancer, where HPV infection has been consistently associated with more favourable outcomes (12).

Figure 1. Anatomical sites of HNSCC development

Head and neck squamous cell carcinoma (HNSCC) arises from the mucosal epithelium of the oral cavity (lips, buccal mucosa, hard palate, anterior tongue, floor of mouth and retromolar trigone), nasopharynx, oropharynx (palatine tonsils, lingual tonsils, base of tongue, soft palate, uvula and posterior pharyngeal wall), hypopharynx (the bottom part of the throat, extending from the hyoid bone to the cricoid cartilage) and larynx. Human papillomavirus-associated HNSCCs arise primarily from the palatine and lingual tonsils of the oropharynx, whereas tobacco-associated HNSCCs arise primarily in the oral cavity, hypopharynx and larynx (7). Source: Johnson et al. 2020 (7).

In England in 2022, there were 9,997 diagnoses of the cancers of cancers of the oral cavity, oropharynx, larynx, and hypopharynx (13). Overall, malignant neoplasm of the lip, oral cavity or pharynx accounted for roughly 2.5% of cancer registrations for that year (14). In England in 2022-23, there were 30,516 finished consultant episodes (FCE), and 27,675 admissions with a primary diagnosis of malignant neoplasm of the lip, oral cavity or pharynx (ICD-10 codes C00-C14), resulting in 17,297 day cases and 79,575 FCE bed days (15). Head and neck cancer is the 8th most common cancer in the UK. Incidence rates in the UK for head and neck cancer are highest in people aged 70-74 (2016-2018). Over the last decade, incidence rates in the UK have increased by almost a sixth (16%) (16), and in the UK between 2017-2019, there were 4,143 deaths from head and neck cancer. The European age-standardised mortality rate per 100,000 of the population in the UK in 2017-2019 was 3.5 in females and 10.2 in males (16).

The symptoms of HNSCC may include a lump in the neck or a sore in the mouth or throat that does not heal, a sore throat that does not go away, difficulty or pain in swallowing and a change or hoarseness in the voice. Other symptoms that may affect specific areas of the head and

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neck include bleeding of the mouth, swelling of the jaw, ear pain, headaches, and paralysis of the muscles in the face, or pain in the face, chin or neck (17). 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 v8 (Figure 2) (18). HNSCC tumour staging is complex and based on the location of the 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.

The long-term survival of patients with HNSCC depends on several factors, mainly the origin/site of the cancer and the stage of the disease at diagnosis; the 5-year survival for localised HNSCC is 86%, decreasing to 69% for locally advanced and 40% for metastatic disease (16, 19). The 10-year survival rate of patients with advanced HNSCC can be as low as 10% (20). If the disease is diagnosed at an early stage the primary treatment is surgical resection of the tumour where possible, however recurrence of the tumour is a major driver of mortality and comorbidities in the management of HNSCC, posing a greater challenge than seen in many other types of cancer. Up to 56% of LA HNSCC patients experience disease recurrence following treatment, either locoregionally or as distant metastases, usually within 2 years following initial treatment, contributing to poor survival outcomes (21, 22). The recurrence rate for LA HNSCC is notably higher than in many other cancers, and is high even among patients who achieved a complete response after initial treatment (23, 24). Treatment of recurrent disease is often especially difficult due to factors such as prior therapies altering tumour cell biology, the infiltrative and multifocal nature of the disease, and the often significant morbidity and deteriorating performance status in patients who progress on initial therapy, further limiting treatment options (25).

Locally advanced HNSCC is associated with considerable burden on patients daily living (26). Depending on the location and size of the tumour, the disease (as well as the effects of treatments, such as surgery and radiotherapy) can have a severe impact on a patient's ability to speak, swallow, breath, see, smell, and taste (27, 28). These can therefore lead to a debilitating impact on patients' general function, including their ability to carry out day-to-day basic self-care, home roles, work, and leisure activities (26).

The disease and its current treatments also often have considerable negative impact on patients' quality of life (29). Severe pain is linked to reduced overall 5-year survival rates in

oral cancer (31% in patients with severe pain vs. 52% in patients without) and pharyngeal cancer (33% in patients with severe pain vs. 52% without) (30). Head and neck cancer is also associated with a higher suicide rate: 37.9 compared to 11.8 per 100,000 person-years for the general population, this is the second highest rate among all cancer types and 3 times higher than the rate for the general population (31, 32). Due to the high likelihood of recurrence of the tumour, patients who have undergone treatment for HNSCC also experience a quality of life impact from the fear of recurrence (24, 33). In addition to the burden on the patients themselves, the caregivers of patients with HNSCC also experience a considerable burden in terms of psychological distress, physical and social functioning, and quality of life (34-36).

Figure 2. TNM staging of HNSCC

		Primary Tumour (T Stage)					Distant metastasis (M Stage)
		T1 <2 cm	T2 2-4 cm	T3 >4 cm	T4a + Invasion	T4b + Invasion	M1
Regional Lymph Nodes (N Stage)	N0	I-II Localised HNSCC (Surgery or RT)		III-Ivb Locoregionally Advanced			Metastatic HNSCC (IVc) Chemotherapy (EXTREME regimen); Erbitux; Keytruda; Opdivo.
	III Locoregionally Advanced (Often resectable; surgery, CRT or RT)			IVa Locoregionally Advanced (Potentially resectable; surgery, CRT or RT)	IVb Locoregionally Advanced (Unresectable, CRT or RT)		
	N1 <3 cm						
	N2 3-6 cm	IVa Locoregionally Advanced (Potentially resectable; surgery, CRT or RT)					
	N3 >6 cm	IVb Locoregionally Advanced (Unresectable, CRT or RT)					

■ Localised HNSCC, Stage I-II

■ Locoregionally Advanced HNSCC, Stage III

■ Locoregionally Advanced HNSCC, Stage IVa

■ Locoregionally Advanced HNSCC, Stage IVb

■ Metastatic HNSCC, Stage IVc

Abbreviations: 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 (18).

Note: The decision problem for this appraisal is in patients with newly diagnosed, nonmetastatic, resectable locally advanced head and neck squamous head and neck squamous cell carcinoma (HNSCC) with stage III oropharyngeal p16-positive disease with tumour size T4 and node stage N0 to N2, or stage III or IVA oropharyngeal p16-negative disease, or stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status, with PD-L1 CPS≥1.

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1.3.2 Treatment pathway and proposed positioning

The treatment pathway used for head and neck cancer in the UK is described in the “*Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition*” and the “*Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up*” (1, 2).

Recommendations on the management of LA HNSCC differ based on tumour site. However, across sites the first consideration is usually whether the tumour is surgically resectable; surgical resection is usually the recommended treatment for tumours in the oral cavity and larynx while organ-preserving approaches tend to be considered first for tumours of the oropharynx and hypopharynx, with surgical resection reserved for larger or more aggressive tumours. HNSCC tumours may be determined to be unresectable if they are too large or have invaded into nearby critical structures such that surgery to remove them is associated with unacceptable risk of severe and irreversible functional deficits (such as the loss of the ability to speak or swallow) or is technically impossible without causing death (such as in cases where the tumour is adjacent to the skull, spine or major blood vessels) (37). AJCC T4a HNSCC are often determined to be resectable while T4b are often determined to be unresectable (37). The standard of care for LA stage III and IV HNSCC cancers not treatable by surgery is concomitant definitive RT with cisplatin.

The current SOC treatment for patients with newly diagnosed Stage III-IV resectable LA HNSCC consists of surgical resection of the tumour and neck lymph node dissection, followed by either RT alone or, for patients with post-surgical high-risk pathological features (extranodal extension and/or positive surgical margins), in combination with cisplatin.

NICE guideline NG36 “*Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over*” was last updated in June 2018 (38). In patients with locally advanced disease eligible for resection and who can tolerate chemotherapy, NG36 makes the recommendations described below for tumours of the larynx and hypopharynx, NG36 does not provide any recommendations for treatment of advanced tumours of the oral cavity or oropharynx. No immune-oncologic therapies are mentioned for these patients.

- Squamous cell carcinoma of the larynx:
 - Offer people with T3 squamous cell carcinoma of the larynx surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.

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- For people with T4a squamous cell carcinoma of the larynx consider surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.
- Squamous cell carcinoma of the hypopharynx:
 - Offer adjuvant radiotherapy to people having surgery as their primary treatment. Add concomitant chemotherapy if appropriate.

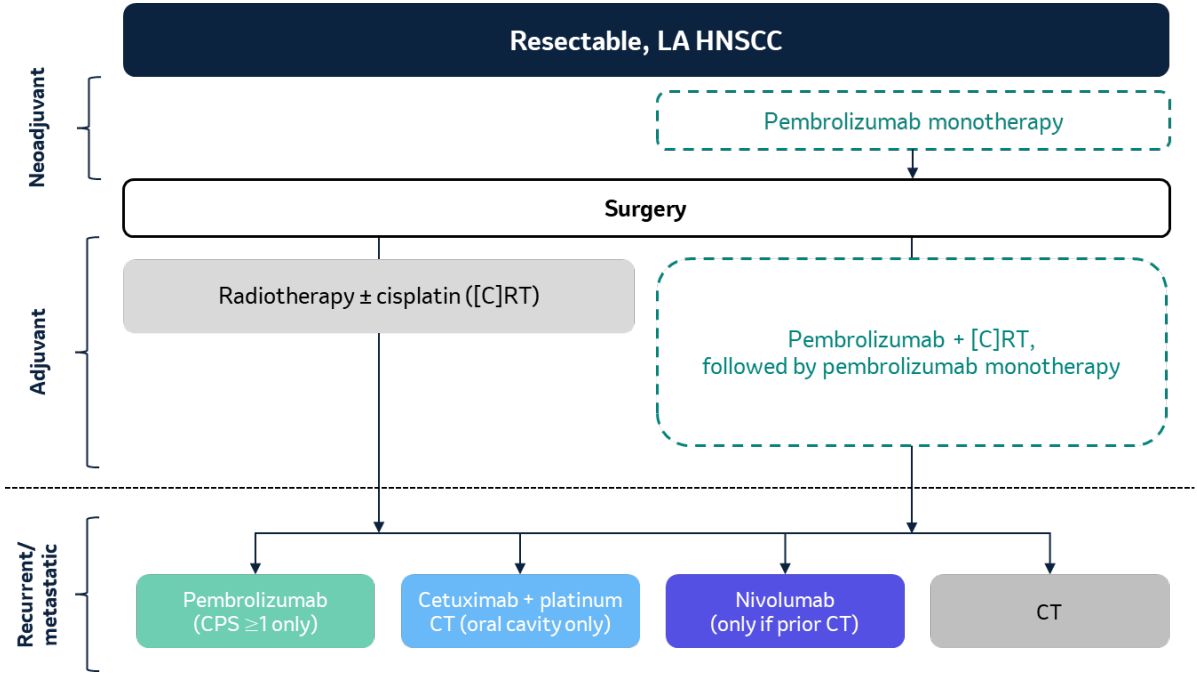
The published NICE technology appraisal guidance for HNSCC, in both LA and recurrent/metastatic settings, is summarised in Table 3. The current UK treatment pathway, including the proposed positioning of pembrolizumab, is illustrated in Figure 3.

Table 3. Published NICE technology appraisal guidance for the management of HNSCC

ID	Recommendation
Similarly positioned therapies (locally advanced HNSCC)	
TA145 (25-JUN-2008)	Cetuximab in combination with radiotherapy is recommended as a treatment option only for patients with locally advanced squamous cell cancer of the head and neck whose Karnofsky performance-status score is 90% or greater and for whom all forms of platinum-based chemoradiotherapy treatment are contraindicated.
Subsequent therapies (recurrent/metastatic HNSCC)	
TA736 (20-OCT-2021)	Nivolumab is recommended as an option for treating recurrent or metastatic squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy, only if: - the disease has progressed within 6 months of having chemotherapy and - the company provides it according to the commercial arrangement.
TA661 (25-NOV-2020)	Pembrolizumab is recommended as an option for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more. This is only if: - pembrolizumab is given as a monotherapy - pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and - the company provides pembrolizumab according to the commercial arrangement.
TA473 (31-AUG-2017)	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 and - when the company provides the drug in line with the commercial access agreement with NHS England.

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Figure 3. The place of perioperative pembrolizumab in the UK treatment pathway for LA HNSCC



Abbreviations: CPS, combined positive score; CT, chemotherapy.
Dotted lines indicated the proposed positioning of perioperative pembrolizumab.

NICE TA145 recommends cetuximab in combination with radiotherapy as a treatment option only for patients with locally advanced squamous cell cancer of the head and neck whose Karnofsky performance-status score is 90% or greater and for whom all forms of platinum-based chemoradiotherapy treatment are contraindicated. The clinical evidence base for TA145 was the Bonner et al. trial for which patients were ineligible if they had undergone surgery or had previously received radiotherapy for head and neck cancer (3). Subsequent clinical trials (e.g. RTOG 1016 and De-ESCaLATE HPV) have indicated that cetuximab in combination with radiotherapy is inferior to platinum-based chemoradiotherapy (5, 6), which further supports the TA145 restriction and is likely to increase clinician hesitancy to use this regimen. Accordingly, clinical expert advice to MSD is that use of cetuximab in this indication is now very rare and it is reserved only for unresectable patients with renal impairment who are not suitable for platinum chemotherapy. Therefore, as the indication under consideration in this appraisal is for patients who are receiving surgery (versus the non-surgical population for which cetuximab is available), and as the practical use of cetuximab in the LA HNSCC setting in UK clinical practice is very low, cetuximab plus radiotherapy is not a relevant comparator for the current decision problem.

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The standard of care (SOC) for resectable locally advanced HNSCC has remained relatively constant since 2004, when two pivotal randomised trials (European Organization for Research and Treatment of Cancer [EORTC] #22931 and Radiation Therapy Oncology Group [RTOG] #9501 (39, 40)) first established the addition of cisplatin to postoperative radiotherapy as the recommended treatment regimen for high-risk disease, and recurrence rates remain high: approximately 50% of patients experience disease recurrence and the 5-year overall survival remains below 50% for high-risk patients. Over the intervening 20 years, the SOC for this patient population has not changed and there continues to be no approved adjuvant therapies that can be administered after completion of postoperative locoregional treatment (41). Several trials of adjuvant immunotherapies have been conducted in this area with few showing meaningful benefit (42, 43).

Furthermore, should the disease recur or progress, this frequently manifests as advanced inoperable or metastatic disease which is linked to complex disease management, and ultimately increased risk of death regardless of any subsequent treatment options. The median survival for recurrent or metastatic HNSCC is only approximately 12 months (21, 44). Accordingly, new treatment strategies to decrease rates of recurrence and distant metastases of HNSCC are needed to improve outcomes for this patient population. Owing to the limited progress in this area, there are currently no NICE-recommended neoadjuvant or adjuvant treatments for HNSCC for use in the NHS. The availability of pembrolizumab as an effective perioperative (neoadjuvant followed by adjuvant) therapy in this indication therefore presents the first meaningful advancement in this setting in over 20 years and represents a considerable step-change in the management of resectable locally advanced HNSCC.

1.3.3 Treatment setting

Pembrolizumab as monotherapy will be administered to patients with resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults [REDACTED]. Pembrolizumab, both as neoadjuvant and adjuvant treatment, will be administered in the secondary care setting.

1.4 Equality considerations

Socioeconomic, sex-based, and racial/ethnic disparities in head and neck cancer have been documented in the UK (16, 45, 46), including:

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- The incidence rate of head and neck cancers in males is more than double that of females.
- Incidence rates for head and neck cancer are lower in the Asian and Black ethnic groups, and in people of mixed or multiple ethnicity, compared with the White ethnic group, in England (however, incidence rates in females are higher in the Asian ethnic group than in the White ethnic group).
- People living in the most deprived areas have almost double the incidence rate of head and neck cancer compared to those living in the least deprived areas.
- People living in the most deprived areas were more likely to be diagnosed with head and neck cancer at a late stage than those living in the least deprived areas (reasons may include lower health literacy, poorer communication of healthcare needs and poorer access to dental services).
- There is significant geographic variation in mortality rates. The integrated care board with the highest mortality rate was double the rate of the integrated care board with the lowest rate and people living in the most deprived areas have more than double the mortality rate of those living in the least deprived areas.

2 Clinical effectiveness

Summary of key clinical effectiveness information

Randomised controlled trial:

- They KEYNOTE-689 study was identified in a SLR conducted with eligibility criteria aligned with the decision problem of this appraisal with a search date of 31-MAR-2025. The SLR identified the KEYNOTE-689 study as the only study that investigated pembrolizumab in the indication of interest to this appraisal.
- KEYNOTE-689 is a phase 3, multicentre, open-label, randomised, active-controlled trial conducted at 192 sites across three geographic regions. Participants were randomly assigned in a 1:1 ratio to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care (pembrolizumab + SOC group) or to receive standard care alone (SOC group). Across the UK, there were six study sites which recruited 19 patients.
- The latest available results from the KEYNOTE-689 study are from the first interim analysis (IA1) with a database cut-off date of 25-JUL-2024, which are reported in this submission. Median actual follow-up time was 2.26 years (range 0.04 years to 5.54 years) for all patients in the study and 2.25 years (range 0.04 years to 5.54 years) in patients with baseline PD-L1 CPS ≥ 1 . The KEYNOTE-689 study is ongoing and may provide additional evidence in the next 12 months for the indication being appraised. Results for the subgroup of patients with PD-L1 ≥ 1 CPS are presented in this section.
- A statistically significant and clinically meaningful improvement in EFS per RECIST 1.1 as assessed by BICR was observed in the pembrolizumab + SOC group compared with the SOC group (HR: 0.70; 95% CI: 0.55, 0.89; $p=0.00140$, which is below the p-value boundary of 0.0124).
- The OS HR estimate favoured pembrolizumab + SOC versus SOC (HR:0.72; 95% CI: 0.56, 0.94; nominal $p=0.00666$) (per prespecified multiplicity strategy, OS was not formally tested in CPS ≥ 1 population at IA1).
- There was a statistically significant and clinically meaningful improvement in mPR based on BIPR in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 9.8% (95% CI: 7.0, 13.3; $p<0.00001$).

- There was an improvement in pCR rate based on BIPR in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 3.1% (95% CI: 1.6, 5.6; nominal p=0.0006).
- Mean change from baseline EORTC QLQ-C30 scores were similar between the pembrolizumab + SOC and SOC groups in the CPS ≥ 1 population at post-adjuvant RT $\pm$ cisplatin Week 25 and Week 51. EQ-5D 5L VAS scores in the pembrolizumab + SOC and in the SOC groups were similar and remained stable at post adjuvant RT $\pm$ cisplatin Week 25 and Week 51.

Meta-analysis and indirect treatment comparison

- No indirect comparisons or mixed treatment comparisons were carried out as the KEYNOTE-689 study provides direct evidence for the treatment comparison of relevance to this appraisal.

Safety

- Pembrolizumab as neoadjuvant and continued as adjuvant treatment in combination with radiotherapy $\pm$ cisplatin followed by pembrolizumab monotherapy in participants with Stage III-VA resectable LA HNSCC has a manageable safety profile that is generally consistent with the well-established safety profile of pembrolizumab monotherapy and the individual safety profiles of RT and cisplatin. No new safety concerns for pembrolizumab are identified.

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 National Institute for Health and Care Excellence (NICE) guidance (47, 48), according to a pre-specified protocol to identify relevant studies that investigated pembrolizumab and any relevant comparator treatments for the indication of interest in this appraisal. Searches for the SLR were executed on 31-MAR-2025, please refer to Appendix B for full details of the process and methods undertaken.

2.2 List of relevant clinical effectiveness evidence

An SLR was performed to identify all relevant published and unpublished RCTs relating to pembrolizumab as per the decision problem of this appraisal. The SLR identified the KEYNOTE-689 study as the only study that investigated pembrolizumab in the indication of

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interest to this appraisal (Table 4). Further details on the findings of the SLR are provided in Appendix B.

Table 4. Clinical effectiveness evidence

Study	KEYNOTE-689
Study design	Phase III, randomised, active-controlled, multicentre, open-label study.
Population	Eligible participants were 18 years of age or older and had newly diagnosed, nonmetastatic, resectable locally advanced HNSCC with either: • Stage III oropharyngeal p16-positive disease with tumour size T4 and node stage N0 to N2, or • Stage III or IVA oropharyngeal p16-negative disease, or • Stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status. Participants had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability), were eligible for primary surgery, and provided newly obtained tumour tissue for programmed death ligand 1 (PD-L1) and human papillomavirus (HPV) analysis.
Intervention(s)	Neoadjuvant and adjuvant pembrolizumab in addition to standard care.
Comparator(s)	Standard care alone. (Standard care was surgery and adjuvant radiotherapy with or without concomitant cisplatin.)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem†	• Event-free survival (EFS) • Overall survival (OS) • Major pathological response (mPR) • Pathological complete response (pCR) • Patients reported outcomes (EORTC QLQ-C30, EQ-5D-5L) • Adverse events

Abbreviations: EFS: event-free survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life questionnaire; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; HNSCC: head and neck squamous cell carcinoma; mPR: major pathological response; OS: overall survival; pCR: pathological complete response; PD-L1 programmed death-ligand 1.

† Outcomes in bold are incorporated into the economic model.

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2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Summary of the methodology of the KEYNOTE-689 study

KEYNOTE-689 is a Phase III, randomised, active-controlled, multisite, open-label study of pembrolizumab as neoadjuvant therapy and pembrolizumab in combination with standard of care radiotherapy with/without cisplatin as post-surgical adjuvant therapy in treatment-naïve participants with newly diagnosed Stage III/IVA, resectable LA HNSCC (Figure 4). A summary of the methodology of the KEYNOTE-689 study is shown in Table 5. A detailed description of the methodology of this study is provided in Appendix L.

Table 5. Summary of trial methodology

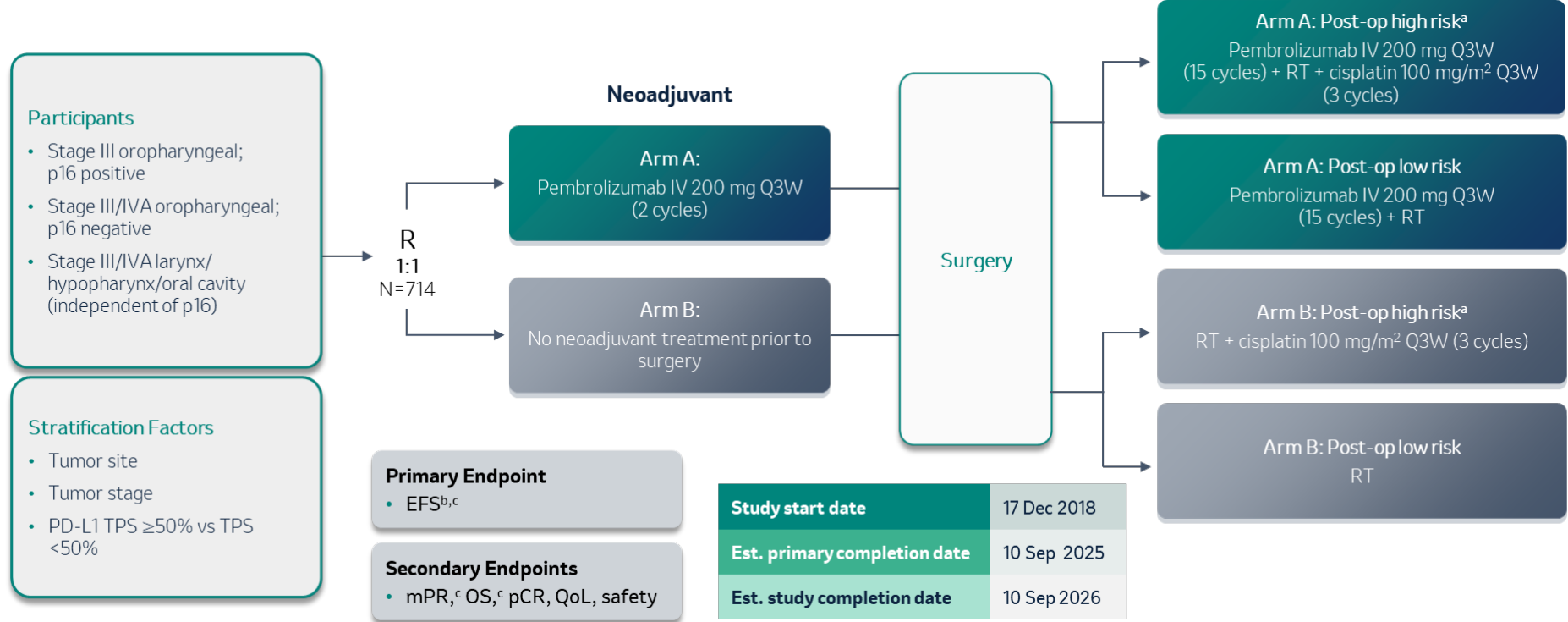
Study name	KEYNOTE-689
Trial design	Phase III, randomised, active-controlled, multicentre, open-label study.
Eligibility criteria for participants	Eligible participants were 18 years of age or older and had newly diagnosed, nonmetastatic, resectable locally advanced HNSCC with either: • Stage III oropharyngeal p16-positive disease with tumour size T4 and node stage N0 to N2, or • Stage III or IVA oropharyngeal p16-negative disease, or • Stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status. Participants had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability), were eligible for primary surgery, and provided newly obtained tumour tissue for programmed death ligand 1 (PD-L1) and human papillomavirus (HPV) analysis.
Settings and locations where the data were collected	Multinational trial with locations in: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Ireland, Israel, Japan, Poland, Portugal, Russian Federation, South Korea, Spain, Switzerland, Taiwan, United Kingdom, Ukraine, United States.
Trial drugs	• Pembrolizumab (200 mg intravenously [IV] every three weeks [Q3W] for two cycles) as neoadjuvant therapy prior to surgery, followed by either pembrolizumab (200 mg IV Q3W for 15 cycles) plus standard-of-care radiotherapy with cisplatin (100 mg/m² IV Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients or pembrolizumab (200 mg IV Q3W for 15 cycles) plus standard-of-care radiotherapy without cisplatin as adjuvant therapy following surgery for low-risk patients; or • No neoadjuvant therapy prior to surgery, followed by either standard-of-care radiotherapy with cisplatin (100 mg/m² IV

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	Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients or standard-of-care radiotherapy without cisplatin as adjuvant therapy following surgery for low-risk patients. (Participants were categorised as high risk if extranodal extension and/or positive margins (<1 mm in the primary resection specimen) of resection were assessed to be present and were categorised as low risk if these pathological features were absent.)
Primary outcomes	The primary end point is event-free survival assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumours, version 1.1.
Other outcomes used in the economic model/specified in the scope	Key secondary end points are major pathological response (mPR), ($\leq 10\%$ residual viable invasive squamous-cell carcinoma) assessed by blinded independent pathological review and overall survival. Other secondary end points include pathological complete response as assessed by blinded independent pathological review and safety and side-effect profile.
Pre-planned subgroups	• Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx) • Tumour Stage (III vs. IVA) • PD-L1 status (TPS $\geq 50\%$ versus TPS < 50%) • Age category (<65 vs. ≥ 65 years) • Sex (female vs. male) • Race (white vs. all others) • Smoking status (never vs. former vs. current) • Geographical regions (North America vs. European Union vs. Rest of the World)

Abbreviations: HPV: human papillomavirus; IV: intravenous; PD-L1: programmed death ligand 1; Q3W: every 3 weeks; TPS: tumour proportion score.

Figure 4. Summary diagram of the KEYNOTE-689 study



EFS: event-free survival; mPR: major pathological response; OS: overall survival; pCR: pathological complete response; PD-L1 TPS: programmed death ligand 1 total positive score; Q3W: every 3 weeks; QoL: quality of life; RT: radiotherapy;
^aHigh-risk definition: Positive margins (<1 mm in the primary resection specimen), positive extranodal extension. ^bEFS: time from the date of randomization to the date of first record of any of the following events: radiographic disease progression; local or distant recurrence, as assessed with imaging or biopsy as indicated; or death due to any cause. ^cAnalysis populations will include CPS cutoffs of CPS ≥ 10 , CPS ≥ 1 , and all participants

2.3.2 Baseline characteristics of trial participants

In participants with PD-L1 CPS $\geq$ 1, demographic and baseline characteristics were generally similar in both treatment groups (Table 6). Most participants were male, white and of not Hispanic or Latino ethnicity. The overall median age was 60.0 (22 to 87) years. Most participants across both groups had an overall cancer staging at baseline of IVA, and 56.9% of participants across both groups had an ECOG-PS score of 0.

Table 6. KEYNOTE-689 study participant baseline characteristics – participants with PD-L1 CPS $\geq$ 1, ITT population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	
Sex						
Male	272	(78.4)	265	(79.1)	537	(78.7)
Female	75	(21.6)	70	(20.9)	145	(21.3)
Age (Years)						
< 65	237	(68.3)	220	(65.7)	457	(67.0)
$\geq$ 65	110	(31.7)	115	(34.3)	225	(33.0)
Mean	59.5		60.4		59.9	
SD	10.0		10.0		10.0	
Median	60.0		61.0		60.0	
Range	29 to 82		22 to 87		22 to 87	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.3)	1	(0.1)
Asian	47	(13.5)	42	(12.5)	89	(13.0)
Black Or African American	8	(2.3)	9	(2.7)	17	(2.5)
Multiple	9	(2.6)	16	(4.8)	25	(3.7)
American Indian Or Alaska Native, Black Or African American, White	2	(0.6)	2	(0.6)	4	(0.6)
American Indian Or Alaska Native, White	1	(0.3)	7	(2.1)	8	(1.2)
Black Or African American, White	4	(1.2)	6	(1.8)	10	(1.5)
Native Hawaiian Or Other Pacific Islander, Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander, White	0	(0.0)	1	(0.3)	1	(0.1)
White, Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	1	(0.3)	2	(0.3)
White	273	(78.7)	260	(77.6)	533	(78.2)
Missing	9	(2.6)	6	(1.8)	15	(2.2)

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	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Ethnicity						
Hispanic Or Latino	54	(15.6)	43	(12.8)	97	(14.2)
Not Hispanic Or Latino	285	(82.1)	285	(85.1)	570	(83.6)
Not Reported	4	(1.2)	4	(1.2)	8	(1.2)
Unknown	0	(0.0)	2	(0.6)	2	(0.3)
Missing	4	(1.2)	1	(0.3)	5	(0.7)
Region						
North America	63	(18.2)	48	(14.3)	111	(16.3)
European Union	134	(38.6)	139	(41.5)	273	(40.0)
Rest of World	150	(43.2)	148	(44.2)	298	(43.7)
PD-L1 Status by TPS Score						
TPS <50%	244	(70.3)	228	(68.1)	472	(69.2)
TPS ≥50%	103	(29.7)	107	(31.9)	210	(30.8)
Primary Tumour Site						
Oropharynx	34	(9.8)	37	(11.0)	71	(10.4)
Oral Cavity	210	(60.5)	205	(61.2)	415	(60.9)
Larynx	77	(22.2)	67	(20.0)	144	(21.1)
Hypopharynx	26	(7.5)	25	(7.5)	51	(7.5)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
ECOG PS						
0	187	(53.9)	201	(60.0)	388	(56.9)
1	160	(46.1)	134	(40.0)	294	(43.1)
HPV Status						
Positive	11	(3.2)	14	(4.2)	25	(3.7)
Negative	336	(96.8)	320	(95.5)	656	(96.2)
Unknown	0	(0.0)	1	(0.3)	1	(0.1)
Overall Cancer Staging at Baseline						
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■
Cancer T Staging at Baseline						
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■
■	■	■	■	■	■	■

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	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Cancer N Staging at Baseline						
Cancer M Staging at Baseline						
Smoking Status						
Cigarette use (packs per year)						
Alcohol use						
SD=Standard deviation. European Union category in this table includes European Economic Area, United Kingdom and Switzerland. Database Cutoff Date: 25JUL2024.						

2.3.3 Description of the methods used for expert elicitation or expert opinion

An advisory board was held on 15-MAY-2025 featuring seven external clinical advisors (5 clinical/medical oncologists, 2 surgeons) experienced in the clinical management of head and neck cancer in the UK. The advisory board objectives were to understand the current treatment UK pathway, discuss the generalisability of the trial data to the UK setting and to

seek advice on key assumptions used to inform the health economic modelling for the NICE submission.

A meeting report was compiled after the advisory board meeting was conducted (49). How the insights from the advisory board we used to inform the cost-effectiveness analyses are described in section 3.

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

A description of the statistical analysis of the KEYNOTE-689 study is provided below. Further details are provided in the KEYNOTE-689 clinical study report and in Appendix M.

2.4.1 Objectives, hypotheses, and endpoints

The objectives, hypotheses, and endpoints of the KEYNOTE-689 study are summarised in Table 7.

Table 7. KEYNOTE-689 study objectives, hypotheses, and endpoints

Objective/Hypothesis	Endpoint(s)
Primary	
- Objective 1: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to EFS per RECIST 1.1 as assessed by BICR in participants whose tumours express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. - Hypothesis #1: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SOC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS per RECIST 1.1 by BICR in participants whose tumours express PD-L1 CPS≥10. - Hypothesis #2: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SOC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS per RECIST 1.1 by BICR in participants whose tumours express PD-L1 CPS≥1. - Hypothesis #3: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to standard of care (SOC) surgical	- EFS – time from the date of randomization to the date of first record of any of the following events: - radiographic disease progression, - radiographic disease progression during the neoadjuvant phase that precludes surgery, - local or distant disease progression or recurrence as assessed with imaging or biopsy as indicated, - death due to any cause (a secondary primary malignancy is not considered an EFS event)

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resection followed by RT ± cisplatin adjuvant therapy with respect to EFS per RECIST 1.1 by BICR in all participants.	
Secondary	
• Objective 2: To compare pembrolizumab neoadjuvant therapy to no neoadjuvant therapy with respect to the rate of major pathological response (mPR) as assessed by the central pathologist at the time of definitive surgery in participants whose tumours express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. ○ Hypothesis #4: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in participants whose tumours express PD-L1 CPS≥10. ○ Hypothesis #5: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in participants whose tumours express PD-L1 CPS≥1. ○ Hypothesis #6: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in all participants.	• mPR – having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumour specimen and all sampled regional lymph nodes
• Objective 3: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to OS in participants whose tumours express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. ○ Hypothesis #7: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SOC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in participants whose tumours express PD-L1 CPS≥10. ○ Hypothesis #8: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SOC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in participants whose tumours express PD-L1 CPS≥1. ○ Hypothesis #9: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SOC surgical resection followed by RT	• OS – time from the date of randomization to the date of death due to any cause

± cisplatin adjuvant therapy with respect to OS in all participants.	
Objective 4: To evaluate the rate of pathological complete response (pCR) as assessed by the central pathologist at the time of definitive surgery in participants whose tumours express PD- L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status.	pCR – having no residual invasive squamous cell carcinoma within the resected primary tumour specimen and all sampled regional lymph nodes
Objective 5: To evaluate global health status/quality of life (QoL) and physical functioning scores using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30, and swallowing, speech and pain symptoms using the EORTC Head and Neck– Specific QoL questionnaire (EORTC QLQ-H&N35) in participants whose tumours express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status.	- EORTC QLQ C30- global health status/QoL scale (items 29 and 30) - EORTC QLQ-C30 physical functioning scale (items 1-5) - EORTC QLQ-H&N35 swallowing scale (items 35-38), speech scale (items 46, 53-54), and pain scale (items 31-34)
Objective 6: To determine the safety and tolerability of pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy.	- AEs - Study drug discontinuations due to AEs

2.4.2 Analysis populations

2.4.2.1 Efficacy analysis population

The Intention-to-Treat (ITT) population was the primary population for efficacy analyses in this study, which consists of all randomised participants. Participants were included in the treatment group to which they are randomised for the analysis of efficacy data using the ITT population.

2.4.2.2 Safety analysis population

Safety analyses were conducted in the All Participants as Treated (APaT) population, which consists of all randomised participants who received at least one dose of study intervention or surgery that is part of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This was the treatment group to which they are randomised except for participants who take incorrect study treatment for the entire treatment period; such participants were included in the treatment group corresponding to the study treatment actually received.

Analyses of laboratory or vital sign measurements included only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis assessed change from baseline, a baseline measurement was also required.

2.4.2.3 PRO analysis population

The PRO analyses are based on the PRO Full Analysis Set (FAS) population, defined as all randomised participants who have at least one PRO assessment available for the specific endpoint and have received treatment. Participants were analysed in the treatment group to which they are randomised.

2.4.3 Statistical methods

The key elements of the statistical analysis plan for the KEYNOTE-689 study are summarised in Table 8. A detailed description of the statistical analysis plan of this study is provided in Appendix M.

Table 8. Summary of the KEYNOTE-689 study statistical methods

Study design and overview	A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant therapy and Pembrolizumab plus Radiotherapy with and without Chemotherapy as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)
Treatment assignment and stratification	In this study, 714 participants have been enrolled, which will result in approximately 462 participants whose tumours express PD-L1 CPS$\geq$10 (based on a prevalence rate of ~65% of the CPS$\geq$10 participants among all participants) and approximately 680 participants whose tumours express PD-L1 CPS$\geq$1 (based on a prevalence rate of ~95% of the CPS$\geq$1 participants among all participants) will be randomized in a 1:1 ratio between 2 treatment arms: 1. Pembrolizumab as neoadjuvant therapy and in combination with RT $\pm$ cisplatin as adjuvant therapy after surgical resection (referred as pembrolizumab arm) 2. No neoadjuvant therapy and RT $\pm$ cisplatin as adjuvant therapy after surgical resection (referred as SOC arm) This study will be conducted as an open-label study. Stratification factors are as follows: - Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx) - Tumour Stage: III vs. IVA - PD-L1 status (TPS $\geq$ 50% vs. TPS<50%) This study will be conducted as an open-label study.
Analysis populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)

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	PRO: Full Analysis Set (FAS)
Primary endpoint	Event-free survival (EFS)
Key secondary endpoint	1. Major pathological response (mPR) 2. Overall survival (OS) 3. Pathological complete response (pCR)
Statistical methods for key efficacy analyses	The primary hypothesis for EFS and key secondary hypothesis for OS will be evaluated by comparing the pembrolizumab arm to the SOC arm using a stratified log-rank test. Estimation of the HR will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The key secondary hypothesis for mPR will be evaluated by comparing the pembrolizumab arm to the SOC arm with respect to the rate of mPR using the stratified Miettinen and Nurminen method with strata weighting by sample size. The between-treatment difference in percentages, its 95% CI and p-value will be provided.
Statistical methods for key safety analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, the analyses will be provided using the Miettinen and Nurminen (M&N) method.
Interim and final analyses	<u>Efficacy:</u> Two IAs will be performed. Results will be reviewed by an eDMC. These IAs and the final analysis (FA) are summarised below. • IA1: ○ Timing: ~207 EFS events in participants whose tumours express PD-L1 CPS$\geq$10 and ~6 months after last participant randomized (estimated to be 64 months after the first participant is randomized) ○ Testing: Inferential analysis for EFS, mPR and OS will be provided • IA2: ○ Timing: ~232 EFS events in participants whose tumours express PD-L1 CPS$\geq$10 and ~22 months after last participant randomized (estimated to be 80 months after the first participant is randomized) ○ Testing: Inferential analysis for EFS and OS will be provided • FA: ○ Timing: ~201 deaths in participants whose tumours express PD-L1 CPS$\geq$10 and ~34 months after last participant randomized (estimated to be 92 months after the first participant is randomized). ○ Testing: Inferential analysis for OS will be provided <u>Safety:</u> An interim safety analysis will be performed and reviewed by the eDMC when the first 15 participants in the pembrolizumab arm have completed RT during the post-surgery adjuvant treatment phase. Afterwards, the eDMC will review safety data periodically in the study.

Multiplicity	The overall Type I error across the primary endpoint (EFS) and the key secondary endpoints (mPR and OS) and across multiple populations is strongly controlled at $\alpha = 2.5\%$ (one-sided), with: $\alpha = 2.5\%$ initially allocated to the hypothesis for EFS in participants whose tumours express PD-L1 CPS≥ 10 (H1) Alpha can be reallocated using the graphical approach of Mauer and Bretz. Group sequential methods will be used to allocate alpha among the interim and final analyses for EFS and OS.
Sample size and power	The planned sample size is 714 participants, which will result in approximately 462 participants whose tumours express PD-L1 CPS≥ 10 and approximately 680 participants whose tumours express PD-L1 CPS≥ 1. For testing EFS in participants whose tumours express PD-L1 CPS≥ 10, the study has ~94.9% power to demonstrate that the pembrolizumab arm is superior to the SOC arm at a one-sided 2.5% alpha-level, if the underlying HR of EFS is 0.62. For the mPR endpoint, the study has >99.9% power to detect a true mPR rate improvement from 2% to 27% (i.e., a difference of 25 percentage points) at $\alpha = 0.05\%$ (one-sided) with ~462 participants whose tumours express PD-L1 CPS≥ 10. For testing OS in participants whose tumours express PD-L1 CPS≥ 10, the study has ~84.9% power to demonstrate that the pembrolizumab arm is superior to the SOC arm at a one-sided 2.45% alpha-level, if the underlying HR of OS is 0.65.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A critical appraisal of the KEYNOTE-689 trial using the Cochrane Collaboration's Risk of Bias tool (Version 2) is presented in Appendix B (section B3).

2.6 Clinical effectiveness results of the relevant studies

Summary of key RCT clinical effectiveness results

- The latest available results from the KEYNOTE-689 study are from the first interim analysis (IA1) with a database cut-off date of 25-JUL-2024, which are reported in this submission. Median actual follow-up time was 117.8 weeks for all patients in the study and 117.4 weeks in patients with baseline PD-L1 CPS ≥ 1 . The KEYNOTE-689 study is ongoing and may provide additional evidence in the next 12 months for the indication being appraised. Results for the subgroup of patients with PD-L1 ≥ 1 CPS are presented in this section.

- A statistically significant and clinically meaningful improvement in EFS per RECIST 1.1 as assessed by BICR was observed in the pembrolizumab + SOC group compared with the SOC group (HR: 0.70; 95% CI: 0.55, 0.89; $p=0.00140$, which is below the p -value boundary of 0.0124).
- The OS HR estimate favoured pembrolizumab + SOC versus SOC (HR:0.72; 95% CI: 0.56, 0.94; nominal $p=0.00666$) (per prespecified multiplicity strategy, OS was not formally tested in CPS ≥ 1 population at IA1, but these results showed a clinically meaningful trend towards significance).
- There was a statistically significant and clinically meaningful improvement in mPR based on BIPR in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 9.8% (95% CI: 7.0, 13.3; $p<0.00001$).
- There was an improvement in pCR rate based on BIPR in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 3.1% (95% CI: 1.6, 5.6; nominal $p=0.0006$).

The latest available results from the KEYNOTE-689 study are from the first interim analysis (IA1) with a database cut-off date of 25-JUL-2024, which are reported in this submission. Results for the subgroup of participants with PD-L1 CPS ≥ 1 are described in this section, results for the entire “all comer” overall KEYNOTE-689 participant population are provided in Appendix N. Patients with CPS ≥ 1 comprised 95.5% of the all comer overall trial population and the proportion of patients with CPS ≥ 1 was balanced between the two trial arms (95.4% in the SOC arm and 95.6% in the pembrolizumab + SOC arm). Note that PD-L1 status, measured using tumour proportion score (TPS), was a stratification factor at randomisation to ensure that the treatment groups were balanced with respect to this potential effect modifier.

2.6.1 KEYNOTE-689 PD-L1 CPS ≥ 1 participants results

2.6.1.1 *Disposition of participants*

The disposition of participants was similar in both treatment groups (Table 9). In the population of participants with PD-L1 CPS ≥ 1 , a total of 682 participants were randomised in the ITT population (347 in the pembrolizumab + SOC group, 335 in the SOC group). Median actual follow-up was 130.4 weeks (range 3.6 weeks to 282.1 weeks) in the pembrolizumab + SOC group and 101.8 weeks (range 2.1 weeks to 289.1 weeks) (Table 11).

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

In the neoadjuvant phase, [REDACTED] participants in the pembrolizumab + SOC group started study treatment, and of the [REDACTED] participants, [REDACTED] completed neoadjuvant study treatment. [REDACTED].

Following surgery, risk categorisation by central assessment found that in the pembrolizumab + SOC group [REDACTED] were at high risk and [REDACTED] were at low risk while in the SOC group [REDACTED] were at high risk and [REDACTED] were at low risk (Table 10).

In the adjuvant phase, [REDACTED] participants in the pembrolizumab + SOC group started study treatment, of which [REDACTED] completed adjuvant study treatment. In the SOC group, [REDACTED] patients started treatment of which [REDACTED] completed adjuvant study treatment.

Table 9. Disposition of participants (participants with PD-L1 CPS≥1, ITT population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	
Status for Neoadjuvant Study Treatment						
Started	[REDACTED]		[REDACTED]		[REDACTED]	
Completed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Discontinued	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Adverse Event	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Clinical Progression	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Lost To Follow-Up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Physician Decision	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Associated with COVID-19	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Progressive Disease	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Withdrawal By Subject	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Status Not Recorded	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Status for In-study Surgery						
Started	[REDACTED]		[REDACTED]		[REDACTED]	
Completed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Discontinued	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Tumour Found To Be Surgically Unresectable	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Status for Adjuvant Study Treatment						
Started	[REDACTED]		[REDACTED]		[REDACTED]	
Completed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Discontinued	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Adverse Event	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Associated with COVID-19	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Clinical Progression	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non-Compliance With Study Drug	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non-Study Anti-Cancer Therapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Physician Decision						
Associated with COVID-19						
Progressive Disease						
Withdrawal By Subject						
Participants Ongoing						
Status for Study Treatment (Overall)						
Started						
Completed						
Discontinued						
Adverse Event						
Associated with COVID-19						
Status for Study Treatment (Overall)						
Clinical Progression						
Lost To Follow-Up						
Non-Compliance With Study Drug						
Non-Study Anti-Cancer Therapy						
Physician Decision						
Associated with COVID-19						
Progressive Disease						
Withdrawal By Subject						
Participants Ongoing						
Status for Trial						
Discontinued						
Death						
Associated with COVID-19						
Lost To Follow-Up						
Withdrawal By Subject						
COVID-19 association unspecified, Subsequently died						
Participants Ongoing						
If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation. Database Cutoff Date: 25JUL2024						

Table 10. Summary of Post-Surgical Risk Categorization by Treatment Group, Participants With CPS $\geq$ 1, (ITT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Risk Category by Central Assessment						
HIGH RISK						
LOW RISK						
Missing						
Post-surgical pathological risk categorization of participants as either high or low risk was completed based on central (BIPR) pathological assessment of the surgically resected specimens from the primary tumour site and neck lymph nodes. Database Cutoff Date: 25JUL2024						

Table 11. Summary of Follow-Up Time (Weeks), Participants With CPS $\geq$ 1, (ITT Population)

	Pembrolizumab	SOC	Total
Participants in population	347	335	682
Theoretical follow-up time (weeks)^a			
Participants with data			
Mean			
SE			
Median			
Range			
Actual follow-up time (weeks)^b			
Participants with data			
Mean			
SE			
Median			
Range			
SE=Standard error. a: Calculated from the date of randomization until the database cutoff date, for all participants. This represents the length of the trial. b: Calculated from the date of randomization until the date of death or the database cutoff date if the participant is still alive. Database Cutoff Date: 25JUL2024			

2.6.1.2 Event free survival (EFS) by BICR

A statistically significant and clinically meaningful improvement in EFS per RECIST 1.1 as assessed by BICR was observed in the pembrolizumab + SOC group compared with the SOC group (HR: 0.70; 95% CI: 0.55, 0.89; p=0.00140, which is below the p-value boundary of 0.0124), representing a 30% reduction in the risk of an EFS event in the pembrolizumab + SOC group versus the SOC group (Table 12).

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Median EFS was 59.7 months in the pembrolizumab + SOC group compared with the median EFS of 29.6 months in the SOC group (Table 12). The EFS rate was higher in the pembrolizumab + SOC group than in the SOC group at all timepoints analysed (Table 12).

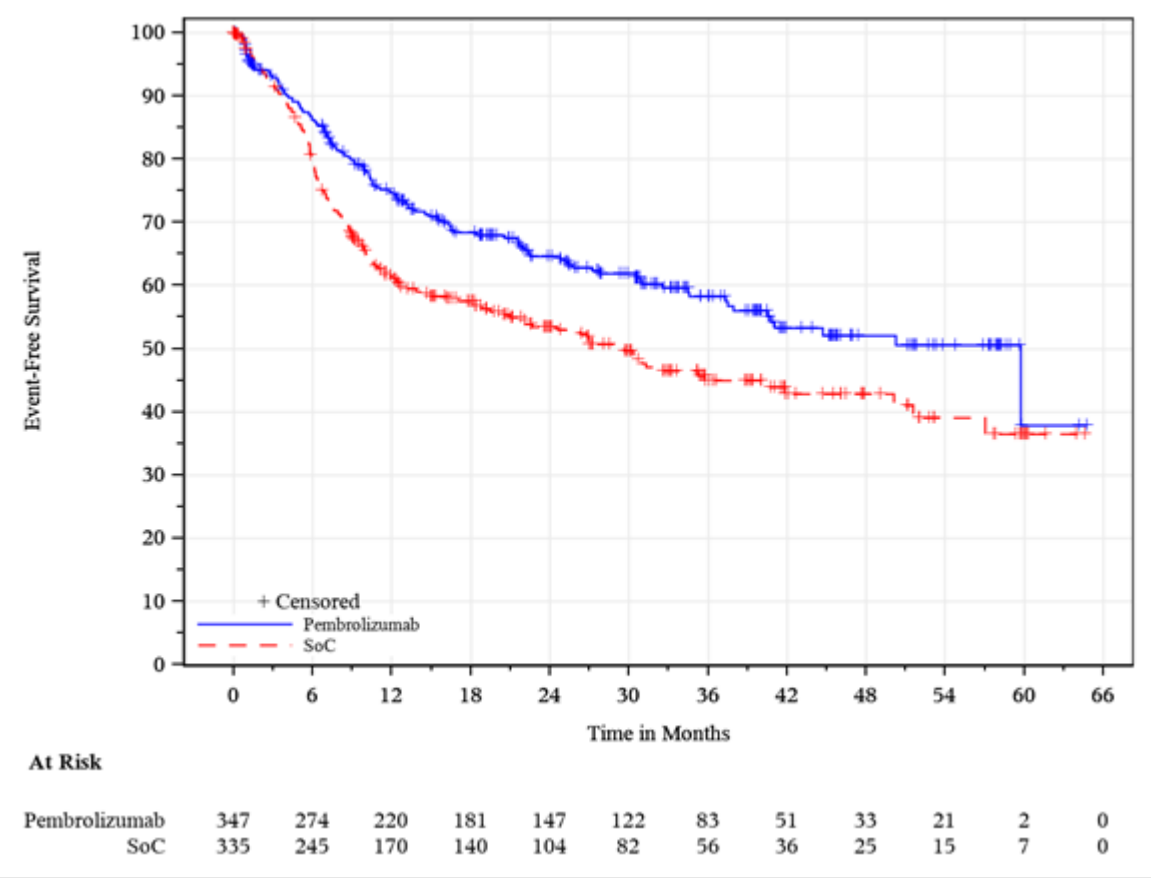
The KM plot for EFS shows that the pembrolizumab + SOC curve separated from the SOC curve at approximately 3 months and remained separated over time (Figure 5).

Table 12. Analysis of Event-Free Survival, Based on BICR per RECIST 1.1, (Participants with CPS $\geq$ 1, ITT Population)

	Pembrolizumab	SOC
	(N=347)	(N=335)
Number of Events (%)	128 (36.9)	156 (46.6)
Death	63 (18.2)	62 (18.5)
Distant PD	24 (6.9)	51 (15.2)
Local And Distant PD	4 (1.2)	6 (1.8)
Local PD/Recurrence	37 (10.7)	37 (11.0)
Number of Censored (%)	219 (63.1)	179 (53.4)
Last assessment showing no progression	216 (62.2)	168 (50.1)
Randomization	3 (0.9)	11 (3.3)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
[Q1, Q3]	[11.9, NR]	[6.9, NR]
Person-months	■	■
Event Rate / 100 Person-months	■	■
vs SOC		
Hazard Ratio (95% CI) ^b	0.70 (0.55, 0.89)	
p-value ^c	0.00140	
EFS Rate at month 6 (%) (95% CI)	■	■
EFS Rate at month 12 (%) (95% CI)	■	■
EFS Rate at month 24 (%) (95% CI)	■	■
EFS Rate at month 36 (%) (95% CI)	58.2 (51.9, 64.0)	44.9 (38.4, 51.2)
EFS Rate at month 48 (%) (95% CI)	■	■

a From product-limit (Kaplan-Meier) method for censored data.
b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
c One-sided p-value based on log-rank test stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
NR = Not reached.
Primary censoring rule.
Database Cutoff Date: 25JUL2024

Figure 5. Kaplan-Meier Plot of Event-Free Survival, Based on BICR per RECIST 1.1, (Participants with CPS≥1, ITT Population)



Primary censoring rule.
Database Cutoff Date: 25JUL2024

2.6.1.3 Overall survival

As per the prespecified multiplicity strategy, OS was not formally tested in the CPS≥1 population at IA1. Median actual follow-up time was 117.4 weeks in patients with baseline PD-L1 CPS ≥1. The OS HR estimate favoured pembrolizumab versus SOC (HR:0.72; 95% CI: 0.56, 0.94; nominal p=0.00666) (Table 13). Median OS was not reached in the pembrolizumab + SOC group compared with a median OS of 61.8 months in the SOC group (Table 13).

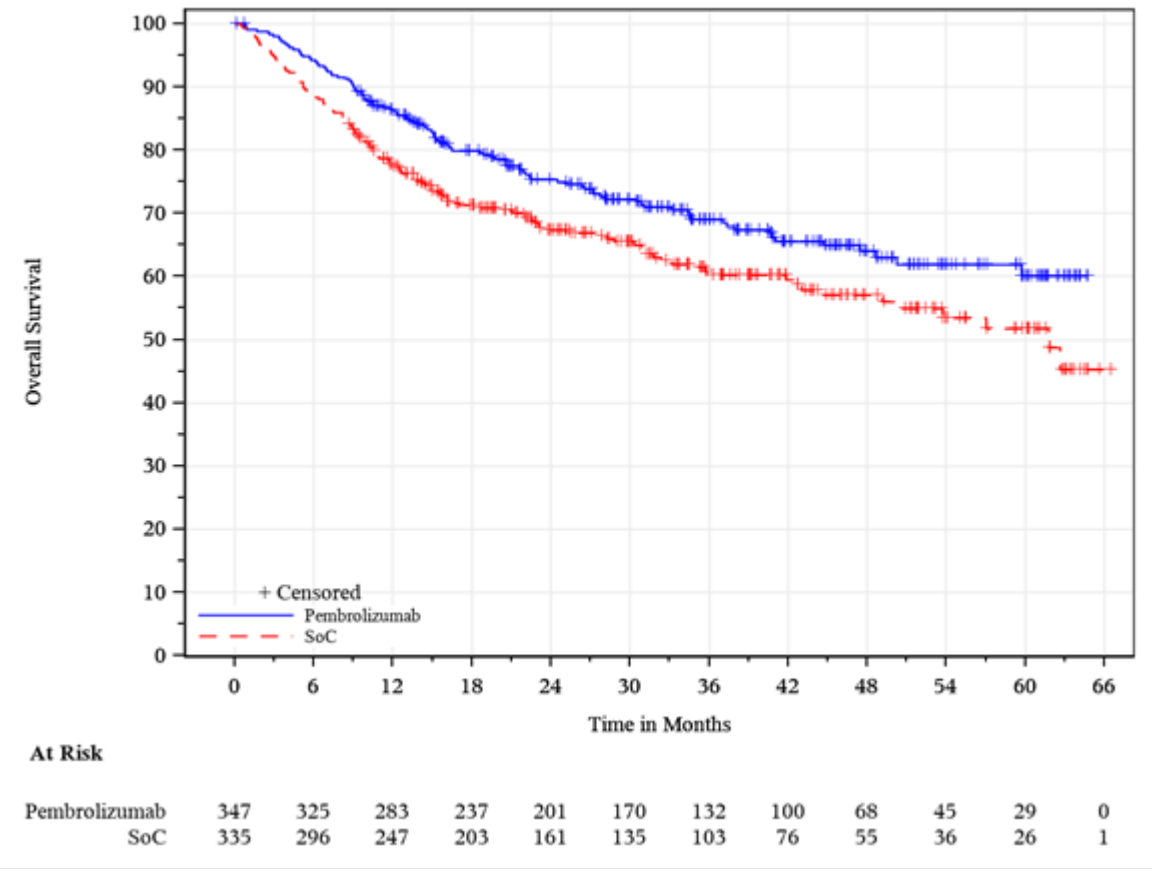
Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

The KM curves separated within the first 2 months and remained separated throughout the evaluation period in favour of pembrolizumab (Figure 6).

Table 13. Analysis of Overall Survival, (Participants with CPS $\geq$ 1, ITT Population)

	Pembrolizumab	SOC
	(N=347)	(N=335)
Number of Events (%)	106 (30.5)	128 (38.2)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
[Q1, Q3]	[24.5, NR]	[14.2, NR]
Person-months	■	■
Event Rate / 100 Person-months	■	■
vs SOC		
Hazard Ratio (95% CI) ^b	0.72 (0.56, 0.94)	
p-value ^c	0.00666	
OS Rate at month 6 (%) (95% CI)	■	■
OS Rate at month 12 (%) (95% CI)	■	■
OS Rate at month 24 (%) (95% CI)	■	■
OS Rate at month 36 (%) (95% CI)	69.0 (63.3, 74.0)	60.2 (54.1, 65.8)
OS Rate at month 48 (%) (95% CI)	■	■
OS Rate at month 60 (%) (95% CI)	■	■
a From product-limit (Kaplan-Meier) method for censored data. b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. c One-sided p-value based on log-rank test stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. NR = Not reached. Database Cutoff Date: 25JUL2024		

Figure 6. Kaplan-Meier Plot of Overall Survival, (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024.

2.6.1.4 Major Pathological Response (mPR) by BIPR

There was a statistically significant and clinically meaningful improvement in mPR based on BIPR in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 9.8% (95% CI: 7.0, 13.3; p<0. 00001), which was below the p-value boundary of 0.0005. The mPR rate was 9.8% for the pembrolizumab + SOC group; there were no participants in the SOC group with mPR (Table 14).

Table 14. Analysis of Major Pathological Response Based on BIPR Assessment, (Participants with CPS≥1, ITT Population)

Treatment	N	Number of mPR	mPR Rate (%) (95% CI)	Difference in % vs. SOC	
				Estimate (95% CI) ^a	p-Value ^b
Pembrolizumab	347	34	9.8 (6.9, 13.4)	9.8 (7.0, 13.3)	<0.00001
SOC	335	0	0.0 (0.0, 1.1)		

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

^a Based on Miettinen & Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
^b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
mPR = Major Pathological Response.
BIPR = Blinded independent pathologist review.
Database Cutoff Date: 25JUL2024.

2.6.1.5 Pathological Complete Response (pCR) by BIPR

There was an improvement in pCR rate based on BIPR in the pembrolizumab + SOC group compared with the SOC group with a difference in response rates of 3.1% (95% CI: 1.6, 5.6; nominal p■■■■). The pCR rate was 3.2% for the pembrolizumab + SOC group; there were no participants with pCR in the SOC group (Table 15).

Table 15. Analysis of Pathological Complete Response Based on BIPR Assessment, (Participants with CPS≥1, ITT Population)

Treatment	N	Number of pCR	pCR Rate (%) (95% CI)	Difference in % vs. SOC	
				Estimate (95% CI) ^a	p-Value ^b
Pembrolizumab	347	11	3.2 (1.6, 5.6)	3.1 (1.6, 5.6)	■■■■
SOC	335	0	0.0 (0.0, 1.1)		

^a Based on Miettinen & Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
^b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
pCR = Pathological Complete Response.
BIPR = Blinded independent pathologist review.
Database Cutoff Date: 25JUL2024.

2.6.1.6 EORTC QLQ-C30 and EORTC QLQ-H&N35

Mean change from baseline global health status/QoL scores ■■■■ (Table 16, Figure 7). The mean change from baseline in the global health status/QoL score showed ■■■■ (Table 16). ■■■■ were observed in the mean change from baseline in the global health status/QoL score ■■■■ (Table 16).

■■■■ were observed in the change in baseline for physical functioning at post adjuvant RT ± cisplatin Week 25 of Week 51 ■■■■ (Table 17).

In all participants, mean change from baseline EORTC QLQ-H&N35 swallowing, speech, and pain symptom scores ■■■■ (Table 18, Table 19). Mean change from baseline pain scores were ■■■■ (Table 20).

Global Health Status/QoL**Table 16. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 25 and Week 51 in EORTC QLQ-C30 Global Health Status/QoL, (Participants with CPS≥1, PRO FAS Population)**

	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■

^a Based on a constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), Tumour Stage: III vs. IVA and PD-L1 status (TPS ≥ 50% vs. TPS<50%) as pre-specified in the sSAP.
For baseline and Post-Adjuvant CRT/RT, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 25JUL2024

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Figure 7. Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group, (Participants with CPS≥1, PRO FAS Population)



Physical Functioning Scale

Table 17. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 25 and Week 51 in EORTC QLQ-C30 Physical Functioning, (Participants with CPS≥1, PRO FAS Population)

	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■

^a Based on a constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), Tumour Stage: III vs. IVA and PD-L1 status (TPS ≥ 50% vs. TPS<50%) as pre-specified in the sSAP.
For baseline and Post-Adjuvant CRT/RT, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 25JUL2024

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Figure 8. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 25 and Week 51 in EORTC QLQ-C30 Physical Functioning, (Participants with CPS≥1, PRO FAS Population)



Database Cutoff Date: 25JUL2024

Swallowing Symptom Score

Table 18. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 25 and Week 51 in EORTC QLQ-HN35 Swallowing, (Participants with CPS≥1, PRO FAS Population)

	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
^a Based on a constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), Tumour Stage: III vs. IVA and PD-L1 status (TPS ≥ 50% vs. TPS<50%) as pre-specified in the sSAP. For baseline and Post-Adjuvant CRT/RT, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group. Database Cutoff Date: 25JUL2024						

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Figure 9. Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-HN35 Swallowing Over Time by Treatment Group, (Participants with CPS≥1, PRO FAS Population)



Database Cutoff Date: 25JUL2024

Speech Symptom Score

Table 19. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 25 and Week 51 in EORTC QLQ-HN35 Speech Symptoms, (Participants with CPS $\geq$ 1, PRO FAS Population)

	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■

^a Based on a constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), Tumour Stage: III vs. IVA and PD-L1 status (TPS $\geq$ 50% vs. TPS<50%) as pre-specified in the sSAP.
For baseline and Post-Adjuvant CRT/RT Week 51, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 25JUL2024

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Figure 10. Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-HN35 Speech Symptoms Over Time by Treatment Group, (Participants with CPS≥1, PRO FAS Population)



Database Cutoff Date: 25JUL2024

Pain Symptom Score

Table 20. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 21 and Week 51 in EORTC QLQ-HN35 Pain, (Participants with CPS $\geq$ 1, PRO FAS Population)

	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■

^a Based on a constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), Tumour Stage: III vs. IVA and PD-L1 status (TPS $\geq$ 50% vs. TPS<50%) as pre-specified in the sSAP.
For baseline and Post-Adjuvant CRT/RT Week 51, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 25JUL2024

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Figure 11. Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-HN35 Pain Over Time by Treatment Group, (Participants with CPS≥1, PRO FAS Population)



Database Cutoff Date: 25JUL2024

2.6.1.7 EQ-5D-5L

EQ-5D 5L VAS scores in the pembrolizumab and in the SOC groups  (Table 21, Figure 12).

VAS score**Table 21. Analysis of Change from Baseline to Post-Adjuvant CRT/RT Week 25 and Week 51 in EQ-5D-5L VAS Score, (Participants with CPS≥1, PRO FAS Population)**

	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab	■	■	■	■	■	■
SOC	■	■	■	■	■	■
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
Pembrolizumab vs. SOC					■	■
^a Based on a constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), Tumour Stage: III vs. IVA and PD-L1 status (TPS ≥ 50% vs. TPS<50%) as pre-specified in the sSAP. For baseline and Post-Adjuvant CRT/RT Week 51, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group. Database Cutoff Date: 25JUL2024						

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Figure 12. Line Plot of Empirical Mean Change from Baseline and 95% CI for the EQ-5D-5L VAS Score Over Time by Treatment Group, (Participants with CPS≥1, PRO FAS Population)



Database Cutoff Date: 25JUL2024

2.7 Subsequent treatments used in the relevant studies

Information on subsequent oncologic therapies received by all the patients in the KEYNOTE-689 study ITT population are shown in Table 22. Additional details of the subsequent treatments used in each arm of the KEYNOTE-689 study are provided in Appendix O.

Table 22. Participants with subsequent oncologic therapies, (Incidence > 0% in one or more treatment groups), all comer population (ITT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Participants in population	████		████	
with one or more subsequent therapies	████	████	████	████
with no subsequent therapy	████	████	████	████
ANTIINFECTIVES FOR SYSTEMIC USE				
ANTIBACTERIALS FOR SYSTEMIC USE	████	████	████	████
cefuroxime	████	████	████	████
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	████	████	████	████
afatinib	████	████	████	████
atezolizumab	████	████	████	████
bevacizumab	████	████	████	████
bleomycin	████	████	████	████
capecitabine	████	████	████	████
carboplatin	████	████	████	████
cetuximab	████	████	████	████
cetuximab sarotalocan sodium	████	████	████	████
cisplatin	████	████	████	████
docetaxel	████	████	████	████
epirubicin hydrochloride	████	████	████	████
evorpacept	████	████	████	████
fluorouracil	████	████	████	████
gemcitabine	████	████	████	████
gimeracil;oteracil potassium;tegafur	████	████	████	████
lenvatinib	████	████	████	████
methotrexate	████	████	████	████
mitomycin	████	████	████	████
nedaplatin	████	████	████	████
nivolumab	████	████	████	████
other monoclonal antibodies and antibody drug conjugates	████	████	████	████
paclitaxel	████	████	████	████
pembrolizumab	████	████	████	████

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
tegafur				
vincristine				
vinorelbine tartrate				
IMMUNOSTIMULANTS				
eftilagimod alfa				
pegenzileukin				
IMMUNOSUPPRESSANTS				
methotrexate				
BLOOD AND BLOOD FORMING ORGANS				
ANTIANEMIC PREPARATIONS				
calcium folinate				
CARDIOVASCULAR SYSTEM				
ANTIHYPERTENSIVES				
tadalafil				
CARDIAC THERAPY				
paclitaxel				
GENITO URINARY SYSTEM AND SEX HORMONES				
OTHER GYNECOLOGICALS				
methotrexate				
UROLOGICALS				
tadalafil				
SENSORY ORGANS				
OPHTHALMOLOGICALS				
bevacizumab				
cefuroxime				
VARIOUS				
ALL OTHER THERAPEUTIC PRODUCTS				
calcium folinate				
INVESTIGATIONAL DRUG				
eftilagimod alfa				
evorpacept				
investigational drug				
pegenzileukin				
THERAPEUTIC RADIOPHARMACEUTICALS				
therapeutic radiopharmaceuticals				

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Every participant is counted a single time for each applicable specific subsequent therapy. A participant with multiple subsequent therapies within a therapy category is counted a single time for that category. Each specific subsequent therapy is listed under all relevant therapy classes based on the therapy's generic name, regardless of route of administration or reason for use. Database Cutoff Date: 25JUL2024.				

2.8 Subgroup analysis

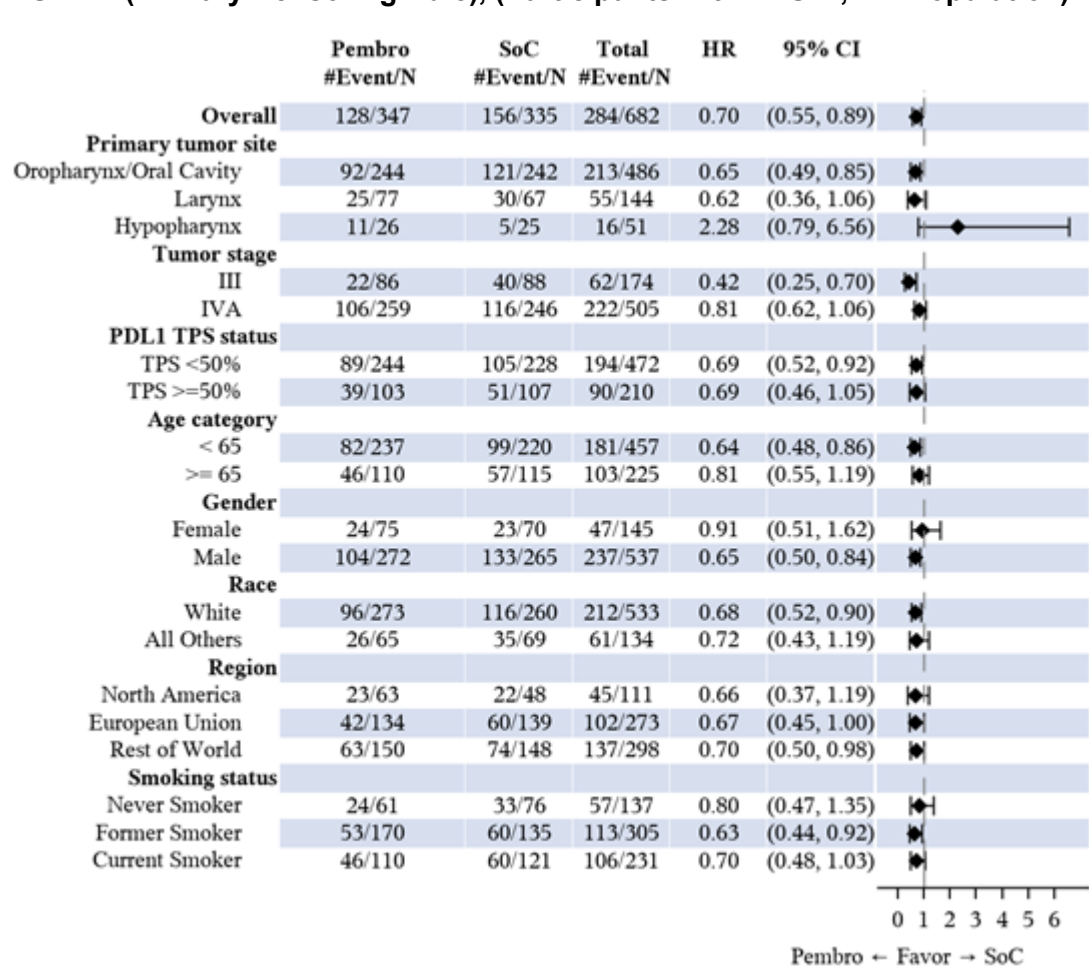
Subgroup analyses of the efficacy endpoints of the KEYNOTE-689 study were conducted according to the subgroups pre-specified in the study protocol and analysis plan (as described in section 2.4). The results of subgroup analyses in the participants with baseline PD-L1 CPS≥1 are presented in this section. In general, the benefit of pembrolizumab over SOC was consistent across prespecified subgroups across the efficacy endpoints. Small sample sizes in some subgroups resulted in wide CIs and therefore the results of those analyses should be interpreted with caution.

2.8.1 KEYNOTE-689 PD-L1 CPS $\geq$ 1 participants – subgroup analyses results

2.8.1.1 Event Free Survival by BICR

The EFS benefit of pembrolizumab over SOC was generally consistent across prespecified subgroups, including tumour stage, PD-L1 TPS status, age, race, smoking status, and geographical region (Figure 13). Note that the small sample sizes in some subgroups (i.e. patients in whom the primary tumour site is the hypopharynx) result in wide CIs and the results should therefore be interpreted with caution.

Figure 13. Forest Plot of EFS Hazard Ratio by Subgroup Factors, Based on BICR per RECIST 1.1 (Primary Censoring Rule), (Participants with CPS $\geq$ 1, ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed. European Union category in this graph includes European Economic Area, United Kingdom and Switzerland. Database Cutoff Date: 25JUL2024

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

2.8.1.2 Overall survival

The OS benefit of pembrolizumab over SOC was generally consistent across prespecified subgroups (Figure 14). Note that the small sample sizes in some subgroups (i.e. patients in whom the primary tumour site is the hypopharynx) result in wide CIs and the results should therefore be interpreted with caution.

Figure 14. Forest Plot of OS Hazard Ratio by Subgroup Factors, (Participants with CPS $\geq$ 1, ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed.

European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.
Database Cutoff Date: 25JUL2024

2.8.1.3 Major Pathological Response (mPR) by BIPR

The treatment differences of the pembrolizumab + SOC group compared with the SOC group across prespecified subgroups were consistent with the findings in the overall CPS $\geq$ 1 population (Figure 15). Note that the small sample sizes in some subgroups result in wide CIs and the results should therefore be interpreted with caution.

Figure 15. Forest Plot of Difference in mPR Rate by Subgroup Factors, Based on BIPR Assessment, (Participants with CPS $\geq$ 1, ITT Population)



For overall population, analysis is based on Miettinen and Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Miettinen and Nurminen method. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed.

European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.
Database Cutoff Date: 25JUL2024

2.8.1.4 Pathological Complete Response (pCR) by BIPR

The treatment differences of the pembrolizumab + SOC group compared with the SOC group across prespecified subgroups were consistent with the findings in the overall CPS $\geq$ 1 population (Figure 16). Note that the small sample sizes in some subgroups result in wide CIs and the results should therefore be interpreted with caution.

Figure 16. Forest Plot of Difference in Pathological Complete Response Rate by Subgroup Factors, Based on BIPR Assessment, Participants With CPS $\geq$ 1, (ITT Population)



Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

For overall population, analysis is based on Miettinen and Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Miettinen and Nurminen method. If total number of participants in one level of a subgroup is <10% of the CPS≥10 population, that particular level will not be displayed.
European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.
Database Cutoff Date: 25JUL2024

2.9 **Meta-analysis**

Meta-analyses were not carried out as only one study (the KEYNOTE-689 study) reported clinical effectiveness data on pembrolizumab in the population of relevance to this appraisal.

2.10 **Indirect and mixed treatment comparisons**

No indirect comparisons or mixed treatment comparisons were carried out as the KEYNOTE-689 study provides direct evidence for the treatment comparison of relevance to this appraisal. Clinical opinion received (elicited as described in section 2.3.3) confirmed that the findings of the KEYNOTE-689 study are generalisable to UK clinical practice, including that the comparator arm of the study is reflective of current UK standard of care.

2.11 **Adverse reactions**

Summary of adverse events information

- Pembrolizumab as neoadjuvant and continued as adjuvant treatment in combination with radiotherapy ± cisplatin followed by pembrolizumab monotherapy in participants with Stage III-IV resectable LA HNSCC has a manageable safety profile that is generally consistent with the well-established safety profile of pembrolizumab monotherapy and the individual safety profiles of RT and cisplatin.
- No new safety concerns for pembrolizumab are identified.

Based on the adverse events observed in the KEYNOTE-689 study, as described in this section, it can be seen that pembrolizumab as neoadjuvant and continued as adjuvant treatment in combination with radiotherapy ± cisplatin followed by pembrolizumab monotherapy in participants with Stage III-IV resectable LA HNSCC has a manageable safety profile that is generally consistent with the well-established safety profile of pembrolizumab monotherapy and the individual safety profiles of RT and cisplatin.

Adverse events of special interest (AEOSI) in the pembrolizumab + SOC group are generally consistent with the established safety profile of pembrolizumab monotherapy in type and

severity. No new indication-specific immune-mediated AEs causally associated with pembrolizumab are identified when pembrolizumab was added to RT $\pm$ cisplatin. No new safety concerns for pembrolizumab are identified.

2.11.1 KEYNOTE-689 all comer overall population

A summary of the adverse events of the KEYNOTE-689 study (at the 25-JUL-2024 database cut-off date) are provided below for the all comer overall population. Detailed adverse event information are provided in Appendix D.

2.11.1.1 Adverse Event Summary

The incidence and types of AEs, including drug-related AEs, AEs leading to death, and Grade 3 to 5 AEs in the pembrolizumab + SOC group were similar to the SOC group (<10% difference in incidence). The incidence of SAEs and AEs leading to treatment discontinuation was higher in the pembrolizumab + SOC group compared with the SOC group ($\geq 10\%$ difference in incidence). In the high-risk category, the incidence of SAEs was higher in the pembrolizumab + SOC group compared with the SOC group. In the low-risk category, SAEs, drug-related SAEs, drug-related Grade 3 to 5, discontinuation due to an AE, discontinuation due to a drug-related AE, and discontinuation due to SAE was higher in the pembrolizumab + SOC group compared with the SOC group.

Table 23. Adverse event summary (all comer overall population, APaT population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	348	(96.4)	305	(96.8)
with no adverse event	13	(3.6)	10	(3.2)
with drug-related ^a adverse events	294	(81.4)	258	(81.9)
with toxicity grade 3-5 adverse events	275	(76.2)	233	(74.0)
with toxicity grade 3-5 drug-related adverse events	161	(44.6)	135	(42.9)
with serious adverse events	179	(49.6)	116	(36.8)
with serious drug-related adverse events	69	(19.1)	33	(10.5)
who died	25	(6.9)	24	(7.6)
who died due to a drug-related adverse event	4	(1.1)	1	(0.3)
discontinued drug due to an adverse event	88	(24.4)	45	(14.3)
discontinued drug due to a drug-related adverse event	64	(17.7)	39	(12.4)
discontinued drug due to a serious adverse event	47	(13.0)	11	(3.5)
discontinued drug due to a serious drug-related adverse event	27	(7.5)	8	(2.5)

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
^a Determined by the investigator to be related to the drug. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Grades are based on NCI CTCAE version 4.03. Database Cutoff Date: 25JUL2024.				

2.12 Ongoing studies

The KEYNOTE-689 study is ongoing and may provide additional evidence in the next 12 months for the indication being appraised (a subsequent interim analysis may be available based on a database lock date in [REDACTED], however as the KEYNOTE-689 study is an event-driven study the database lock date for predefined interim analyses cannot be definitively determined beforehand).

2.13 Interpretation of clinical effectiveness and safety evidence

Efficacy results from KEYNOTE-689 at IA1 show that perioperative pembrolizumab provides a statistically significant and clinically meaningful improvement in EFS and a statistically significant improvement in mPR compared with adjuvant SOC RT ± cisplatin in treatment-naïve participants with newly diagnosed Stage III-IVA resectable locoregionally advanced HNSCC. The point estimate of OS HR favours perioperative pembrolizumab versus SOC. The improvements in EFS and mPR, and favourable trend in OS, were consistent across the PD-L1 CPS ≥1, and all participant populations.

There [REDACTED] in the change from baseline in EORTC QLQ-C30 of EQ-5D VAS scores between the pembrolizumab and SOC groups in the CPS ≥1 population at post adjuvant RT ± cisplatin Week 25 and Week 51, indicating no negative effects of adding pembrolizumab treatment.

The results of the KEYNOTE-689 study also showed that pembrolizumab as neoadjuvant and continued as adjuvant treatment in combination with RT ± cisplatin followed by pembrolizumab monotherapy in participants with Stage III-IVA resectable LA HNSCC has a manageable safety profile that is generally consistent with the well-established safety profile of pembrolizumab monotherapy and the individual safety profiles of RT and cisplatin. No new safety concerns for pembrolizumab are identified.

Standard care for resectable locally advanced HNSCC has remained relatively constant since 2004, when two pivotal randomized trials (European Organization for Research and Treatment of Cancer [EORTC] #22931 and Radiation Therapy Oncology Group [RTOG] #9501 (39, 40)) first established the addition of cisplatin to postoperative radiotherapy as the recommended treatment regimen for high-risk disease. The KEYNOTE-689 trial showed that the addition of neoadjuvant and adjuvant pembrolizumab to standard care conferred a significant improvement in event-free survival, reducing the risk of recurrence or progression by 30% among patients with resectable locally advanced HNSCC (41). The neoadjuvant pembrolizumab phase is a meaningful contributor to efficacy, potentiating early immune engagement to influence long-term outcomes, while the KEYNOTE-689 study also delivers positive results after previous trials in other adjuvant therapies in this indication have failed. This perioperative strategy increases immune system surveillance and demonstrably decreases the risk of disease recurrence. The availability of pembrolizumab as an effective perioperative therapy in this indication therefore presents the first meaningful advancement in this setting in over 20 years, re-establish immunotherapy as a potential option in the curative setting, and represents a considerable step-change in the management of resectable locally advanced HNSCC.

3 Cost effectiveness

Summary of key cost effectiveness information

Objective:

- To model the cost-effectiveness of perioperative pembrolizumab plus standard of care (SOC; surgical resection followed by adjuvant radiotherapy $\pm$ chemotherapy) compared to SOC alone for patients with CPS $\geq$ 1 resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC), [REDACTED].

Model structure:

- A systematic literature review (SLR) was conducted to identify cost-effectiveness analyses relevant to this decision problem. No previous studies or NICE technology appraisals were identified in the neoadjuvant or perioperative setting for LA HNSCC.
- A *de novo* four state Markov model was developed; event-free [EF], local/salvageable recurrence [L/SR], incurable recurrence/progression [IRP], and death. This structure captures the main elements of the disease course and heterogeneity in management of patients with LA HNSCC.

Model inputs:

Patient population inputs:

- The baseline characteristics were sourced from the KEYNOTE-689 trial.

Clinical efficacy inputs:

- Transition probabilities from the EF, L/SR, and IRP health states were derived from patient-level data from the KEYNOTE-689 trial.
- Adverse event data were from the KEYNOTE-689 trial, pooled across both arms.

Utility inputs:

- The EQ-5D-5L was collected in the KEYNOTE-689 trial and mapped to EQ-5D-3L.
- Measurements were pooled across treatment arms for the EF, L/SR and IRP pre-progression health states, and a disutility for adverse events was applied.
- Utility for the IRP state is split into pre-progression and post-progression to reflect the impact of progression on HRQoL. Due to limited events in the KEYNOTE-689 trial, utility for the IRP post-progression state was sourced from NICE TA473 (based on HRQoL data in the EXTREME trial).

Costs and resource use inputs:

- Resource use associated with management in the EF state was obtained from UK clinical experts at an advisory board, meanwhile resource use in the downstream L/SR and IRP states was based on previous NICE appraisals in (recurrent/metastatic [R/M]) HNSCC.
- Unit costs were sourced primarily from NHS reference costs, and drug acquisition costs were taken from the BNF and eMIT.

Base-case results and sensitivity analyses:

- The base case incremental cost-effectiveness ratio (ICER) and ICERs in all one-way sensitivity and scenario analyses were below £20,000/QALY gained.
- The probabilistic sensitivity analysis generated an ICER of [REDACTED], showing the model results to be robust, and indicated that there was a [REDACTED]% probability that perioperative pembrolizumab is cost-effective at the £30,000/QALY threshold.

Cost effectiveness conclusions:

- Treatment with perioperative pembrolizumab accrues quality-adjusted life years (QALYs) by increasing the number of years patients spend event-free. Similar to other (neo)adjuvant treatments, it is expected to increase the proportion of patients who achieve functional cure. The initial costs are offset to some degree by a reduction in the need for downstream care.
- The model results demonstrate that perioperative pembrolizumab is a cost-effective addition to adjuvant standard of care for patients with resectable LA HNSCC.

3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted on 9th April 2025. Searches were run from database inception, to identify economic evaluations in previously untreated, resectable patients with LA HNSCC. Full details on the methodology and findings are detailed in Appendix E. Three full-text publications met the inclusion criteria,(50-52) however none were from a UK perspective nor evaluated perioperative treatment regimens. No additional studies meeting the inclusion criteria were identified from the grey literature (bibliographic, conference, or HTA agency databases).

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Due to the limited records meeting the inclusion criteria, the scope of the search was expanded to include all interventions in LA HNSCC regardless of resectability (i.e. to include studies considering interventions for patients who did not undergo tumour resection), resulting in an additional 10 studies (11 publications) meeting the broader inclusion criteria (North America, n=2; Europe, n=6, Asia Pacific, n=2). Of the six identified studies in Europe, two studies were in the overall head and neck cancer population, 3 across the oropharynx, hypopharynx, and larynx, and one study specific to the oropharynx only. Study interventions included induction chemotherapy, radiotherapy, and cetuximab + radiotherapy. Further details of identified studies can be found in Appendix E.

No UK studies were identified relevant to the population in the current decision problem, reflecting the unmet need for patients with resectable LA HNSCC.

3.2 Economic analysis

No previous economic evaluations specific to the neoadjuvant or perioperative treatment setting in LA HNSCC have been identified (Appendix E), reflecting the lack of advancements and unmet need in this population. Only one previous technology, cetuximab in combination with RT for treatment of patients with LA HNSCC for whom all forms platinum-based chemotherapy are contraindicated, has previously been appraised by NICE in the LA setting (TA145).(4) As discussed in Section 1.1, the company does not consider TA145 to be applicable to the current decision problem as the population in the pivotal trial is based on patients who are not undergoing surgical resection; in addition, clinical experts expressed that cetuximab in LA HNSCC is very rarely used in practice and is reserved for patients with renal failure.

In addition, pembrolizumab is the first perioperative (neoadjuvant followed by adjuvant) treatment for LA HNSCC to be evaluated by NICE in the UK. In the absence of published models in the perioperative setting, a *de novo* economic model was developed to assess the cost-effectiveness of pembrolizumab as a neoadjuvant treatment followed by pembrolizumab and radiotherapy, plus or minus chemotherapy, as an adjuvant treatment for resectable LA HNSCC.

3.2.1 Patient population

The population for the current economic evaluation consists of adult (18 years or older) patients newly diagnosed with treatment-naïve resectable stage III-IVa LA HNSCC who have

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

PD-L1 CPS≥1. [REDACTED] The population for the economic model aligns with the NICE scope for this decision problem and no other subgroups are applicable to this evaluation.

The starting age, gender distribution, and histology distribution of the model cohort in cycle 0 was based on the reported characteristics of the KEYNOTE-689 all comer trial population (N=714) (Table 24). The CPS≥1 population of KEYNOTE-689 made up 95.5% (N=682) of the trial all comer population and the baseline characteristics are consistent between the two trial populations (see Appendix N for data for the all comer population). Means and standard errors of body surface areas (BSA) and body weight are also based on KEYNOTE-689. The source for glomerular filtration rate (GFR) is based on a UK study assessing GFR in head and neck cancer patients before initiation of chemotherapy, identified by a targeted review, as this characteristic was not available from KEYNOTE-689. The BSA, weight and GFR were used within the economic model to compute the required dosage of cisplatin in the adjuvant setting and other subsequent treatment options.

Table 24. Baseline characteristics of the patients in the economic model

Characteristic	Mean	SE	Source
Age (years)	59.9	-	KEYNOTE-689 (all comer population)
Female (%)	21.1%	-	
Body surface area (m ²)	[REDACTED]	[REDACTED]	
Weight (kg)	[REDACTED]	[REDACTED]	
Glomerular filtration rate (GFR) (ml/min/1.73m ²)	96.0	-	Akmar et al. (2020)(53)

Abbreviations: SE, standard error

3.2.2 Model structure

A four-state Markov cohort structure model was developed in Microsoft Excel®. In contrast to the partitioned survival model often used to model advanced cancer, Markov models have commonly been used for appraisals of treatments in the earlier-stage settings including both perioperative (e.g. TA851, TA1017)(54, 55) and adjuvant (e.g. TA830, TA837, TA766, TA1037)(56-59) appraisals of pembrolizumab as they allow greater flexibility in modelling downstream treatment outcomes.

Only one previous LA HNSCC indication has previously been appraised by NICE (TA145), however this was in a non-surgically resected population,(4) with no appraisals in the perioperative setting. Table 25 presents a summary of the key features of this *de novo* model versus the model used in TA145. Whilst TA145 is not relevant for this decision problem as the recommendation is in the unresected population, nonetheless it was reviewed for

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completeness and with the aim of understanding the different modelling approaches utilised. Further details of the previous evaluation are presented in Table 25.

Table 25. Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	Cetuximab in LA HNSCC (TA145)(4)	Chosen values	Justification
Population	Patients with LA HNSCC with no surgical resection	Patients with resectable LA HNSCC undergoing surgical resection	N/A
Model structure	Individual patient-level model with four primary health states (Acute phase, Loco-regional control, Progressive disease, Death) whereby the acute phase consists of 7 sub-states representing the worst adverse event(s) a patient experienced during the treatment.	Markov with four health states (EF, L/SR, IRP, and death).	There is no standard approach to modelling early HNSCC as there have been no previous evaluations in the neoadjuvant/adjuvant setting. This model structurally reflects the impact of the disease on patients with LA HNSCC as per the KEYNOTE-689 pivotal trial. Specifically, the health states capture the type of recurrence as the primary endpoint of the KEYNOTE-689 trial (EFS) encompasses both types of recurrence events (L/SR and IRP). The model captures key aspects of the clinical pathway and patient experiences, accounting for the heterogeneity in management of patients with HNSCC, while adhering to the principles of transparency.
Time horizon	Lifetime	40.1 years	A lifetime time horizon based on mean age in KEYNOTE-689 of 59.9 years. After 40.1 years, virtually all patients have died and so lifetime cost and benefits are captured in the economic model, reflecting the NICE methods guide.
Cycle length	N/A	1 week	The model uses a weekly cycle length to allow for precise calculation of drug acquisition and administration costs.
Half-cycle correction	N/A	Yes	Half cycle correction was applied to costs and effectiveness for additional precision. As an exception, half-cycle correction was not applied to cost components that are incurred at the beginning of a cycle, including neoadjuvant/adjuvant drug acquisition and administration costs (recurring costs starting from week 0) and AE-related costs in each model arm (applied as a lump-sum cost at week 0).

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Source of utilities	EQ-5D-3L from a study of 50 oncology nurses in the UK.(60)	EQ-5D-5L from KEYNOTE-689 mapped to EQ-5D-3L using the Hernandez-Alava mapping algorithm(61) for all states apart from IRP post-progression taken from TA473 of cetuximab in R/M HNSCC.(62)	The EQ-5D-5L from the KEYNOTE-689 pivotal trial is the most appropriate data and has been mapped to EQ-5D-3L in line with recommendations in the NICE methods guide. Due to trial follow-up and EQ-5D collection protocol, no utility value for the IRP post-progression health state could be derived and therefore this input was taken from TA473,(62) identified through additional searches (see Section 3.4.3.2).
Source of costs	NHS Reference costs, BNF	NHS Reference costs (2023/24), BNF, eMIT	Standard cost databases that reflect the perspective of the NHS and PSS, in line with NICE reference case.
Discount rate	3.5% to costs and benefits	3.5% to costs and effects	In line with the NICE reference case.

Abbreviations: AE, adverse event; BNF, British National Formulary; EF, event-free; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; IRP, incurable recurrence or progression; L/SR, local or salvageable recurrence; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; R/M, recurrent or metastatic; SLR, systematic literature review.

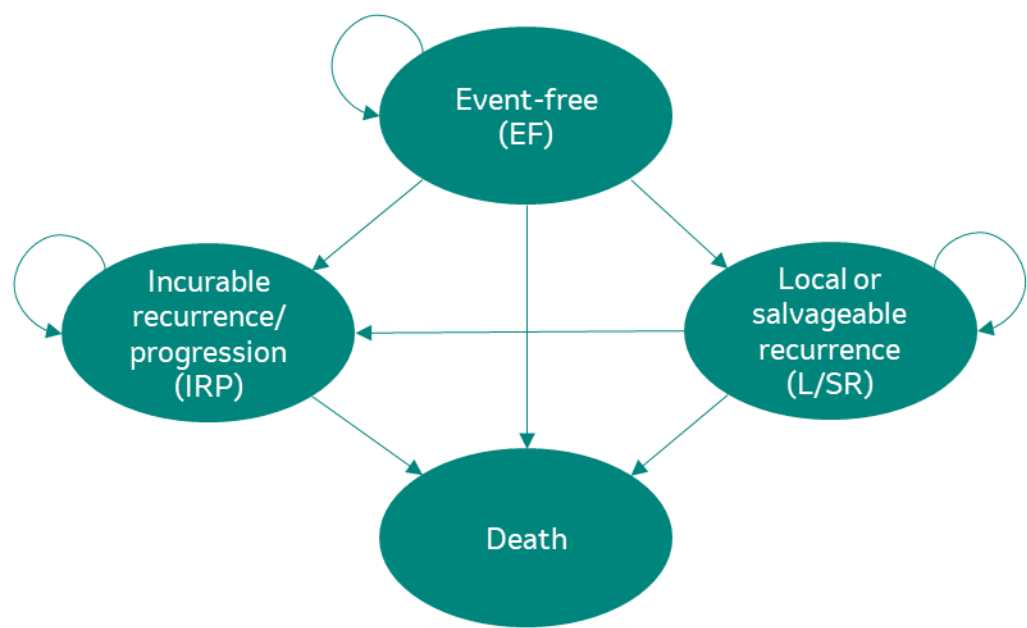
Figure 17 illustrates the specific health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states (i.e., event-free [EF], local or salvageable recurrence [L/SR], incurable recurrence/progression [IRP], and death) to track the disease course and survival of patients over time.

The model structure differentiates health states by type of recurrence (either L/SR or IRP) depending on the site of recurrence (local or distant) and whether it is considered to be salvageable or not. The definition of the two recurrence health states is as follows:

- **Local or salvageable recurrence (L/SR):** A patient has an EFS event of recurrence or progression and has received any subsequent surgery, or any subsequent oncological systemic therapy or radiation recorded as ‘with *Curative Intent*’ in the patient case report form, or none of the above and the EFS event is recorded as ‘Local PD/Recurrence’ confirmed with clinical approval
- **Incurable recurrence/progression (IRP):** A patient has an EFS event of recurrence or progression and received either subsequent oncological systemic therapy or oncological radiation recorded as ‘*Recurrent/Metastatic/Incurable*’ in the patient case report form, or none of the above and EFS event is recorded as ‘*Distant PD*’ or ‘*Local and Distant PD*’

This definition of the recurrence health states reflects the management of patients in the KEYNOTE-689 trial post-recurrence or progression, differentiating patients who received subsequent treatment with ‘curative intent’. As such, patients in the IRP state are non-salvageable and therefore would not be eligible for subsequent surgery. This structure allows the economic model to account for the heterogeneity in management of HNSCC patients, whilst retaining the principles of model parsimony and transparency. These two types of recurrence are expected to have different implications on patients’ prognosis and therefore result in different health outcomes and costs.

Figure 17. Model schematic



Note: Arrows indicate allowable transitions between health states

All patients entered the model in the EF state following diagnosis of resectable stage III-IVa LA HNSCC, with characteristics consistent with the KEYNOTE-689 trial patient population at baseline (see Table 24). Neoadjuvant/adjuvant therapy affects patients' risks of transitioning directly from EF to L/SR, IRP, or death. Patients who enter the L/SR state may receive salvage surgery, radiotherapy or systemic oncologic therapy, and are at risk of transitioning from L/SR to IRP or death. Following IRP, patients are assumed to receive first-line therapy for recurrent/metastatic HNSCC and may also receive second-line therapy in this setting. The distribution of individuals across health states is used in conjunction with state-specific costs and utility values to estimate life years (LYs), quality-adjusted life years (QALYs), and costs.

The health states and allowable transitions were defined such that EFS and OS curves can be generated using the Markov trace. This facilitated validations of the model against observed Kaplan-Meier curves from the trial and external data sources, where available.

The model uses a weekly cycle length to allow for precise calculation of drug acquisition and administration costs. Half cycle correction was applied to costs and effectiveness for additional precision. As an exception, half-cycle correction was not applied to cost components that are incurred at the beginning of a cycle, including neoadjuvant/adjuvant drug acquisition and administration costs (recurring costs starting from week 0) and AE-related costs in each model arm (applied as a lump-sum cost at week 0).

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The cost-effectiveness analysis was conducted using a lifetime time horizon to comprehensively capture differences in costs and outcomes between perioperative pembrolizumab + SOC and its comparator arm, consistent with the *“NICE Guide to the Methods of Technology Appraisal”* which recommends that the time horizon should be long enough to reflect the differences in costs and outcomes between the technologies being considered.⁽⁶³⁾ The starting age of the patient cohort at model entry was based on the average age of the KEYNOTE-689 trial population at baseline. To approximate a lifetime horizon, the base-case model was run for 40.1 years (equal to 100 years minus the starting age), by which point virtually all patients [REDACTED] in the Markov cohort have reached the death state.

The impact of alternative time horizons was explored via sensitivity analyses.

3.2.3 Intervention technology and comparators

3.2.3.1 Perioperative pembrolizumab + SOC

The intervention, perioperative pembrolizumab + SOC (adjuvant radiotherapy [RT] with or without cisplatin), is implemented in the economic model as per the KEYNOTE-689 trial, adjusted for the anticipated administration regimen in UK clinical practice. Of note, and in line with current SOC, the addition of cisplatin to radiotherapy in the adjuvant setting is determined by whether or not a patient has high-risk pathological features as assessed post-surgery. High-risk pathological features as per KEYNOTE-689 include the presence of positive margins (<1mm in the primary resection specimen) or positive extranodal extension (ENE; defined as an extension of SCC from within a lymph node through the fibrous capsule and into the surrounding connective tissue). UK clinical experts confirm these are reflective of UK practice.⁽⁴⁹⁾

In KEYNOTE-689, the perioperative pembrolizumab + SOC regimen was administered as follows:

- Neoadjuvant phase:
 - Pembrolizumab 200 mg intravenous (IV) every three weeks (Q3W) for a maximum of 2 cycles
- Adjuvant phase, following surgical resection:
 - Patients with high-risk pathological features receive pembrolizumab 200 mg IV on day 1 of each Q3W cycle for up to fifteen cycles plus standard of care radiotherapy

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(see Section 3.2.3.2 below) and cisplatin 100 mg/m² intravenously on day 1 of each 3-week cycle for three cycles.

- Patients without high-risk pathological features receive pembrolizumab 200 mg IV on day 1 of each Q3W cycle for fifteen cycles plus standard of care radiotherapy as adjuvant therapy

Due to service capacity constraints, UK clinical experts indicated that in the adjuvant setting pembrolizumab is expected to be administered every 6 weeks (Q6W) at a flat dose of 400 mg. This is reflected in the base case economic model, whereby pembrolizumab administered in the adjuvant setting is assumed to be administered as 1 cycle of pembrolizumab 200 mg followed by up to 7 cycles of 400 mg Q6W. The initial dose was assumed to be 200 mg to reflect closer patient monitoring as they reinitiate treatment with pembrolizumab after surgery, and to prevent delivering a higher total dose of pembrolizumab over the full treatment schedule than is specified in the protocol. A scenario analysis is provided where adjuvant pembrolizumab is administered as 200 mg Q3W for up to 15 cycles as per the trial to evaluate the impact on model results.

Some variation in cisplatin use is seen across clinical practice in the UK whereby cisplatin may be administered 40 mg/m² once weekly (QW). However, UK clinical experts advised that many centres use the Q3W regimen as this allows for better treatment persistence and flexibility in administration, therefore the dosing as per KEYNOTE-689 trial is considered generalisable to the UK.(49)

3.2.3.2 SOC

The comparator included in the economic model mirrors the KEYNOTE-689 trial, consisting of surgical resection followed by adjuvant radiotherapy plus a maximum of 3 cycles of cisplatin 100 mg/m² Q3W for patients with high-risk pathological features (as defined above) or radiotherapy alone for patients without high-risk pathological features.

As part of SOC in both arms, radiotherapy consists of 2 Gy per day in 30 fractions (total of 60 Gy) for low-risk patients, 33 fractions (total of 66 Gy) for high-risk patients, and 35 fractions (total of 70 Gy) for patients with gross residual disease. Radiotherapy is costed based on the proportion of patients in both arms from KEYNOTE-689 who started RT and the mean number of fractions received in the adjuvant setting, pooled across both arms (further details of implementation in section 3.5.4).

3.3 Clinical parameters and variables

Where available, clinical parameters informing the economic model use patient level data from the KEYNOTE-689 trial (IA1, database cutoff [DCO] 25th July 2024).

3.3.1 Overview of transition and clinical data used in the model

The set of allowable transitions and corresponding data sources are summarized in Table 26. All transitions from the EF, L/SR, and IRP health states are estimated directly using patient-level data from the KEYNOTE-689 trial for both the perioperative pembrolizumab + SOC and SOC arms.

Table 26: Summary of health state transitions considered in the economic model

Transition(s)	Estimation approach	Data source(s)
EF → L/SR EF → IRP EF → Death*	Based on a parametric multistate modelling approach in which different parametric functions were fitted to each of the three individual transitions starting from EF, accounting for competing risks, for both the intervention and comparator arm.	- Patient-level data from KEYNOTE-689 - National life tables – <i>for transitions to death*</i>
L/SR → IRP L/SR → Death*	Exponential rates of L/SR → IRP and L/SR → death were estimated using KEYNOTE-689 data.	- Patient-level data from KEYNOTE-689 - National life tables – <i>for transitions to death*</i>
IRP → Death*	Exponential models of IRP→death were fitted using KEYNOTE-689 data. The survival analysis was conducted in the subset of patients who experienced IRP either as their first EFS failure event or following an earlier L/SR. Separate exponential models were fitted for each trial arm.	- Patient-level data from KEYNOTE-689 - National life tables – <i>for transitions to death*</i>

Abbreviations: EF, event free; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; L/SR, local or salvageable recurrence; IRP, incurable recurrence/progression.

*Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from national life tables given the age and gender distribution of the cohort at each cycle.

3.3.2 Modelling transitions from the EF state

Transition probabilities starting from the EF state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-689 trial, following the parametric multistate modelling approach described by Williams et al. (2017a & 2017b).^(64, 65) Parametric models were used to estimate the cause-specific hazards of each transition (i.e., EF → L/SR, EF → IRP, and EF → death) over time within the perioperative pembrolizumab + SOC and SOC arms of the trial. Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any EFS failure event) were calculated as a function of all three cause-specific hazards.

3.3.2.1 *Estimation of cause-specific hazards for each individual transition starting from the EF state*

In order to fit parametric models to each of the three health state transitions, standard survival analysis methods were used with one modification to account for competing risks: when analysing time to each specific type of EFS failure, the two competing failure types were treated as censoring events.⁽⁶⁶⁾ For example, to model the transition from EF to IRP, patients who experience a L/SR or death prior to IRP were censored at the time of the earlier competing event. After these additional censoring criteria were applied to the patient-level time-to-event data for each transition, parametric curve fitting was performed using the survival analysis package *flexsurvreg* in R software.

The following three parametric modelling approaches were used to explore uncertainty in the estimation of transition probabilities starting from the EF state:

- Approach #1: Parametric models separately fitted to each treatment arm: Transition probabilities were estimated based on parametric models that were fitted individually to each treatment arm of the KEYNOTE-689 trial. Seven different parametric functions (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalized gamma) were considered to model each transition from the EF state (i.e., EF → L/SR, EF → IRP, EF → death) in each treatment arm.
- Approach #2: Parametric proportional hazards models with a time-constant treatment effect: Transition probabilities in the neoadjuvant pembrolizumab / adjuvant pembrolizumab + SOC and SOC arms were estimated based on jointly fitted models from the proportional hazards class (i.e., exponential, Weibull, or Gompertz) that incorporated a time-constant binary indicator equal to 1 in the perioperative

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pembrolizumab + SOC arm and 0 in the SOC arm of KEYNOTE-689. The models thus assumed a time-constant hazard ratio (HR) for perioperative pembrolizumab + SOC versus SOC in KEYNOTE-689.

- Approach #3: Parametric proportional hazards models with a time-varying treatment effect (before and after year 1): Transition probabilities in the perioperative pembrolizumab + SOC and SOC arms of the model were estimated based on jointly fitted models from the proportional hazards class that used a time-varying HR for pembrolizumab versus observation in KEYNOTE-689. Specifically, the parametric models under Approach #3 incorporated a time-constant binary indicator equal to 1 in the perioperative pembrolizumab arm and 0 in the SOC arm of KEYNOTE-689. Beyond the first year follow up a time-varying binary indicator equal to 1 in the perioperative pembrolizumab + SOC arm and 0 for the SOC arm was applied. The models thereby allowed the treatment effect to differ during versus after the first year following initiation of adjuvant therapy. The allowance of a differing treatment effect during the first year versus following years is based on the protocol-defined maximum treatment duration of approximately 1 year.

Parameter estimates associated with all parametric models under Approaches #1, 2, and 3 are reported in Appendix J1.

For each of the two model arms, probabilities of each transition from the EF state were calculated based on all three cause-specific hazard functions. The predicted EFS curve over time in each treatment arm similarly depended upon all three cause-specific hazard functions. Therefore, in order to select base-case parametric functions, and across the three approaches described above, a total 397 (possible parametric functions combinations for EF → L/SR, EF → IRP, and EF → death) were considered (Appendix J1). Criteria for the selection of base-case parametric functions are described below in Section 3.3.2.3.

3.3.2.2 Calculation of transition probabilities based on cause-specific hazards

For each individual transition starting from the EF state, transition probabilities in each weekly cycle were calculated within the model as a function of the cause-specific hazards for all three types of EFS failure. The following calculation steps were performed:

1. For each cause of EFS failure k (i.e., L/SR, IRP, or death), the average cause-specific hazard within the cycle from week $(t-1)$ to t was calculated as:

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$$\bar{h}_k(t) = H_k(t) - H_k(t-1),$$

where $H_k(.)$ is the cause-specific cumulative hazard of cause k (based on the parametric function selected to model cause k).

2. The average hazard of any EFS failure within the cycle from week $(t-1)$ to t , denoted $\bar{h}_{EFS}(t)$, was calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard was converted into a probability using the formula:

$$1 - e^{-\bar{h}_{EFS}(t)}$$

3. In each cycle, the relative contribution of each cause k to the overall hazard of EFS failure was derived as:

$$\frac{\bar{h}_k(t)}{\bar{h}_{EFS}(t)}$$

This represents the probability of having had an EFS failure of type k given that an EFS failure has occurred within the cycle.(67) The relative contribution of cause k was then multiplied by the probability of any EFS failure within the cycle to obtain the transition probability corresponding to cause k .

Within each cycle, the transition probability from EF → death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in the UK were obtained from the Office for National Statistics (ONS) life tables 2021-2023.(68)

3.3.2.3 Selection of base-case parametric models for transitions from EF state

As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, assessing model fit is more challenging in the context of multistate models than partitioned survival models, as the target outcomes of interest (e.g., the proportions of individuals experiencing the composite endpoint) are determined by a combination of survival models rather than by a single survival model.(66)

Therefore, to select base case parametric functions, all 397 possible combinations of parametric functions for EF → L/SR, EF → IRP, and EF → death (across the 3 approaches, as described in section 3.3.2.1) were considered (see Appendix J1). In accordance with

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recommendations in the NICE DSU TSD 14 which states that unless there is clear and strong evidence against (i.e. pathophysiological, clinical or other rationale), base-case parametric functions should be selected such that the same functional form is used to model each health state transition in both the perioperative pembrolizumab + SOC and SOC arms. The rationale for this approach is to prevent the extrapolated portion of the EFS curves from following drastically different trajectories between these two model arms, as noted in NICE DSU TSD 14.(69)

The appropriateness of the base case parametric functions was assessed using the following criteria:

- Statistical fit based on mean squared error (MSE) vs. observed EFS

Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks.(64) MSE was therefore used as an alternative diagnostic test to assess fit of the predicted EFS curve versus the observed Kaplan-Meier curve during the within-trial period in each treatment arm. Specifically, MSE was calculated based on the average of the squared difference in predicted versus observed EFS at weekly intervals across the within-trial period, with weighting by number of patients at risk in each weekly interval.

In addition, the assumption of proportional hazards was assessed through formal statistical tests to evaluate the potential suitability of Approach #2. Namely, for each transition, the function *cox.zph()* in R was used to test for independence between time and the scaled Schoenfeld residuals from a Cox proportional hazards model with a time-constant treatment covariate. The proportional hazard assumption is supported by a non-significant relationship between residuals and time.

- Visual assessment of modelled vs. observed EFS

Predictions generated by different combinations of parametric functions were visually verified against the observed data in each trial arm, following the approach used by Williams et al. (2017).(64) Specifically, predicted versus observed cumulative incidence curves were plotted for each of the three individual transitions starting from the EF state. The resulting predictions of EFS as a composite endpoint were also compared against the observed EFS Kaplan-Meier curve in each arm. Of note, the KEYNOTE-689 trial provided ~5 years of follow-up data which allowed for a robust assessment of modelled versus observed EFS during the trial period.

- Clinical plausibility and external validity of long-term extrapolations

A targeted literature review was used to identify real-world studies reporting long-term EFS and OS for SOC conducted in the resectable LA HNSCC population for external validation of modelled longer-term extrapolations from the economic model. A summary of identified studies is presented in Appendix J1.4. Due to the heterogeneity evident in head and neck cancer patients, none of the identified studies were considered generalisable to the KEYNOTE-689 population, in particular with regards to anatomical site which can be a strong determinant of prognosis. Regardless, these studies demonstrate the range of plausible outcomes for LA HNSCC to inform the long-term pattern of recurrence and survival.

Due to the lack of previous neoadjuvant or perioperative treatment strategies in resectable LA HNSCC, identified studies reflect the adjuvant setting only and report disease-free survival (DFS), as is common practice in the adjuvant setting. This causes a discrepancy between the starting time (randomisation post-surgery for patients that have survived and are disease free at study entry) and the time at risk for a subsequent recurrence event, for the adjuvant studies vs the perioperative KEYNOTE-689 study. In adjuvant studies, early progressions precluding surgical resection, or deaths directly associated with surgery, are by definition excluded from the study population, and as such the trials may report improved survival outcomes compared with studies where follow-up starts prior to surgery as in KEYNOTE-689. No studies were identified reporting EFS to allow for external validation of SOC. As such no direct comparisons between DFS and EFS can be made. However, KEYNOTE-689 has substantial follow-up vs other early-stage studies (approximately 5 years) which enables a robust internal validation for EFS.

With regards to OS, the extensive trial follow-up also enabled assessment of the internal validity of the OS extrapolations. As the primary censoring rules used in the EFS and OS analyses of the KEYNOTE-689 trial differed, it was necessary to reconcile the censoring rules used for EFS and OS to enable this validation – further details are provided in section 3.14 and Appendix J4. In addition, three studies (albeit with similar limitations as described above for EFS) reported long-term survival beyond the KEYNOTE-689 trial follow-up period to allow some validation of extrapolated long-term OS outcomes on SOC in current clinical practice.

Although external data sources were unavailable to inform validation of the perioperative pembrolizumab + SOC arm, the clinical plausibility of the predicted OS benefit for this perioperative treatment strategy (vs. SOC) was assessed based on the observed OS Kaplan-Meier curves from KEYNOTE-689.

Curve selection process:

The distribution selection process first selected the distribution for the cause-specific hazards of EF → death, in line with the approach previously taken and accepted in NICE TA1017.⁽⁵⁵⁾ An assessment of summarised fit statistics led to the reduction of the number of candidate combinations from 397 to 67. Subsequent steps in the process identified the most suitable distributions for the cause-specific hazards of EF → L/SR and EF → IRP, based on a close inspection of statistical and visual fit in conjunction with clinical plausibility among the 67 remaining combinations.

1. Statistical fit of EF→death based on MSE: The MSE for predicted versus observed EFS was computed for each of the 397 candidate combinations of distributions, and divided into thirteen sets defined by approach and EF→death distribution (seven sets of 49 combinations under Approach #1 [combinations of models individually fitted to each arm], three sets of 9 combinations under Approach #2 [combinations of models that can be parameterised under proportional hazards], and three sets of 9 combinations under Approach #3 [combinations of models that can be parameterised under time-varying proportional hazards beyond year 1]). The average and minimum MSE was summarised across all combinations of distributions within each set (see Appendix J1.1 for further details) with the conclusions summarised below:

- Under Approach #1, MSE statistics for predicted vs. observed EFS supported the 49 combinations of distributions that used generalized gamma for EF→death. In both arms of KEYNOTE-689, these 49 combinations had the lowest average MSE and lowest minimum MSE out of the seven sets of 49 combinations using different EF→death distributions under Approach #1.
- Under Approach #2, MSE statistics supported the 9 combinations of distributions that used Gompertz for EF→death, which in both arms had the lowest average MSE and lowest minimum MSE out of the three sets of 9 combinations using different distributions for EF→death under Approach #2

- Under Approach #3, MSE statistics suggested that the 9 combinations of distributions using Gompertz for EF→death provide the best balance between statistical fit in the perioperative pembrolizumab + SOC and SOC arms

The subsequent steps therefore focused on the 67 combinations of distributions identified above.

2. **Visual assessment of fit vs observed EF failure events:** Cumulative incidence graphs were generated to compare observed versus predicted curves from the 67 different combinations of parametric functions remaining after Step 1 (see Appendix J1.2 for further details and associated figures). Visual inspection led to the exclusion of all but 16 combinations of parametric distributions under approaches #1-3:

- Under Approach #1, 12 combinations that use Gompertz or generalized gamma for EF→IRP and that do not use exponential for EF→L/SR
- Under Approach #2, 2 combinations that use Gompertz for EF→IRP and that do not use exponential for EF→L/SR
- Under Approach #3, 2 combinations that use Gompertz for EF→IRP and that do not use exponential for EF→L/SR

3. **Statistical assessment of fit:** All 67 combinations of parametric functions that modelled EF→ death using generalized gamma under Approach #1 or Gompertz under Approach #2 or #3 were ranked for statistical fit based on MSE for predicted versus observed EFS (full details available in Appendix J1.3. Consistent with findings from the visual assessment, the corresponding 16 combinations identified all ranked in the top half for best statistical fit.

Of note, the proportional hazards assumption could not be rejected for EF→IRP or EF→death, but was rejected for EF→L/SR ($p=0.0351$). Schoenfeld residual plots, presented in Appendix J1.3, are non-horizontal suggesting potential violation of the proportional hazards assumption. Thus, the 2 combinations of parametric functions under Approach #2 were excluded from further consideration for the base case, but were assessed further in scenario analyses.

MSE values were generally higher in magnitude in the SOC arm than the perioperative pembrolizumab + SOC arm, and therefore the choice of base case distributions prioritised statistical fit in SOC. Subsequent assessments of external validity and clinical plausibility therefore focused primarily on the 10 of the remaining 14

combinations that were in the top 10 best-fitting combinations (among the 67 combinations remaining after Step 1) in the SOC arm.

4. **Internal and external validations of predicted OS for SOC:** Predicted OS in the SOC arm for the remaining 10 best-fitting combinations was validated against observed OS data from KEYNOTE-689; all combinations provided an excellent fit to the observed OS data. OS data from published real-world cohort studies (see Appendix J1.4 for summary of real-world studies) among patients with resectable LA HNSCC, presented in Figure 18, were also used to assess external validity of extrapolations.

As previously discussed, there is a wide heterogeneity amongst the LA HNSCC population that is reflected in the patient characteristics of the identified real-world studies, resulting in a wide range of long-term OS outcomes and limiting generalisability to the KEYNOTE-689 population (see Appendix J1.4). Specifically, Burbure et al and Chen et al included only hypopharyngeal patients who historically have a worse prognosis compared with other anatomical sites,(70, 71) whilst Leeman et al primarily included patients with oropharyngeal disease,(22) of which 48% were HPV-positive which is known to have better prognosis than HPV-independent disease.

Consequently, no further exclusions could be concluded based on external validations of OS; however, the modelled OS for the SOC arm falls within the range of the external studies and is consistent with the comparative outcomes expected based on the differences in anatomical site described above, demonstrating that the predicted outcomes are within the range of plausible outcomes. Regardless of the magnitude of OS, all external studies demonstrate a consistent shape in the long-term survival curves, which are supportive of the modelled extrapolations for the SOC arm in the short-term and long-term OS prediction.

Figure 18. External validation of OS in the SOC arm



Abbreviations: EF, event free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; OS, overall survival; SOC, standard of care

Note: In this figure, the 10 finalist curves presented are all using Approach #1 and cause-specific hazards of EF → death are modelled using Generalized gamma. Published OS curves from external studies were digitised.

Where KM curves from subgroups were reported separately (Leeman et al. 2017; Burbure et al. 2021), a weighted average was derived as the sum product of the OS at each time point and the proportion of the population in each subgroup as per the KEYNOTE-689 study baseline characteristics.

5. **Clinical plausibility of the predicted EFS and OS benefit:** The incremental EFS and OS benefit of perioperative pembrolizumab + SOC relative to SOC was assessed under the 10 finalist combinations of parametric distributions (see Appendix J1.5).

All 10 combinations yielded reasonably close predictions of the observed incremental EFS and OS benefit during the available trial period. Beyond the trial period, at the 10-year time point, all but 1 of the 10 finalist combinations predicted incremental EFS and OS benefits of ≥ 8 percentage points, and ≥ 9 percentage points under 8 of the 10 finalist combinations. The log-normal / Gompertz / generalized gamma combination under Approach #1 yielded outlying estimates of incremental EFS and OS benefits (6.7 and 6.8 percentage points, respectively) relative to the other combinations of distributions, in addition to a clinically implausible implied EFS HR that exceeds 1 by 4 years (contradicting the observed trial data); this combination was nevertheless retained for further consideration in a highly conservative scenario analysis to represent the lower bound of incremental effectiveness.

Of note, clinical expert opinion to the company indicated that patients remaining EF at 5 years would be considered cured, and subsequently discharged, and an observed plateau in EFS would be expected in both arms. The EFS curve using Gompertz / Gompertz / Generalised gamma demonstrates a plateau in EFS in line with clinical experts' expected cure pattern, however this same plateau is not observed in the log-normal / Gompertz / generalized gamma combination under Approach #1 (see Figure 22).

Base case

Based on the findings described above, one of the 10 finalist combinations of distributions was chosen as the base case.

The selected base case combination was Gompertz / Gompertz / generalized gamma under Approach #1, based on both visual and statistical fit, and clinical plausibility. The Gompertz function from EF $\rightarrow$ IRP was the preferred choice of distribution on the basis of visual inspection. Further, the combination of Gompertz / Gompertz / generalized gamma under Approach #1 had the best MSE ranking in the SOC arm among the combinations of distributions that used Gompertz for EF $\rightarrow$ IRP, and provides a mid-range incremental benefit amongst the finalist combinations. Although four of the other finalist combinations had marginally better MSE ranking in the SOC arm (indicating better statistical fit between

predicted vs. observed EFS), these combinations yielded worse visual fit to the EF → IRP transition in the SOC arm (see Figure 8 in Appendix J1.2).

Out of the 67 candidate combinations remaining after Step 1, this combination was the 5th best-fitting in the SOC arm and the 16th best-fitting in the perioperative pembrolizumab + SOC arm. Out of the entire original 397 candidate combinations, this combination was the 5th best-fitting in the SOC arm and the 36th best-fitting in the perioperative pembrolizumab + SOC arm.

Under the base case parametric distribution selected, Figure 19 presents the predicted versus observed cumulative incidence of transitions from the EF state. Of note, patients in the perioperative pembrolizumab + SOC arm remain in the EF state for longer, without having a recorded recurrence, and thus the modelled cumulative incidence of EF→death is moderately higher in the perioperative pembrolizumab + SOC arm compared to the SOC arm. Figure and Table 28, and Figure and Table 29, present the modelled and observed EFS and OS, respectively.

Of the 9 remaining combinations, the two resulting in the most and least incremental EFS and OS benefit are presented as scenario analyses to demonstrate the range of plausible cost-effectiveness. The best-fitting combinations from each of Approach #2 and Approach #3 are also presented, to explore the impact of assuming time constant and time-varying proportional hazards, respectively. The final set of combinations used in the base case and explored in scenarios is shown in Table 27 and Figure 22.

Table 27. Combinations of distributions selected for base case and scenarios

Description	Distributions [†]	Comments
Base case	Approach #1: Gompertz / Gompertz / generalized gamma	Best balance of statistical fit, visual fit and clinical plausibility. Captures the EFS plateau in both arms described by clinical experts and predicts a mid-range estimate of treatment incremental benefit.
Scenarios		
Largest incremental EFS/OS benefit:	Approach #1: Generalized gamma / generalized gamma / generalized gamma	Plateau in SOC arm not captured
Smallest incremental EFS/OS benefit:	Approach #1: log-normal / Gompertz / generalized gamma	Plateau in pembrolizumab arm not captured
Best-fitting under Approach #2:	Approach #2: Gompertz / Gompertz / Gompertz	Best-fitting to explore impact of proportional hazards

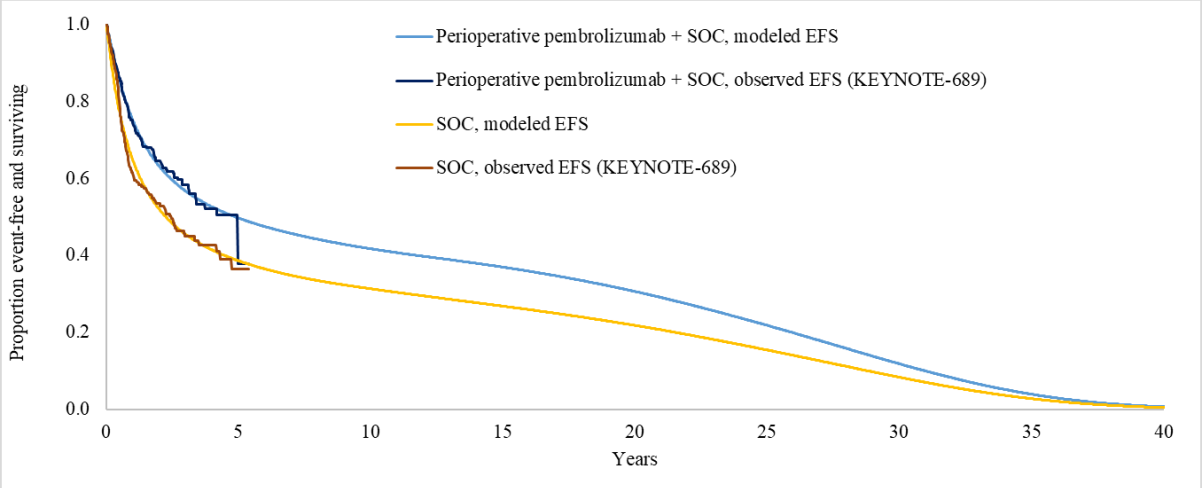
Best-fitting under Approach #3:	Approach #3: Gompertz / Gompertz / Gompertz	Best-fitting to explore impact of time-varying proportional hazards

Abbreviations: EFS, event-free survival; OS, overall survival; SOC, standard of care.
† Distributions are presented in the format: Approach # / EF→L/SR / EF→IRP / EF→ death.

Figure 19. Predicted vs. observed cumulative incidences of transitions from the EF state under the base case (CPS $\geq$ 1 population)

■ *Abbreviations:* CPS, combined positive score; EF, event-free; IRP, incurable recurrence/progression; L/SR, local and/or salvageable recurrence; SOC, standard of care.

Figure 20. Base case modelled and observed EFS over model time horizon (CPS≥1 population)



Abbreviations: CPS, combined positive score; EFS, event-free survival; SOC, standard of care

Figure 21. Base case modelled and observed OS over model time horizon (CPS≥1 population)

Abbreviations: CPS, combined positive score; OS, overall survival, SOC, standard of care
Note: In this figure, observed OS is based on the censoring rule used in the primary EFS analysis. See Section 3.14.1.1 for further details.

Table 28. Base case predicted EFS

Outcome	EFS by year, %									
	1	2	3	4	5	10	15	20	30	40
SOC										
KM	■	■	■	■	■	-	-	-	-	-
Modelled	■	■	■	■	■	■	■	■	■	■
Perioperative pembrolizumab + SOC										
KM	■	■	■	■	■	-	-	-	-	-
Modelled	■	■	■	■	■	■	■	■	■	■

Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; SOC, standard of care.
Note: The Kaplan-Meier EFS curve from KEYNOTE-689 IA1 beyond year 3 is subject to a high degree of censoring as a result of immature trial data and should be interpreted with caution.

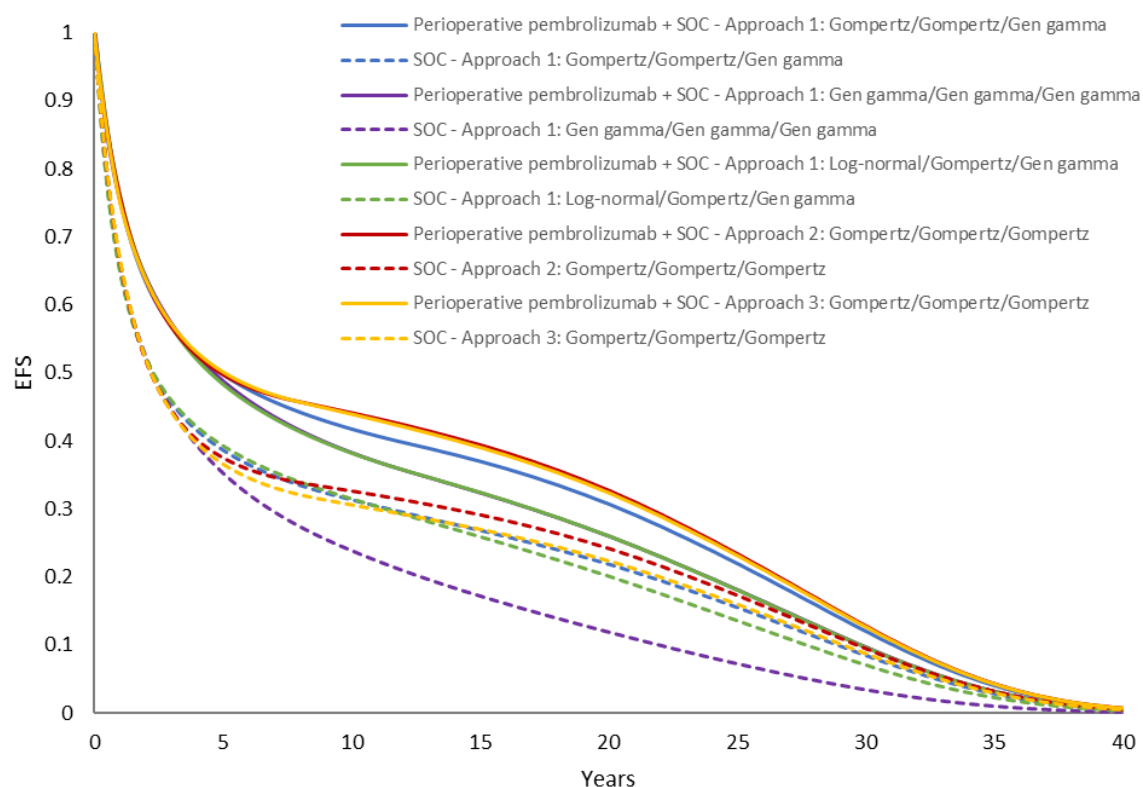
Table 29. Base case predicted OS

Outcome	OS by year, %								
	1	2	3	4	5	10	20	30	40
SOC									
KM						-	-	-	-
Modelled									
Perioperative pembrolizumab + SOC									
KM						-	-	-	-
Modelled									

Abbreviations: KM, Kaplan-Meier; OS, overall survival; SOC, standard of care.

Note: The Kaplan-Meier OS curve from KEYNOTE-689 IA1 beyond year 3 is subject to a high degree of censoring as a result of immature trial data and should be interpreted with caution. Observed OS landmark estimates are based on the censoring rule used in the primary EFS analysis. See Section 3.14.1.1 for further details.

Figure 22. Incremental EFS benefit in base case and alternative distribution scenarios



Abbreviations: EFS, event-free survival; SOC, standard of care

Blue curves represent the base case distributions (Approach #1 Gompertz/Gompertz/Gen gamma); other colours represent curves presented in scenario analyses.

Note that some curves may overlay one another. A detailed figure of the EFS curves in the base case and scenario analysis up to year 10 is presented in Appendix J1.5.

Cure point

Clinical expert opinion to the company indicated that the majority of recurrences in LA HNSCC would occur in the first two years and that patients remaining EF at 5 years after the initiation of treatment would be considered functionally cured and subsequently discharged (although they noted that the risk of recurrence never becomes zero).⁽⁴⁹⁾ The modelled EFS, under the base case selection of curves for transitions from the EF health state, for both arms (Figure) demonstrates a plateau from approximately 5 years, in addition to the implied hazard rates of EFS failure in both arms showing a very low risk of recurrence or death by year 5 in the economic model (Figure 23). This suggests that potential for cure is already accounted for. Thus, in this instance the application of an additional cure assumption in the base case

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economic model may overestimate, and potentially double count, for the likelihood of cure. Therefore, and in contrast to several previous appraisals in early-stage cancer indications (TA569, TA632, TA746, TA837, TA1017, TA1037)(55, 57, 59, 72-74) no explicit cure assumption is applied in the base case economic model. A scenario analysis explores the impact of applying an instantaneous cure assumption at 5 years with a 95% risk reduction in recurrence or death on model results.

Of note, the plateau in EFS and implied hazard rates of EFS failure seen in the base case are specific to the distributions selected for transitions from the EF health state. Therefore, the decision to apply a cure assumption is determined by the combination of curves selected in terms of hazard profile and predicted survival. This same profile is not seen across all the finalist combinations, such as those included in the scenario analysis (see Figure 22), and therefore under different distribution selections it may be appropriate to apply a cure assumption in order to capture the expected plateau in EFS across both arms.

Figure 23. Implied hazard rate of EFS failure in the perioperative pembrolizumab + SOC and SOC arms in the base case economic model



Abbreviations: EFS, event-free survival; SOC, standard of care

3.3.3 Modelling transitions from the L/SR state

To estimate the cause-specific hazards of transitions from the L/SR state (L/SR → IRP and L/SR → death), exponential models were fitted to patient-level data from the KEYNOTE-689 CPS≥1 population for each arm. The exponential distribution is commonly assumed when estimating transition probabilities starting from intermediate health states in a Markov model, as the hazard rate does not depend on time since entry into the health state.(75) In the PD-L1 CPS ≥1 population, the analytical sample included [REDACTED] who experienced L/SR as their first EFS failure event. Among these patients, exponential parametric functions were fitted to time (in weeks) from L/SR state entry until IRP to estimate the cause-specific hazard of L/SR → IRP, and similarly time from L/SR state entry until death for L/SR → death. Patients were censored at the last date that the patient was known to be alive or upon experiencing the competing event type (for example, when modelling the cause-specific hazards of L/SR → IRP, patients were censored at the earliest of death or date that the patient was last known to be alive).

Within each model cycle, the transition probability from L/SR → death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality.

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The cause-specific hazards of L/SR → IRP and L/SR → death are shown in Table 30. Internal validations of predicted versus observed cumulative incidences of L/SR → IRP and L/SR → death are presented for each arm in Figure 24 and Figure 25, respectively, demonstrating good alignment.

As noted above, the proportion of patients who have an L/SR as their first EF event is small and comparable across both study arms, and therefore transition probabilities from the L/SR health state are not expected to be a major driver of cost-effectiveness model results. The impact of changing the exponential rate of transitions from L/SR→IRP and L/SR→Death is tested in the sensitivity analysis.

Table 30. Transition probabilities from L/SR state (CPS≥1 population)

Adjuvant regimen	L/SR → IRP		L/SR → Death	
	Log(rate)	SE	Log(rate)	SE
Perioperative pembrolizumab + SOC	■	■	■	■
SOC	■	■	■	■

Abbreviations: CPS, combined positive score; IRP, incurable recurrence or progression; L/SR, local or salvageable recurrence; SE, standard error; SOC, standard of care.

Figure 24. Internal validation of predicted vs. observed cumulative incidences of transitions from the L/SR to IRP health states (CPS≥1 population)

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence, SOC, standard of care
Source: KEYNOTE-689 (IA1, data cutoff: 25 July 2024).

Figure 25. Internal validation of predicted vs observed cumulative incidences of transitions from L/SR to death (CPS≥1 population)

Abbreviations: CPS, combined positive score; L/SR, local or salvageable recurrence; SOC, standard of care
Source: KEYNOTE-689 (IA1, data cutoff: 25 July 2024)

3.3.4 **Modelling transitions from the IRP state**

Similar to the approach used to model transitions starting from L/SR (Section 3.3.3), exponential models fitted to patient-level data from KEYNOTE-689 were used to estimate the cause-specific hazard of the IRP → death transition in each trial arm. The analytical sample included a total of [REDACTED] patients who experienced IRP either as their first EFS failure event ([REDACTED]; [REDACTED] in the perioperative pembrolizumab + SOC arm and [REDACTED] in the SOC arm) or who first experienced L/SR followed by IRP as a subsequent recurrence event [REDACTED]; [REDACTED] in the perioperative pembrolizumab + SOC arm and [REDACTED] in the SOC arm). Among these patients, exponential parametric functions were fitted to time from IRP state entry until death (or until censoring at the end of data or loss of follow-up). The resulting hazard rates are presented in Table 31.

As with other transitions to death, the transition probability from IRP → death in each weekly model cycle was set equal to the maximum of the estimated probability based on parametric modelling and background mortality. Of note, as with the transitions starting from the L/SR state, the transition from IRP to death was modelled using exponential distributions, as the memoryless property of Markov models prevents the use of transition probabilities that depend on time spent in an intermediate health state.(75) Internal validations of predicted versus observed cumulative incidences IRP → death are presented for each arm in Figure 26 and demonstrate that the exponential models provide a good fit to the observed data.

The impact of varying the exponential rate for transitions from IRP→Death within the 95% confidence intervals is explored in the sensitivity analyses. In addition, the potential impact of using longer- or shorter-tailed distributions for this transition was explored in sensitivity analyses that varied the rates of OS and PFS failure associated with first-line treatments in the IRP state. As OS is modelled using trial data directly in the base case, this only impacts the ratio of OS and PFS which in turn determines costs and utilities based on pre- and post-progression in the IRP health state.

Table 31. Transition probabilities from IRP to death (CPS≥1 population)

Adjuvant regimen	IRP → Death	
	Exponential rate	SE
Perioperative pembrolizumab + SOC	[REDACTED]	[REDACTED]
SOC	[REDACTED]	[REDACTED]

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; SE, standard error; SOC, standard of care.
Source: KEYNOTE-689 (IA1, data cutoff: 25 July 2024)

Figure 26. Internal validation of predicted vs. observed cumulative incidences of transitions from IRP to death (CPS $\geq$ 1 population)

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; SOC, standard of care.
Source: KEYNOTE-689 (IA1, data cutoff: 25 July 2024)

As a scenario analysis, an alternative approach is considered in which the transition probabilities from IRP to death in each treatment arm are assumed to depend on the efficacy and market shares of subsequent treatments in the IRP state. Specifically, in each treatment arm, mean progression-free survival (PFS) and OS within the IRP state were estimated based on the market shares and efficacy of first-line treatments for recurrent/metastatic HNSCC received in that arm. The model included first-line treatment options that had relevant PFS and OS inputs available (Table 52 in Section 3.5.2.3) and that are recommended in UK clinical practice. Further details on this scenario analysis are provided in Appendix J2. Despite its complexities and data limitations, this is a common approach in previous NICE TA for early-stage indications due to immature trial data precluding estimation of this transition directly from the trial. However, the IA1 DBL of KEYNOTE-689 has sufficient follow-up and events to enable estimating transitions from IRP $\rightarrow$ death using trial data directly, which reduces the modelling complexity and reliance on external data.

3.3.5 Adverse events

The inclusion of specific AEs within the economic model was based on a combination of the risk and severity of each event. The model considered AEs occurring in the neoadjuvant and adjuvant (i.e. perioperative) settings only; AEs associated with subsequent treatments in the metastatic setting were not considered due to their expected small impact on the cost-effectiveness results. The model considered all-cause grade 3+ AEs that occurred with a frequency of $\geq$ 5% in either treatment arm.

Risks of the included AEs for patients treated with perioperative pembrolizumab + SOC and SOC were obtained from KEYNOTE-689 (all comer population), based on the proportions of patients with all-cause grade 3-5 AEs reported for the all-participants-as-treated (APaT) population (Table 18).

Mean duration per AE episode and mean number of episodes per patient with each included AE were collected from KEYNOTE-689 (pooling across both trial arms) and were used within the model to estimate the duration of the disutility impact from each AE regardless of treatment arm. The percent of AEs resulting in hospitalizations were also collected from KEYNOTE-689 (pooling across both trial arms) and used to calculate the cost per AE episode (see Section

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3.5.3). AE-related disutility and costs are applied in the first cycle of the model (in-line with standard practice) and are described further in Section 3.4.4 and Section 3.5.3, respectively.

Table 32. Adverse event incidence and durations (all cause grade 3+)

AE type	AE risk (%), by treatment arm		Mean number of episodes per patient with AE†	Mean duration of AE per episode (weeks)†	% of AE episodes resulting in hospitalization†
	Perioperative pembrolizumab + SOC	SOC			
Anaemia	████	████	████	████	████
Dysphagia	████	████	████	████	████
Hypokalaemia	████	████	████	████	████
Hyponatraemia	████	████	████	████	████
Lymphocyte count decreased	████	████	████	████	████
Neutrophil count decreased	████	████	████	████	████
Pneumonia	████	████	████	████	████
Radiation skin injury	████	████	████	████	████
Stomatitis	████	████	████	████	████
Weight decreased	████	████	████	████	████
White blood cell count decreased	████	████	████	████	████
Source	KEYNOTE-689 IA1, data cutoff: 25 July 2024 (APaT population)				

Abbreviations: AE, adverse event; APaT, all patients as treated; SOC, standard of care.
† Pooled across treatment arms and used within the model to estimate the duration of the disutility impact, and cost, associated with each AE.

3.4 Measurement and valuation of health effects

An SLR was conducted to identify published studies reporting health-related quality of life (HRQoL) or utility data for patients with LA HNSCC. Additional searches were conducted to identify utility data for the recurrent/metastatic setting to help inform the economic model. Full details on the methodology and findings of the SLR, including search terms, PRISMA diagram and outcomes are detailed in Appendix F, and a summary of identified studies is provided in 3.4.3.

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

3.4.1.1 KEYNOTE-689

HRQoL was measured in KEYNOTE-689 using the EORTC-QLQ-C30, EORTC-QLQ-H&N35 instrument, and the EuroQoL EQ-5D-5L instruments. The NICE STA guidelines state that the EQ-5D is the preferred tool to measure HRQoL and that the economic model should consider HRQoL data collected directly from patients in the relevant clinical study to inform the utility weights,(63) therefore the EQ-5D trial data were analysed for use in the economic evaluation.

In KEYNOTE-689, the EQ-5D-5L questionnaire was completed by participants at various time points, including the pre-surgery and post-surgery periods. During the pre-surgery period, the EQ-5D-5L questionnaire was administered on weeks 1 and 4 (± 3 days) and then again in week 6 (± 10 days) in the perioperative pembrolizumab + SOC arm. The EQ-5D-5L questionnaire was administered once before surgery in the SOC arm. During the post-surgery treatment period, the EQ-5D-5L questionnaire was completed in conjunction with radiotherapy $\pm$ cisplatin treatment prior to treatment administration. During post-treatment follow-up period, the EQ-5D-5L questionnaire was completed 30 days (± 14 days) from the last dose, and then every three months from last scan (± 7 days) for up to end of year 3 and every 12 months (± 14 days) in years 4 and 5.

Aligned with the economic model, utility values were calculated for the following states based on the average across all patient visits with an EQ-5D-5L measurement within that state, within the all comer population:

- EF (without grade 3+ AEs; which includes patient-visits in the EF state while patients had no AEs or solely grade 1-2 AEs);
- EF (with grade 3+ AEs; which includes patient-visits in the EF state while patients had grade 3+ AEs);

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- L/SR
- IRP

Utility values were estimated via descriptive analyses of patient-level EQ-5D-5L data from the IA1 data cut of KEYNOTE-689 and consisted of the PRO full analysis set (PRO-FAS), defined as all randomized participants who received at least one dose of study treatment and have at least one valid EQ-5D endpoint assessment. Each EQ-5D response from KEYNOTE-689 was categorised into one of these health states (based on a determination of the patient's health state at the time of collection of each response) and included in the utility analysis accordingly. At each available patient-visit, the corresponding EQ-5D-5L score was used to characterize utility. Baseline measurements were excluded from the analysis, along with patient-visits with missing EQ-5D-5L responses. Compliance to the EQ-5D assessments was very good and remained over █████% in both treatment arms for all timepoints up to week 129 (see Appendix K). Summary statistics were computed based on multiple records per participant, which were treated as independent observations.

The analyses were pooled across treatment arms to estimate the average utility for all patients in the trial, as there was no clinically meaningful difference in HRQoL observed between the treatment arms in either the neoadjuvant or adjuvant phases of the KEYNOTE-689 trial (section 2.6.1.6 and 2.6.1.7). Any differences in HRQoL as a result of adverse events of treatment were captured by the application of treatment-specific adverse event disutilities (section 3.4.4). It is therefore assumed that any HRQoL impact of a reduction in adjuvant cisplatin use in the pembrolizumab arm is captured by the adverse event disutility, however this may not fully capture the HRQoL benefit of avoiding of adjuvant chemotherapy. This approach also maximises the available data and is consistent with previous appraisals of early-stage cancers (e.g. NICE TA766, TA830, TA837, TA851, TA1017).(54-58) To reflect health preferences in the general UK population, patient responses to the EQ-5D-5L questionnaire were mapped onto the UK EQ-5D-3L value set using the crosswalk developed by Hernández Alava et al. (2023) in accordance with Section 4.3.16 of NICE's updated manual for health technology evaluations.(61, 63)

It was not possible to generate utility values for pre- versus post-progression in the IRP health state as the available follow-up data from KEYNOTE-689 required to inform such analysis to date were too limited, and related to too few patients, to reliably capture the average utility over the entire post-progression disease course until death. The utility value for the IRP state

from KEYNOTE-689 may therefore be used as an approximation of utility in the pre-progression IRP sub-state only.

Health state utility values derived from the trial are presented below in Table 33.

Table 33. Health state utilities derived from KEYNOTE-689

Health state	Patients, n	Records, n	EQ-5D-3L		Source
			Value	SE	
EF (without grade 3+ AEs)	■	■	■	■	KEYNOTE-689 IA1 (all comers)
EF (with grade 3+ AEs)	■	■	■	■	
L/SR	■	■	■	■	
IRP	■	■	■	■	

Abbreviations: AE: Adverse events; EF, event-free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; SE, standard error.

3.4.2 Mapping

As per NICE’s manual for reference case analyses, the EQ-5D-3L value set is preferred for the reference case analysis.(63) Therefore, the EQ-5D-5L measurements collected in KEYNOTE-689 were mapped to the EQ-5D-3L tool from which utilities from derived, using the mapping function and UK value set developed by the Decision Support Unit,(Hernández Alava et al. 2023) as recommended in the NICE methods guide.(61, 63)

3.4.3 Health-related quality-of-life studies

3.4.3.1 LA HNSCC

The SLR described in Appendix F was conducted to identify studies reporting utility values for patients with previously untreated LA HNSCC. No studies were identified that reported utility data specifically for resectable/resected LA HNSCC (i.e. aligned with the KEYNOTE-689 population); however, four publications reporting utilities for LA HNSCC, irrespective of resection status, were included.

Of these, only one study was fully aligned with the NICE reference case. Smith et al, 2017 reported an EQ-5D utility value (disease-free: 0.7 [SD 0.03], n=564) for UK patients with N2-3 M0 HNSCC (including oropharyngeal, laryngeal, oral, hypopharyngeal or occult) within the PET-Neck pragmatic trial who had planned neck dissection either before or after primary chemoradiotherapy, or chemoradiotherapy with PET-CT management.(76) A range of utility values were available from the M-TAG utility study conducted to inform the NICE TA145 appraisal,(4) however whilst these were measured using the EQ-5D, the population surveyed

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was nursing staff in oncology centres rather than HNSCC patients, and therefore the resulting values, while informative, are not aligned with the reference case. One additional study, TAX-323/EORTC-24971 (Parthan et al, 2009), reported utility values collected via EORTC-QLQ-C30 and mapped to EQ-5D, from patients with unresectable LA HNSCC (stable, 0.7; progressive, 0.67; response, 0.79);(77) whilst not specified, as a UK CEA it is assumed to use the UK value set.

3.4.3.2 *Progressed, recurrent HNSCC*

As noted in section 3.4.1, it was not possible to generate utility values specifically for pre-versus post-progression in the IRP health state as the available follow-up from KEYNOTE-689 trial was too limited to capture the average utility over the entire post-progression disease course until death. Therefore, external sources were considered to inform the IRP post-progression health state.

A range of potential sources were identified via the utility SLR, targeted searches and internal MSD datasets. These are summarised in Table 34, and additional details are provided in Appendix F. Utility data available to MSD from KEYNOTE-048, a Phase 3 RCT of pembrolizumab ± chemotherapy versus cetuximab + chemotherapy in patients with incurable untreated R/M HNSCC, report a pooled post-progression utility that is higher than the IRP pre-progression utility in KEYNOTE-689 (■■■■). Whilst this may seem counterintuitive, feedback from clinical experts to MSD was that whilst they would expect HRQoL to decrease on progression, in this specific case this observation is plausible as they would expect patients with *de novo* metastatic disease to have better HRQoL than patients who recurred or progressed from LA disease, as a result of high morbidity following major surgery and CRT in the LA-recurrent group.(49) Only 27-32% of patients in KEYNOTE-048 had recurrent disease,(78) therefore a higher HRQoL in this study versus KEYNOTE-689 is not unexpected. However, consequently KEYNOTE-048 is not a useful source to inform the IRP post-progression utility in the current economic model.

In NICE TA172/TA473, which assessed cetuximab for treating recurrent or metastatic HNSCC, EQ-5D-3L utility values obtained by mapping EORTC QLQ-C30 data collected from patients in the EXTREME trial were used.(62) For the post-progression state, the estimated utility value was 0.52; this could represent a suitable source to inform the IRP post-progression state, as it is logically consistent with the KEYNOTE-689 utility data and adequately captures the limited effective treatment options for patients at that stage of the treatment pathway.

Singh et al, 2021 report a patient preference study and a utility value of 0.57 for Stage III-IV R/M HNSCC,(79) however, this is not specific to post-progression and limited details of patient characteristics are provided. A bespoke study (M-TAG utility study) conducted to inform NICE TA145 (cetuximab for LA HNSCC) reports a utility of 0.129 for post-progression,(60) however utilities were estimated from nurses rather than patients, and this value seems remarkably low and may not hold face validity. Parthan et al, 2009 also report a utility for progressive disease, however this is progression from LA HNSCC,(77) and therefore has similar limitations as the IRP utility from KEYNOTE-689 in that it does not specifically represent progression after a recurrence.

Table 34: External utility estimates for progressive disease

Study	Measurement instrument Valuation Participants, N	Health state definition	Utility estimate, mean (SE) [95% CI]
KEYNOTE-048	EQ-5D-3L TTO, UK value set Patients with incurable untreated R/M HNSCC, n=466	Progressive disease (pooled)	
NICE TA172, 2009/ TA473, 2017 (EXTREME RCT)(62)	EORTC QLQ-C30 mapped to EQ-5D-3L NR Patients with R/M HNSCC with no prior chemotherapy, N=NR	Progressive disease	0.52 [0.11-0.93]
Singh 2021(79)	EQ-5D-3L Patients with Stage III-IV R/M HNSCC, N=577	Stage III-IV R/M HNSCC	0.570 (NR)
NICE TA145, 2008 (M-TAG utility study)(60)	EQ-5D-3L TTO, UK value set Nurses in British oncology centres, N=50	Post-treatment Progressive or worsening disease (unsuccessful treatment)	0.129 (0.040)
Parthan 2009(77)	EORTC QLQ-C30 mapped to EQ-5D-3L NR Patients with Stage III-IV, unresectable LA HNSCC, N=NR	Progressive stage (Note: progression from LA, not specific to R/M post-progression)	0.67 [0.60-0.74]

Abbreviations: CI, confidence interval; HNSCC, head and neck squamous cell carcinoma; LA, locally advanced; NR, not reported; RCT, randomized controlled trial; R/M, recurrent/metastatic; SE, standard error; TTO, time trade off.

3.4.4 Adverse reactions

AE-related disutility was applied as a one-time QALY decrement in the first model cycle. This disutility associated with AEs was calculated in each treatment arm as a function of treatment-

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specific AE risks; the mean duration per AE episode; the mean number of episodes per affected patient in KEYNOTE-689; and the estimated disutility associated with an active grade 3+ AE. This disutility of an active grade 3+ AE was calculated as the difference between the mean utility for “EF with grade 3+ AE” minus the mean utility for “EF without any AE”, as estimated from KEYNOTE-689 (Table 35).

Inputs and assumptions related to AE incidence, duration and number of episodes are described in section 3.3.5.

Table 35. Estimated AE disutility for grade 3+ AEs, derived from KEYNOTE-689

Health state	Patients, n	Records, n	EQ-5D-3L		Source
			Mean	SE	
EF (without grade 3+ AEs)	■	■	■	■	KEYNOTE-689 IA1 (all comers)
EF (with grade 3+ AEs)	■	■	■	■	
Disutility for grade 3+ AEs†	-	-	■	■	

Abbreviations: AE, adverse event; SE, standard error.
† Calculated as the difference between the mean utility across patient-visits in the EF state with any grade 3+ AE minus the mean utility in the EF state with no grade 3+ AE.

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

As stated in the NICE methods guide, the preferred approach for incorporating HRQoL into the economic model is to collect health state measurements from patients relevant to the decision problem using the EQ-5D-3L tool, and the utility weights should be elicited from the UK general population.(63) Accordingly, for the EF, L/SR, and pre-progression IRP health states the base case analysis used utility values derived from the analyses of patient-level EQ-5D-5L data collected from the KEYNOTE-689 trial. The EQ-5D-5L measurements were mapped back to the EQ-5D-3L version of the tool using the NICE DSU algorithm(61) and utilities derived using the UK value set. A disutility for AEs was also estimated from the KEYNOTE-689 trial and applied as a one-off decrement in the first model cycle (Table 36).

In line with the model structure, the IRP health state was comprised of two sub-states (pre-progression and post-progression) to capture differences in outcomes and costs of patients who develop incurable recurrent/metastatic disease. As discussed in 3.4.1, EQ-5D data corresponding to post-progression were not available from KEYNOTE-689 as the available follow-up from the trial was too limited to enable a robust analysis of post-progression utility. Alternate sources were therefore reviewed for suitability to inform this parameter (see section

3.4.3 for details and discussion). The utility value for progressive disease estimated based on EORTC-QLQ-C30 data collected in the EXTREME trial and mapped to EQ-5D (used in NICE TA172/TA473) was deemed the most appropriate source to inform the IRP post-progression health state, based on good general alignment with the NICE reference case and health state definition, and face validity with respect to the utilities from KEYNOTE-689 used to model the other health states.

In each treatment arm, utility for the IRP state was then calculated as a weighted average of utility values in the pre- and post-progression IRP sub-states, based on the expected proportion of time spent pre- versus post-progression estimated using PFS and OS failure rates of first-line treatments as outlined in Appendix J2. A scenario using the KEYNOTE-689 IRP utility for both pre- and post-progression IRP states was also conducted.

A summary of the utilities used in the base case analysis is provided in Table 36.

Table 36. Summary of utility values for cost-effectiveness analysis

State	Utility, mean	SE	Reference in submission	Source and justification
EF (without AEs)	■	■	3.4.1	EQ-5D-3L values derived from patients directly relevant to the decision problem (from KEYNOTE-689) using UK value set, in line with the NICE reference case
L/SR	■	■		
IRP (pre-progression)	■	■		
IRP (post-progression)	0.52	0.209 [†]	3.4.3	EORTC-QLQ-C30 from EXTREME mapped to EQ-5D-3L, reported in NICE TA172/TA473(62) Alignment with NICE reference case and to ensure face validity with KEYNOTE-689 values
	■	■	3.4.1	Scenario analysis (assuming no HRQoL decrement on progression)
Grade 3+ AE	■	■	3.4.4	KEYNOTE-689, in line with the NICE reference case

Abbreviations: AE, adverse event; EF, event-free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; SE, standard error.

[†] Calculated based on 95% CI reported in ERG report.

3.4.5.1 Age-related disutility

The economic model accounted for disutility related to aging of the cohort over time, based on expected EQ-5D-3L by age and sex in the UK, as derived from Health Survey for England

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(HSE) 2014 data.(80) Age-related disutility is applied starting from the end of the available within-trial period (i.e., 2.6 years, based on mean actual follow-up in KEYNOTE-689 at IA1), as the health state utilities derived from KEYNOTE-689 data already reflect the mean age of participants during the trial period. In each cycle i thereafter, age-related disutility was computed as the utility corresponding to patients' age and gender distribution in cycle i (as estimated using the general population utilities from HSE) minus the utility corresponding to patients' age and gender distribution at the end of the trial period (also estimated using the general population utilities from HSE).

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify healthcare resource use and costs associated with treatment of LA HNSCC. All relevant search strategies, search identification, and methodology are presented in Appendix G.

In line with the NICE reference case, the model took a UK National Health Service (NHS) and Personal Social Services (PSS) perspective and therefore only direct healthcare costs related to the treatment and management of LA HNSCC were considered. Evidence on resources used by patients in the treatment pathway were sourced from the KEYNOTE-689 trial and the published literature. Where trial data are used to inform inputs, the APaT population is used to account for the open-label nature of the KEYNOTE-689 trial and better reflect expected outcomes of patients receiving the respective treatment regimen. Healthcare costs were obtained from publicly available sources which primarily included the British National Formulary (BNF),(81) NHS Reference Costs,(82) and the Personal Social Services Research Unit (PSSRU) to ensure the model used the most up to date costs relevant to UK practice. These were supplemented by costs from published studies where relevant inputs from the public sources were not available. All costs are reported in 2024 GBP.

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition and administration costs per infusion of neoadjuvant/adjuvant treatments were calculated in the model as a function of the list price per drug unit, defined dosing schedule and unit cost of drug administration. The proportions of patients remaining on each neoadjuvant/adjuvant drug component over time were based on observed data from KEYNOTE-689.

3.5.1.1 Drug acquisition costs

In the perioperative pembrolizumab + SOC and SOC treatment arms, the defined dosing schedules of drug components reflected the KEYNOTE-689 trial and anticipated licence (Table 37):

- In the perioperative pembrolizumab + SOC arm, pembrolizumab is administered as a flat dose of 200 mg IV Q3W for up to 2 cycles in the neoadjuvant setting before surgery. In the adjuvant setting, to reflect clinical expert opinion that Q6W administration would be preferred to manage capacity,(49) pembrolizumab was assumed to be administered

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as a flat dose of 400 mg IV Q6W. However, to reflect closer patient monitoring as they reinitiate treatment with pembrolizumab after surgery, and to prevent delivering a higher total dose of pembrolizumab over the full treatment schedule than is specified in the protocol, it is assumed that the first dose in this setting will be 200 mg with the first 400 mg dose administered 3 weeks later. A scenario assuming only 200 mg Q3W dosing in the adjuvant phase for up to 15 cycles was also explored.

- In both arms, high-risk patients received adjuvant cisplatin administered IV as a dose of 100 mg/m² Q3W for up to 3 cycles.

Table 37. Perioperative regimens dosing schedule (PD-L1 CPS≥1 population)

Regimen	Component	Dosing schedule description	% receiving component
Perioperative pembrolizumab + SOC	Pembrolizumab (neoadjuvant)	200 mg IV Q3W up to 2 cycles, followed by surgery	100.0%
	Pembrolizumab (adjuvant)	After surgery, 200 mg IV for 1 cycle, then 3 weeks later, 400 mg IV Q6W for up to 7 cycles	
	Cisplatin (adjuvant)	After surgery, 100 mg/m ² IV Q3W up to 3 cycles	
SOC	Cisplatin (adjuvant)	After surgery, 100 mg/m ² IV Q3W up to 3 cycles	

Abbreviations: IV, Intravenous; N/A, not applicable; QxW, every x weeks; SOC, standard of care.
Source: KEYNOTE-689 (25 July 2024 data cut-off), APaT (all patients as treated).
† Reflects patients starting adjuvant therapy after surgery – see section 3.5.1.3 for details.

Unit acquisition costs for the perioperative treatments (as well as drugs used as subsequent treatments in the L/SR and IRP states), are presented in Table 38 (and Appendix I). Unit drug prices were retrieved from the British National Formulary (BNF) for branded drugs and the electronic market information tool (eMIT) for generically available drugs.(81, 83) For generic drugs with multiple eMIT price listings for the same strength, the minimum price per unit was used. Additionally, price listings for a given strength were not used if a higher strength was available at a lower price per unit. A PAS with a simple discount is currently in place for pembrolizumab, reported in Appendix I; list prices are used for all other drugs, as any discounts in place are unavailable to MSD.

For IV-administered drugs with weight-, AUC-, or BSA-based dosing, the base-case analysis assumed that vial-sharing is allowed. Under this assumption, the number of vials required per infusion was calculated based on average body weight, GFR, or BSA of patients in the model cohort. For example, the number of vials for a treatment dosed according to BSA was calculated as mean BSA (m²) multiplied by the required dose per m² (i.e., mg/m²) divided by

the strength per vial (i.e., mg/vial, based on the vial strength associated with the lowest cost per mg). A scenario assuming no vial-sharing was also explored, in which the number of vials required per infusion is similarly calculated based on average body weight, GFR, or BSA, and then rounded up to the nearest whole vial.

No reductions in neoadjuvant/adjuvant drug acquisition costs were applied based on relative dose intensity (i.e., relative dose intensity was set to 100%). As described in section 3.5.1.3, the model considered the exact proportions of patients receiving each cycle of the KEYNOTE-689 trial regimens, an approach which implicitly captures any missed doses.

Table 38: List price unit drug costs for all drug regimens used in model (perioperative or in L/SR or IRP states)

Drug	Unit drug costs		Sources
	Strength per vial or tablet (mg)	List price per package	
5-FU	5,000	£6.27	eMIT (accessed March 2025)
Carboplatin	450	£23.18	eMIT (accessed March 2025)
Cetuximab	100	£178.10	BNF (accessed March 2025)
Cisplatin	10	£3.67	eMIT (accessed March 2025)
Docetaxel	80	£9.73	eMIT (accessed March 2025)
Gemcitabine	2,000	£19.74	eMIT (accessed March 2025)
Ipilimumab	50	£3,750.00	BNF (accessed March 2025)
Methotrexate	500	£12.23	eMIT (accessed March 2025)
Nivolumab	40	£439.00	BNF (accessed March 2025)
Paclitaxel	300	£31.89	eMIT (accessed March 2025)
Pemetrexed	850	£41.78	eMIT (accessed March 2025)
Pembrolizumab	100	£2,630.00	BNF (accessed March 2025)

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool.

3.5.1.2 Drug administration costs

Unit costs of drug administration for both neoadjuvant/adjuvant and subsequent treatments were obtained from the NHS Reference Costs (Table 39),(82) and were applied according to the following principles:

- For IV drug component(s) delivered on the first day of a treatment cycle, the unit cost for SB12Z (simple parenteral chemotherapy) in the outpatient setting was applied once if only one drug component (other than 5-FU) is delivered on that day. If multiple drug components are delivered on that day and 5-FU is not one of the drug components, the unit cost for SB13Z (complex parenteral chemotherapy) in the outpatient setting was applied once (covering the administration of all IV drug components delivered on that

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day). If multiple drug components are delivered on that day and 5-FU is one of the drug components, the unit cost for SB14Z (complex parenteral chemotherapy, including prolonged infusional treatment) in the outpatient setting was applied once (covering the administration of all IV drug components delivered on that day, as well as the prolonged administration of 5-FU spanning multiple days via a device such as a take-home pump). This approach is in line with the approach advised by the Cancer Drugs Fund lead in a recent pembrolizumab submission (TA983).(84)

- For IV drug component(s) other than 5-FU that are delivered on subsequent days of a treatment cycle, the unit cost for SB15Z (subsequent elements of a chemotherapy cycle) in the outpatient setting was applied once per each subsequent day of the treatment cycle in which ≥ 1 IV drug component(s) are administered.

Table 39. Unit costs of drug administration

Route	Type of administration	Unit cost per administration or pharmacy dispensing	Source(82)
IV (simple)	Simple parenteral chemotherapy (1 IV component)	£152.13	NHS Reference Costs 2023/2024 - SB12Z: Deliver simple parenteral chemotherapy at first attendance (OP procedures)
IV (complex)	Complex parenteral chemotherapy (2+ IV components, excluding 5-FU)	£201.66	NHS Reference Costs 2023/2024 - SB13Z: Deliver more complex parenteral chemotherapy at first attendance (OP procedures)
IV (complex prolonged)	Complex parenteral chemotherapy, prolonged infusion (2+ IV components & includes 5-FU)	£352.31	NHS Reference Costs 2023/2024 - SB14Z: Deliver complex parenteral chemotherapy, including prolonged infusional treatment, at first attendance (OP procedures)
IV (subsequent)	Subsequent elements of a chemotherapy cycle	£250.77	NHS Reference Costs 2023/2024 - SB15Z: Deliver subsequent elements of a chemotherapy cycle (OP procedures)
Oral	Oral drug dispensing	£247.13	NHS Reference Costs 2023/2024 - SB11Z: Deliver exclusively oral chemotherapy (OP procedures)

Abbreviations: IV, intravenous; NHS, National Health Service; OP, outpatient.

3.5.1.3 Time on treatment

Time on treatment (ToT) for each drug component of the perioperative pembrolizumab + SOC and SOC arms was based on the observed proportions of patients who received each scheduled cycle of treatment in each arm in the KEYNOTE-689 trial (Table 40). Based on the

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maximum number of cycles for each drug component in each arm, there was sufficient follow-up data from the trial to directly observe the proportions of patients who received each treatment cycle, without the need for extrapolation. To account for the treatment-free period pre- and post-surgery observed in KEYNOTE-689 (Table 40), the first dose of adjuvant treatment was applied at week 13 in the perioperative pembrolizumab + SOC arm and at week 7 in the SOC arm.

Table 40: Proportion of patients receiving each scheduled cycle of perioperative treatment (PD-L1 CPS $\geq$ 1 population, APaT)

Treatment cycle			Perioperative pembrolizumab + SOC			SOC		
			Weeks from model start	% of patients who received each cycle			Weeks from model start	% of patients who received each cycle
				Pembrolizumab (Q3W → Q6W) [†]	Pembrolizumab (Q3W → Q3W); <i>scenario</i>	Cisplatin		Cisplatin
% assigned to component			100.0%	100.0%				
Neo	1	0	100%	100%	-	-	-	
	2	3			-	-	-	
% of patients assigned who receive adjuvant					100%		100%	
Adjuvant	1	13				7		
	2	16				10		
	3	19	-			13		
	4	22			-	-	-	
	5	25	-		-	-	-	
	6	28			-	-	-	
	7	31	-		-	-	-	
	8	34			-	-	-	
	9	37	-		-	-	-	
	10	40			-	-	-	
	11	43	-		-	-	-	
	12	46			-	-	-	
	13	49	-		-	-	-	
	14	52			-	-	-	
	15	55	-		-	-	-	

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Abbreviations: APaT, all patients as treated; CPS, combined positive score; QxW, every x weeks; SOC, standard of care.
Note: Proportions shown in the columns for adjuvant therapy refer to the proportions of patients who receive each scheduled adjuvant dose among those who receive the first scheduled adjuvant dose. Within the model, these proportions are multiplied by the percentage of patients who received the first scheduled dose of adjuvant therapy.
† To reflect closer patient monitoring as they reinitiate treatment with pembrolizumab after surgery, and to prevent delivering a higher total dose of pembrolizumab over the full treatment schedule than is specified in the protocol, it is assumed that the first adjuvant dose will be 200 mg with the first 400 mg dose administered 3 weeks later
Source: KEYNOTE-689 (25 July 2024 DCO).

Table 41. Treatment-free period pre- and post-surgery in KEYNOTE-689

	Weeks, mean	
	Perioperative pembrolizumab + SOC	SOC
Time from first neoadjuvant dose to surgery	■	N/A
Time from surgery to first adjuvant dose	■	■

Abbreviations: N/A, not applicable.

3.5.1.4 Initial surgery and adjuvant radiotherapy costs

Costs associated with the initial surgery following neoadjuvant therapy and any post-surgery adjuvant radiotherapy were calculated based on the observed proportions of patients who underwent surgery as planned and who received post-surgery radiotherapy in KEYNOTE-689 (Table 42). Unit costs per surgery and per radiotherapy regimen were based on NHS Reference Costs. The cost per radiotherapy regimen was calculated as a fixed cost of initiating a radiotherapy regimen, plus an additional cost per week of radiotherapy multiplied by the observed average duration of a radiotherapy regimen (~6.4 weeks) among patients in KEYNOTE-689 who received adjuvant radiotherapy. The additional cost per week of radiotherapy was calculated as the cost per fraction of radiation multiplied by the planned number of fractions per week (i.e., 5 fractions/week, based on the KEYNOTE-689 trial protocol).

Within the model, the timing of the costs of the initial surgery and any post-surgery radiotherapy was based on their average observed timing in KEYNOTE-689.

Table 42: Utilization and unit costs of initial surgery and adjuvant radiotherapy in the EF state (PD-L1 CPS ≥1 population)

	Perioperative pembrolizumab + SOC	SOC	Source
Initial surgery			
% of patients	■	■	KEYNOTE-689 (25-Jul-2024 DCO), APaT
Unit cost	£8,051.66		NHS Reference Costs 2023/24. CA93A (Elective Inpatient): Major Maxillofacial Procedures, 19 years and over, with CC Score 1+
Week of first neoadjuvant dose	0	N/A	KEYNOTE-689 (25-Jul-2024 DCO)
Weeks from first neoadjuvant dose to surgery, mean	■	N/A	

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	Perioperative pembrolizumab + SOC	SOC	Source
Apply initial surgery cost at week [†]	6	0	-
Adjuvant radiotherapy			
% of patients	■	■	KEYNOTE-689 (25-Jul-2024 DCO); APaT
Unit cost	£10,095.39		NHS Reference Costs 2023/2024 - SC41Z (Daycase and Reg Day/Night): Preparation for Intensity Modulated Radiation Therapy, with Technical Support (£2,460); and SC23Z (Daycase and Reg Day/Night): Deliver a Fraction of Complex Treatment on a Megavoltage Machine (£238) Preparation + (Cost per fraction multiplied by mean 6.4 weeks × 5 fractions/week) (£2,460 + (£238*6.4*5))
Weeks from initial surgery to start of adjuvant radiotherapy, mean	■	■	KEYNOTE-689 (25-Jul-2024 DCO)
Apply adjuvant radiotherapy cost at the following week [‡]	13	7	-

Abbreviations: APaT, all patients as treated; DCO, data cut-off.

[†] The week of initial surgery is calculated as the sum of the week of first neoadjuvant dose + mean weeks from this dose to the initial surgery), rounded to the nearest whole week.

[‡] The week of adjuvant radiotherapy costs is calculated as the sum of the (week of first neoadjuvant dose + mean weeks from this dose to the initial surgery + mean weeks from initial surgery to adjuvant radiotherapy), rounded to the nearest whole week.

3.5.2 Health-state unit costs and resource use

3.5.2.1 Disease management costs by health state

Medical resource use in the EF, L/SR, and IRP states includes outpatient provider visits, laboratory tests, and imaging procedures. Unit costs of medical resources were obtained from NHS Reference Costs (Table 45).(82)

In the EF state, weekly frequencies of routine outpatient visits, laboratory tests, and CT scans were initially informed by clinical guidelines in head and neck cancer (UK National Multidisciplinary Guidelines)(1) and then refined based on clinical expert opinion obtained by

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MSD.(49, 85) Resource use in this state was modelled separately by treatment arm to capture the expected additional resource use associated with delivering and managing perioperative pembrolizumab. Other resources, such as dieticians and speech and language therapists, were not expected to differ by treatment and were therefore not included in the model. Frequencies were time-varying to account for the recommended change in the frequency of monitoring over time; monitoring would decrease after completion of adjuvant therapy (i.e. approximately year 2 onwards) and clinicians agreed that patients who remained event-free after 5 years would be discharged (Table 44).

The IRP state encompasses both pre- and post-progression IRP. Therefore, in each model arm, disease management costs per week in the IRP state were computed as a weighted average of resource use associated with pre- versus post-progression IRP, based on the estimated proportion of time spent progression-free within the IRP state. Medical resource use frequencies per week before and after progression within the IRP state were based on sources and assumptions used in previous NICE submissions in the recurrent/metastatic HNSCC setting (including NICE TA490 and TA661) (Table 35).(86, 87) Specifically, TA490 assumed a monthly frequency of 1 oncologist visit, 1 cell blood count test, and 1 CT scan during initial therapy for recurrent/metastatic disease, and a monthly frequency of 0.33 oncologist visits and 0.33 cell blood count tests after discontinuation of initial therapy. These frequencies during and after initial therapy in NICE TA490 were applied to pre-progression and post-progression IRP, respectively, in the present model. Monthly frequencies were converted to weekly by dividing by (365.25/12/7). For other outpatient services, the percentages of patients using each service before and after progression were based on a medical chart review among UK patients with metastatic HNSCC who received ≥ 3 lines of systemic therapy (Nash Smyth et al. 2015),(88) the same source used to inform these inputs in TA490. As in TA490, the healthcare resource utilization results from Nash Smyth et al. were assumed to represent the monthly probability of using each service. These monthly probabilities were accordingly converted to weekly probabilities using the formula:

$$P_{weekly} = 1 - \exp\left(\frac{\ln(1 - P_{monthly})}{\frac{365.25}{12 \times 7}}\right)$$

Medical resource use frequencies per week in the L/SR state were assumed equal to those in the IRP state, based on clinical expert opinion that resource use would be similar between these health states.(49)

Table 43: Unit costs of medical resource use

Resource use element	Unit cost (£)	Sources
Outpatient visits		
Consultant visit	149.41	NHS Reference Costs 2023/2024 (Outpatient Care) - WF01A - (800) Non-Admitted Face-to-Face Attendance, Follow-up
Clinical nurse specialists	115.36	NHS Reference Costs 2023/2024 (Summary: Other Currencies) - N10AF - Specialist Nursing, Cancer Related, Adult, Face to face
Dieticians	364.97	NHS Reference Costs 2023/2024 (Summary: Other Currencies) - N16AF - Specialist Nursing, Enteral Feeding Nursing Services, Adult, Face to face
Speech and language therapy	119.95	NHS Reference Costs 2023/2024 (Summary: Other Currencies) - A13A1 - Speech and Language Therapist, Adult, One to One
Dentistry	160.28	NHS Reference Costs 2023/2024 (Summary Outpatient Attendances) - 450 - Dental Medicine Service
Psychological support	126.69	NHS Reference Costs 2023/2024 (Summary: Other Currencies) - A06A1 - Occupational Therapist, Adult, One to One
Pain and symptom management/any supportive care	142.34	NHS Reference Costs 2023/2024 (Summary: Other Currencies) - N21AF - Specialist Nursing, Palliative/Respite Care, Adult, Face to face
Xerostomia management	41.14	BNF 2025. Pilocarpine hydrochloride 5 mg (assumed 5-10mg 3 times a day)
Antiemetics	0.67	eMIT. Ondansetron 8mg (10 pack) DDF029 (assumed up to 8mg per day for 5 days)
Management of oral and gastrointestinal mucositis	14.08	BNF 2025. 300ml Benzydamine hydrochloride 1.5 mg per 1 ml. Assumed one 300ml bottle per cycle (take 15ml 8 times a day for 7 days)
Hematologic growth factor/transfusions	183.78	NHS Price List 2024/2025 - Blood and Components
Laboratory tests		
Cell blood count	6.77	NHS Reference Costs 2023/2024 (Directly Access Pathology Services) - PATH05 - Haematology
Imaging		
CT scan	142.33	NHS Reference Costs 2023/2024 (Diagnostic Imaging) - RD22Z - Computerised Tomography Scan of One Area, with Pre- and Post-Contrast

Abbreviations: CT, computerized tomography; ER, emergency room; NHS, National Health Services.

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Table 44: Resource use in the EF health state

Resource use element	Perioperative pembrolizumab + SOC						SOC					
	EF year 1		EF years 2-5		EF years 5+		EF year 1		EF years 2-5		EF years 5+	
	%	# per week	%	# per week	%	# per week	%	# per week	%	# per week	%	# per week
Consultant visit	100%	0.167 (Q6W)	100%	0.057 (Q4M)	0%	0	80%	0.115 (Q2M)	80%	0.057 (Q4M)	0%	0
Clinical nurse specialist visit	100%	0.167 (Q6W)	100%	0.057 (Q4M)	0%	0	80%	0.115 (Q2M)	80%	0.057 (Q4M)	0%	0
Blood tests	100%	0.333 (1/cycle)	100%	0.019 (1/year)	0%	0	██████†	0.057 (1/cycle)	100%	0.019 (1/year)	0%	0
CT scan	100%	0.077 (Q3M)	100%	0.005 (one-off)	0%	0	0%	0	100%	0.005 (one-off)	0%	0

Abbreviations: CT, computed tomography; EF, event-free; QxW, every x weeks; QxM, every x months; SOC, standard of care.

Frequencies based on clinical expert opinion obtained by MSD.(49, 85)

† Represents the proportion of patients who get adjuvant cisplatin in the SOC arm of KEYNOTE-689.

Table 45: Resource use in the L/SR and IRP states

Resource use element	L/SR and IRP (pre-progression) – one-time resource use upon entering health state		L/SR and IRP (pre-progression) – subsequent weekly resource use		IRP (post-progression) – weekly resource use	
	% Patients	# per week	% Patients	# per week	% Patients	# per week
Outpatient visits						
Oncologist visit	100%	0.23	100%	0.23	100%	0.08
Dental therapy for radiotherapy effects	6%	1.00	6%	1.00	2%	1.00
Depression assessment and management	3%	1.00	3%	1.00	3%	1.00

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Nutritional support	18%	1.00	18%	1.00	15%	1.00
Pain and symptom management/any supportive care	16%	1.00	16%	1.00	18%	1.00
Speech and swallowing therapy	6%	1.00	6%	1.00	2%	1.00
Xerostomia management	6%	1.00	6%	1.00	3%	1.00
Antiemetics	19%	1.00	19%	1.00	11%	1.00
Management of oral and gastrointestinal mucositis	8%	1.00	8%	1.00	4%	1.00
Hematologic growth factor/transfusions	7%	1.00	7%	1.00	3%	1.00
Laboratory tests						
Cell blood count	100%	0.23	100%	0.23	100%	0.08
Imaging						
CT scan	100%	0.11	100%	0.11	0%	0.00
<i>Totals:</i>	£177.81 one-off cost		£177.81 per week		£107.39 per week	
<i>Sources & notes:</i>	Nash Smyth et al. (2015); NICE TA490 ^{†‡}		Nash Smyth et al. (2015); NICE TA490 ^{†‡}		Nash Smyth et al. (2015); NICE TA490 ^{†‡}	

Abbreviations: CT, computerized tomography; ER, emergency room; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence.

† NICE TA490 assumed a monthly frequency of 1 oncologist visit, 1 cell blood count test, and 0.5 CT scans during initial therapy for recurrent/metastatic disease, and a monthly frequency of 0.33 oncologist visits and 0.33 cell blood count tests after discontinuation of initial therapy. These frequencies during and after initial therapy in NICE TA490 were applied to pre-progression and post-progression IRP, respectively, in the present model. Monthly frequencies were converted to weekly by dividing by (365.25/12/7).

‡ For other outpatient services, the percentages of patients using each service before and after progression were based on a medical chart review among UK patients with metastatic HNSCC who received ≥3 lines of systemic therapy (Nash Smyth et al. 2015), the same source used to inform these inputs in NICE TA490.(87, 88) As in NICE TA490, the healthcare resource utilization results from Smyth Nash et al. were assumed to represent the monthly probability of using each service. These monthly probabilities were accordingly converted to weekly probabilities using the formula: $P_{\text{weekly}} = 1 - \exp(\ln(1 - P_{\text{monthly}})/(365.25/12/7))$.

3.5.2.2 L/SR health state

Patients who entered the L/SR health state were eligible for a range of treatment options including radiotherapy, salvage surgery or systemic therapies, as per the health state definition (section 3.2.2). As such, treatment in the L/SR state included one-time costs of radiotherapy, salvage surgery and/or systemic therapy for a proportion of patients who entered this state, based on the proportions of patients who received each of these therapies within this health state in the KEYNOTE-689 trial.

Subsequent radiotherapy and salvage surgery costs in the L/SR state

Frequencies of radiotherapy and salvage surgery were based on observed percentages of patients with each type of treatment in the KEYNOTE-689 trial. The percentages of patients with salvage surgery and radiotherapy in the L/SR state were calculated using as the denominator the number of patients in KEYNOTE-689 who experienced L/SR as their first EFS failure event, pooling across both treatment arms (Table 46).

Unit costs per salvage surgery and per radiotherapy course in the L/SR state were based on the same sources as those used to inform the unit costs of initial surgery and adjuvant radiotherapy, respectively, with the exception that the duration of salvage radiotherapy was conservatively assumed to be half that of the primary treatment course to reflect increased morbidity after recurrence (Table 46).

Table 46: One-time costs of salvage surgery and radiotherapy in the L/SR state (PD-L1 CPS $\geq$ 1 population)

Resource use element in L/SR state	% of patients	Unit cost	Source of unit cost
Salvage surgery	■	£8,051.66	NHS Reference Costs 2023/2024 - CA93A (Elective inpatient): Major Maxillofacial Procedures, 19 years and over, with CC Score 1+
Radiotherapy	■	£6,277.62	NHS Reference Costs 2023/2024 - SC41Z (Daycase and Reg Day/Night): Preparation for Intensity Modulated Radiation Therapy, with Technical Support (£2,460); and SC23Z (Daycase and Reg Day/Night): Deliver a Fraction of Complex Treatment on a Megavoltage Machine (£238) (£2,460 + (£238 * 3.2 weeks x 5 fractions/week)); mean duration of radiotherapy in L/SR state

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			conservatively assumed to be half that of adjuvant radiotherapy to reflect increased morbidity and treatment drop-off
Source (% of patients):	KEYNOTE-689 (25-Jul-2024 DCO) [†]	-	-

Abbreviations: CPS, combined positive score; L/SR, local recurrence; PD-L1, programmed death-ligand 1.

[†] Frequencies of surgery and radiotherapy were based on observed percentages of patients with each type of treatment in KEYNOTE-689 among those who experienced L/SR as their first EFS failure event.

Subsequent systemic therapy in the L/SR state

Drug acquisition and administration costs associated with systemic therapies in the L/SR state were applied as a one-time cost upon entry into the state. Treatment options in the L/SR state and their dosing schedules were assumed to be the same as in the first-line IRP setting (see section 3.5.2.3).

For systemic treatment regimens in the L/SR state, mean treatment durations were based on the observed mean durations of systemic treatments received in the L/SR state among patients in KEYNOTE-689 who experienced L/SR as their first EFS failure type (pooling across both treatment arms) (Table 47). Based on the estimated mean duration of each drug component in a regimen, the model estimated the mean total cost of the entire treatment regimen.

In the base case analysis, in both arms the mix of systemic treatments in the L/SR state was based on observed subsequent treatment data among patients in KEYNOTE-689 who experienced L/SR as their first EFS failure event (Table 48), to ensure costs were aligned with the efficacy of drugs received by patients in the trial. As pembrolizumab + chemotherapy is not available in England, the observed market share of this regimen in the L/SR state in KEYNOTE-689 was redistributed to the other included regimens.

However, UK clinical experts advised that the approach to managing patients with *non-salvageable* local recurrence in practice may not fully align with the approaches observed in the trial, as often these patients would be treated as per patients in the IRP state (i.e. systemic therapy without curative intent) and as such the degree of systemic therapy use in the L/SR state may underestimate what would be expected in UK clinical practice. Therefore, a scenario analysis was conducted in which the costs of systemic therapy in the L/SR state were assumed to equal the costs of systemic therapy in the IRP state.

Table 47. Time on treatment for systemic regimens in the L/SR state

Regimen	Component	ToT (weeks), mean
Pembrolizumab monotherapy	Pembrolizumab (Q3W)	
	Pembrolizumab (Q6W)	
Nivolumab	Nivolumab	
Cisplatin + 5-FU	Cisplatin	
	5-FU	
Cetuximab + cisplatin + docetaxel	Cetuximab (first cycle)	
	Cetuximab (chemo phase)	
	Cetuximab (maintenance)	
	Cisplatin	
	Docetaxel	
Cisplatin + paclitaxel	Cisplatin	
	Paclitaxel	
Cetuximab + cisplatin	Cetuximab (first cycle)	
	Cetuximab (chemo phase)	
	Cetuximab (maintenance)	
	Cisplatin	
Cisplatin	Cisplatin	

Abbreviations: Q#W, every # weeks; ToT, time on treatment.

Sources for mean ToT: KEYNOTE-689 (data cutoff date: 25-Jul-2024).

Note: Week of initiating each drug component, maximum ToT, percentage receiving each drug component, and relative dose intensity are assumed to be the same as in the first-line IRP state (see Table 49).

Table 48. Treatment mix of systemic regimens in the L/SR state by treatment arm (PD-L1 CPS $\geq$ 1 population)

Treatment regimen	% of patients, by perioperative treatment arm	
	Perioperative pembrolizumab + SOC	SOC
Pembrolizumab monotherapy		
Pembrolizumab + chemotherapy [†]		
Nivolumab		
Cetuximab + platinum + 5-FU		
Cisplatin + 5-FU		
Carboplatin + 5-FU		
Cetuximab + cisplatin + docetaxel		
Cisplatin + paclitaxel		
Gemcitabine + paclitaxel		
Cetuximab + platinum + paclitaxel		
Cetuximab + cisplatin		
Cisplatin + pemetrexed		
5-FU		

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Cisplatin				
Methotrexate				
No active treatment				

Abbreviations: CPS, combined positive score; PD-L1, programmed death-ligand 1; SOC, standard of care.
Source: KEYNOTE-689 (data cutoff date: 25-Jul-2024)
Note: The market shares of systemic treatment regimens in the LR state were obtained from KEYNOTE-689 among patients who experienced LR as their first EFS failure event. The set of treatment options was assumed to be the same as in the first-line recurrent/metastatic HNSCC setting. The market shares of other systemic regimens (as observed in KEYNOTE-689) were distributed among the regimens listed above.
† Additionally, because pembrolizumab + chemotherapy is not reimbursed in the UK, the observed market share of this regimen in the L/SR state in KEYNOTE-689 was also redistributed to the other included regimens.

3.5.2.3 **IRP health state**

Within the model, drug acquisition and administration costs associated with subsequent therapies (including both first-line and second-line subsequent therapies) were applied as a one-time cost upon entry into the IRP state. A proportion of patients who entered the IRP state were assumed to receive an active first-line treatment for recurrent/metastatic HNSCC. The costs of second-line treatments for recurrent/metastatic HNSCC were also considered. Additional details are provided in the sub-sections below.

Unit drug costs and dosing schedules

Drug acquisition cost per administration or pharmacy dispensing was calculated for drugs in the recurrent/metastatic HNSCC setting based on unit drug costs (Table 38) and defined dosing schedules (Table 49). The dosing schedules were based on prescribing information, treatment protocols in pivotal clinical trials, or clinical guidelines.

Drug administration costs were applied according to the sources and principles described in section 3.5.1.2 (Table 39).

Table 49: Dosing schedules for first-line and second-line therapies in the IRP state

Regimen	Drug component	Dosing schedule	Week of initiating drug component after IRP entry	Max ToT (weeks)	RDI (%)	% receiving drug component	Sources
First-line therapies							
5-FU	5-FU	1,000 mg/m ² /day IV on days 1-4 of each Q3W cycle	0	No max	91.0%	100.0%	Jacobs et al. (1992)(89)
Cisplatin + 5-FU	Cisplatin	100 mg/m ² IV Q3W	0	No max	76.0%	100.0%	Jacobs et al. (1992);(89) similar dosing schedule used in Forastiere et al. (1992)(90) and Gibson et al. (2005)(91)
	5-FU	1,000 mg/m ² /day IV on days 1-4 of each Q3W cycle	0	No max	76.0%	100.0%	
Carboplatin + 5-FU	Carboplatin	300 mg/m ² IV Q4W	0	No max	100.0%	100.0%	Forastiere et al. (1992)(90)
	5-FU	1,000 mg/m ² /day IV on days 1-4 of each Q4W cycle	0	No max	100.0%	100.0%	
Cetuximab + cisplatin	Cetuximab (first cycle)	Initial dose of 400 mg/m ² IV over 2 hours	0	1	100.0%	100.0%	Bossi et al. (2017) [B490](92)
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during chemo phase	1	17	100.0%	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during maintenance phase	18	No max	100.0%	100.0%	
	Cisplatin	100 mg/m ² IV Q3W	0	18	100.0%	100.0%	
Cetuximab + cisplatin + docetaxel	Cetuximab (first cycle)	Initial dose of 400 mg/m ² IV over 2 hours	0	1	100.0%	100.0%	Guigay et al. (2021) [TPExtreme](93)
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during chemo phase	1	17	100.0%	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during maintenance phase	18	No max	100.0%	100.0%	
	Cisplatin	75 mg/m ² IV Q3W	0	18	81.0%	100.0%	
	Docetaxel	75 mg/m ² IV Q3W	0	18	90.0%	100.0%	
Cetuximab + platinum + 5-FU	Cetuximab (first cycle)	Initial dose of 400 mg/m ² IV over 2 hours	0	1	■	100.0%	KEYNOTE-048
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during chemo phase	1	17	■	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during maintenance phase	18	No max	■	100.0%	

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	Cisplatin	100 mg/m2 IV Q3W	0	18	■	■	
	Carboplatin	AUC 5 mg/ml/min IV Q3W	0	18	■	■	
	5-FU	1,000 mg/m2/day IV on days 1-4 of each Q3W cycle	0	18	■	100.0%	
Cetuximab + platinum + paclitaxel	Cetuximab (first cycle)	Initial dose of 400 mg/m2 IV over 2 hours	0	1	100.0%	100.0%	Bossi et al. (2017) [B490];(92) carboplatin dosing was assumed to be the same as in cetuximab + platinum + 5-FU
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m2 IV QW over 1 hour during chemo phase	1	17	100.0%	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m2 IV QW over 1 hour during maintenance phase	18	No max	100.0%	100.0%	
	Cisplatin	75 mg/m2 IV Q3W	0	18	100.0%	100.0%	
	Carboplatin	AUC 5 mg/ml/min IV Q3W	0	18	100.0%	0.0%	
	Paclitaxel	175 mg/m2 IV Q3W	0	18	100.0%	100.0%	
Cisplatin	Cisplatin	100 mg/m2 IV Q3W	0	No max	96.0%	100.0%	Jacobs et al. (1992)(89)
Cisplatin + paclitaxel	Cisplatin	75 mg/m2 IV Q3W	0	No max	100.0%	100.0%	Gibson et al. (2005)(91)
	Paclitaxel	175 mg/m2 IV Q3W	0	No max	100.0%	100.0%	
Cisplatin + pemetrexed	Cisplatin	500 mg/m2 IV Q3W	0	18	91.0%	100.0%	Urba et al. (2012)(94)
	Pemetrexed	75 mg/m2 IV Q3W	0	18	94.0%	100.0%	
Gemcitabine + paclitaxel	Gemcitabine	3,000 mg/m2/day IV on days 1 and 15 of each Q4W cycle	0	No max	100.0%	100.0%	Malhotra et al. (2014) [S0329](95)
	Paclitaxel	150 mg/m2/day IV on days 1 and 15 of each Q4W cycle	0	No max	100.0%	100.0%	
Methotrexate	Methotrexate	40 mg/m2 IV QW	0	No max	100.0%	100.0%	Forastiere et al. (1992)(90)
Pembrolizumab monotherapy	Pembrolizumab (Q3W)	200 mg IV Q3W	0	105	■	100.0%	KEYNOTE-048
	Pembrolizumab (Q6W)	400 mg IV Q6W	0	102	■	0.0%	
Second-line therapies							
Carboplatin + 5-FU	Carboplatin	300 mg/m2 IV Q4W	0	No max	100.0%	100.0%	Forastiere et al. (1992)(90)
	5-FU	1,000 mg/m2/day IV on days 1-4 of each Q4W cycle	0	No max	100.0%	100.0%	
Cetuximab	Cetuximab (first cycle)	Initial dose of 400 mg/m2 IV over 2 hours	0	1	100.0%	100.0%	Vermorken et al. (2007)(96)

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	Cetuximab (subsequent cycles)	Subsequent doses of 250 mg/m ² IV QW over 1 hour	1	No max	100.0%	100.0%	
Cetuximab + carboplatin + paclitaxel	Cetuximab (first cycle)	Initial dose of 400 mg/m ² IV over 2 hours	0	1	100.0%	100.0%	Bossi et al. (2017) [B490];(92) carboplatin dosing was assumed to be the same as in cetuximab + platinum + 5-FU
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during chemo phase	1	17	100.0%	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during maintenance phase	18	No max	100.0%	100.0%	
	Carboplatin	AUC 5 mg/ml/min IV Q3W	0	18	100.0%	100.0%	
	Paclitaxel	175 mg/m ² IV Q3W	0	18	100.0%	100.0%	
Cetuximab + paclitaxel	Cetuximab (first cycle)	Initial dose of 400 mg/m ² IV over 2 hours	0	1	100.0%	100.0%	Assumption based on Bossi et al. (2017) [B490](92)
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during chemo phase	1	17	100.0%	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during maintenance phase	18	No max	100.0%	100.0%	
	Paclitaxel	175 mg/m ² IV Q3W	0	18	100.0%	100.0%	
Cetuximab + platinum + 5-FU	Cetuximab (first cycle)	Initial dose of 400 mg/m ² IV over 2 hours	0	1	■	100.0%	KEYNOTE-048
	Cetuximab (chemo phase)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during chemo phase	1	17	■	100.0%	
	Cetuximab (maintenance)	Subsequent doses of 250 mg/m ² IV QW over 1 hour during maintenance phase	18	No max	■	100.0%	
	Cisplatin	100 mg/m ² IV Q3W	0	18	■	■	
	Carboplatin	AUC 5 mg/ml/min IV Q3W	0	18	■	■	
	5-FU	1,000 mg/m ² /day IV on days 1-4 of each Q3W cycle	0	18	■	100.0%	
Cisplatin	Cisplatin	100 mg/m ² IV Q3W	0	No max	96.0%	100.0%	Urba et al. (2012)(94)
Cisplatin + 5-FU	Cisplatin	100 mg/m ² IV Q3W	0	No max	76.0%	100.0%	Jacobs et al. (1992);(89) similar dosing schedule used in Forastiere et al. (1992)(90) and Gibson et al. (2005)(91)
	5-FU	1,000 mg/m ² /day IV on days 1-4 of each Q3W cycle	0	No max	76.0%	100.0%	
Docetaxel	Docetaxel	75 mg/m ² IV Q3W	0	18	100.0%	100.0%	Docetaxel SPC
Methotrexate	Methotrexate	40 mg/m ² IV QW	0	No max	100.0%	100.0%	Forastiere et al. (1992)(90)

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Nivolumab	Nivolumab	240 mg IV Q2W	0	No max	100.0%	100.0%	Nivolumab SPC
Paclitaxel	Paclitaxel	175 mg/m2 IV Q3W	0	18	100.0%	100.0%	Assumption based on paclitaxel dosing in other 1L/2L regimens
Pembrolizumab	Pembrolizumab (Q3W)	200 mg IV Q3W	0	105	■	100.0%	KEYNOTE-048
	Pembrolizumab (Q6W)	400 mg IV Q6W	0	102	■	0.0%	
Platinum + paclitaxel	Cisplatin	75 mg/m2 IV Q3W	0	18	100.0%	12.5%	Gibson et al. (2005);(91) carboplatin dosing was assumed to be the same as in cetuximab + platinum + 5-FU
	Carboplatin	AUC 5 mg/ml/min IV Q3W	0	18	100.0%	87.5%	
	Paclitaxel	175 mg/m2 IV Q3W	0	18	100.0%	100.0%	

Abbreviations: IRP, incurable recurrence/progression; IV, intravenous; HNSCC, head and neck squamous cell carcinoma; Q#W, once every # weeks; RDI, relative dose intensity; ToT, time on treatment.

Note: Where applicable, for second-line regimens in the IRP state, the relative usage of cisplatin vs. carboplatin is based on subsequent treatment data from KEYNOTE-048 (data cutoff date: 21-Feb-2022).

Time on treatment of subsequent therapies

First- and second-line treatments were selected for inclusion in the model based on available treatment options in the UK, verified by clinical experts,(49) and the second-line treatments observed in KEYNOTE-048 following 'progressed disease' state entry.

The model estimated the mean total cost of each first- and second-line treatment regimen over the expected duration of each therapy. Durations of first-line treatment regimens for recurrent/metastatic HNSCC were modelled using the exponential rates of PFS failure to approximate treatment discontinuation rates for each treatment. Exponential rates of PFS failure for three reference treatments (including cetuximab + platinum + 5-FU from KEYNOTE-048) were sourced from clinical trials and rates for all other treatments were estimated by applying HRs sourced from a network meta-analysis (NMA) of clinical trials to one of these reference regimens (Table 50).(97) See appendix J4 for further details of the NMA. Some regimens or components of regimens were subject to a maximum treatment duration based on recommended dosing schedules (Table 49). For second-line treatments, mean treatment durations were based on the observed mean durations of specific treatments received in the next line of therapy among patients in the KEYNOTE-048 trial (database cutoff date: 21-Feb-2022)(Table 51).

Table 50: Exponential rates of PFS failure used to model ToT for first-line treatments in metastatic setting

	Weekly exponential rate of PFS failure	HR	Source
Cetuximab + platinum + 5-FU		-	KEYNOTE-048, PD-L1 CPS $\geq$ 1 (data cutoff date: 21-Feb-2022)
Cisplatin + pemetrexed	0.0443	-	Urba et al. (2012) (all-comers)(94)
Gemcitabine + paclitaxel	0.0399	-	Malhotra et al. (2014) (all-comers)(95)
	Reference treatment		
Pembrolizumab monotherapy	Cetuximab + platinum + 5-FU		1L R/M HNSCC NMA with pembro mono, PD-L1 CPS $\geq$ 1 (97)
Pembrolizumab + chemotherapy [†]	Cetuximab + platinum + 5-FU		1L R/M HNSCC NMA with pembro + chemo, PD-L1 CPS $\geq$ 1 (97)
Nivolumab	Cetuximab + platinum + 5-FU		HRs assumed equal to those of pembrolizumab monotherapy
Cisplatin + 5-FU	Cetuximab + platinum + 5-FU		

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Carboplatin + 5-FU	Cetuximab + platinum + 5-FU	■	1L R/M HNSCC NMA with pembro mono, PD-L1 CPS≥1 (97)
Cetuximab + cisplatin + docetaxel	Cetuximab + platinum + 5-FU	■	
Cisplatin + paclitaxel	Cetuximab + platinum + 5-FU	■	
Cetuximab + platinum + paclitaxel	Cetuximab + platinum + 5-FU	■	
Cetuximab + cisplatin	Cetuximab + platinum + 5-FU	■	
5-FU	Cetuximab + platinum + 5-FU	■	
Cisplatin	Cetuximab + platinum + 5-FU	■	
Methotrexate	Cetuximab + platinum + 5-FU	■	
No active treatment	Cetuximab + platinum + 5-FU	■	Assumed equal to treatment with highest HR

Abbreviations: 1L, first line; CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; R/M, recurrent or metastatic.

† Not available in England.

Table 51. Time on treatment for second-line treatment regimens in the metastatic HNSCC setting

Second-line treatment regimen	Component	Second-line
		ToT (weeks), mean
Pembrolizumab	Pembrolizumab (Q3W or Q6W)	■
Nivolumab	Nivolumab	■
Cetuximab + platinum + 5-FU	Cetuximab (first cycle)	■
	Cetuximab (chemo phase)	■
	Cetuximab (maintenance)	■
	Cisplatin	■
	Carboplatin	■
	5-FU	■
Cisplatin + 5-FU	Cisplatin	■
	5-FU	■
Carboplatin + 5-FU	Carboplatin	■
	5-FU	■
Platinum + paclitaxel	Cisplatin	■
	Carboplatin	■
	Paclitaxel	■
Cetuximab + paclitaxel	Cetuximab (first cycle)	■
	Cetuximab (chemo phase)	■
	Cetuximab (maintenance)	■

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	Paclitaxel		■
Cetuximab + carboplatin + paclitaxel	Cetuximab (first cycle)		■
	Cetuximab (chemo phase)		■
	Cetuximab (maintenance)		■
	Carboplatin		■
	Paclitaxel		■
Cetuximab	Cetuximab (first cycle)		■
	Cetuximab (subsequent cycles)		■
Paclitaxel	Paclitaxel		■
Docetaxel	Docetaxel		■
Cisplatin	Cisplatin		■
Methotrexate	Methotrexate		■

Abbreviations: Q#W, every # weeks; ToT, time on treatment.

Sources for mean ToT: KEYNOTE-048 (data cutoff date: 21-Feb-2022).

Mix of subsequent therapies

The mean costs of first- and second-line treatments were then calculated for each perioperative treatment arm as a weighted average based on the first- and second-line treatment mix within each arm. In the base case, first-line treatment mix reflected observed first subsequent treatment use amongst patients who experienced IRP as their first EFS failure event in KEYNOTE-689. The model included first-line treatment options that had relevant PFS and OS inputs available, that are recommended by EHNS–ESMO–ESTRO clinical guidelines,(2) and may be used in the UK. The treatment mix of other first-line regimens (as observed in KEYNOTE-689) were distributed among the selected regimens in proportion to their observed usage as patients' first systemic treatment in the IRP state. Additionally, because pembrolizumab + chemotherapy is not recommended by NICE for this indication, the observed share of this regimen as first-line treatment in the IRP state in KEYNOTE-689 was also redistributed to the other included first-line regimens (note that the share was redistributed across all regimens rather than specifically pembrolizumab monotherapy, as patients who would receive the pembrolizumab + chemotherapy regimen are typically those with more aggressive disease who require rapid treatment, and may not be able to wait for the benefits of single-agent immunotherapy to kick in).

The subsequent treatment use observed in the trial, and used in the base case model, was validated with UK clinical experts to ensure it was suitably reflective of clinical practice in the UK.(49) The experts advised that:

- Approximately 70% of patients with IRP receive systemic first-line therapy, which is broadly aligned with patterns observed in the trial

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- Of those receiving systemic therapy in current practice (i.e. after adjuvant SOC only), most patients (approximately 80%) would get anti-PD-1 treatment at first-line, which would usually be pembrolizumab monotherapy, but may be nivolumab in a few cases (and only if they had previously received adjuvant cisplatin)
 - The overall pattern of anti-PD-1 use amongst treated patients with IRP in the trial (████) was reasonably well aligned with UK practice, although it was slightly underestimated vs clinical opinion. However, nivolumab use may be overestimated in the trial vs UK practice, therefore a scenario reallocating nivolumab use to pembrolizumab was explored
- Rechallenge with anti-PD-1 therapy may be permitted if the recurrence occurred at least 6 months after completing adjuvant treatment with pembrolizumab
 - Patients who recurred within the first 18 months of the model start were therefore assumed to be ineligible for further anti-PD-1 therapy – the proportions of pembrolizumab and nivolumab use in the pembrolizumab arm were set to 0% for this period and proportionally redistributed. After 18 months, treatment mix proportions were set as per observed use in the pembrolizumab arm of the trial. As it is plausible that the trial subsequent treatment use disproportionately reflects early recurrences, a scenario assuming a treatment mix as per the SOC arm applied for recurrences after 18 months was conducted to explore the impact of higher pembrolizumab and cetuximab use in patients with later recurrence.
- Approximately 20-35% of patients would get active therapy at second-line, but there are few suitable options once at that stage. This aligned well with patterns observed in the trial. However, as pembrolizumab is not approved for second-line use in the UK, any pembrolizumab shares were redistributed to nivolumab.

Base-case treatment mix in the first-line setting is presented in Table 52. Base-case treatment mix in the second-line setting is shown in Table 53.

Table 52. Treatment mix of first-line regimens for recurrent/metastatic HNSCC by neoadjuvant/adjuvant treatment arm (PD-L1 CPS $\geq$ 1 population)

First-line regimens in IRP state	% of patients, by perioperative treatment		
	Perioperative pembrolizumab + SOC		SOC
	IO eligible	IO-ineligible	
Pembrolizumab monotherapy	████	████	████
Pembrolizumab + chemotherapy†	████	████	████
Nivolumab	████	████	████

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Cetuximab + platinum + 5-FU			
Cisplatin + 5-FU			
Carboplatin + 5-FU			
Cetuximab + cisplatin + docetaxel			
Cisplatin + paclitaxel			
Gemcitabine + paclitaxel			
Cetuximab + platinum + paclitaxel			
Cetuximab + cisplatin			
Cisplatin + pemetrexed			
5-FU			
Cisplatin			
Methotrexate			
No active treatment			

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; PD-L1, programmed death-ligand 1; SOC, standard of care.

Source: KEYNOTE-689 (data cutoff date: 25-Jul-2024)

Note: The shares of first-line regimens in the IRP state were obtained from KEYNOTE-689 among patients who experienced IRP as their first EFS failure event. Proportions account for the proportion of patients who receive no active treatment, therefore if rebased to consider only patients who had active therapy (i.e. denominator is 100%), all proportions would be higher.

As a result of rounding, some columns may not sum to 100%.

† As pembrolizumab + chemotherapy is not reimbursed in the UK for this indication, the observed share of this regimen as first-line treatment in the IRP state in KEYNOTE-689 was redistributed to the other first-line regimens.

Table 53. Treatment mix of second-line regimens in the IRP state by treatment arm (PD-L1 CPS $\geq$ 1 population)

Second-line regimens in IRP state	% of patients, by treatment arm		
	Perioperative pembrolizumab + SOC		SOC
	IO eligible	IO-ineligible	
Pembrolizumab			
Nivolumab			
Cetuximab + platinum + 5-FU			
Cisplatin + 5-FU			
Carboplatin + 5-FU			
Platinum + paclitaxel			
Cetuximab + paclitaxel			
Cetuximab + carboplatin + paclitaxel			
Cetuximab			
Paclitaxel			
Docetaxel			
Cisplatin			
Methotrexate			
No active treatment			

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; PD-L1, programmed death-ligand 1; SOC, standard of care.

Source: KEYNOTE-689 (data cutoff date: 25-Jul-2024)

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Note: The shares of second-line regimens in the IRP state were obtained from KEYNOTE-689 among patients who experienced IRP as their first EFS failure event. The set of second-line treatment options was selected based on the second-line regimens recommended for recurrent/metastatic HNSCC by clinical guidelines and verified based on UK clinical expert opinion. The shares of other second-line regimens (as observed in KEYNOTE-689) were distributed among the regimens listed above in proportion to their observed usage as patients' second systemic treatment in the IRP state.

3.5.3 Adverse reaction unit costs and resource use

Costs associated with the management of AEs were applied as a lump-sum cost at model entry. In each model arm, this lump-sum cost was calculated as the sum-product of AE risks, mean number of episodes per patient with the AE (Table 32), and mean cost per episode of the AE (Table 54). For a given AE, the mean cost per episode was based on the proportion of patients with hospitalization due to this AE and AE-specific hospitalization and outpatient visit costs.

For each AE, the mean cost per episode resulting in hospitalization was obtained from NHS Reference Costs. For AEs that do not result in hospitalization, the cost of an outpatient visit was assigned.

Table 54: Unit costs of AE management

AE type	Cost per AE episode (£)	Source(82)
AEs not resulting in hospitalisation		
Cost per episode	159.94	NHS Reference Costs 2023/2024: 800 - Clinical Oncology (Previously Radiotherapy) total outpatient attendance
AEs resulting in hospitalisation		
Anaemia	766.57	NHS reference costs 2023/2024: SA01K, J, H, G Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. (Non-elective short stay)
Dysphagia	1,039.41	NHS Reference Costs 2023/2024, FE12A: Endoscopic Insertion of Gastrostomy Tube, 19 years and over (Non-elective short stay)
Hypokalaemia	809.00	NHS Reference Costs 2023/2024, KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+. (Non-elective short stay)
Hyponatraemia	809.00	NHS Reference Costs 2023/2024, KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+. (Non-elective short stay)
Lymphocyte count decreased	329.38	NHS Reference Costs 2023/2024, WH13: Abnormal Findings without Diagnosis (Non-elective short stay)
Neutrophil count decreased	329.38	NHS Reference Costs 2023/2024, WH13: Abnormal Findings without Diagnosis (Non-elective short stay)

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AE type	Cost per AE episode (£)	Source(82)
Pneumonia	685.00	NHS Reference Costs 2023/2024, DZ11T Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9 (Non-elective short stay)
Radiation skin injury	511.89	NHS Reference Costs 2023/2024, JD07: Skin Disorders (Non-elective short stay)
Stomatitis	591.09	NHS Reference Costs 2023/2024, CA86A: Minimal, Mouth or Throat Procedures, 19 years and over (Non-elective short stay)
Weight decreased	0.00	Assuming zero cost
White blood cell count decreased	329.38	NHS Reference Costs 2023/2024, WH13: Abnormal Findings without Diagnosis (Non-elective short stay)

Abbreviations: AE, adverse event; NHS, National Health Service.

3.5.4 Miscellaneous unit costs and resource use

3.5.4.1 PD-L1 testing costs

Therefore, at model entry in the perioperative pembrolizumab + SOC arm, the model applied the cost of the expected number of PD-L1 tests needed to identify one patient with PD-L1 CPS ≥ 1 (i.e., $1.05 = 1 / \text{proportion of patients with PD-L1 CPS} \geq 1$ in the KEYNOTE-689 trial population, 95.5%). Given the transient nature of the PD-L1 biomarker and uncertainty regarding the prevalence of CPS ≥ 1 in UK practice, a scenario assuming the proportion of patients with PD-L1 CPS ≥ 1 is equal to the prevalence in the KEYNOTE-048 trial (72%, expected number of tests = 1.39) was also conducted.

Additionally, in both arms, the model applied the cost of one PD-L1 test upon entry into the IRP state to determine patients' eligibility for subsequent PD-L1 treatments in that state. Clinical experts at the advisory board stated that a repeat test would still be required for patients in the pembrolizumab arm as anti-PD-L1 treatment rechallenge is permitted for recurrences that occur at least 6 months after completing adjuvant treatment, and it is possible for the disease pathology of recurrent tumours to differ to the primary tumour.(49)

The unit cost per PD-L1 test was based on the weighted average of NHS Reference Costs with currency code PATH02 (histopathology and histology). PD-L1 testing assumptions are presented in Table 55.

Table 55. One-time costs of PD-L1 testing in the EF and IRP states

	Perioperative pembrolizumab + SOC	SOC	Source
Number of PD-L1 tests to identify one patient eligible to initiate regimen at model entry	1.05	0	Expected number of tests needed to identify one patient with PD-L1 CPS ≥ 1 (i.e., 1 / prevalence of CPS ≥ 1 in the KEYNOTE-689 trial population).
Number of PD-L1 tests upon IRP state entry	1.00	1.00	PD-L1 test is assumed to be required to determine eligibility for subsequent treatments(49)
Unit cost	£36.20		NHS Reference Costs 2023/2024 - PATH02: Histopathology and histology
Totals			
One-time costs of PD-L1 testing upon model entry in the EF state	£37.90	0.00	Calculated, based on unit cost and number of tests required to identify one eligible patient
One-time costs of PD-L1 testing upon entry in the IRP state	£36.20	£36.20	-

Abbreviations: CPS, combined positive score; EF, event-free; IRP, incurable recurrence/progression; PD-L1, programmed death-ligand 1; SOC, standard of care.

3.5.4.2 Terminal care costs

Patients who transitioned to death were assumed to incur a one-time cost associated with palliative/terminal care in the last ~90 days of life. Terminal care costs (£8,498.27 after inflation-adjustment) were obtained from Georghiou & Bardsley (2014),(98) and inflated to the current cost year.

3.6 Severity

MSD considers that pembrolizumab does not qualify for a severity modifier in this indication as the expected QALY loss for standard of care versus the general population does not meet any severity modifier threshold.

3.7 Uncertainty

MSD considers that key areas of uncertainty relating to this indication have been adequately captured in the economic model and explored through sensitivity and scenario analyses.

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3.8 Managed access proposal

MSD considers that this intervention is a candidate for baseline NHS funding. However, MSD remains committed to patient access as a priority and are willing to discuss options for managed access should it prove necessary.

The later interim analyses and final analysis of the ongoing KEYNOTE-689 trial may allow for additional data collection to further reduce uncertainties identified during the technology appraisal, although it should be noted that the study follow up is already extensive.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

The list of parameters used in the base case cost-effectiveness analysis is presented in Table 56, along with the parameters used to vary the base case inputs in sensitivity analyses, if applicable.

Table 56. Summary of variables applied in the economic model

Table 30. Summary of variables applied in the economic model				
Variable	Value	SE	Distribution for PSA	Section in submission
Cycle length	1 week	-	Not varied	3.2.2
Time horizon, years	40.1 years	-	Not varied	
Discount rate: Costs	3.5%	-	Not varied	
Discount rate: Outcomes	3.5%	-	Not varied	
Starting age, years	59.9 years	-	Not varied	3.2.1
Female, %	21.1%		Not varied	
Body surface area, m ²			Not varied	
Weight, kg			Not varied	
Glomerular filtration rate (GFR) (mL/min/1.73 m ²)	96.0	-	Not varied	
Parameter estimates for EF→L/SR; Gompertz				
Parameter A, SOC		-	Multivariate normal	3.3.2
Parameter B, SOC		-		
Parameter C, SOC		-		
Parameter A, Pembrolizumab		-		
Parameter B, Pembrolizumab		-		
Parameter C, Pembrolizumab		-		
Parameter estimates for EF→IRP; Gompertz				
Parameter A, SOC		-	Multivariate normal	3.3.2
Parameter B, SOC		-		
Parameter C, SOC		-		

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Parameter A, Pembrolizumab		-		
Parameter B, Pembrolizumab		-		
Parameter C, Pembrolizumab		-		
Parameter estimates for EF→death; Generalized Gamma				
Parameter A, SOC		-	Multivariate normal	3.3.2
Parameter B, SOC		-		
Parameter C, SOC		-		
Parameter A, Pembrolizumab		-		
Parameter B, Pembrolizumab		-		
Parameter C, Pembrolizumab		-		
Exponential rates of L/SR→IRP				
Pembrolizumab			Normal	3.3.3
SOC				
Exponential rates of L/SR→death				
Pembrolizumab			Normal	3.3.3
SOC				
Exponential rates of IRP→death				
Pembrolizumab			Normal	3.3.4
SOC				
Medical management costs				
Initial surgery costs in the EF state: Pembrolizumab			Gamma	3.5.1.4
Initial surgery costs in the EF state: SOC				
Initial RT costs in the EF state: Pembrolizumab				
Initial RT costs in the EF state: SOC				
Medical management costs in EF state for Pembrolizumab + SOC per week, up to year 1	57.30	11.46		3.5.2
Medical management costs in EF state for Pembrolizumab + SOC per week, years 1-5	16.03	3.21		
Medical management costs in EF state for SOC per week, up to year 1	24.53	4.91		
Medical management costs in EF state for SOC per week, years 1-5	12.99	2.60		
Medical management costs in EF state per week, years 5 onward	0.00	0.00		

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Medical management costs in EF state per week, years 40.1 onward	0.00	0.00		
Medical management costs in EF state per week, years 40.1 onward	0.00	0.00		
Salvage surgery costs upon L/SR state entry (one-time cost)	■	■		
Salvage RT costs upon L/SR state entry (one-time cost)	■	■		
Medical management costs in L/SR state (per week)	177.81	35.56		
Medical management costs upon IRP state entry (one-time cost)	177.81	35.56		
Medical management costs in pre-progression IRP state (per week)	177.81	35.56		
Medical management costs in post-progression IRP state (per week)	107.39	21.48		
Terminal care cost (one-time cost)	8,498.27	1,699.65		
Drug administration costs				
Unit costs of IV drug administration, simple	152.13	30.43	Gamma	3.5.1.2
Unit costs of IV drug administration, complex	201.66	40.33		
Unit costs of IV drug administration, complex prolonged	352.31	70.46		
Unit costs of IV drug administration, subsequent	250.77	50.15		
Unit costs of oral drug dispensing	247.13	49.43		
AE costs				
Perioperative pembrolizumab + SOC	■	■	Gamma	3.5.3
SOC	■	■		
Utilities				
Utility of EF (without toxicity)	■	■	Beta	3.4.5
Utility of L/SR	■	■		
Utility of pre-progression IRP	■	■		
Utility of post-progression IRP	0.52	0.209		
Disutility from AEs	■	■	Normal	

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3.9.2 Assumptions

A summary of the key assumptions used in the economic evaluation is provided in Table 57.

Table 57. Assumptions used in the economic evaluation

Parameter	Assumption	Justification
Comparator	SOC; surgery followed by adjuvant radiotherapy with or without chemotherapy	The population in this decision problem is patients with resectable LA HNSCC who have a CPS$\geq$1. In current practice, these patients are treated by surgery followed by adjuvant radiotherapy with or without cisplatin. This was validated with UK clinical experts as the current SOC for this patient population, and thus the appropriate comparator for this appraisal. To date, the only previous NICE Technology Appraisal in LA HNSCC is TA145, cetuximab in addition to primary/definitive RT for patients in whom platinum-based chemotherapy is contraindicated. The use of cetuximab is specific to the <u>unresected</u> LA HNSCC population, as per its pivotal trial, and thus is not relevant to the current decision problem. In addition, clinical experts advised that the use of cetuximab in the LA setting is limited to the small subset of patients with unresectable tumours and renal impairment making them ineligible for platinum-based chemotherapy.
Cure	No cure assumption applied	Due to the length of follow-up data available from KEYNOTE-689 (DCO: 25 July 2024), when fitting parametric distributions to transition from the EF state a clear plateau is already evident in the EFS curve in the base case model and the implied hazard of a recurrence or death event is close to 0 from ~5 years. This suggests that the probability of cure is already captured in the model and therefore no further application of a cure assumption is applied.
Transitions from the IRP state	Estimated using patient level data from KEYNOTE-689 (CPS $\geq$ 1 population)	Due to immature trial data, a common approach to estimating transitions for the later health state in early-stage cancer indications is to use an NMA based on the efficacy and market shares of 1L subsequent treatments. However, the long follow-up period from the KEYNOTE-689 trial allows for transitions from IRP→Death to be directly estimated from trial patient-level data. This is the best available data to inform this approach as it is reflective of the KEYNOTE-689 patient population and outcomes. Of note, the IRP health state is stratified by pre- and post-progression to more accurately reflect costs and quality of life. Data on progression in the IRP state are not captured in the KEYNOTE-689 trial and therefore the proportion of time in the IRP state spent pre- vs post-progression is informed by an NMA of PFS of 1L subsequent treatments.

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Distribution of treatments for IRP state	As observed in KEYNOTE-689, with minor adjustments to account for availability of treatments in the UK	The treatment mix of subsequent treatments in the IRP state is based on the use observed in KEYNOTE-689. The list of treatments was restricted to treatment options listed in clinical guidelines and available in the UK, and validated with UK clinical experts. Pembrolizumab + chemotherapy is not available in England, therefore this was proportionally distributed across other available regimens. This approach ensures the costs and efficacy applied in the model are aligned as far as possible, whilst accounting for local variations in treatment practices.
Retreatment with IO in the IRP state	IO retreatment following pembrolizumab permitted 18 months after the model start	The use of an anti-PD-L1 as retreatment in the recurrent/metastatic setting is permitted in UK clinical practice 6 months after completing adjuvant treatment with pembrolizumab at an earlier stage of disease. Allowing IO retreatment after 18 months in the economic model is a simplified approach that ensures no patients are retreated with IO as a subsequent treatment before the eligibility period. The mix of subsequent treatments in the IRP state is informed by the KEYNOTE-689 trial and adjusted in line with treatments recommend in England and Wales in the base case, accounting for patients considered IO-eligible or IO-ineligible.
Post-L/SR recurrence efficacy	Informed by KEYNOTE-689 data using treatment-arm specific patient-level data and exponential modelling	The RCT remains the most useful source to provide onward transitions specific to the patient population included in the decision problem. Considering the similar rates of L/SR between the treatment arms, pooled estimates informing this input would have limited impact. Uncertainty is testing by varying the exponential rate used to model this transition.
Adverse events	Based on treatment-specific AE incidence rates as per KEYNOTE-689 and applied as a one-off cost in the first model cycle. The impact of AE disutilities in the EF state are applied over the mean observed duration in the trial. No L/SR or IRP AEs have been applied for subsequent treatments	As AEs account for a very small proportion of costs in the model, AEs associated with L/SR and IRP treatments are excluded to avoid additional model complexity. This simplification is in line with usual assumptions in submissions to NICE.
Pembrolizumab administration	Q6W in adjuvant setting and subsequent treatment	UK clinical experts advised that a Q6W administration regimen is likely to be used in the adjuvant setting to better manage capacity constraints and more efficient resource allocation.

Utilities	EF, L/SR, Pre-progression IRP, AE disutility: KEYNOTE-689	All health state utility values in the economic model, except for post-progression IRP, were informed by the KEYNOTE-689 trial. EQ-5D-5L assessments were collected in the trial and were subsequently mapped to EQ-5D-3L as per the NICE reference case.
	Post-progression IRP: informed by the EXTREME trial used in TA483	The available follow-up from the KEYNOTE-689 trial was too limited to capture the average utility over the entire post-progression disease course until death. Therefore, the utility value for this substate was sourced from the EXTREME trial which informed NICE TA483 (cetuximab for recurrent/metastatic HNSCC), which ensured logical validity with the KEYNOTE-689 utilities for the other health states and was consistent with the NICE reference case.
Vial sharing	Permitted	To reflect clinical practice in the UK. Note that this assumption applies to weight-based treatments only; pembrolizumab is given as a fixed dose and therefore vial sharing is not required.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness results are presented in Table 58. The model estimated that perioperative pembrolizumab + SOC resulted in [REDACTED] discounted additional life years compared with SOC. This translated into an additional cost of [REDACTED] and 1.28 QALYs. The incremental cost-effectiveness ratio (ICER) was [REDACTED] indicating that perioperative pembrolizumab + SOC is a highly cost-effective strategy.

Table 58. Base-case deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.28	[REDACTED]
SOC	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-

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

Table 59. Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Perioperative pembrolizumab + SOC	[REDACTED]	[REDACTED]	[REDACTED]	1.28	[REDACTED]	[REDACTED]

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SOC			-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

3.11 Exploring uncertainty

A series of sensitivity and scenario analyses were conducted to explore the uncertainty around the parameters and assumptions used in the economic model.

3.11.1 Probabilistic sensitivity analysis

To explore the uncertainty around the variables included in the economic model, probabilistic sensitivity analysis (PSA) was performed by running the analysis over 1,000 simulations. The distributions used to vary model parameters are presented in section 3.9.1 (Table 56). Whenever available, the standard error of the selected distribution was based on the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the standard error for each cost parameter was assumed to be equal to 20% of the mean value.

The cost-effectiveness results obtained from the PSA are shown in Table 60; the corresponding scatterplots of PSA results and cost-effectiveness acceptability curves (CEAC) are shown in Figure 27 and Figure 28, respectively. The probabilistic results are very similar to those in the deterministic base case. The PSA results demonstrate that, under base case assumptions, there is a probability that perioperative treatment with pembrolizumab is a cost-effective treatment strategy SOC at a threshold of £30,000/QALY gained and at £20,000/QALY gained.

Table 60. Probabilistic cost-effectiveness results (mean of 1,000 iterations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC						1.31	
SOC				-	-	-	-

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

Figure 27: PSA scatterplot at £30,000/QALY willingness to pay

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 28. Cost-effectiveness acceptability curve

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Abbreviations: QALY, quality-adjusted life year; SOC, standard of care.

3.11.2 Deterministic sensitivity analysis

To further assess the robustness of the model results, deterministic sensitivity analyses (DSAs) were conducted by individually varying modelling inputs between the upper and lower limits of their plausible range. Parameters were varied by their 95% confidence intervals, or by $\pm 20\%$ if measures of variance were not available. The following variables were explored in the DSA:

- Exponential rates of transitions from L/SR and IRP health states
- Exponential rates of OS and PFS failure with first-line treatments for metastatic HNSCC indications using the 1L metastatic NMA
- Unit costs of drug administration
- Patient weight, body surface area and GFR
- Initial surgery and adjuvant radiotherapy costs in the EF state
- Medical management costs in the EF state
- Chemotherapy, salvage surgery and radiotherapy costs on L/SR state entry
- Medical management costs in the L/SR state
- Medical management costs in the IRP state (upon entry, pre-progression and post-progression)
- Terminal care costs
- Adverse event costs
- Health state utilities and disutilities from adverse events

The results of the DSA are presented in a tornado diagram (Figure 29) which illustrates the 10 parameters that had the most impact on the ICER.

The parameters which had the greatest impact on the ICER were the post-progression IRP utility value and the rate of transitions from the L/SR to IRP health state in the SOC arm. The post-progression IRP utility value was sourced from TA473 identified through a targeted literature review, in the absence of mature data from the KEYNOTE-689 trial. The impact in this one-way sensitivity analysis is a reflection of the wide reported confidence intervals informed by a small sample size contributing to the utility value calculation. An alternative

scenario, assuming the utility value is equal for pre- and post-progression in IRP using data from KEYNOTE-689, is also presented in Section 3.11.3 below. The rate of transitions was estimated by fitting an exponential curve to patient level data from KEYNOTE-689, the best available data to inform this parameter. In addition, the predicted versus observed transition from L/SR → IRP showed good alignment. The impact of this on the overall model results is small. The inputs with the next biggest impact were the cost of surgery and radiotherapy in the EF state, medical management cost in the EF state for the first year (i.e. while on treatment), and the OS and PFS failure rate for treatments in the IRP setting. All other parameters demonstrated a negligible impact on model results.

Figure 29. Tornado diagram featuring top 10 individually influential parameters

Abbreviations: CI, confidence interval; EF, event free; HNSCC, head and neck squamous cell carcinoma; ICER, incremental cost-effectiveness ratio; IRP, incurable recurrence/progression; IV, intravenous; L/SR, local or salvageable recurrence; OS, overall survival; QALY, quality-adjusted life year

3.11.3 Scenario analysis

A series of scenario analyses was conducted to explore the uncertainty around key structural and methodological assumptions, and sources of data used to inform model inputs. The results of all scenarios are presented in Table 61.

The combination of parametric distributions used to estimate transitions from the EF state had the biggest impact on the ICER. Out of the 10 best fitting combinations using Approach #1, based on the selection process detailed in Section 3.3.2.3, the distributions resulting in the greatest and least incremental EFS and OS benefit at 10 years (see Table 65 in Appendix J1.5), are presented as a scenario analysis to demonstrate the range of outcomes on the model results (■■■■/QALY to ■■■■/QALY). All scenarios of alternative long-term extrapolations are within the range of cost-effectiveness as per the £20,000 per QALY willingness-to-pay threshold, and it should be noted that the base case selection of extrapolations falls in the middle of this range.

As discussed in section 3.3.2.3, no cure assumption was applied in the base case based on the implied hazard rate for EFS in both arms and the presence of a plateau in the EFS curve which aligned with clinical expert feedback received. However, alternative distributions of curve for transition from the EF state do not resemble the same patterns of recurrence and application of a cure assumption should be considered based on the hazard rates and modelled EFS. Therefore, two additional scenarios (scenarios 3 and 4) include a cure assumption applied at 5 years in addition to the alternative curve selections using Approach #1.

The scenarios with the next greatest impact on the model results are using an alternative censoring rule for transitions from the EF health state and using a shorter time horizon of 20 years. The base case model reflects transitions from the EF health state based on the per protocol censoring criteria for EFS (censored at date of last disease assessment), to reflect the KEYNOTE-689 trial and the expected patient follow-up in real world practice. To help validate the modelled outcomes, an alternative approach to censoring for EF events, based on the OS analysis, is presented in Section 3.14.1.1. As per the NICE methods guide, the time horizon used in the economic model should reflect a lifetime time horizon to sufficiently capture all relevant benefits and costs. In the base case, there are ■■■■% of patients alive at the end of the model time horizon and therefore 40.1 years reflects the NICE reference case.

All scenario analyses produced ICERs under £20,000/QALY, showing the economic model outputs to be very robust to changes in the model assumptions and inputs.

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Table 61. Scenario analyses

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
-	Base case				■	1.28	■	-
1	Distributions used to model transitions from EF (<i>EF→L/SR/IRP/death</i>)	Approach #1, Gompertz/ Gompertz/ Gen gamma	Approach #1: Gen gamma/ Gen gamma/ Gen gamma (pessimistic incremental EFS and OS benefit)	Explore range of impact based on most and least incremental EFS and OS benefit of the 10 finalist curve combinations.	■	1.73	■	■
2			Approach #1: Log normal/ Gompertz/ Gen gamma (optimistic incremental EFS and OS benefit)		■	1.00	■	■
3			Scenario 1 + Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years	Explore the impact of applying a cure assumption to alternative distributions using Approach #1 to model transitions for EF, to ensure a modelled pattern of recurrence in line with clinical expert opinion.	■	1.49	■	■
4			Scenario 2 + Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years		■	1.09	■	■
5			Approach #2: Gompertz/ Gompertz/ Gompertz (proportional hazards)	Test impact of assuming proportional hazards Best-fitting combination under Approach #2.	■	1.38	■	■
6			Approach #3: Gompertz/ Gompertz/ Gompertz (time-varying proportional hazards)	Test impact of adopting a time-varying HR approach, given violation of proportional hazards for EF→L/SR. Best-fitting combination under Approach #3 (but not	■	1.54	■	■

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
				included in the final 10 combination of distributions).				
7	Cure	No cure point applied	Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years	Reflect clinical expert opinion that patients are functionally cured at 5 years; similar to previous appraisals	■	1.26	■	■
8	Censoring of transitions from EF state	Censoring rule as per protocol for KEYNOTE-689 trial (last disease assessment, as per EFS analysis)	Alternative censoring rule (last known date alive, as per OS analysis) – Approach #1: Gompertz/Gompertz/Gen Gamma	Explore impact of different censoring rules applied for per protocol analyses of EFS and OS in trial. Base case selection for alternative censoring rule (see Appendix J3)	■	1.12	■	■
9			Alternative censoring rule (last known date alive, as per OS) – Approach #1: Gompertz/Gen Gamma/Gen Gamma	Explore impact of different censoring rules applied for per protocol analyses of EFS and OS in trial. Most optimistic for incremental EFS and OS benefit out of final combinations (see Appendix J3.4)	■	1.44	■	■
10	Transitions from IRP→death	Based on PLD from KEYNOTE-689	Based on efficacy (from NMA) and market shares of 1L treatments for R/M HNSCC	Explore impact of approach to modelling IRP transitions, and aligned with method in previous appraisals	■	1.25	■	■

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
11	IRP post-progression utility	EORTC-QLQ-C30 from EXTREME mapped to EQ-5D-3L, used in NICE TA172/TA473	As per pre-progression IRP utility in KEYNOTE-689 (assumes no HRQoL decrement on progression)	Consistent utility source across all health states	■	1.26	■	■
12	Pembrolizumab dosing (adjuvant)	200 mg Q3W for 1 dose, followed by 400 mg Q6W for up to 7 cycles	200 mg Q3W for up to 15 cycles	Reflect dosing in trial and possible variation in clinical practice	■	1.28	■	■
13	Vial sharing (for weight-based treatments)	Permitted	Not permitted	Explore variation in practice in the UK NHS	■	1.28	■	■
14	Mix of systemic treatment in L/SR state	Based on treatment patterns as observed for patients with L/SR in KEYNOTE-689	As per the IRP state	Explore impact of assuming more patients in L/SR are treated systemically, equal to patients in IRP	■	1.28	■	■
15	1L treatment for IRP (SOC arm)	SOC arm: Nivolumab share as per trial SOC arm	SOC arm: Nivolumab share in trial SOC arm redistributed to pembrolizumab	Clinical advice indicates that most patients on anti-PD-1 get pembrolizumab rather than nivolumab	■	1.28	■	■

Company evidence submission template for Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
16	1L treatment for IO-eligible patients in IRP (pembro arm)	IO-eligible (recurrences post-18 months): 1L treatment mix as per trial pembrolizumab arm	IO-eligible (recurrences post-18 months): 1L treatment mix as per trial SOC arm	Subsequent treatments in trial may disproportionately reflect early recurrences, and later recurrences may be more likely to receive further IO (as observed in SOC arm)	■	1.28	■	■
17	PD-L1 tests required to identify 1 CPS≥1 patient	Based on prevalence of CPS≥1 in KEYNOTE-689 (95.5%)	Based on prevalence of CPS≥1 in KEYNOTE-048 (72%)	Prevalence of CPS≥1 in the real-world population is unknown	■	1.28	■	■
18	Time horizon	Lifetime (40.1 years)	20 years	Understand impact of shorter time horizon (note: does not capture full lifetime costs and effects [■% still alive at 30 years])	■	1.05	■	■
19			30 years		■	1.25	■	■
20	Discount rate	3.5% for costs & effects	1.5% for costs and effects	As per NICE guidance	■	1.61	■	■
21	Apply relative dose intensity	Yes	No		■	1.28	■	■

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SOC, standard of care.

3.12 Subgroup analysis

Subgroup analysis was not performed as it is not considered relevant for this indication.

3.13 Benefits not captured in the QALY calculation

MSD consider that wider patient, family and societal benefits of pembrolizumab in this indication exist that are not strictly captured within the NICE reference case and the formal QALY framework. Nonetheless these remain relevant for the purposes of decision making and are summarised below. MSD urges the NICE committee to account for these wider benefits in its decision making.

Innovation in a disease that has had few advancements and limited treatment options

The KEYNOTE-689 trial of perioperative pembrolizumab is the first study to demonstrate a statistically significant EFS benefit and a strong positive trend for OS in a therapeutic area that has seen limited advances in the last 20 years. Clinical experts have highlighted the clinical significance of the results, with the inclusion of the neoadjuvant phase considered a clear differentiator.⁽⁴⁹⁾ It should be noted that the current SOC requires extensive surgery in complex anatomical areas which can affect daily functional activities (e.g. speaking, swallowing), all of which directly or indirectly negatively impact patients, families and their caregivers.

Resectable LA HNSCC patients are prone to high rates of recurrence even after aggressive surgery and radiotherapy ($\pm$ cisplatin), and any such recurrences are very aggressive in nature. The limited number of effective treatment options downstream (primarily IO monotherapies) mean that long-term survival post recurrence beyond 5 and 10 years remains low when compared to many other cancers. In England and Wales, pembrolizumab + chemotherapy is not recommended for advanced/metastatic disease, in contrast to Scotland where Scottish clinicians note its use in patients with urgent clinical need. This often includes patients who experience early recurrences from LA disease which is typically indicative of more aggressive disease that would benefit from combined treatment with immunotherapy and fast-acting chemotherapy. This highlights the need for more effective treatments to delay or prevent patients developing recurrent disease.

Potential benefits of neoadjuvant component of treatment

The neoadjuvant component of the pembrolizumab treatment ensures patients receive an active and effective treatment whilst their surgery is being scheduled. This can reduce the tumour burden (i.e. downstaging of the tumour) which may in turn reduce the complexity of

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the surgery and enable it to be more organ-sparing in nature (i.e. de-escalation of surgery). Consequently, the impact of surgery on morbidity and psychosocial factors may be reduced, resulting in HRQoL improvements versus SOC.(49) However, this de-escalation of surgery was not permitted according to the KEYNOTE-689 trial protocol, and therefore any cost or HRQoL benefits of this are not factored into the economic model. In addition, the active neoadjuvant treatment may also reduce the fear of disease progression whilst the surgery is being scheduled.

Reduced fear of recurrence

The aggressive nature of HNSCC, and the invasiveness of treatment, means that there is frequently a substantial psychological impact at the point of diagnosis as well as throughout and post-treatment. Compared with other cancer types, patients with HNSCC are disproportionately affected by issues related to psychological distress, frequently reporting particularly high rates of anxiety, depression, and substance abuse.(33, 36) Amongst cancer patients and survivors, fear of recurrence is widely seen as a key concern resulting from, and contributing to, psychological distress, and one which appears to be especially prevalent in HNSCC;(33) patients with LA HNSCC are therefore particularly vulnerable to fears relating to recurrence risk. Patients having to endure the fear of developing a new HNSCC and the regular follow-up examinations may (re)activate and contribute to these fears. The availability of an active treatment option, such as perioperative pembrolizumab, which has been shown to significantly reduce the risk of recurrence may contribute to lessening the psychological impact of a new cancer diagnosis and a wider value of hope for these patients.

Impact on families and caregivers

Beyond the patient, a cancer diagnosis also often has a negative impact on the HRQoL of families and carers of patients due to the additional caring responsibilities as well as anxieties relating to the fear of recurrence and understanding downstream implications of advanced disease.(99) Therefore, any benefits of pembrolizumab that result in a longer time spent event-free and a reduced fear of recurrence for the patient are likely to extend to the family and other informal caregivers.

Impact on indirect and societal factors

Recurrences from early-stage disease often have a negative impact to both patients and carers in terms of work productivity, employment, finances and increases in out-of-pocket expenditure, in addition to the captured health care utilisation. This negative impact is observed in both patients and caregivers and is regardless of the recurrence type (local or

distant), although its magnitude could vary.(100) These parameters are not captured in the NICE reference case, but the reduction in the incidence of recurrence events expected with the use of perioperative pembrolizumab is likely to reduce the impact of the disease on these factors.

Bereavement QALY due to increased suicide rates of HNSCC

The need to perform extensive surgery in complex anatomical areas which may be visible and affect daily functioning activities such as speech, chewing and swallowing, can result in stigma, isolation and lower levels of community engagement. Some patient testimonies relating to these issues are presented extensively in “The Swallows” charity organisation website.(101) Such aspects associate head and neck cancer with a higher suicide rate: 37.9 per 100,000 compared to 11.8 per 100,000 person-years for the general population. This is the second highest rate among all cancer types and 3 times higher than the rate for the general population.(31, 32) This is more likely to take place within the first 5 years since diagnosis and younger or middle-aged patient cohorts are more likely to be affected. Indirect effects of this such as a bereavement QALY due to sudden family loss and family spill over are long term effects not factored in the economic evaluation.(102)

Impact of reduced adjuvant cisplatin use on HRQoL

Whilst the study was not formally powered to ascertain cisplatin utilisation differences in the adjuvant setting, a lower proportion of patients requiring adjuvant cisplatin after surgery in the pembrolizumab arm, as a result of reducing the proportion of patients with high-risk pathological features, may reduce the negative impact of treatment on HRQoL due to reduced toxicity. Due to the open-label trial design, the trial not being powered for cisplatin use, and the application of pooled utilities, any HRQoL impact of reduced cisplatin use in the pembrolizumab arm is not captured in the economic model.

Severity modifier thresholds across the head and neck pathway

To date, all other NICE STAs for inoperable or metastatic disease (i.e. TA661, TA736)(86, 87) have been appraised and approved under end of life criteria (pre-2022 STA process). Whilst this indication using the strict NICE criteria does not qualify for a severity modifier, the downstream head and neck patient pathway itself qualifies for severity weighting to account for the end of life nature of all downstream treatments. As such the decision ICER for this technology could be argued to exceed that of a standard technology without end-of-life given the aggressive nature of recurrent disease.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

To verify the results of the cost-effectiveness model, quality control procedures were undertaken to ensure that the mathematical calculations are performed correctly and are consistent with the model's specifications, and that parameter input values are correctly populated throughout the model. Additionally, internal and external validation was also assessed comparing modelled outcomes with the observed trial data and data from external sources, respectively.

3.14.1.1 Internal validation

The internal validity of the model was assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs. The present economic model was developed using data from the first interim analysis of KEYNOTE-689 (data cutoff date: 25-Jul-2024), representing 3.2 years of median follow-up (defined as the time between the date of randomization until the database cutoff date) in the all-comer population. Comparison of the predicted and observed cumulative incidence curves for each individual transition from the EF state (i.e., EF to L/SR, EF to IRP, and EF to death; Figure 19), the L/SR state (i.e., L/SR to IRP and L/SR to death; Figure 24 and Figure 25), and IRP state (i.e., IRP to death; Figure 26) showed an excellent fit for all transitions in both trial arms. In addition, the EFS and OS curves predicted for the two arms of KEYNOTE-689 were plotted alongside the observed Kaplan-Meier curves for EFS and OS to ensure that the curves are well-aligned during the trial period (Figure 20 and Figure 21). These demonstrated that the modelled curves for both EFS and OS had excellent alignment with the observed trial data.

It should be noted however that, per the protocol of KEYNOTE-689 trial, differing censoring rules for EFS and OS were specified whereby EFS was censored at the date of last disease assessment and OS was censored at the last date known alive. The date of the patient's last disease assessment is typically earlier than the last date that the patient was known to be alive. In other words, for patients who are censored with respect to both EFS and OS (i.e., those without any disease recurrence or death), the censoring date in the per-protocol Kaplan-Meier analysis of EFS is typically earlier than the censoring date in the per-protocol Kaplan-Meier analysis of OS. As of the 25-Jul-2024 DBL, in the all-comer population, a total of [REDACTED] patients ([REDACTED] patients in the KEYNOTE-689 CPS $\geq$ 1 population) were censored in the Kaplan-Meier analysis of OS, and [REDACTED] of these patients ([REDACTED] in the CPS $\geq$ 1 population) were also

censored in the Kaplan-Meier analysis of EFS. Among those [REDACTED] patients, the date of the last disease assessment was, on average, [REDACTED] days before the last date that the patient was known to be alive.

It is necessary for validation purposes to reconcile the two censoring rules as they are structurally linked in the economic model. When estimating the transition probabilities from the EF state, the per protocol censoring rule for EFS is used, and the resulting EFS endpoint is jointly determined by the three transition probabilities from the EF state (i.e., $EF \rightarrow L/SR$, $EF \rightarrow IRP$, and $EF \rightarrow \text{death}$). Meanwhile, the OS endpoint is jointly determined by all transition probabilities in the model (i.e., $EF \rightarrow L/SR$, $EF \rightarrow IRP$, $EF \rightarrow \text{death}$, $L/SR \rightarrow IRP$, $L/SR \rightarrow \text{death}$, and $IRP \rightarrow \text{death}$). Therefore, if the [REDACTED] patients without any disease recurrence or death are censored at the last disease assessment when fitting the transition probabilities for $EF \rightarrow L/SR$, $EF \rightarrow IRP$, and $EF \rightarrow \text{death}$, they are effectively also censored at the last disease assessment with respect to OS. This would result in a discrepancy between the modelled and observed curves for OS whereby modelled OS is censored at the date of last disease assessment whereas observed OS is censored at the last date known to be alive (Figure 30).

Figure 30. Discrepancy in modelled vs observed OS resulting from differing per protocol censoring rules used for EFS and OS



Abbreviations: EFS, event-free survival; OS, overall survival; SOC, standard of care.

Modelled base case OS is a function of all modelled transitions, based on the per protocol censoring rule for EFS (censored at date of last disease assessment).

Whilst the discrepancy is relatively small and affects both treatment arms, to enable internal validation of the modelled OS curves in the base case analysis versus the observed Kaplan-Meier OS curves from KEYNOTE-689, it was necessary to align the censoring rule used in the OS analysis with that used in the EFS analysis by censoring patients at:

- Last disease assessment for patients who are censored with respect to both EFS and OS
- Last date known to be alive for patients who are censored with respect to OS but not EFS

Alternatively, the censoring rules could instead be reconciled by applying the censoring rules used in the OS analysis (i.e. censor at last date known alive) to the EFS analysis, and recalculating the transitions from the EF health state, enabling the modelled OS to be validated against the per protocol observed OS. To test the impact of this approach, an alternative scenario is presented whereby EFS is censored at the last date known to be alive, in line with the per protocol censoring rule for OS (see Appendix J3 for full details). MSD considers the

censoring rule used in the EFS analysis to be appropriate as EFS is the primary endpoint of the trial and reflects how patients are followed up in clinical practice, whereas the OS analysis has not yet been formally tested and data are less mature. However, as the application of censoring rules impacts both arms in the economic model equally, the resulting impact on the cost-effectiveness is small.

3.14.1.2 External validation

Model predictions were also compared against observed long-term data from three identified external studies. As this is the first treatment in the perioperative setting for LA HNSCC, no real-world data were identified to validate EFS in this population. As discussed in Section 3.3.2.3, external real-world studies contained a range of patients across anatomical sites in HNSCC, with two studies in hypopharyngeal SCC only and one by Leeman et al., 2017 with a high proportion of HPV-positive oropharyngeal SCC (~48% HPV+ve and 43% of the sample with HPV status “unknown”). Anatomical site is an important prognostic indicator of outcomes and thus differences in the populations limits the usefulness of these studies to validate numerical modelled OS outcomes. In addition, all three real world studies with long-term outcomes were in the adjuvant setting, post-resection, which further impacts the generalisability to KEYNOTE-689. However, the shape of the long-term OS curves supported modelled predictions in both the SOC and intervention arm of the model.

Figure 31. External validation of OS in the SOC arm



Abbreviations: OS, overall survival; SOC, standard of care

Additionally, a total of 8 clinical experts treating LA HNSCC within the UK NHS were consulted via an advisory board and individual follow-up engagements to validate and inform the key model assumptions from a clinical perspective.

3.15 Interpretation and conclusions of economic evidence

To date, NICE have only conducted one Technology Appraisal in the locally advanced HNSCC setting, which was in the unresected population and therefore is not relevant to this decision problem. Perioperative pembrolizumab in addition to current SOC (surgery followed by adjuvant radiotherapy with or without cisplatin) will be the first Technology Appraisal in the perioperative setting for patients with resectable disease. This represents a step change in the current treatment pathway and offers an innovative treatment option that addresses the high unmet need in this population.

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A four-state Markov model was used to assess the cost-effectiveness of perioperative pembrolizumab. The four-state structure has been used in many previous NICE Technology Appraisals for early-stage cancers as it allows flexibility in modelling in the disease pathway to account for heterogeneity, whilst maintaining transparency and model parsimony. The KEYNOTE-689 pivotal trial provided randomised evidence to inform the primary treatment effect in the model, as well as other key model parameters. A key strength in the economic evaluation is the availability of approximately 5 years of follow-up data from the trial, which substantially reduces any uncertainty regarding the long-term outcomes. Where RCT evidence was not available, inputs were sourced through systematic literature reviews and clinical expert opinion. Both model inputs and outcomes were validated with clinical experts at an advisory board.

Perioperative pembrolizumab is modelled to impact QALYs by delaying recurrence and by increasing the proportion of patients who are functionally cured. The increase in upfront costs of perioperative treatment is partially offset by reducing the proportion of patients with high-risk pathological features following surgery and subsequently requiring adjuvant chemotherapy, in addition to the large downstream savings in the management of incurable recurrence/progression.

A limitation in this appraisal is the lack of real-world evidence to allow for external validation of modelled outcomes in the SOC arm. This is a reflection of the heterogeneity in HNSCC and pembrolizumab being the first perioperative treatment, that limits the generalisability of the external literature to the population in this decision problem. This was accounted for through extensive scenario testing to explore the impact of model extrapolations on long-term outcomes and model results. In addition, the availability of follow-up data from KEYNOTE-689 is extensive compared to previous early-stage indications and provides increased confidence in long-term OS modelled outcomes.

The value of perioperative pembrolizumab was demonstrated in a robust economic analysis where the addition of perioperative pembrolizumab to current SOC was shown to be cost-effective at a willingness-to-pay threshold of £20,000/QALY compared to current SOC alone. The sensitivity and scenario analyses conducted indicated that perioperative pembrolizumab plus SOC is cost-effective when tested against a range of inputs and assumptions. Incremental QALY gains were in the range of [REDACTED] to [REDACTED], with ICERs in the range of [REDACTED] to [REDACTED] per QALY. All sensitivity or scenario analyses were under the £20,000/QALY threshold, with a [REDACTED] probability of perioperative pembrolizumab being a cost-effective treatment in addition to SOC for patients with resectable LA HNSCC at the £30,000/QALY threshold.

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Taken together, the cost-effectiveness evidence shows that perioperative pembrolizumab in addition to SOC offers an innovative treatment option for patients with resectable LA HNSCC that is a cost-effective use of NHS resources compared to current standard of care.

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5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality-of-life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: Additional information on clinical parameters and variables informing the economic model

Appendix K: Utility analyses

Appendix L: KEYNOTE-689 additional methodological details

Appendix M: KEYNOTE-689 additional statistical analysis details

Appendix N: KEYNOTE-689 all comer population results

Appendix O: KEYNOTE-689 study subsequent therapies by health state

**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

**Pembrolizumab before surgery (neoadjuvant)
then with radiotherapy after surgery (adjuvant)
for newly diagnosed, resectable, locally
advanced, squamous cell head and neck
cancer ID6477**

Summary of Information for Patients (SIP)



September 2025

File name	Version	Contains confidential information	Date
[ID6477] Pembro LA HNSCC SIP v1.0	1.0	No	01-SEP-2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Pembrolizumab Brand name: KEYTRUDA

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

Pembrolizumab is being appraised as neoadjuvant treatment and then continued as adjuvant treatment for patients with newly diagnosed locally advanced head and neck cancer tumours which can be surgically removed. A neoadjuvant treatment is used before surgery, and an adjuvant treatment is used after surgery.

In the neoadjuvant treatment phase, two cycles of pembrolizumab are used. In the adjuvant phase 15 cycles of pembrolizumab are used in combination with the current standard of care, which is radiotherapy with or without chemotherapy given at the same time (in this case cisplatin). Use of chemotherapy (cisplatin) would depend as to whether evidence of high-risk features are identified based on local clinical guidelines and an assessment after the surgery.

The goal of adding treatments to surgery and radiotherapy (with or/without chemotherapy) is to reduce the risk of the cancer coming back. Even if all the tumour is removed during surgery, there might be some cancerous cells left behind, which might move through the body to other sites. The body has something called an immune response, which is a reaction to protect the body against anything unusual that enters the body. Drugs called immunotherapies act by triggering the immune response and helping the immune system to fight, amongst other things, cancer. Pembrolizumab is an immunotherapy drug. Giving pembrolizumab before and after surgery (also known as 'perioperative' treatment) helps the body to target and kill any cells that are there before the surgery and that might be released during the surgery. Pembrolizumab may also shrink the tumour and keep it from spreading, which can make surgery easier and less complicated. By doing this, there is a better chance that surgery will remove all the cancer, and patients may be less likely to need extra treatments like chemotherapy afterwards.

The type of patient who will be able to have pembrolizumab is described in section 1c of the main company evidence submission.

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

UK marketing authorisation for pembrolizumab is pending. Further details are available in the main submission (section B.1.2, table 2 of the main company evidence submission).

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

Existing collaborations between MSD and patient/carer groups relevant to pembrolizumab in the indication under consideration in this appraisal are listed below:

Cancer52:

MSD is a Cancer 52 member.

Head and Neck Cancer UK:

MSD had previously sponsored an awareness campaign involving Head and Neck Cancer UK, this was before 2023.

Macmillan Cancer Support:

MSD and Macmillan Cancer Support have met to share annual plans/projects, discuss policy and landscape, and share learnings.

Maggie's Centres:

MSD's clinical trials team has met Maggie's Centres to provide insight into the clinical trial process from concept to data readout.

Oracle Head and Neck Cancer UK:

MSD have both met with and provided financial transactions to Oracle Head and Neck Cancer UK in 2023/2024 as Oracle Head and Neck Cancer UK are the convenor of the Head and Neck Cancer Coalition (which MSD continue to be a member of as of 2025).

Swallows Head & Neck Cancer Support Group:

MSD are planning to sponsor the Swallows Head and Neck Cancer Conference later this year (2025).

Tenovus Cancer Care:

MSD sponsored a roundtable event for thought leaders to discuss upper gastrointestinal and oesophageal cancer issues in Wales. MSD have met to share annual plans/projects, discuss policy and landscape, and share learnings. MSD have also participated in meetings where both parties were supporting a lung health check project.

MSD has no other collaborations with any of the listed patient/carer groups stakeholders listed for this appraisal, relevant to pembrolizumab in the indication under consideration in this appraisal.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

Head and neck cancer is a term used for several different cancers that start in the tissues in the head and neck area. This includes the oral cavity (the lips, mouth, tongue, gums), pharynx (throat, nasopharynx, oropharynx and hypopharynx) and larynx (the voice box) (1, 2).

Like other cancers, head and neck cancer happen when cells in these areas start to grow out of control. These abnormal cells can form lumps, called tumours. Head and neck cancers can be divided into two main groups: squamous cell cancers (which affect the surface of tissues) and non-squamous cell cancers. Around 9 out of 10 head and neck cancers are squamous cell cancers (3).

Doctors describe cancer by its stage, which shows how advanced it is (4).

- Stage I cancer is small and has not spread to other parts of the body.
- Stage IV is the most advanced stage, where the cancer has spread to other areas or organs (known as secondary or metastatic cancer).
- Stages II and III are in-between, where the cancer may be bigger or have spread to nearby tissues or lymph nodes.

Some head and neck cancers are linked to infection with the human papilloma virus (HPV), especially cancers in the oropharynx (the part of the throat just behind the mouth). These HPV-related cancers are often linked to better outcomes compared to those not caused by HPV (5, 6).

Head and neck cancer is the 8th most common cancer in the UK. It is more likely to be diagnosed in people aged 70-74 years (2016-2018) (7). Over the past 10 years, the number of people diagnosed with head and neck cancer has increased by almost 16%. Between 2017-2019, there were 4,143 deaths from head and neck cancer in the UK (7).

The main risk factors for developing this cancer are (8):

- Tobacco use (smoking or chewing tobacco)
- Heavy alcohol use
- Infection with HPV

Cancers linked to HPV may have better survival rates, but they can still cause serious health problems and affect quality of life (6).

When head and neck cancer is found at an early stage, the chances of living for many years after diagnosis are much higher. However, the 10-year survival rate of patients with advanced HNSCC can be as low as 10% (9). The disease often comes back, and this a major reason for poor outcomes. Up to 56% of people with locally advanced head and neck cancer have their cancer return after treatment, sometimes spreading to other areas of the body (10, 11).

The treatments for head and neck cancer include surgery, radiotherapy and chemotherapy (12-14). These can all affect a person's ability to speak, swallow, breathe, see, smell and taste (15). This can have a big impact on daily life, making it harder to eat, talk, work and enjoy social activities, alongside their ability to carry out day-to-day basic self-care, home roles, work, and leisure activities (16).

People who have head and neck cancer also face a higher risk of suicide - about three times higher than the general population (17). Many also live with a constant fear that the cancer will return, which can affect their wellbeing (18, 19).

Common symptoms may include a lump in the neck or a sore in the mouth or throat that does not heal, a sore throat that does not go away, difficulty or pain in swallowing and a change or hoarseness in the voice. Other symptoms that may affect specific areas of the head and neck include bleeding of the mouth, swelling of the jaw, ear pain, headaches and, paralysis of the muscles in the face, or pain in the face, chin or neck {National Cancer Institute, 2021 #66.

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

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

In the UK, if a GP or dentist suspects head and neck cancer based on the above-mentioned symptoms, the patient will usually be referred urgently to a specialist within two weeks. This will often be an ear, nose and throat (ENT) surgeon or an oral and maxillofacial surgeon (OMFS), depending on where the symptoms are.

The specialist will examine the head and neck area, including the lymph nodes, and may arrange further test to confirm the diagnosis and see how advanced the cancer is. These tests may include:

- Imaging scans - such as CT, MRI, PET-CT, or ultrasound, to assess the size of the tumour and whether it has spread.
- Biopsy - taking a small tissue sample to confirm cancer under the microscope.

Once the cancer is confirmed, further tests help doctors decide on the most suitable treatment. For some treatments, including certain immunotherapies like pembrolizumab, the biopsy sample may be tested for a protein called PD-L1, which can help guide treatment decisions.

For the specific use of pembrolizumab being considered here, before and after surgery for head and neck cancer, PD-L1 testing is expected to be required before starting treatment.

2c) Current treatment options:

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

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

For most people with LA HNSCC, the aim is to remove the cancer completely and reduce the chance of it coming back.

Current main treatment options include (12-14):

- Surgery: This involves removing the tumour and, in many cases, some of the surrounding tissue and lymph nodes in the neck. Surgery is usually carried out by an ENT surgeon or an oral and maxillofacial surgeon (OMFS).
- Radiotherapy: High-energy X-rays are used to destroy any cancer cells that may be left after surgery, or sometimes as the main treatment if surgery is not suitable.
- Chemoradiotherapy: A combination of chemotherapy and radiotherapy given together. Chemotherapy uses drugs to make cancer cells more sensitive to radiotherapy and to treat any cells that may have spread elsewhere.
- Rehabilitation and support: Many people need help with swallowing, speech, nutrition, and emotional wellbeing during and after treatment.

Where pembrolizumab may fit in:

- Pembrolizumab is an immunotherapy, which is a type of treatment that helps the body's own immune system to find and attack cancer cells. NICE is currently reviewing its use before and after surgery in patients with resectable LA HNSCC. This could be added to the current treatment pathway alongside surgery and radiotherapy, with the aim of improving the chances of long-term cure and reducing the risk of the cancer coming back.

Other points to consider:

- Not all treatments are suitable for everyone: the MDT considers age, other health conditions and the patient's wishes.
- There can be side effects from surgery, radiotherapy, chemotherapy, or immunotherapy, which will be discussed with the patient before treatment begins.
- Drug interactions are uncommon in this setting, but all current medications will be checked before starting treatment.

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

Context:

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

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

Locally advanced HNSCC poses a considerable burden on patients daily living (15). Depending on the location and size of the tumour, the disease (as well as the effects of treatments, such as surgery and radiotherapy) can have a severe impact on a patient’s ability to speak, swallow, breath, see, smell, and taste (20, 21). These can have a debilitating impact on patients' ability to carry out day-to-day basic self-care, home roles, work, and leisure activities (15).

The disease and its current treatments also often have considerable negative impact on patients' quality of life (16). Severe pain is linked to reduced overall 5-year survival rates in oral cancer (31% in patients with severe pain vs. 52% in patients without) and pharyngeal cancer (33% in patients with severe pain vs. 52% without) (22). Head and neck cancer is also associated with a higher suicide rate: 37.9 compared to 11.8 per 100,000 person-years for the general population, this is the second highest rate among all cancer types and 3 times higher than the rate for the general population (17, 23). Due to the high likelihood of recurrence of the tumour, patients who have undergone treatment for HNSCC also experience a quality of life impact from the fear of recurrence (18, 19). In addition to the burden on the patients themselves, the caregivers of patients with HNSCC also experience a considerable burden in terms of psychological distress, physical and social functioning, and quality of life (24-26).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Our immune system is designed to protect us by recognising and attacking things that don’t belong in the body, such as bacteria, viruses or abnormal (cancer) cells. Immune cells called T cells play a key role in this defence.

Cancer cells can sometimes hide from the immune system. One way they do this is by using a protein called PD-L1, which sits on their surface. PD-L1 can attach to a “brake” on T cells called PD-1. When P--L1 and PD-1 connect, the T cells receive a “stop” signal, telling them not to attack. This helps protect normal cells in the body, but cancer cells use this trick to avoid being destroyed.

Pembrolizumab is a type of treatment called an immunotherapy and specifically a PD-1 inhibitor. It works by blocking the connection between PD-1 (on T cells) and PD-L1 (on cancer cells). By doing

this, pembrolizumab takes the brakes off the immune system, allowing T cells to recognise and attack the cancer cells.

Pembrolizumab does not attack the cancer directly like chemotherapy or radiotherapy. Instead, it helps the patient's own immune system do the work. This approach can lead to longer-lasting control of the cancer in some patients, even after treatment stops.

The summary of product characteristics (SmPC) and the patient information leaflet (PIL) for pembrolizumab can be found by following this link: <https://products.mhra.gov.uk/search/?search=keytruda&page=1&doc=Spc%7CPil>

3b) Combinations with other medicines

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

- Yes / No

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

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

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

In the UK, treatment for locally advanced head and neck squamous cell carcinoma (LA HNSCC) is planned by a multidisciplinary team (MDT). This is a group of specialists including surgeons, cancer doctors (oncologists), radiologists, pathologists, dietitians, and speech and language therapists, who work together to decide the best treatment for each patient.

The treatment approach depends on:

- The exact location of the cancer
- How far it has spread
- The patient's overall health and preferences

In this treatment approach, pembrolizumab is given together with the current standard treatments for patients with locally advanced head and neck squamous cell carcinoma (LA HNSCC) that can be removed by surgery.

The standard treatment is surgery followed by radiotherapy, sometimes combined with chemotherapy (often a drug called cisplatin), depending on the risk of the cancer coming back.

Why are these medicines used together?

- Pembrolizumab is an immunotherapy. It works by helping the body's own immune system to recognise and attack cancer cells by blocking the PD-1 "brake" on immune cells.
- Radiotherapy uses targeted high-energy X-rays to kill any cancer cells left behind after surgery.
- Chemotherapy (when given) works by damaging the cancer cells' ability to grow and divide, making them more likely to die. Chemotherapy can also make radiotherapy work better.

By combining pembrolizumab with radiotherapy (and chemotherapy if needed), the aim is to attack the cancer in different ways:

- Surgery removes the main tumour.

- Pembrolizumab boosts the immune system to find and destroy any cancer cells that might remain in the body.
- Radiotherapy (and chemotherapy, if given) targets any cancer cells left at the original site or nearby lymph nodes.

Availability of the other medicines:

- Radiotherapy and cisplatin chemotherapy are standard NHS treatments for LA HNSCC. These treatments are already widely available in specialist cancer centres across the UK.

Main side effects:

- Pembrolizumab: Can cause tiredness, skin rash, itching, diarrhoea, and effects linked to increased immune activity (such as inflammation of the lungs, liver, or thyroid).
- Radiotherapy to the head and neck: Can cause sore mouth/throat, dry mouth, changes in taste, difficulty swallowing, and skin redness in the treated area.
- Cisplatin chemotherapy: Can cause nausea, vomiting, loss of appetite, hearing changes, kidney effects, and changes in blood counts.

Patients will be closely monitored throughout treatment to manage any side effects quickly.

3c) Administration and dosing

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

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

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This treatment is given in two phases: one before surgery and one after surgery and is usually provided in a hospital cancer centre.

Phase 1: Before surgery (neoadjuvant treatment):

- Two cycles (or treatment sessions) of pembrolizumab are given every 3 weeks by a drip into a vein (intravenous infusion).
- Each cycle takes around 30–60 minutes for pembrolizumab.
- The aim of giving pembrolizumab before surgery is to help the immune system attack the cancer early, possibly shrinking the tumour and lowering the risk of it coming back.

Surgery:

- The tumour is removed, often with some surrounding tissue and lymph nodes, by an ENT surgeon or oral and maxillofacial surgeon (OMFS).

Phase 2: After surgery (adjuvant treatment):

- Pembrolizumab is given again by intravenous drip for up to 15 cycles.
- Patients also receive radiotherapy to the area where the tumour was, sometimes combined with cisplatin chemotherapy if there is a higher risk of the cancer returning.
- The aim is to kill any cancer cells that may be left behind and to boost the immune system's ability to keep the cancer away long term.

Treatment schedule:

- Pembrolizumab is typically given once every 3 weeks.
- Patients are monitored closely throughout for side effects and to check how well the treatment is working.

How this differs from current standard treatment:

- Standard treatment for resectable LA HNSCC usually involves surgery followed by radiotherapy with or without chemotherapy.
- In this new approach, pembrolizumab is added both before and after surgery, aiming to improve long-term cure rates by using the immune system as well as standard treatments to fight the cancer.

3d) Current clinical trials

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

The KEYNOTE-689 study is currently ongoing for the treatment for this indication (27). The KEYNOTE-689 study is ongoing Phase III, randomised, active-controlled, multi-site, open-label study of pembrolizumab given as a perioperative treatment in treatment naïve participants with newly diagnosed Stage III/IVA, resectable, locoregionally advanced, head and neck squamous cell carcinoma. The study evaluated pembrolizumab as neoadjuvant therapy, then continued after surgery in combination with standard-of-care radiotherapy (with or without cisplatin) as adjuvant therapy, followed by pembrolizumab as maintenance therapy, compared to adjuvant radiotherapy (with or without cisplatin) alone. The primary end point is event-free survival. Key secondary end points are major pathological response ($\leq 10\%$ residual viable invasive squamous-cell carcinoma) assessed by blinded independent pathological review and overall survival in the CPS-10 population, the CPS-1 population, and the total population. Other secondary end points include pathological complete response as assessed by blinded independent pathological review and safety and side-effect profile.

Results from the KEYNOTE-689 study are available from the first interim analysis, with a database cut-off date of 25-JUL-2024 (27, 28).

3e) Efficacy

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

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

The KEYNOTE-689 study tested whether adding the immunotherapy pembrolizumab before and after surgery, alongside the usual standard of care of radiotherapy with or without chemotherapy, could help people with newly diagnosed locally advanced head and neck cancers that can be surgically removed, stay cancer-free for longer than the standard treatment alone (27).

Efficacy: How well does the treatment work?

In the UK, most people with resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC) are treated with surgery to remove the cancer, followed by radiotherapy (RT) to the head and neck area. If there is a higher risk of the cancer returning, chemotherapy (usually cisplatin) is also given with the radiotherapy. This is called “risk-adapted” treatment.

The KEYNOTE-689 study looked at whether adding pembrolizumab (an immunotherapy that helps the body’s immune system attack cancer cells) to this standard approach could improve outcomes. People in the study either:

- Had pembrolizumab before and after surgery, along with the usual radiotherapy (and chemotherapy if needed), then continued pembrolizumab for up to a year.
- Or had the usual NHS treatment only.

What did the study find?

The main measure the researchers looked at was event-free survival (EFS) – how long people live without their cancer coming back, growing, spreading, or causing death.

- Pembrolizumab helped people stay cancer-free for longer than standard care alone.
- In all patients, the chance of the cancer returning or causing death was reduced by 27%.
- In patients whose tumours had a PD-L1 score (CPS) of 1 or more (something that is tested in the NHS), the chance was reduced by 30%.
- In those with a PD-L1 CPS of 10 or more, the chance was reduced by 34%.
- For people with PD-L1 CPS ≥ 1 , the average time without cancer problems more than doubled (around 60 months with pembrolizumab vs 30 months with standard care).

Other important results

- Tumour shrinkage before surgery: More people given pembrolizumab had a “major pathological response”, meaning most of the cancer was already destroyed by the time of surgery.
- Getting to surgery: Almost everyone in both groups went ahead with surgery as planned, meaning pembrolizumab given before surgery did not delay or prevent operations.
- Overall survival: At the time the results were first reported, it was too early to say for certain whether people lived longer overall. Follow-up is ongoing.

What this means for patients in the UK

This is the first large study to show that adding pembrolizumab before and after surgery can significantly increase the time people with resectable LA HNSCC stay cancer-free, especially if their tumour is PD-L1 positive. It did not stop people from having surgery and did not add unexpected side effects. The biggest benefits were seen in those whose cancers expressed PD-L1, so testing for PD-L1 is an important step when considering this treatment.

More information is provided in the main company evidence submission document, section 2.6.

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

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

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

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

Quality of life data such as patient reported outcomes (PROs) were collected in the KEYNOTE-689 study by using three types of questionnaire, the EORTC QLQ-C30, that looks specifically at the quality of life of cancer patients, the EORTC QLQ-H&N35, that looks specifically at the quality of life in head and neck cancer patients, and the EQ-5D, that looks at the general health status of a patient (28).

The EQ-5D consists of 2 sections: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system has five questions on mobility, self-care, pain, usual activities, and psychological status with the latest version of the questionnaire enabling five possible answers for each item (1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem and 5=extreme problem). Results from these questions can then be combined and scaled to produce a single score with a maximum score of 1. Scores can vary from 0, which represents death, to 1 which represents the best possible health state. The EORTC QLQ-C30 uses different questions, however, it also produces a score that is meant to represent a patient's quality of life. The EORTC QLQ-H&N35 focuses specifically on the impact on patients ability to swallow and to speak as well as the impact of pain. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. From this we can gather three scores (from the EQ-5D questionnaire, the EQ-5D VAS and the EORTC questionnaire) that can assess how a patient feels throughout their treatment.

In the KEYNOTE-689 study these outcomes were collected before the study patients received the treatment (baseline), at post-adjuvant treatment week 25, and at post-adjuvant treatment week 51. In terms of the change from baseline to post-adjuvant treatment week 25 and post-adjuvant treatment week 51 in each of these PROs, no significant differences between the patients treated with pembrolizumab in addition to standard of care and the patients treated with standard of care without pembrolizumab were observed, indicating no negative effects of adding pembrolizumab treatment.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The side effects of neoadjuvant and adjuvant pembrolizumab in addition to standard of care were observed in the KEYNOTE-689 study (27). The overall number of patients with adverse events (side effects) was generally similar in the pembrolizumab group (96.4%) and standard of care group (96.8%). The most frequently side effects were stomatitis, radiation skin injury, weight decreased, anaemia, dysphagia, and constipation in the pembrolizumab group and stomatitis, radiation skin injury, anaemia, dysphagia, nausea, weight decreased, and dry mouth in the standard of care group. These side effects are known risks of radiotherapy or cisplatin.

Potentially immune-mediated side effects occurred in 43.2% of the patients in the pembrolizumab group and 10.2% of those in the standard of care group. In both groups, the most common such event was hypothyroidism (24.7% in the pembrolizumab group and 5.4% in the control group). Potentially immune-mediated side effects of grade 3 or higher occurred in 10.0% of the patients in the pembrolizumab group and 0.6% of those in the standard of care group.

Pembrolizumab as neoadjuvant and continued as adjuvant treatment in combination with radiotherapy with to without cisplatin has a manageable safety profile that is consistent with the well-established safety profile of pembrolizumab monotherapy and the individual safety profiles of radiotherapy and cisplatin. No new safety concerns for pembrolizumab were identified in the study.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Pembrolizumab reduces the risk of the cancer coming back. This means that it may stop the cancer from progressing to stages where treatments aiming to cure the disease are not available.
- Most of the side effects that patients can experience while on treatment or after treatment are of mild or moderate severity. Overall, the benefit-risk ratio for pembrolizumab in this indication is considered positive.
- While treatment requires infusion every three or six weeks for up to a year, resulting in more frequent visits to hospital compared to active monitoring, pembrolizumab does not negatively affect quality of life.
- The infusion time of pembrolizumab is short and there is the potential for pembrolizumab to be given every 6 weeks in the adjuvant setting, which could result in short and less frequent visits to a hospital for patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Mode of Action - Immune System Activation:

- Pembrolizumab “switches on” the immune system to attack cancer, but this can also result in the immune system harming healthy organs. Immune-related side effects can be unpredictable, occur during or long after treatment, and may require ongoing immune-suppressing drugs, adding further risk and complexity for patients and carers. Please note there is clear guidance provided in the SmPC that instructs healthcare providers on how to manage these side effects.

Side Effects - Added Burden and Risks:

- Pembrolizumab does bring risks of immune-related side effects (e.g., affecting skin, bowels, liver, lungs, hormone glands, kidneys, nerves, heart, or pancreas), which are not typical with current standard treatments. These complications may prolong recovery, require further treatment and increase the care burden.

Mode of Administration and Treatment Disruption:

- Immune activation around surgery or radiotherapy may worsen inflammation and, rarely, complicate recovery by delaying wound healing or causing breaks in treatment. This can extend the physical and emotional strain on patients and caregivers and disrupt planned care schedules.

Most Important Disadvantages for Patients and Carers:

- These are:
 - Potential for unpredictable immune side effects
 - Possible delays in recovery or interruptions to planned treatments

Community Impact:

- Greater need for complex care, additional monitoring, and support resources, with potential for increased strain on healthcare services compared to standard treatments.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness relates to how much new health (or quality-adjusted life years [QALYs]) the new medicine produces compared to its additional cost (vs. current care), for a typical/average patient and whether the new health is worth the extra cost required to pay for it.

The cost-effectiveness of perioperative pembrolizumab in addition to standard of care compared to standard of care alone (radiotherapy with or without chemotherapy after surgery) is evaluated for the typical/average patient via modelling that uses trial data from KEYNOTE-689 to predict clinical effectiveness (efficacy) and costs over 40.1 years. The model comprises of four-health states: event-free, local and/or salvageable recurrence, incurable recurrent or progression, and death.

In early-stage appraisals, the efficacy and costs of downstream or subsequent treatments are an important consideration and were therefore captured in the KEYNOTE-689 model. Due to length of follow-up in the KEYNOTE-689 trial, the efficacy of treatments in recurrence/progression health state was modelled based on trial data directly.

Quality-of-life data (event-free and local and/or salvageable recurrence, and pre-progression incurable recurrence or progression health states and adverse events) were available from the KEYNOTE-689 trial of pembrolizumab. The utility for the post-progression incurable recurrence or progression health state was informed by data from a previous NICE appraisal of cetuximab in recurrent/metastatic HNSCC (TA473).

Differences in costs in the model are driven by the cost of pembrolizumab, which is offset by lower subsequent treatment and disease management costs in the recurrence health state compared with radiotherapy with or without chemotherapy alone. Differences in QALYs gained are largely driven by greater QALYs in the pembrolizumab arm in the event-free health state. This is because of pembrolizumab increasing the number of years patients spend event free, and the number of patients cured.

MSD does not believe this indication qualifies for a Severity Modifier as expected QALY loss on SoC vs. the general population does not meet any Severity Modifier threshold.

The results of the economic analysis show that pembrolizumab given before and after surgery, in addition to the current standard of care after surgery, is cost-effective compared with radiotherapy with or without cisplatin after surgery. The base-case results cannot be shared due to

confidentiality, but pembrolizumab is cost-effective compared to NICE's normal threshold of £20,000-£30,000 per QALY gained. Additional scenario analyses were all under the normal threshold. The results demonstrate that pembrolizumab is clinically effective and, based on the modelling results, highly likely to be a cost-effective addition to standard care.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

As explained in sections 1b and 2c, there are no perioperative treatments in established clinical practice available for the treatment of locally advanced HNSCC. This means that there is still a high chance for the disease to progress to stages where curative treatments are no longer possible. Pembrolizumab would represent a 'step-change' in the management of the condition for this population, by providing HNSCC patients with locally advanced disease with a treatment plan that reduces the risk of the cancer coming back.

Implementation of an immunotherapy would allow shifting of treatment pathways towards earlier preventative treatment enabling more patients to remain disease-free.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues [here](#)

Socioeconomic, sex-based, and racial/ethnic disparities in head and neck cancer have been documented in the UK (7, 29, 30), including:

- The incidence rate of head and neck cancers in males is more than double that of females.
- Incidence rates for head and neck cancer are lower in the Asian and Black ethnic groups, and in people of mixed or multiple ethnicity, compared with the White ethnic group, in England (however, incidence rates in females are higher in the Asian ethnic group than in the White ethnic group).
- People living in the most deprived areas have almost double the incidence rate of head and neck cancer compared to those living in the least deprived areas.
- People living in the most deprived areas were more likely to be diagnosed with head and neck cancer at a late stage than those living in the least deprived areas.
- There is significant geographic variation in mortality rates. People living in the most deprived areas have more than double the mortality rate of those living in the least deprived areas.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

ADL - (activities of daily living) Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

AJCC - (American Joint Committee on Cancer) collaboration of professional organizations that develop and update cancer staging systems and education.

CPS - Combined Positive Score (used in PD-L1 testing)

CT - Computed Tomography

ENT - Ear, Nose and Throat

HPV - Human Papillomavirus

LA HNSCC - Locally Advanced Head and Neck Squamous Cell Carcinoma

MDT - Multidisciplinary Team

MRI - Magnetic Resonance Imaging

OMFS - Oral and Maxillofacial Surgery

PD-1 - Programmed Cell Death Protein 1

PD-L1 - Programmed Death-Ligand 1

PET-CT - Positron Emission Tomography - Computed Tomography

PIL - Patient Information Leaflet

PROs - Patient Reported Outcomes

SmPC - Summary of Product Characteristics

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single Technology Appraisal

**Pembrolizumab before surgery
(neoadjuvant) then with radiotherapy after
surgery (adjuvant) for newly diagnosed
resectable, locally advanced, squamous cell
head and neck cancer [ID6477]**

Clarification questions

September 2025

File name	Version	Contains confidential information	Date
ID6477 Pembro LAHNSCC CQs MSD response [CON]	1.0	Yes	9 October 2025

Section A: Clarification on effectiveness data

Literature searches

A1. Appendix B, section B1.1.1: The submission states that searches were conducted of clinicaltrials.gov and clinicaltrialsregister.eu. Was the WHO International Clinical Trials Registry Platform (ICTRP) also searched?

MSD response:

No, the WHO ICTRP was not searched. Clinicaltrials.gov and clinicaltrialsregister.eu are the largest contributors to ICTRP and index the majority of trials globally. Therefore, searching these two platforms is very likely to capture the same core data that ICTRP would provide, with minimal risk of missing relevant studies.

A2. Appendix B, section B1.1.1 and Table 1, Table 2, Table 3. Please clarify which platforms or interfaces were used to search Embase, MEDLINE and CENTRAL, as this information is not stated in either section B1.1.1 or the tables reporting the individual search strategies.

MSD response:

As noted in Appendix B, section B.1.1.1, Embase, MEDLINE, and CENTRAL were searched using the Ovid portal. The portal is accessible via <https://ovidsp.ovid.com/>.

A3. Appendix B, section B1.1.1 and section B1.1.2. Please clarify whether hand searching of the bibliographies of relevant systematic reviews or meta-analyses took place and how this was conducted. The search strategy section B1.1.1 does not explicitly mention that this was done, but in the study eligibility criteria section, the submission states that '*Relevant SLRs and meta-analyses of clinical trials were included at the abstract screening stage for the purpose of cross-checking*'.

MSD response:

Yes, hand searching of bibliographies from relevant systematic reviews and meta-analyses was conducted. Systematic reviews and meta-analyses identified through database searches (Embase, MEDLINE, and CENTRAL) and meeting the PICOTS eligibility criteria were included at the abstract screening stage. Full-text publications of these reviews were retrieved, and their reference lists were screened to identify any additional studies that may not have been

captured by the primary database searches. Any citation that was identified (and included) via this approach was counted under the “Hand searches” category of the PRISMA flow diagram.

A4. Appendix E, section E1.3, Table 22. This search appears to have been performed simultaneously for two databases (MEDLINE and Embase) but without changing the subject headings (MeSH or Emtree as appropriate) to suit each database. Please comment on the possible implications for retrieval.

The Embase.com platform contains both (a) native Embase citations (unique Embase citations that are not in MEDLINE and common citations that are available in both Embase and MEDLINE), as well as (b) imported MEDLINE citations that are not initially available in Embase.

The native Embase citations (unique Embase citations and common MEDLINE citations) are directly indexed in Embase, with Emtree terms, in alignment with the Embase indexing guide. For MEDLINE citations that are licensed or imported from the National Library of Medicine (NLM), their index terms assigned by the NLM from the MeSH thesaurus are automatically mapped to Emtree. This automated mapping process ensures consistency in searching across all citations in the Embase.com interface, regardless of their original source. The Embase platform handles the mapping from MeSH to Emtree. Further details can be found on the Mendeley Support Center (1).

A single search on the Embase platform therefore enables both databases to be searched comprehensively without the need to manually adapt the search terms and subsequently remove duplicate citations.

A5. Appendix B, Table 1, Table 2, Table 3; Appendix E, Table 23; Appendix F, Table 33. These database searches from both the clinical and economic systematic literature reviews (SLRs) have been conducted with an English language limit. Given the dangers of language bias, please provide a justification for the decision to apply this limit and, in particular, for doing so at the searching rather than screening/reviewing stage. Please also clarify why some of the database searches (listed above) had an English language limit applied and others (Appendix B, Table 4; Appendix E, Table 22, Table 24; Appendix F, Table 32, Table 34) did not.

MSD response:

With regard to Appendix B, Table 1, Table 2, Table 3, and Table 4 (the SLR to identify relevant studies reporting clinical-effectiveness data relevant to the decision problem of this appraisal):

The effective primary objective of this review was to identify the KEYNOTE-689 study as this is the only clinical trial that has investigated pembrolizumab in the context/indication of this decision problem. We know this with certainty as KEYNOTE-689 is an MSD study, pembrolizumab is an MSD medicine, and MSD is necessarily aware of all clinical trials using pembrolizumab especially those in indications for which regulatory approval had not been granted at the time of the trial. KEYNOTE-689 is also the most recent and only perioperative study to date which offers recent and transferable data for SoC. As stated in section 2.10 of the company evidence submission, no indirect comparisons or mixed treatment comparisons were required as the KEYNOTE-689 study provides direct evidence for the treatment comparison of relevance to this appraisal. Clinical opinion received confirmed that the findings of the KEYNOTE-689 study are generalisable to UK clinical practice, including that the comparator arm of the study is reflective of current UK standard of care. Consequently there is no need to explore/identify any other SoC studies, and English language filter was applied to balance specificity with sensitivity, to help contain the number of citations to screen.

We were aware that the conference abstract on the KEYNOTE-689 results that had been published at the time of the searches was published in the English language (Uppaluri et al. American Association for Cancer Research 2025 [<https://doi.org/10.1158/1538-7445.AM2025-CT001>]). Accordingly, in the case of this review for this appraisal, there is no real risk of missing the relevant clinical evidence by including an English language limit in the database search strategies.

The search strategy for the Northern Light database (Northern Light Life Sciences Conference Abstracts 2010 – 2025 Week 12) (i.e. that shown in Appendix B, Table 4, of the company evidence submission) did not include an English language limit as the final search results to screen from that search were already modest enough in number so no additional restriction to increase the specificity of the search was required.

With regard to Appendix E, Table 23 and Table 24; Appendix F, Table 32, Table 33, and Table 34 (the SLRs for economic and HRQoL/utility evidence):

For the economic and HRQoL/utility SLRs, the English language filter was not applied to the main Embase and MEDLINE searches to ensure comprehensive coverage and maximise search sensitivity. For these specific SLRs, the language filter was only applied to the PubMed searches used to search MEDLINE In Process. The searches of this database supplemented the SLRs to identify the most recent citations not yet indexed in the main MEDLINE database. However, the overwhelming majority of citations identified by the PubMed search strategies in each SLR were indexed with the English language filter (Economic SLR, 1,586/1,593;

HRQoL SLR, 2,239/2,636) therefore the impact of the filter was minimal. MEDLINE In Process citations primarily consist of English language publications and for the purposes of informing the economic model, studies that are most relevant to the UK healthcare setting are most likely to be those published in English.

A6. Appendix, E section E1.1; Appendix F, section F1.1. In the database searches for these reviews, search terms have been used to identify studies of the types eligible for inclusion (economic evaluations and cost and resource use data sources; studies reporting health related quality of life (HRQoL) data and health state utility values (HSUVs) respectively); however there is no indication that these are based on published filters which have been validated for sensitivity/precision in identifying eligible studies. Please indicate whether this was the case (providing a supporting citation to relevant validation studies).

The search filters used for identifying economic and HRQoL studies were based on the search terms from Scottish Intercollegiate Guideline Network (SIGN; <https://www.sign.ac.uk/what-we-do/methodology/search-filters/>) and the Canadian Agency for Drugs and Technologies in Health (CADTH; <https://www.cadth.ca/resources/finding-evidence/strings-attached-cadth-database-search-filters#health/>), accessed on 15th April 2024. The filters applied to the economic, cost/HCRU and HRQoL SLRs included all the key terms from these sources, adapted slightly to align with the objective of the SLRs.

A7. Appendix E, section E1.1 and Table 24. Please clarify which platform was used to search the EconLit database, as the search narrative in E1.1 and the legend for Table 24 are not consistent in the reporting of this.

EconLit was searched via www.aeaweb.org/econlit/; the legend for Table 24 was incorrect.

A8. Appendix E, section E1.1, and Figure 2. The search strategy states that database searches included NHS EED, DARE, International HTA database and Tufts CEA registry. Please provide the search strategies that were used to search these databases. In addition, the PRISMA diagram at Figure 2 does not indicate how many studies were retrieved from these databases. Please provide clarification on the number of results from these database searches.

The search strategies for NHS EED, DARE and International HTA databases are provided in Table 1, Table 2, and Table 3, respectively. The updated PRISMA diagrams are provided in Figure 1, Figure 2 and Figure 3.

Table 1: Search strategy for NHS EED and DARE using www.crd.york.ac.uk/CRDWeb/ResultsPage.asp (database inception to March 31, 2015)

#	Search string	Search hits
#1	<i>"head and neck squamous cell carcinoma"</i>	27
#2	<i>HNSCC</i>	5
#3	#1 OR #2	27

Table 2: Search strategy for International HTA database using database.inahta.org (database inception to April 09, 2025)

#	Search string	Search hits
#1	<i>"head and neck squamous cell carcinoma"</i>	19
#2	<i>HNSCC</i>	0
#3	#1 OR #2	19

Table 3: Search strategy for Tufts CEA registry using <https://cevr.tuftsmedicalcenter.org/databases/cea-registry> (database inception to April 09, 2025)

#	Search string	Search hits
#1	<i>"head and neck squamous cell carcinoma"</i>	21
#2	<i>HNSCC</i>	10
#3	#1 OR #2	21

Figure 1: PRISMA flow diagram for economic evaluation studies

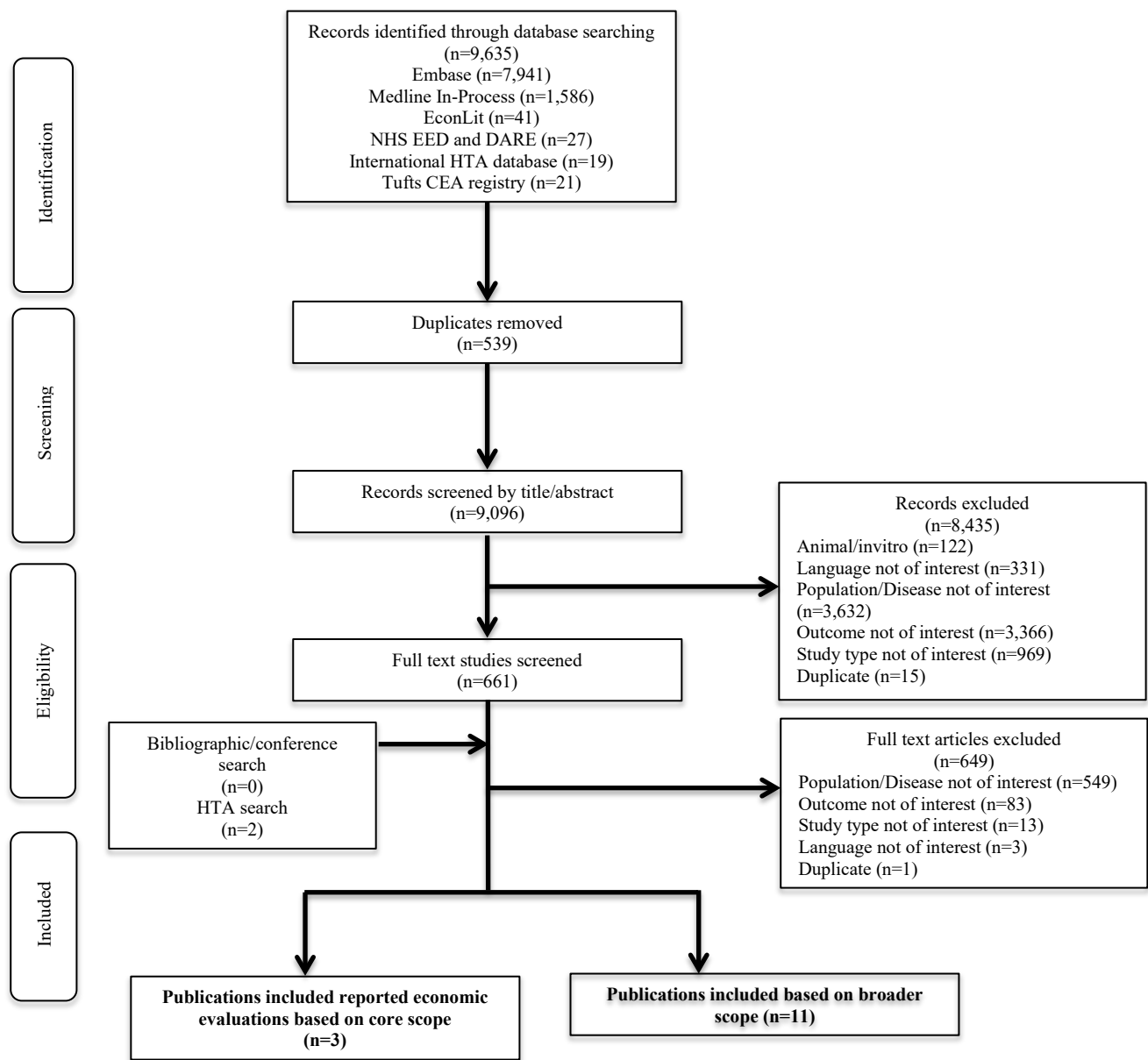


Figure 2. PRISMA flow diagram for cost studies

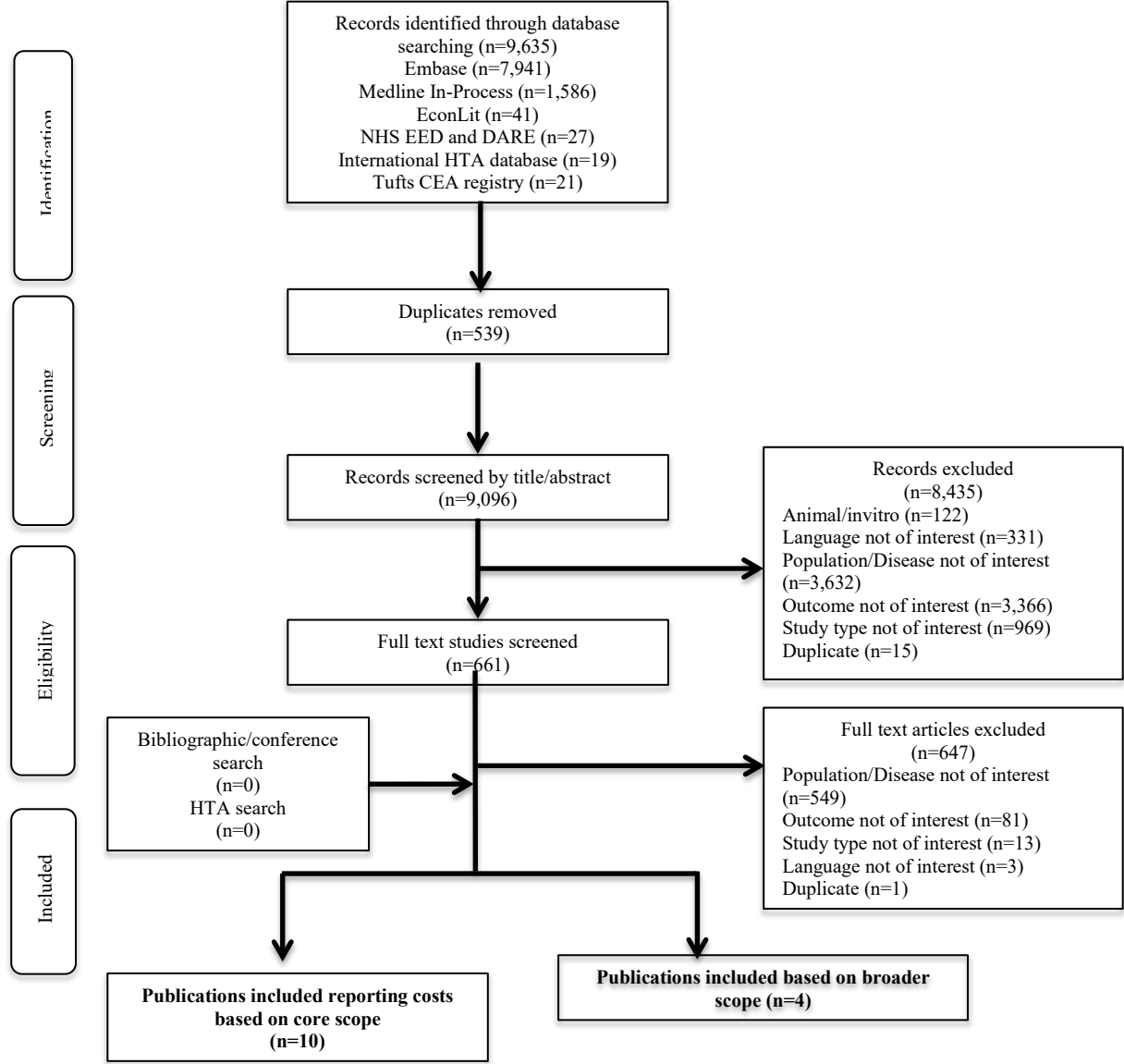
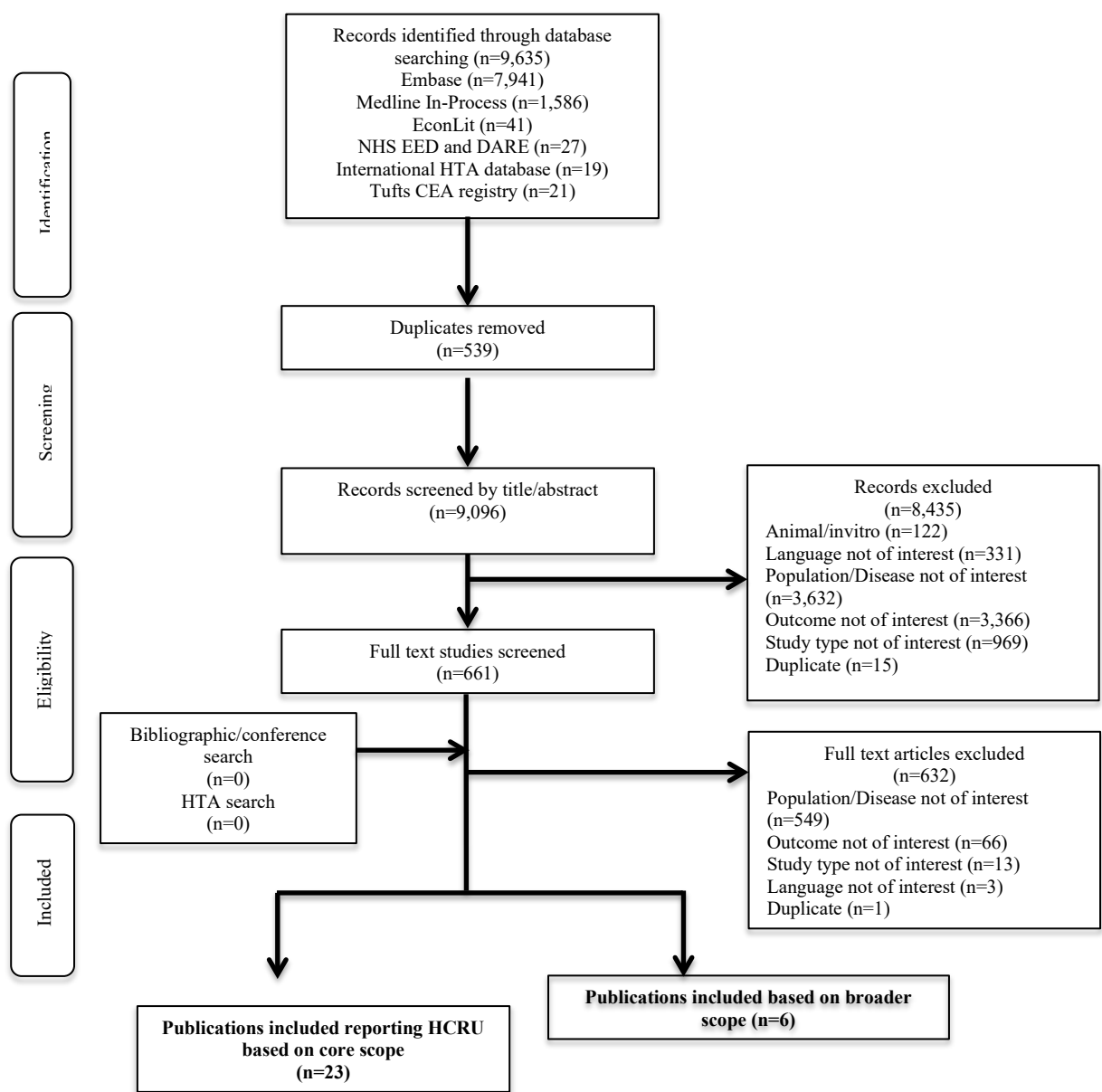


Figure 3. PRISMA flow diagram for HCRU studies



Literature review methods

A9. Please clarify why the principal KEYNOTE-689 publication (Uppaluri et al 2025) is not listed in the included studies (Appendix B, Table 7). Its publication appears to post-date the searches (31st March 2025), but the publication is cited (#41) in

section B.1.3.2 on treatment pathways. Please also clarify why the SLR was not updated to include this publication.

MSD response:

The Uppaluri et al. 2025 full journal publication was first published in the New England Journal of Medicine on 18-JUN-2025 (<https://www.nejm.org/doi/full/10.1056/NEJMoa2415434>) and does indeed post-date the searches of the SLR.

The SLR conducted to identify studies reporting clinical-effectiveness data relevant to the decision problem of this appraisal (i.e. that described in section 2.1 and Appendix B of the company evidence submission) had its searches last executed on 31-MAR-2025 (as described in section 2.1 and Appendix B section B.1.1.1), which is within 6 months of the company evidence submission date of 01-SEP-2025. The SLR was not updated post 18-JUN-2025 as the current SLR already fulfils NICE's requirements of it being conducted using searches execute no earlier than 6 months from the time of company evidence submission.

The KEYNOTE-689 study is MSD's own trial, and so all the relevant data on this trial (including trial results from the 25-JUL-2024 data cut-off date) has been in MSD's possession, data presented on/from the KEYNOTE-689 trial used in the submission are taken from MSD's own protocol, statistical analysis plan, and clinical study report (CSR). The Uppaluri et al 2025 publication (which also report results from the 25-JUL-2024 data cut-off date) does not include any information that MSD did not already possess at the time of submission. Consequently, there was no need to update the SLR specifically to include this publication.

A10. The only cited source for the data appears to be the unpublished clinical study report (CSR), and the principal KEYNOTE-689 publication (Uppaluri et al 2025) is not listed in the included studies (Appendix B, Table 7). Please clarify the source of the data being reported in this section, e.g. in each Table.

MSD response:

The KEYNOTE-689 is MSD's own trial, data presented on/from the KEYNOTE-689 trial used in the submission are taken from MSD's own protocol, statistical analysis plan, and clinical study report (CSR). The source of all methodological and clinical effectiveness data from the 25-JUL-2024 data cut-off date of the KEYNOTE-689 study (i.e. in sections 2.2 to 2.11 and Appendices C, D, L, M, N, and O of the company evidence submission) is directly from MSD, including from the referenced CSR.

A11. The clinical effectiveness review presented in the company submission (CS) identified for inclusion 85 reports covering 49 studies (CS, Appendix B, p.14, Figure 1 and Table 7). However, only evidence from one trial was presented in the clinical effectiveness section of the CS: KEYNOTE-689. Please clarify – for each study – the reason for its exclusion from the review in CS, Section 2 with specific reference to the Decision problem in CS, Section 1.1.

MSD response:

As stated in section 1.1 of the company evidence submission, the decision problem for this appraisal covers the full anticipated marketing authorisation of for this indication in the UK which is:

- [REDACTED]
[REDACTED]
[REDACTED]

The decision problem is not restricted to patients with tumours in specific sites of the head and neck.

The systematic literature review to identify relevant clinical effectiveness evidence for this appraisal was conducted initially with an objective to identify randomised controlled trials (RCTs) evaluating the efficacy, safety, and health-related quality of life (HRQoL) outcomes of surgery with neoadjuvant and/or adjuvant treatments in newly diagnosed patients with resectable LA-HNSCC (as described in Appendix B section B1 of the company evidence submission). This is a broader scope than that of the decision problem for this appraisal as stated above and is specific to the anticipated marketing authorisation (peri-operative setting). Accordingly, the initial findings of this review were then further restricted to only those studies that specifically reported results of treatment using neoadjuvant and adjuvant pembrolizumab in the indication of interest, and consequently only the KEYNOTE-689 study is of relevance and considered further as part of the clinical effectiveness evidence for this appraisal (as described in Appendix B section B1.2 of the company evidence submission).

The reason for the exclusion of each of the other 48 studies initially included in the review after full-text screening is that they do not report results of treatment using neoadjuvant and adjuvant pembrolizumab in the indication of interest.

It was not necessary for the final step to consider for inclusion evidence from studies that did not directly investigate pembrolizumab (for the purposes of e.g. use in indirect treatment

comparison) because no indirect comparisons or mixed treatment comparisons were carried out as the KEYNOTE-689 study provides direct and contemporary evidence for the treatment comparison of relevance to this appraisal (as described in section 2.10 of the company evidence submission, including for both pembrolizumab and the SoC relevant to the UK). Clinical opinion received confirmed that the findings of the KEYNOTE-689 study are generalisable to UK clinical practice, including that the comparator arm of the study is reflective of current UK standard of care.

A12. Appendix B.1.1.2: Study selection: The CS states, *‘Two reviewers working independently reviewed all abstracts identified in the literature search. Studies deemed eligible for inclusion by both investigators were advanced to full-text screening.’* Please clarify the process in the event that one investigator alone deemed a study eligible for inclusion? Were all such reports excluded?

MSD response:

At each screening stage (abstract and full-text), any disagreement between the two primary reviewers was first discussed to reach consensus. If consensus could not be achieved, a third reviewer was consulted to resolve the conflict. Therefore, no study was excluded solely because only one reviewer deemed it eligible.

Clinical evidence from KEYNOTE-689

A13. CS, Table 9: Please clarify what is meant by “*Status for Adjuvant Study Treatment*” for both study arms in this table. For the standard of care (SoC) arm, does it relate to any adjuvant treatment including radiotherapy or cisplatin? Similarly for the pembrolizumab arm, does it relate to any adjuvant treatment including pembrolizumab, radiotherapy or cisplatin? Please also clarify, how the start and end of treatment are reported if patients did not start/complete all elements of the planned adjuvant treatment.

MSD response:

Yes, “Status for Adjuvant Study Treatment” relates to any adjuvant treatment in each arm.

The start of treatment is from the initiation of any treatment components. For discontinuation of adjuvant treatment, the patient needs to discontinue all study treatments. Participants who start adjuvant treatment are marked as “completed” by the site when the participant completes adjuvant treatment as planned/expected. If a participant started adjuvant treatment and didn’t

complete all elements of it, the reason for discontinuation is captured and reported as shown in Table 9 of the Company evidence submission.

A14. PRIORITY CS, Table 9. Please clarify if patients who did not start neoadjuvant treatment in the pembrolizumab arm could progress to surgery? If so, please provide the numbers in the Combined Positive Score (CPS)≥1 population who did this? Please also clarify if patients who did not have surgery could receive treatments that were planned to be given as adjuvant treatment e.g. radiotherapy ± cisplatin ± pembrolizumab. If so, then please provide the numbers in the CPS≥1 population, by trial arm, who received such treatments without having surgery and the treatments received. (A narrative similar to that provided on page 260-263 of Appendix N for the whole trial population would be helpful).

MSD response:

With regard to whether patients who did not start neoadjuvant treatment in the pembrolizumab arm could progress to surgery, and if so, the numbers in the Combined Positive Score (CPS)≥1 population who did this:

Patients who did not start neoadjuvant treatment in the pembrolizumab arm could not progress to surgery.

With regard to whether patients who did not have surgery could receive treatments that were planned to be given as adjuvant treatment e.g. radiotherapy ± cisplatin ± pembrolizumab, and if so, the numbers in the CPS≥1 population, by trial arm, who received such treatments without having surgery and the treatments received:

Patients who did not have surgery could receive treatments that were planned to be given as adjuvant treatment e.g. radiotherapy ± cisplatin ± pembrolizumab. A narrative of flow for patients with PD-L1 CPS≥1 in the KEYNOTE-689 study is below:

A total of 682 participants had CPS $\geq$ 1 (347 in the pembrolizumab group, 335 in the SoC group). The median follow-up duration was longer in the pembrolizumab group compared with the SoC group (■■■ months vs ■■■ months)

In the neoadjuvant phase, [REDACTED] participants in the pembrolizumab group started study treatment, and of the [REDACTED] participants, [REDACTED] completed neoadjuvant study treatment. [REDACTED]

In the pembrolizumab arm, a total of [REDACTED] participants did not have surgery. The most common reason for not having in-study surgery for the pembrolizumab group was [REDACTED]. The remaining participants [REDACTED] did not have surgery and proceeded to either receive pembrolizumab + RT + cisplatin [REDACTED], or RT only [REDACTED], or did not receive any study treatment after randomization [REDACTED].

In the SoC arm, a total of [REDACTED] of the [REDACTED] participants randomized did not have surgery: [REDACTED] received neither surgery nor RT ± cisplatin and [REDACTED] were treated with RT ± cisplatin without surgery (Table 4 and Table 5).

Table 4: Surgery Status, Participants With CPS≥1, (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[REDACTED]		[REDACTED]		[REDACTED]	
With in-study Surgery	[REDACTED]		[REDACTED]		[REDACTED]	
Without in-study Surgery	[REDACTED]		[REDACTED]		[REDACTED]	
Reason for in-study surgery not performed						
Adjuvant Treatment without Surgery^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Adverse Event	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Physician Decision	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Tumor Found To Be Surgically Unresectable	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Withdrawal By Subject	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Discontinued Treatment Prior to Surgery^b	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Adverse Event	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Lost To Follow-Up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non-Study Anti-Cancer Therapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Physician Decision	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Progressive Disease	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Withdrawal By Subject	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Randomized but Not Treated^c	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

^a SoC participants in this category were eligible to receive radiation ± cisplatin. Pembrolizumab participants were eligible to receive pembrolizumab ± radiation ± cisplatin.

^b Participants in this group received at least one dose of pembrolizumab and discontinued treatment before surgery.

^c Participants in this group did not continue to any phase of treatment (including surgery) following randomization.

Database Cutoff Date: 25JUL2024

Table 5: Treatment Received During Adjuvant Phase for Participants Without in-study Surgery, Participants With CPS $\geq$ 1, (All-Participants-as-Treated Population)

Treatment Received	Study: KEYNOTE 689 ^a		
	Pembrolizumab	SoC	Total
	N ^b =8	N ^b =7	N ^b =15
Adjuvant Treatment, n (%)			
Radiation	■	■	■
Cisplatin+Radiation	■	■	■
Pembrolizumab+Cisplatin+Radiation	■	■	■
a: Database Cutoff Date: 25JUL2024			
b: Number of participants who received treatment during adjuvant phase without in-study surgery			

Among the ■ pembrolizumab participants who completed surgery, ■ were discontinued prior to initiation of adjuvant treatment. The most common reason for discontinuation was progressive disease ■. Among the ■ SoC participants who completed surgery, ■ were discontinued prior to initiation of adjuvant treatment. The most common reason for discontinuation was adverse event (■) and withdrawal by subject (■) (Table 6).

Table 6 Disposition of Participants, (Participants who Completed Surgery but Did Not Receive Adjuvant Therapy), Participants With CPS $\geq$ 1, (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	50		39		89	
Status for Study Treatment (Overall)						
Discontinued	■	■	■	■	■	■
Adverse Event	■	■	■	■	■	■
Clinical Progression	■	■	■	■	■	■
Non-Compliance With Study Drug	■	■	■	■	■	■
Non-Study Anti-Cancer Therapy	■	■	■	■	■	■
Physician Decision	■	■	■	■	■	■
Progressive Disease	■	■	■	■	■	■
Withdrawal By Subject	■	■	■	■	■	■
Participants in population is used as the denominator for the percentage calculation.						
Database Cutoff Date: 25JUL2024						

In the adjuvant phase following surgery, ■ participants in the pembrolizumab group started study treatment of which ■ completed study treatment. A total of ■ of the ■ participants received adjuvant pembrolizumab, ■ completed 3 or less cycles of pembrolizumab and ■ completed more than 3 cycles of pembrolizumab while ■ of the ■ participants received RT ± cisplatin only.

Table 7 Summary of Drug Exposure to Pembrolizumab, Adjuvant Phase, (Participants Who Received Adjuvant Treatment), Participants With CPS $\geq$ 1, (All-Participants-as-Treated Population)

	Pembrolizumab (N=264)	SoC (N=262)
Study Days on Therapy (months)		
n	■	■
Mean (SD)	■	■
Median	■	■
Range	■	■
Number of Cycles		
n	■	■
Mean (SD)	■	■
Median	■	■
Range	■	■
n (%)	■	■
≤ 3	■	■
> 3	■	■
Database Cutoff Date: 25JUL2024		

In the SoC group, ■ participants started study treatment, and ■ participants completed study treatment consisting of RT $\pm$ 3 cycles of cisplatin.

For participants who underwent surgery, ■ participants in the pembrolizumab group and ■ participants in the SoC group received in-study surgery and RT. Of the participants who underwent surgery, ■ in the pembrolizumab group and ■ in the SoC group received in-study surgery and RT + cisplatin (Table 8).

Table 8: Summary of Surgery, (Participants Who Underwent Surgery), Participants With CPS $\geq$ 1

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	■		■		■	
Surgery Procedure						
Lip and oral cavity surgery	■	■	■	■	■	■
Larynx surgery	■	■	■	■	■	■
Pharynx surgery	■	■	■	■	■	■
Surgery Outcome						
Complete Resection	■	■	■	■	■	■
Incomplete Resection-R1	■	■	■	■	■	■
Incomplete Resection-R2	■	■	■	■	■	■
Attempted Resection	■	■	■	■	■	■
Time Since Start of Neoadjuvant^a to Surgery (weeks)						

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
< 4 weeks	■	■	■	■	■	■
4 to <5 weeks	■	■	■	■	■	■
5 to <6 weeks	■	■	■	■	■	■
>=6 weeks	■	■	■	■	■	■
Participants with data	■		■		■	
Mean	■		■		■	
SD	■		■		■	
Median	■		■		■	
Range	■		■		■	
Time Since End of Neoadjuvant^a to Surgery (weeks)						
< 4 weeks	■	■	■	■	■	■
4 to <5 weeks	■	■	■	■	■	■
5 to <6 weeks	■	■	■	■	■	■
>=6 weeks	■	■	■	■	■	■
Participants with data	■		■		■	
Mean	■		■		■	
SD	■		■		■	
Median	■		■		■	
Range	■		■		■	
Time since Surgery to First Adjuvant Treatment (weeks)						
Participants with data	■		■		■	
Mean	■		■		■	
SD	■		■		■	
Median	■		■		■	
Range	■		■		■	
Days of Hospitalization from Surgery to Discharge						
Participants with data	■		■		■	
Mean	■		■		■	
SD	■		■		■	
Median	■		■		■	
Range	■		■		■	
Surgery Delay Status						
Yes	■	■	■	■	■	■
Adverse Experience	■	■	■	■	■	■
Scheduling Change	■	■	■	■	■	■
Patient Non-Compliance	■	■	■	■	■	■
Other Due to COVID-19	■	■	■	■	■	■

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Other Not Due to COVID-19	■	■	■	■	■	■
No	■	■	■	■	■	■
Post Surgery Adjuvant CRT/RT						
With in-study surgery and adjuvant CRT	■	■	■	■	■	■
With in-study surgery and adjuvant RT	■	■	■	■	■	■
^a Time since randomization to surgery is summarized for participants who did not receive neoadjuvant treatment. Database Cutoff Date: 25JUL2024						

The proportion of participants who discontinued overall study treatment was greater in the pembrolizumab group compared with the SoC group (pembrolizumab group: ■; SoC group: ■). The most common reasons for discontinuing overall study treatment among participants who discontinued all study treatment in the pembrolizumab group were progressive disease (■) and AE (■) and in the SoC group were AE (■) and withdrawal by subject (■). The longer duration of exposure in the pembrolizumab group should be taken into consideration when interpreting the difference in discontinuation rates and the most common reasons for treatment discontinuation between treatment groups. As of the data cutoff date, ■ participants in the pembrolizumab group and ■ participants in the SoC group were ongoing with overall study treatment.

A15. Appendix N, Table 96. Please clarify the numbers of discontinuations in the pembrolizumab arm between surgery and starting adjuvant treatment. Table 96 reports, n=321 completed surgery and n=275 started adjuvant treatment suggesting that 46 discontinued prior to adjuvant treatment (321-275=46), but the text of p.260 states “54 were discontinued prior to initiation of adjuvant treatment”. Is this discrepancy because 8 patients did not have surgery but went on to have treatments that were classified as adjuvant treatments (radiotherapy ± cisplatin ± pembrolizumab)?

MSD response:

Yes, that is correct. The discrepancy is indeed due to the 8 patients who did not have surgery but went on to have treatments that were classified as adjuvant treatments.

A16. Appendix N2, p.260 states, ‘Among the 321 pembrolizumab participants who completed surgery, 54 were discontinued prior to initiation of adjuvant treatment. The

most common reason for discontinuation was progressive disease (27 [50.0%]). Among the 308 SoC participants who completed surgery, 41 were discontinued prior to initiation of adjuvant treatment. The most common reason for discontinuation was adverse event (11 [26.8%])'. Please clarify the reason for the high proportion of patients discontinuing treatment due to progressive disease in the pembrolizumab arm between surgery and starting adjuvant treatment compared with the SoC arm.

MSD response:

The higher proportion of patients discontinuing treatment prior to the start of adjuvant therapy is as expected due to the event classification and treatment discontinuation guidelines of earlier versions of the KEYNOTE-689 study protocol prior to Amendment 08 of that protocol (made on 07-SEP-2023). Amendment-08 revised the EFS definition to state that progressions occurring in presurgical phase will be counted as events if there is a preclusion to curative intent surgery. Prior to this amendment, progressions occurring the presurgical phase were counted as events independent of curative intent surgery and these participants subsequently discontinued from study.

Additionally, per the KEYNOTE-689 schedule of scan activities (described in the response to question A17), in the pembrolizumab group, the first radiographic assessment is the pre-surgery scan which is required for all participants within 2 weeks prior to the date of surgery. However, in the SoC group, the first radiographic assessment required for all participants is a post-surgery scan (12 weeks after the end of adjuvant RT/CRT treatment). In the SoC group, only if the baseline scans are done more than 2 weeks prior to the date of surgery, the pre-surgery scan is required. Because of the difference in time of the first radiographic assessment required per protocol between treatment groups, a comparison of the radiographic disease progression pre-surgery is biased in favour of the SoC group with an increased likelihood of capturing more events in the pembrolizumab arm.

The impact of these differences should be considered when interpreting the discontinuations prior to the start of adjuvant therapy between treatment groups.

A17. Please describe the schedule of routine scans to detect recurrence/progression in both arms and highlight any differences in the number or timing of scans required by the study protocol pre- and post- surgery.

MSD response:

The schedule of scans (tumour imaging) followed that of the protocol of the KEYNOTE-689 study, described below.

Initial tumour imaging prior to randomisation:

Initial tumour imaging at Screening (contrast enhanced head and neck, chest, and upper abdomen computer tomography [CT] scan or chest CT scan plus head and neck and abdomen magnetic resonance imaging [MRI], and fluorodeoxyglucose-positron emission tomography [FDG-PET or FDG-PET/CT]) must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the participant has evaluable disease per RECIST 1.1 prior to submitting to central imaging vendor.

The screening images must be submitted to the central imaging vendor for retrospective review.

Scans performed as part of routine clinical management are acceptable for use as screening tumour imaging if they are of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the central imaging vendor.

FDG-PET or FDG-PET/CT scans will only be performed at screening to help guide potential SoC neck dissections, if required. Diagnostic quality CT can be acquired on the PET/CT scanner while performing FDG-PET if that is the local standard practice.

Tumour imaging during the study:

The same modality (CT/MRI head and neck, chest, and upper abdomen) used at screening should be used during neoadjuvant and adjuvant treatment and during the post-treatment follow-up visits at the scheduled time points described below.

For participants in the pembrolizumab arm (Arm A), the first on-study imaging assessment should be performed after completion of 2 cycles of pembrolizumab treatment, at approximately Week 6 (± 10 days) from the date of randomization and before surgery. If the presurgery scan shows tumour flare this should not alter the timing or decision to proceed to surgery unless the tumour is unresectable. In the SoC arm (Arm B), the screening imaging will

serve as the presurgery imaging. If the presurgery scans for Arm A or baseline scans for Arm B are done > 14 days prior to the date of surgery, then repeat imaging prior to surgery will be required.

The first post-surgery imaging should be performed 12 weeks (± 7 days) after the end of RT $\pm$ cisplatin. Subsequent tumour imaging should then be performed every 3 months (91 ± 7 days), or more frequently if clinically indicated, until the end of Year 3 after randomization, then every 6 months (182 ± 14 days) until the end of Year 5. For all postsurgery imaging, the clock will start at the end of RT $\pm$ cisplatin (ie, last dose of). All of these visits should stay on track using the last dose of RT $\pm$ cisplatin as the starting clock, ie, if one of the imaging visits is late (even the first scan post-surgery), the participants will stay on the original schedule starting with the last dose of RT $\pm$ cisplatin for all future visits; do not recalculate. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. When the investigator identifies radiographic progression per RECIST 1.1, the site should submit the imaging with verification of progression (VOP) request to the central imaging vendor as soon as possible. Expedited VOP read will be performed by BICR and the results will be communicated to the site and Sponsor via email. If initial site-assessed PD was not verified by BICR, each subsequent imaging must be submitted to central imaging vendor with VOP request until PD has been verified. Treatment should continue until PD has been verified by BICR, initiation of a new anticancer treatment, pregnancy, death, withdrawal of consent, study conclusion or early termination, whichever occurs first. Of note, a participant will only discontinue from study treatment during the neoadjuvant phase if PD precludes surgery.

End of treatment and follow-up tumour imaging:

For participants who discontinue study treatment without a documented event/disease progression, every effort should be made to continue monitoring their disease status by tumour imaging using the same imaging schedule used while on treatment (every 3 months [91 ± 7 days] until the end of Year 3, thereafter every 6 months [182 ± 14 days] until the end of Year 5) to monitor disease status until an event/disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. For participants who discontinue study treatment due to an event/documented disease progression, this is the final required tumour imaging.

A18. Appendix N, Table 97 reports data for the 'all comers' (i.e. whole trial) population. Please provide equivalent data for the CPS ≥ 1 population. These data are required to verify the proportions receiving radiotherapy and cisplatin in the

model. In addition to this, please provide information on the proportion of high and low risk patients who started treatment with cisplatin in each study arm.

MSD response:

Please find the requested information in the two tables (Table 9 and Table 10) below:

Table 9: Study population (trial flow) – all comer population

	Pembrolizumab	SoC	Total
Number of Participants Screened			1044
Number of Participants Randomized (Planned Treatment) (ITT)	363	351	714
Number of Participants Randomized and Did Not Receive Treatment	3	35	38
Number of Participants Who Received Treatment (Actual Treatment) (APaT)	361	315	676
Number of Participants Who Received Neoadjuvant Treatment	■	I	■
Number of Participants Who Underwent In-Study Surgery	■	■	■
Number of Participants Who Received the Adjuvant Treatment	■	■	■
Number of Participants Who Received In-Study Radiation Therapy	■	■	■
Number of Participants Who Received Cisplatin	■	■	■
Number of High-Risk Participants Who Received Cisplatin	■	■	■
Number of Low-Risk Participants Who Received Cisplatin	■	■	■
Number of Participants Who Received Cisplatin + In-Study Radiation Therapy	■	■	■
Database Cutoff Date: 25JUL2024			

Table 10: Study population (trial flow) – PD-L1 CPS $\geq$ 1 population

	Pembrolizumab	SoC	Total
Number of Participants Screened			889
Number of Participants Randomized (Planned Treatment) (ITT)	■	■	■
Number of Participants Randomized and Did Not Receive Treatment	I	■	■
Number of Participants Who Received Treatment (Actual Treatment) (APaT)	■	■	■
Number of Participants Who Received Neoadjuvant Treatment	■	I	■

	Pembrolizumab	SoC	Total
Number of Participants Who Underwent In-Study Surgery	■	■	■
Number of Participants Who Received the Adjuvant Treatment	■	■	■
Number of Participants Who Received In-Study Radiation Therapy	■	■	■
Number of Participants Who Received Cisplatin	■	■	■
Number of High-Risk Participants Who Received Cisplatin	■	■	■
Number of Low-Risk Participants Who Received Cisplatin	■	■	■
Number of Participants Who Received Cisplatin + In-Study Radiation Therapy	■	■	■
Database Cutoff Date: 25JUL2024			

A19. Appendix N, Table 100 reports data for the ‘all comers’ population. Please provide the equivalent data for the CSP ≥ 1 population.

MSD response:

These data are provided across the three tables (Table 11, Table 12, and Table 13) below:

Table 11: Summary of Drug Exposure (Overall), Participants With CPS ≥ 1 , (All-Participants-as-Treated Population)

	Pembrolizumab (N=345)	SoC (N=300)
Study Days on Therapy (months)		
n	■	■
Mean (SD)	■	■
Median	■	■
Range	■	■
Treatment includes study drugs, in-study surgery and in-study radiotherapy. Database Cutoff Date: 25JUL2024		

Table 12: Summary of Drug Exposure to Pembrolizumab, Neoadjuvant Phase, Participants With CPS ≥ 1 , (All-Participants-as-Treated Population)

	Pembrolizumab (N=345)	SoC (N=1)
Study Days on Therapy (months)		
n	■	■
Mean (SD)	■	■
Median	■	■
Range	■	■

	Pembrolizumab	SoC
	(N=345)	(N=1)
Number of Cycles		
n	■	■
Mean (SD)	■	■
Median	■	■
Range	■	■
Database Cutoff Date: 25JUL2024		

Table 13: Summary of Drug Exposure, Adjuvant Phase, (Participants Who Received Adjuvant Treatment), Participants With CPS $\geq$ 1, (All-Participants-as-Treated Population)

	Pembrolizumab	SoC
	(N=264)	(N=262)
Study Days on Therapy (months)		
n	■	■
Mean (SD)	■	■
Median	■	■
Range	■	■
Treatment includes study drugs, in-study surgery and in-study radiotherapy.		
Database Cutoff Date: 25JUL2024		

A20. CS, Table 23; Please clarify why the number of SoC patients in the safety analysis in Table 23 (N=315) is lower than the number available for baseline characteristics (Table 6, N=335). Please also clarify why the number of patients for the safety analyses in the pembrolizumab arm is higher than for the baseline characteristics (N=361 for safety vs 347 for baseline). Please also describe how any patients who received treatment different from their randomised allocation were handled for the safety analysis.

MSD response:

Table 23 shows data for the all comer overall population in the all patients as treated (APaT) population, whereas Table 6 shows data for the subgroup of patients with PD-L1 CPS $\geq$ 1 in the intention-to-treat (ITT) population. These are quite different groups of patients and so the numbers are different for both the pembrolizumab and SoC arms (see Table 14 below for additional clarification of these numbers).

Table 14: Comparison of ITT and APaT numbers for relevant KEYNOTE-689 populations

	Pembrolizumab	Soc
All comer population		
Intention-To-Treat (ITT) population	363	351
All Patients as Treated (APaT) population	361	315
PD-L1 CPS$\geq$1 population		
Intention-To-Treat (ITT) population	347	335
All Patients as Treated (APaT) population	345	300

With regard to how any patients who received treatment different from their randomised allocation were handled for the safety analysis, this only occurred in the case of two participants in the SoC group received neoadjuvant pembrolizumab in error (protocol deviations). One received 1 cycle pembrolizumab and was returned to standard-of-care treatment for the remainder of the study (included in the control group for both efficacy and safety analysis); the other received 2 cycles pembrolizumab, underwent surgery, and discontinued study treatment thereafter without adjuvant therapy (included in the control group for efficacy analysis and the pembrolizumab group for safety analysis).

A21 Please clarify and define the term ‘clinically meaningful’, e.g. CS, Section B.2, p.37 and multiple instances.

MSD response:

“Clinically meaningful” in these instances refers to the results being impactful as it relates to the clinical state or outcome. No specific quantitative thresholds etc. were considered.

The KN-689 data have been considered clinically meaningful through insights gained at an MSD advisory board, undertaken on 15th May 2025. The data has demonstrated, for the first time in over two decades, a clear peri-operative treatment benefit in patients with resectable locally advanced HNSCC, with significant improvement in event-free survival rates versus standard surgery and adjuvant therapy alone across all biomarker populations. The advisors recognised the neoadjuvant pembrolizumab phase as a key driver of efficacy, enabling early immune activation and reduction in EFS events - which was statistically significant. However, it was also acknowledged that the overall strength of the KN-689 regimen lies in the peri-operative design, where continuation of adjuvant pembrolizumab after surgery serves to sustain immune engagement and consolidate the benefit achieved in the neoadjuvant phase, to support long-term disease control in the curative intent setting.

This was seen as redefining what could be achieved alongside radiotherapy. Overall, KN-689 was recognised as a pivotal advancement that not only delivers meaningful efficacy but also validates the role of immunotherapy in a new treatment paradigm.

From the MSD advisory board report:

- KN-689 was recognised as an important advancement in the treatment of resectable LA HNSCC, with advisors highlighting the significance of the EFS improvement observed in the interim analysis.
- The neoadjuvant pembrolizumab phase was widely seen as a meaningful contributor to efficacy, with many participants noting the potential for early immune engagement to influence long-term outcomes alongside the adjuvant component.
- EFS was generally considered an appropriate endpoint for this peri-operative trial.
- The study was felt to re-establish immunotherapy in the peri-operative setting as a potential option in the curative setting, following previous challenges seen in the adjuvant-only context.

Anonymised advisor quotes from MSD advisory board report:

- “The first time we've seen improvement in recurrence rates for this population,” noting the clear benefit over surgery and adjuvant [chemo]radiotherapy alone.
- The neoadjuvant approach itself was “exciting,” highlighting that previous adjuvant trials with IO had failed to deliver similarly impactful results.
- The KN-689 study was also described as “the first in over 20 years” to show a clear (neo)adjuvant treatment benefit”
- Advisors also reflected on the impact of the findings from a radiotherapy (RT) standpoint: “It’s really stretched what we can do alongside RT,” noting the limited impact that current systemic treatments have previously had on survival curves. It was also stated that many clinicians had “lost hope” in IO from negative results of previous trials in the curative setting, but KN-689 reintroduced confidence for IO in the radical treatment setting in a meaningful way.
- It was also emphasised that KN-689 not only shows efficacy but also corrects some of the uncertainties surrounding IO use, as “it proves we don’t really understand how IO works,”, noting that past trials in the adjuvant setting were difficult to interpret. Advisors

also praised the data for showing neoadjuvant IO treatment providing efficacious response in “a new setting for the first time”.

- It was also suggested that the benefit may derive from prevention of early disease dissemination: “It seems like it does quite a lot in that earlier disease phase, and makes quite a bit of difference in that early period. I feel that it brings IO back to the radical setting, in a way”.

A22. PRIORITY Appendix B.3: Critical appraisal of each study, Table 8: Please clarify the judgement that there were ‘*No deviations [from the intended intervention(s)] reported*’. Appendix N2, pp.260-261 states that 2 patients in the comparator arm were exposed to therapy that they should not have received (*‘In the SoC group, there was no neoadjuvant treatment, however, 2 participants received neoadjuvant treatment mistakenly. One of these 2 participants received 1 cycle of neoadjuvant treatment and was returned to SoC treatment for the remainder of the study, while the other participant received 2 neoadjuvant cycles of pembrolizumab, underwent surgery, and was discontinued from study treatment; this participant did not receive any adjuvant treatment’*) and 20 patients in the intervention arm did not receive the planned adjuvant pembrolizumab treatment: *‘A total of 255 of the 275 participants received adjuvant pembrolizumab, 36 completed 3 or less cycles of pembrolizumab and 219 completed more than 3 cycles of pembrolizumab while 20 of the 275 participants received RT ± cisplatin only’*.

MSD response:

When assessing this domain, the Cochrane RoB 2 guidance was applied, which considers whether deviations from intended interventions were likely to affect the outcome and whether they occurred because of the trial context. In the KEYNOTE-689 study, clinically important protocol deviations were defined as those that could compromise primary efficacy/safety analyses or participant safety (2).

Of the two patients in the SoC arm who mistakenly received neoadjuvant pembrolizumab, only one was classified as a clinically important protocol deviation (2). In the pembrolizumab + SoC arm, although 20 participants did not receive adjuvant pembrolizumab, the total number of clinically important protocol deviations in this arm (for any reason) was smaller than 20 (2). This indicates that these cases were not clinically important deviations (due to e.g. acceptable reasons such as medical decisions) and were unlikely to be related to the trial context.

It is also noteworthy to mention that the likely direction of bias from both types of deviations (SoC patients receiving pembrolizumab and intervention patients missing adjuvant pembrolizumab) would be toward the null effect, favouring the comparator. Given the small number of clinically important deviations and the use of an intention-to-treat analysis, it was initially judged this domain as “low risk.” However, to address any residual concerns, we can update the judgment to “some concerns” and revised our responses in this domain to explicitly acknowledge these deviations if necessary.

A23. PRIORITY Appendix B.3: Critical appraisal of each study, Table 8: For missing outcome data, please clarify which outcome or outcomes were considered when completing the risk of bias assessment. Please specifically comment on whether any of the judgements would differ for the patient reported outcomes (PROs) versus the outcomes based on BICR/BIPR.

MSD response:

The risk of bias assessment for missing outcome data was based on the trial’s primary endpoint, event-free survival (EFS) as assessed by BICR. For patient-reported outcomes (PROs), compliance was high throughout the study. For example, for EORTC QLQ-C30, more than 90% of patients completed the questionnaire at baseline, with over 94% compliance during the neoadjuvant phase at Weeks 4 and 6, and more than 88% compliance in both arms during the post-adjuvant phase at Week 51. Given these high completion and compliance rates, our judgment would not differ for PROs. We would maintain the assessment as “Outcome available for all or nearly all patients,” corresponding to a low risk of bias for this domain.

A24. PRIORITY Appendix B.3: Critical appraisal of each study, Table 8: For measurement of outcome, please clarify the judgement ‘*Probably not*’ in response to the question, ‘*Could assessment of the outcome have been influenced by knowledge of intervention received?*’, given the open-label nature of the trial and the presence of some subjective PROs for quality of life and safety.

MSD response:

Although the trial was open-label, the primary endpoint (EFS) and key secondary endpoints (major pathological response and OS) were based on objective measures such as death events and assessments performed by blinded independent central review (BICR) or blinded independent pathologist review (BIPR). Another secondary endpoint, pathological complete

response, was also assessed by BICR. These outcomes were therefore unlikely to have been influenced by knowledge of the intervention received.

However, because some subjective endpoints (e.g., PROs and safety outcomes) could theoretically be affected by the open-label design, we selected “Probably not” rather than “No” in response to this question, even though these endpoints were not part of the hypothesis-testing hierarchy.

A25. Appendix D.1.1, Table 11 summarises adverse events of special interest (AEOSI) but does not provide any details on the specific nature of these adverse events and instead pools frequencies according to whether they were grade 3+, whether they were classified as serious or drug-related or whether they led to discontinuation. Please provide further details of the specific AEOSI occurring including:

- a) The frequency of the specific AEOSIs that were classified as drug related toxicity grade 3-5 (9.4% for pembrolizumab vs 0% in the ScC arm)

MSD response:

This is provided in the table (Table 15) below:

Table 15: Participants With Drug-Related Grade 3-5 Adverse Events of Special Interest (AEOSI), (Incidence > 0% in One or More Treatment Groups), (All-Participants-as-Treated Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	■	■	■	■
with no adverse events	■	■	■	■
Adrenal Insufficiency	■	■	■	■
Adrenal insufficiency	■	■	■	■
Colitis	■	■	■	■
Colitis	■	■	■	■
Hepatitis	■	■	■	■
Hepatitis acute	■	■	■	■
Immune-mediated hepatitis	■	■	■	■
Hypophysitis	■	■	■	■
Hypophysitis	■	■	■	■
Myocarditis	■	■	■	■
Myocarditis	■	■	■	■

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Nephritis	1	3	1	3
Immune-mediated nephritis	1	3	1	3
Tubulointerstitial nephritis	1	3	1	3
Pancreatitis	1	3	1	3
Autoimmune pancreatitis	1	3	1	3
Pancreatitis	1	3	1	3
Pancreatitis acute	1	3	1	3
Pneumonitis	1	3	1	3
Interstitial lung disease	1	3	1	3
Pneumonitis	1	3	1	3
Severe Skin Reactions	1	3	1	3
Dermatitis exfoliative	1	3	1	3
Erythema multiforme	1	3	1	3
Severe Skin Reactions	1	3	1	3
Pruritus	1	3	1	3
Rash	1	3	1	3
Rash maculo-papular	1	3	1	3
Every participant is counted a single time for each applicable row and column. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 Database Cutoff Date: 25JUL2024				

b) The frequency of the specific AEOSI leading to discontinuation (7.8% for pembrolizumab vs 0% in ScC arm)

MSD response:

This is provided in the table (Table 16) below:

Table 16: Participants With Adverse Events of Special Interest (AEOSI) Leading to Treatment Discontinuation, (Incidence > 0% in One or More Treatment Groups), (All-Participants-as-Treated Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	1	3	1	3
with no adverse events	1	3	1	3
Adrenal Insufficiency	1	3	1	3
Primary adrenal insufficiency	1	3	1	3
Colitis	1	3	1	3

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Colitis	█	██	█	██
Hepatitis	█	██	█	██
Hepatitis acute	█	██	█	██
Immune-mediated hepatitis	█	██	█	██
Nephritis	█	██	█	██
Immune-mediated nephritis	█	██	█	██
Tubulointerstitial nephritis	█	██	█	██
Pancreatitis	█	██	█	██
Pancreatitis	█	██	█	██
Pancreatitis acute	█	██	█	██
Pneumonitis	█	██	█	██
Interstitial lung disease	█	██	█	██
Pneumonitis	█	██	█	██
Severe Skin Reactions	█	██	█	██
Dermatitis exfoliative	█	██	█	██
Rash	█	██	█	██
Every participant is counted a single time for each applicable row and column. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 Database Cutoff Date: 25JUL2024				

c) The frequency of the most common immune-mediated (or potentially immune-mediated) adverse events of any grade as these are described as adverse events of special interest (AEOSI) in Appendix M2.1.

MSD response:

This is provided in the table (Table 17) below. The immune-mediated (or potentially immune-mediated) adverse events were those ones designated as the AEOSI.

Table 17: Participants With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade, (Incidence > 0% in One or More Treatment Groups), (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	█	██	█	██
Grade 1	█	██	█	██
Grade 2	█	██	█	██
Grade 3	█	██	█	██
Grade 4	█	██	█	██
Grade 5	█	██	█	██

	Pembrolizumab		SoC	
	n	(%)	n	(%)
with no adverse events	■	■	■	■
Adrenal Insufficiency	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Adrenal insufficiency	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Primary adrenal insufficiency	■	■	■	■
Grade 2	■	■	■	■
Colitis	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Grade 4	■	■	■	■
Colitis	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Grade 4	■	■	■	■
Gastritis	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Gastritis	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Hepatitis	■	■	■	■
Grade 1	■	■	■	■
Grade 3	■	■	■	■
Grade 4	■	■	■	■
Autoimmune hepatitis	■	■	■	■
Grade 3	■	■	■	■
Hepatitis	■	■	■	■
Grade 1	■	■	■	■
Hepatitis acute	■	■	■	■
Grade 4	■	■	■	■
Immune-mediated hepatitis	■	■	■	■
Grade 3	■	■	■	■
Grade 4	■	■	■	■

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Hyperthyroidism	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Hyperthyroidism	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Hypoparathyroidism	■	■	■	■
Grade 2	■	■	■	■
Hypoparathyroidism	■	■	■	■
Grade 2	■	■	■	■
Hypophysitis	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Hypophysitis	■	■	■	■
Grade 3	■	■	■	■
Hypopituitarism	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Hypothyroidism	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Hypothyroidism	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Infusion Reactions	■	■	■	■
Grade 1	■	■	■	■
Drug hypersensitivity	■	■	■	■
Grade 1	■	■	■	■
Hypersensitivity	■	■	■	■
Grade 1	■	■	■	■
Infusion related reaction	■	■	■	■
Grade 1	■	■	■	■
Myocarditis	■	■	■	■
Grade 3	■	■	■	■
Myocarditis	■	■	■	■
Grade 3	■	■	■	■

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Myositis	1	1	1	1
Grade 2	1	1	1	1
Myositis	1	1	1	1
Grade 2	1	1	1	1
Nephritis	1	1	1	1
Grade 1	1	1	1	1
Grade 3	1	1	1	1
Grade 4	1	1	1	1
Glomerulonephritis acute	1	1	1	1
Grade 1	1	1	1	1
Immune-mediated nephritis	1	1	1	1
Grade 4	1	1	1	1
Tubulointerstitial nephritis	1	1	1	1
Grade 3	1	1	1	1
Pancreatitis	1	1	1	1
Grade 2	1	1	1	1
Grade 3	1	1	1	1
Autoimmune pancreatitis	1	1	1	1
Grade 3	1	1	1	1
Pancreatitis	1	1	1	1
Grade 2	1	1	1	1
Grade 3	1	1	1	1
Pancreatitis acute	1	1	1	1
Grade 3	1	1	1	1
Pneumonitis	1	1	1	1
Grade 1	1	1	1	1
Grade 2	1	1	1	1
Grade 3	1	1	1	1
Grade 4	1	1	1	1
Grade 5	1	1	1	1
Interstitial lung disease	1	1	1	1
Grade 2	1	1	1	1
Grade 3	1	1	1	1
Pneumonitis	1	1	1	1
Grade 1	1	1	1	1
Grade 2	1	1	1	1
Grade 3	1	1	1	1
Grade 4	1	1	1	1
Grade 5	1	1	1	1

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Severe Skin Reactions	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Dermatitis exfoliative	■	■	■	■
Grade 3	■	■	■	■
Erythema multiforme	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Exfoliative rash	■	■	■	■
Grade 1	■	■	■	■
Pruritus	■	■	■	■
Grade 3	■	■	■	■
Rash	■	■	■	■
Grade 3	■	■	■	■
Rash maculo-papular	■	■	■	■
Grade 3	■	■	■	■
Skin necrosis	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Thyroiditis	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Thyroiditis	■	■	■	■
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Uveitis	■	■	■	■
Grade 1	■	■	■	■
Iridocyclitis	■	■	■	■
Grade 1	■	■	■	■
Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term. Only the highest reported grade of a given adverse event is counted for the individual participant. Grades are based on NCI CTCAE version 4.03. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 Database Cutoff Date: 25JUL2024.				

A26. In Section 2, “*summary of key clinical effectiveness information*”, the overall survival hazard ratio is stated to equal 0.72, with a nominal p-value equal to 0.00666. It was stated that “*per prespecified multiplicity strategy*”, overall survival was not formally tested in the CPS $\geq$ 1 population. Can the company confirm that this is due to the inability to reject H7 (overall survival [OS] within the CPS $\geq$ 10 population) as per Figure 26 and Section M.6.1.3 in the Appendices?

MSD response:

Yes, we confirm that is correct.

Section B: Clarification on cost-effectiveness data

Model structure

B1. CS, Page 121 states, “*The utility value for the IRP state from KEYNOTE-689 may therefore be used as an approximation of utility in the pre-progression IRP sub-state only.*” Please clarify how the pre-progression and post-progression Incurable Recurrence/Progression (IRP) sub-states are defined. Please clearly describe the data that are used to determine the transition from pre- to post-progression in the IRP state, and transitions to death from both IRP sub-states.

The two substates within the IRP health state are not modelled as separate health states, rather they are intended only to allow the costs and HRQoL implications of the IRP state to be more accurately captured. Consequently, transitions to and from the pre- to post-progression IRP substates are not explicitly modelled; the model only considers transitions to and from the IRP state as a whole (in the base case, transitions from IRP to death are estimated based on exponential models fitted to patient-level data from KEYNOTE-689, as described in CS section 3.3.4).

Once in the IRP state, in each model arm weekly utility and disease management costs for the IRP state are calculated as a weighted average of the weekly utility and costs for the pre- and post-progression substates, based on the ratio of time spent pre- vs post-progression (Table 18, and ‘Effectiveness’ sheet in model). This is estimated based on the ratio of mean PFS to OS in each arm, determined by the efficacy and mix of first-line treatments applied in the IRP state (as per CS Table 52). Details on the data and assumptions used to calculate the efficacy (i.e. mean PFS and OS) of first-line treatments are provided in CS Appendix J2 (note that the appendix also discusses estimation of the hazard rate for the transition from IRP to

death based on the OS efficacy of first-line treatments, as this method is explored in a scenario analysis as an alternative approach to estimating transitions from the IRP state; however, only the PFS:OS ratio is relevant for the purposes of calculating utilities and disease management costs in the base case analysis).

Table 18. Ratio of PFS to OS based on expected survival in IRP state

Model arm	Eligibility for IOs in the metastatic setting [†]	Mean survival in IRP state (weeks): Weighted average based on first-line IRP treatment market shares [‡]		
		OS	PFS	Ratio of PFS to OS
Perioperative pembrolizumab + SOC	IO-eligible	■	■	■
	IO-ineligible	■	■	■
SOC [§]	IO-eligible	■	■	■

Abbreviations: IO, immunotherapy; IRP, incurable recurrence/progression; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

[†] IO eligibility in the pembrolizumab arm is determined based on time of recurrence – recurrences occurring in the first 18 months after initiation of neoadjuvant pembrolizumab (i.e. model start) are assumed to be IO-ineligible; [‡] Mean survival for each first line IRP treatment is estimated using exponential models fitted to OS and PFS data; [§] Longer OS in the IRP state for SOC likely reflects higher use of immunotherapy in the SOC arm

Survival curves

B2. PRIORITY: When modelling the transitions from the event free (EF) state, in Approach 1, only the standard parametric model fits are implemented. However, for the transition from the EF state to the IRP state in the SoC arm, the visual comparison to the cumulative incidence curves suggests poor fitting of these models (Appendix J1.2, Figure 8). Please therefore explore the use of more flexible models (spline odds model, spline normal model, spline hazard model) with one, two and three knots within the curve selection process for the EF state.

MSD Response

The parametric multistate modelling approach used in this submission represents a different type of flexible parametric model, described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21 as a “poly-hazard model” (3). In a poly-hazard model, the overall hazard function (in this case, the overall hazard of EFS failure) is modelled as the sum of different cause-specific hazards (in this case, the cause-specific hazards of EF → L/SR, EF → IRP, and EF → death), each of which can be modelled using different distributions. The resulting overall hazard function is far more flexible than if standard parametric distributions were fitted to the overall hazard (see Section 3.2.5 of NICE DSU TSD 21). The existing set of candidate distributions resulted in 397 different combinations of

parametric distributions for transitions from the EF state, each resulting in unique extrapolation of EFS and of the EF → L/SR, EF → IRP, and EF → death cumulative incidence curves. Nesting additional flexible parametric distributions such as spline models within this flexible parametric modelling approach would have further complicated the base-case curve selection process and potentially led to overfitting.

As shown in CS Figure 19 (Section 3.3.2), the base-case combination of parametric distributions resulted in close alignment between each predicted versus observed cumulative incidence curve throughout the large majority of the modelled timeframe, including at the tail. In the case of EF → IRP in the SOC arm, there was a slight deviation between the predicted vs. observed cumulative incidence curve during the first ~32 weeks due to a sharp upward bend in the observed curve around weeks 23-30. However, the deviation occurred early on and over a small proportion of the overall trial period and therefore is not expected to appreciably affect the cost-effectiveness results. Moreover, the abrupt increase in the observed hazard of EF → IRP during weeks 23-30 (relative to weeks 0-23) is likely to have been an artifact of the first scheduled CT/MRI at 12 weeks (± 7 days) after the end of radiotherapy $\pm$ cisplatin treatment; in this respect, the smoothed hazard of EF → IRP implied by the predicted cumulative incidence may in fact be a more realistic representation of the underlying disease process during the first ~30 weeks after surgery.

Nevertheless, to assess the impact of this short-term deviation in the EF → IRP cumulative incidence, the model has been updated to include functionality for a scenario analysis in which the transition probabilities from the EF state are based on the **observed cumulative incidence curves during the first 32 weeks**, with base-case parametric distributions used in subsequent weeks. The observed versus predicted cumulative incidence curves from this scenario are presented in Figure 4. This approach allows the nuanced curve shape in the early stages of the model to be more accurately captured than if spline models were used, without the need for the additional complexity that inclusion of spline models would introduce.

This scenario analysis has been presented in Table 19 using the updated company economic model, demonstrating results that are comparable to base case analysis.

Table 19. Scenario analysis: Transition probabilities from EF state based on based on observed cumulative incidence in the first 32 weeks of the model

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	■	■	■	■	■	1.33	■

SOC				-	-	-	-

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

Figure 4. Observed versus predicted cumulative incidence of transitions from the EF state using observed cumulative incidence during the first 32 weeks

Abbreviations: EF, event-free; IRP, incurable recurrence/progression; L/SR, local /salvageable recurrence; SOC, standard of care.

B3. In Appendix J1.3, Figure 13, the Schoenfeld residual plots are presented to support the assumption of proportional hazards. Please can the company provide further comment on why the proportional hazards (PH) assumption is assumed to hold for the EF→IRP transition, where there appears to be a peak in the residuals. In addition, please report the p-values for all three transitions included in Figure 13. Please also provide the assessment of the PH assumption by assessing the clog-log plots. If indeed the PH assumption is not appropriate for two out of three types of transition, please can the company provide further explanation on why this approach was explored.

MSD Response

To clarify, the model does not rely on the proportional hazards assumption as it uses parametric distributions independently fitted to treatment-specific patient level data. The appropriateness of the proportional hazards assumption was assessed as part of the process of determining the most appropriate approach to model survival in each arm, from the three approaches defined *a priori* (i.e., Approach #1, independently fitted models; Approach #2, jointly fitted proportional hazards models ; Approach #3, time-varying proportional hazards models), as outlined in NICE DSU TSD 14 (4).

Jointly fitted parametric proportional hazards models with a time-constant treatment effect (i.e., Approach #2) were among the list of candidate distributions that were considered for each transition from the EF state. The combinations of distributions under Approach #2 represented 27 of the 397 candidate combinations of distributions that were considered overall. While the combinations of distributions under Approach #2 were included as candidates *a priori*, they were excluded from base-case consideration due to rejection of the PH assumption for at least one of the three transitions (EF→L/SR), based on formal statistical testing. The p-values for each transition are presented in Table 20, in addition to the Schoenfeld residual plots presented in CS Appendix J1.3, as further support for the exclusion of the candidate distributions under Approach #2. Log cumulative hazard plots for each cause-specific transition are presented in Figure 5. P-values are considered a more objective assessment than Schoenfeld residual plots or log hazard plots, and therefore these figures should not be assessed in isolation but rather as additional evidence.

As discussed in CS Section 3.3.2, the PH assumption for the transition EF→L/SR was rejected based on formal statistical testing (p-value of 0.0351, see Table 20). For the remaining two

transitions, EF→IRP and EF→death, the CS did not conclude that the PH assumption holds, but rather that it could not be formally rejected based on statistical testing (p-value of 0.4414 and 0.0558, respectively). Given that the PH assumption was concluded to **not** hold for at least one of the three transitions from the EF state, combinations of distributions under Approach #2 were excluded from consideration for the base case analysis. Scenario analyses using Approach #2 and Approach #3 were retained in the scenario analysis to demonstrate that these were all explored in the curve selection process, despite not being retained, to show the full range of impact on the cost-effectiveness results. As presented in the CS, after undergoing the full curve selection process, all parametric functions for the 10 finalist combinations used Approach #1 (parametric models fitted individually to each treatment arm, not reliant on the PH assumption) with Gompertz/Gompertz/Generalized gamma selected as the base case.

Table 20. P-values for PH testing of transitions from EF health state

Transition	P-value from PH testing
EF→L/SR	0.0351
EF→IRP	0.4414
EF→death	0.0558

Abbreviations: EF, event-free; IRP, incurable recurrence/progression; L/SR, local/salvageable recurrence; PH, proportional hazards.

Figure 5. Cumulative log hazard plots for cause-specific transitions from EF state (CPS≥1 population)

A. EF→L/SR



B. EF→IRP



C. EF→death



Parallel log-cumulative hazard curves suggest hazards are proportional. The vertical distance between the curves across the x-axis should be constant
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B4. It appears that Approach 3, outlined in Section 3.3.2.1, introduces a time varying treatment effect (before and after 1 year) within a proportional hazards model. From the ‘Parameter Estimates’ sheet in the model this appears to be a piecewise proportional hazard model where a different hazard ratio is applied before and after one year. Please can the company confirm if this is the case, and justify this choice of time point. Can the

company also confirm why this approach was explored as opposed to alternative models which can account for more complex hazard shapes such as spline models?

MSD response:

MSD confirms that the above description of Approach #3 is accurate. The allowance of a differing treatment effect during the first year versus following years was specified *a priori* to reflect the hypothetical possibility of a change in the treatment effect at the approximate end of adjuvant pembrolizumab treatment in the perioperative pembrolizumab + SOC arm. As with Approach #2, the combinations of distributions under Approach #3 represented only 27 of the 397 total candidate combinations of distributions. The 343 combinations of distributions under Approach #1 (parametric models separately fitted to each arm) were considered to account for potentially more complex shapes of the hazard function. However, Approach #3 was considered a useful addition to explore the possibility of an abrupt change in the relative treatment effect beyond the maximum treatment duration.

As noted in response to question B2, the parametric multi-state modelling approach in and of itself represents a type of flexible parametric modelling (termed as a “poly-hazard model” in NICE DSU TSD 21) (3). Close alignment between predicted vs. observed EFS curves was thus expected to be achievable without nesting additional flexible distributions such as spline models within this flexible modelling approach.

B5. PRIORITY In Section 3.3.2.3 of the CS the company outlines how the base-case parametric models for transitions from the EF state are selected. It is stated that “*The distribution selection process first selected the distribution for the cause-specific hazards of EF → death, in line with the approach previously taken and accepted in NICE TA1017*”. Please can the company provide an explanation as to why this transition was initially chosen to drive the first selection of candidate models in this appraisal. In TA1017 it is stated that this choice of selecting models for EF→Death did not alter the final choice of distribution. Please can the company demonstrate this by selecting an alternative transition in the initial stage of model selection (EF→L/SR or IRP states). Please present the alternative model choices that would be selected following this strategy, along with comment on the base case and the models that would have been chosen as scenario analyses.

MSD response:

The selection process for base-case distributions started with the selection of EF → death distribution as Step 1, rather than starting with the selection of EF → L/SR or EF → IRP distributions, as the summarized MSE results in Step 1 of the distribution selection process provided a clear indication of the most appropriate EF → death distribution under each approach: In both arms, the sets of combinations using generalized gamma under Approach #1, Gompertz under Approach #2, or Gompertz under Approach #3 for EF → death ranked as #1 best-fitting (in terms of both average MSE and minimum MSE) among the various sets of combinations defined by the EF → death distribution. In contrast, EF → L/SR and EF → IRP distributions were less amenable to upfront selection based on the summarized MSE results (i.e., because the ranking of the various sets of combinations differed between the two treatment arms, or because the ranking differed when based on minimum MSE vs. average MSE). This challenge is illustrated in Step 1 of the alternative distribution selection process described below, in which the EF → L/SR distribution is selected first. See response to B8 for further details.

Regardless, the full curve selection process starting with EF → L/SR is carried out to demonstrate that, as was the case for TA1017, the same base case combination would still be concluded if the process started with the transition that was informed by the fewest number of events.

Alternative distribution selection process (starting with the distribution selection for EF → L/SR rather than EF → death)

Step 1: Initial assessment of statistical fit based on MSE to select the EF→L/SR cause-specific hazards distribution

Table 21, below, presents a summary of fit statistics for different sets of combinations defined by approach and EF → L/SR distribution. As shown, under Approach #1, in the perioperative pembrolizumab + SOC arm the average and minimum of MSEs were lowest for combinations using generalized gamma for EF → L/SR; for the SoC arm, MSEs were lowest for combinations using log-normal for EF → L/SR. Combinations using Gompertz for EF → L/SR under Approach #1 ranked second-best fitting in both arms.

Thus, unlike with EF → death, the most suitable distribution for EF → L/SR under Approach #1 is less straightforward to select upfront in Step 1. Overall, combinations using Gompertz for EF → L/SR under Approach #1 provide the best balance between statistical fit in the two arms, and we therefore proceed to Step 2 focusing on 67 combinations of distributions using Gompertz under Approach #1, 2, or 3 for EF → L/SR. As seen in the remaining steps below, this upfront selection

ultimately leads to the same base-case combination of distributions as our original selection process; however, due to the upfront exclusion of combinations using generalized gamma or log-normal under Approach #1 for EF → L/SR, this alternative process excludes several combinations that were considered finalists, and presented in scenario analyses, in the original CS selection process.

Step 2: Visual assessment of fit

As illustrated in Figure 6 and Figure 7 below, visual assessment most strongly favoured combinations of distributions using generalized gamma for EF → death and Gompertz for EF → IRP. Combinations using Gompertz for EF → death and/or generalized gamma for EF → IRP also warranted further consideration. Step 3 below therefore focused on the 6 combinations of distributions that used generalized gamma or Gompertz for EF → death and generalized gamma or Gompertz for EF → IRP (including 4 combinations under Approach #1, 1 combination under Approach #2, and 1 combination under Approach #3).

Step 3: Further assessment of statistical fit based on MSE vs. observed EFS

As in the original selection process, combinations of distributions under Approach #2 were excluded due to evidence against the proportional hazards assumption. Therefore, 1 of the 6 remaining combinations after Step 2 was excluded. In both arms, the remaining 5 finalist combinations of distributions (shaded green in Table 22 and Table 23) had excellent MSE ranking among the 67 combinations that remained after Step 2. Because visual assessment most strongly supported combinations of distributions using generalized gamma for EF → death and Gompertz for EF → IRP, the selected base-case combination was Gompertz for EF → LR, Gompertz for EF → IRP, generalized gamma for EF → death under Approach #1, consistent with the original base case.

Among the other 4 finalist combinations, 1 was also a finalist under the original selection process; the remaining 3 finalist combinations were newly selected under the alternative selection process. The two new finalist combinations that use Approach #1 are presented as a scenario analysis in Table 24, demonstrating cost-effectiveness within the range of the original finalists. The remaining new finalist combination, Approach #3 using Gompertz / Gompertz / Gompertz, was already presented as a scenario in the CS and is included in Appendix B.

Table 21. Step 1: Summary of statistical fit under different distributions of the EF → L/SR cause-specific hazards (CPS ≥1 population)

Distribution for EF → L/SR	Unique combinations of distributions for EF → death and EF → IRP with this EF → L/SR distribution	Average of MSEs vs. observed EFS across combinations with this EF → L/SR distribution		Minimum of MSEs vs. observed EFS across combinations with this EF → L/SR distribution		Rank based on average of MSEs (among all EF → L/SR distributions under each approach)		Rank based on minimum of MSEs (among all EF → L/SR distributions under each approach)	
		Perioperative pembrolizumab +SOC	SOC	Perioperative pembrolizumab +SOC	SOC	N Perioperative pembrolizumab +SOC	SOC	Perioperative pembrolizumab +SOC	SOC
Under approach #1 (separately fitted)									
Exponential	49 (=7×7)	0.0011628	0.0022843	0.0004453	0.0006469	7	7	7	7
Weibull	49 (=7×7)	0.0005504	0.0020291	0.0001402	0.0006227	5	5	5	5
Gompertz	49 (=7×7)	0.0003435	0.0019763	0.0001195	0.0006020	2	2	2	2
Log-normal	49 (=7×7)	0.0004842	0.0018070	0.0001264	0.0005357	3	1	3	1
Log-logistic	49 (=7×7)	0.0005335	0.0019974	0.0001372	0.0006099	4	4	4	4
Generalized gamma	49 (=7×7)	0.0003324	0.0019858	0.0001127	0.0006049	1	3	1	3
Gamma	49 (=7×7)	0.0005665	0.0020415	0.0001433	0.0006277	6	6	6	6
Under approach #2 (jointly fitted, time-constant HR)									
Exponential	9 (=3×3)	0.0011424	0.0030503	0.0002733	0.0010762	3	3	3	3
Weibull	9 (=3×3)	0.0006993	0.0024062	0.0001435	0.0008649	2	2	2	2
Gompertz	9 (=3×3)	0.0005866	0.0021887	0.0001386	0.0007577	1	1	1	1
Under approach #3 (jointly fitted, time-varying HR)									
Exponential	9 (=3×3)	0.0000969	0.0031960	0.0000715	0.0010420	2	3	1	3
Weibull	9 (=3×3)	0.0001126	0.0027067	0.0000818	0.0008830	3	2	3	2
Gompertz	9 (=3×3)	0.0000949	0.0025875	0.0000736	0.0008214	1	1	2	1

Abbreviations: CPS, combined positive score; EF, event-free; EFS, event-free survival; HR, hazard ratio; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; MSE, mean squared error; PD-L1, programmed death-ligand 1; SOC, standard of care.

Green highlighting indicates best balance of ranking by MSE between the two arms. Yellow highlighting indicates distribution with best ranking in one arm but not the other.

Figure 6. Step 2: Predicted vs. observed cumulative incidence of EF → Death

Abbreviations: EF, event-free; IRP, incurable recurrence/progression; SOC, standard of care

Figure 7. Step 2: Predicted vs. observed cumulative incidence of EF → IRP

Abbreviations: EF, event-free; IRP, incurable recurrence/progression; SOC, standard of care

Table 22. Step 3: Mean squared error of different parametric functions used to model EFS in the perioperative pembrolizumab + SOC arm (PD-L1 CPS ≥ 1 population)

Rank by MSE (out of all 67 combinations under approaches 1-3)	Parametric functions			MSE vs. observed EFS
	EF → Death	EF → IRP	EF → L/SR	
Approach #1: Parametric models separately fitted to each treatment arm				
10*	Generalized gamma	Generalized gamma	Gompertz	0.0001195
11	Gompertz	Generalized gamma	Gompertz	0.0001308
12	Gompertz	Gompertz	Gompertz	0.0001330
13*	Generalized gamma	Gompertz	Gompertz	0.0001344
15	Log-normal	Generalized gamma	Gompertz	0.0001454
16	Log-normal	Gompertz	Gompertz	0.0001478
17	Generalized gamma	Log-normal	Gompertz	0.0001494
18	Generalized gamma	Log-logistic	Gompertz	0.0001605
19	Generalized gamma	Weibull	Gompertz	0.0001626
20	Generalized gamma	Gamma	Gompertz	0.0001689
22	Log-logistic	Gompertz	Gompertz	0.0001755
23	Log-logistic	Generalized gamma	Gompertz	0.0001826
24	Weibull	Gompertz	Gompertz	0.0001934
25	Gompertz	Log-normal	Gompertz	0.0002022
26	Weibull	Generalized gamma	Gompertz	0.0002087
27	Gamma	Gompertz	Gompertz	0.0002113
28	Gamma	Generalized gamma	Gompertz	0.0002286
29	Log-normal	Log-normal	Gompertz	0.0002320
30	Gompertz	Log-logistic	Gompertz	0.0002339
31	Gompertz	Weibull	Gompertz	0.0002444
32	Gompertz	Gamma	Gompertz	0.0002561
33	Log-normal	Log-logistic	Gompertz	0.0002624
34	Exponential	Gompertz	Gompertz	0.0002654
35	Log-normal	Weibull	Gompertz	0.0002713
36	Log-normal	Gamma	Gompertz	0.0002838
37	Exponential	Generalized gamma	Gompertz	0.0002861
39	Log-logistic	Log-normal	Gompertz	0.0002985
40	Weibull	Log-normal	Gompertz	0.0003395
41	Log-logistic	Log-logistic	Gompertz	0.0003423
42	Log-logistic	Weibull	Gompertz	0.0003567
43	Gamma	Log-normal	Gompertz	0.0003693
44	Log-logistic	Gamma	Gompertz	0.0003728
45	Weibull	Log-logistic	Gompertz	0.0003915
47	Generalized gamma	Exponential	Gompertz	0.0004041
48	Weibull	Weibull	Gompertz	0.0004111

49	Gamma	Log-logistic	Gompertz	0.0004241
50	Weibull	Gamma	Gompertz	0.0004302
51	Gamma	Weibull	Gompertz	0.0004448
52	Exponential	Log-normal	Gompertz	0.0004518
53	Gamma	Gamma	Gompertz	0.0004651
55	Exponential	Log-logistic	Gompertz	0.0005125
56	Gompertz	Exponential	Gompertz	0.0005324
57	Exponential	Weibull	Gompertz	0.0005353
59	Exponential	Gamma	Gompertz	0.0005583
60	Log-normal	Exponential	Gompertz	0.0006061
61	Log-logistic	Exponential	Gompertz	0.0007295
62	Weibull	Exponential	Gompertz	0.0008061
64	Gamma	Exponential	Gompertz	0.0008596
66	Exponential	Exponential	Gompertz	0.0010016
Approach #2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect				
14	Gompertz	Gompertz	Gompertz	0.0001386
21	Weibull	Gompertz	Gompertz	0.0001734
38	Gompertz	Weibull	Gompertz	0.0002893
46	Exponential	Gompertz	Gompertz	0.0003999
54	Weibull	Weibull	Gompertz	0.0004854
58	Gompertz	Exponential	Gompertz	0.0005541
63	Weibull	Exponential	Gompertz	0.0008390
65	Exponential	Weibull	Gompertz	0.0009372
67	Exponential	Exponential	Gompertz	0.0014623
Approach #3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect				
1	Exponential	Gompertz	Gompertz	0.0000736
2	Gompertz	Exponential	Gompertz	0.0000743
3	Gompertz	Weibull	Gompertz	0.0000853
4	Weibull	Gompertz	Gompertz	0.0000914
5	Weibull	Exponential	Gompertz	0.0000974
6	Exponential	Exponential	Gompertz	0.0001018
7	Exponential	Weibull	Gompertz	0.0001026
8	Weibull	Weibull	Gompertz	0.0001111
9	Gompertz	Gompertz	Gompertz	0.0001161

Abbreviations: CPS, combined positive score; EF, event-free; IRP, incurable recurrence/progression; L/SR, local/salvageable recurrence; MSE, mean-squared error; PD-L1, programmed death-ligand 1; SOC, standard of care.

Green highlighting indicates combination is in remaining top 5 finalist combinations.

*Combinations that were also identified in the top 10 finalist distribution when starting selection with the EF→death transition

Table 23. Step 3: Mean squared error of different parametric functions used to model EFS in the SOC arm (PD-L1 CPS ≥1 population)

Rank by MSE (out of all 67 combinations under approaches 1-3)	Parametric functions			MSE vs. observed EFS
	EF → Death	EF → IRP	EF → L/SR	
Approach #1: Parametric models separately fitted to each treatment arm				

1*	Generalized gamma	Generalized gamma	Gompertz	0.0006020
2*	Generalized gamma	Gompertz	Gompertz	0.0006207
3	Gompertz	Gompertz	Gompertz	0.0007087
5	Log-normal	Gompertz	Gompertz	0.0007780
7	Gompertz	Generalized gamma	Gompertz	0.0008477
8	Log-logistic	Gompertz	Gompertz	0.0009039
10	Log-normal	Generalized gamma	Gompertz	0.0009631
11	Weibull	Gompertz	Gompertz	0.0009844
12	Gamma	Gompertz	Gompertz	0.0010305
14	Generalized gamma	Log-normal	Gompertz	0.0011013
15	Log-logistic	Generalized gamma	Gompertz	0.0011145
16	Generalized gamma	Log-logistic	Gompertz	0.0011890
17	Weibull	Generalized gamma	Gompertz	0.0012214
18	Generalized gamma	Weibull	Gompertz	0.0012857
20	Gamma	Generalized gamma	Gompertz	0.0013012
21	Generalized gamma	Gamma	Gompertz	0.0014024
23	Gompertz	Log-normal	Gompertz	0.0014843
24	Exponential	Gompertz	Gompertz	0.0015107
25	Gompertz	Log-logistic	Gompertz	0.0015649
27	Log-normal	Log-normal	Gompertz	0.0016599
28	Gompertz	Weibull	Gompertz	0.0016643
29	Log-normal	Log-logistic	Gompertz	0.0017507
30	Gompertz	Gamma	Gompertz	0.0018102
31	Log-normal	Weibull	Gompertz	0.0018710
32	Log-logistic	Log-normal	Gompertz	0.0018743
33	Log-logistic	Log-logistic	Gompertz	0.0019767
34	Weibull	Log-normal	Gompertz	0.0020213
35	Log-normal	Gamma	Gompertz	0.0020296
36	Generalized gamma	Exponential	Gompertz	0.0020496
39	Log-logistic	Weibull	Gompertz	0.0021162
40	Weibull	Log-logistic	Gompertz	0.0021274
41	Gamma	Log-normal	Gompertz	0.0021290
42	Exponential	Generalized gamma	Gompertz	0.0022001
43	Gamma	Log-logistic	Gompertz	0.0022337
44	Log-logistic	Gamma	Gompertz	0.0022863
45	Weibull	Weibull	Gompertz	0.0022974

46	Gamma	Weibull	Gompertz	0.0024162
47	Weibull	Gamma	Gompertz	0.0024807
48	Gamma	Gamma	Gompertz	0.0026085
49	Gompertz	Exponential	Gompertz	0.0026153
53	Log-normal	Exponential	Gompertz	0.0028754
55	Log-logistic	Exponential	Gompertz	0.0031702
57	Exponential	Log-normal	Gompertz	0.0032633
58	Exponential	Log-logistic	Gompertz	0.0033229
59	Weibull	Exponential	Gompertz	0.0033979
61	Exponential	Weibull	Gompertz	0.0035304
62	Gamma	Exponential	Gompertz	0.0035581
63	Exponential	Gamma	Gompertz	0.0037932
67	Exponential	Exponential	Gompertz	0.0050964
Approach #2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect				
4	Gompertz	Gompertz	Gompertz	0.0007577
9	Weibull	Gompertz	Gompertz	0.0009518
19	Exponential	Gompertz	Gompertz	0.0012935
26	Gompertz	Weibull	Gompertz	0.0016287
37	Weibull	Weibull	Gompertz	0.0020640
50	Gompertz	Exponential	Gompertz	0.0026791
52	Exponential	Weibull	Gompertz	0.0027830
56	Weibull	Exponential	Gompertz	0.0032440
65	Exponential	Exponential	Gompertz	0.0042971
Approach #3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect				
6	Gompertz	Gompertz	Gompertz	0.0008214
13	Weibull	Gompertz	Gompertz	0.0010917
22	Exponential	Gompertz	Gompertz	0.0014061
38	Gompertz	Weibull	Gompertz	0.0021001
51	Weibull	Weibull	Gompertz	0.0027246
54	Gompertz	Exponential	Gompertz	0.0031008
60	Exponential	Weibull	Gompertz	0.0034055
64	Weibull	Exponential	Gompertz	0.0038769
66	Exponential	Exponential	Gompertz	0.0047601

Abbreviations: CPS, combined positive score; EF, event-free; IRP, incurable recurrence/progression; L/SR, local/salvageable recurrence; MSE, mean-squared error; PD-L1, programmed death-ligand 1; SOC, standard of care.

Green highlighting indicates combination is in remaining top 5 finalist combinations.

*Combinations that were also identified in the top 10 finalist distribution when starting selection with the EF→death transition

Table 24. Scenario analysis: top two new curve combinations for transitions from EF state starting selection with EF→L/SR

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Approach #1: Gompertz / Gompertz / Gompertz							
Perioperative pembrolizumab + SOC	■	■	■	■	■	1.13	■
SOC	■	■	■	-	-	-	-
Approach #1: Gompertz / Generalized gamma / Gompertz							
Perioperative pembrolizumab + SOC	■	■	■	■	■	1.42	■
SOC	■	■	■	-	-	-	-

Abbreviations: EF, event-free; ICER, incremental cost-effectiveness ratio; IRP, incurable recurrence/progression; L/SR, local/salvageable recurrence; LYG, life-years gained; QALY, quality-adjusted life-year; SOC, standard of care.

Combinations presented in format EF→L/SR / EF→ IRP / EF→ death.

Note: All other finalist combinations identified via this alternative selection process (starting with selection of EF→L/SR transition) have previously been identified and presented as scenarios in the CS. The same base case combination (Approach #1: Gompertz / Gompertz / Generalised gamma) resulted from both selection processes.

B6. Please provide the smoothed hazard plots for event free survival (EFS) and overall survival (OS) for the pembrolizumab and SoC arms (CPS ≥ 1 population). Please also provide the predicted hazard plots for EFS and OS for the base case (as in Figure 23), and the 10 best-fitting combinations of models (for both arms). Please also provide the predicted hazards for any additional models identified in the response to question B5.

The smoothed hazard plots, based on kernel density estimation, for EFS and OS are presented in Figure 8 and Figure 9, respectively.

The predicted hazard plots for EFS for the 10 best-fitting combinations are shown in Figure 10 with the equivalent plots for OS presented in Figure 11. In addition, implied hazard plots for EFS and OS based on the additional curve distribution combinations identified in response to question B5 are presented in Figure 12 and Figure 13, respectively.

Figure 8. Smoothed hazard plots for EFS (CPS ≥ 1)



Abbreviations: EFS, event-free survival; SOC, standard of care.

Figure 9. Smoothed hazard plots for OS (CPS ≥ 1)



Abbreviations: OS, overall survival; SOC, standard of care.

Figure 10. Implied hazard rate of EFS failure for 10 best-fitting combinations

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Figure 11. Implied hazard rate of OS failure for 10 best-fitting combinations

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Figure 12. Implied hazard rate of EFS failure for 3 additional combinations identified in B5

Note: The kink in the hazards for the combination using Approach #3 is due to the use of time-varying hazards before and after 1 year.

Figure 13. Implied hazard rate of OS failure for 3 additional combinations identified in B5

Note: The kink in the hazards for the combination using Approach #3 is due to the use of time-varying hazards before and after 1 year.

B7. In Section 3.3.2.3, page 107, it is stated that “*Of the 9 remaining combinations, the two resulting in the most and least incremental EFS and OS benefit are presented as scenario analyses to demonstrate the range of plausible cost-effectiveness.*” Please can the company clarify how the “most” and “least” incremental EFS was assessed. For instance the Generalized gamma / generalized gamma / generalized gamma has the lowest incremental difference in EFS/OS at year 1, and then the maximum at year 10. Similarly the log-normal / Gompertz / generalized gamma model has the largest incremental difference at year 1 and then the smallest at 10 years (for EFS and OS).

MSD response:

The assessment of incremental EFS benefit is based on the timepoint at 10 years. As discussed in the CS Section 3.3.2 curve selection process (page 105), all of the 10 finalist combinations resulted in similar predictions of incremental EFS and OS benefit during the trial period which were also reasonably in line with observed incremental EFS and OS benefit from the KEYNOTE-689 trial (see Table 65 in Appendix J1.5). Therefore, the timepoint at year 10 was used to distinguish long-term incremental EFS benefit between the remaining combinations of distributions.

B8. CS, p102 states, “*The distribution selection process first selected the distribution for the cause-specific hazards of EF → death, in line with the approach previously taken and accepted in NICE TA1017*”. However, in TA1017 this was because this transition had the fewest number of events in the KEYNOTE-671 trial, which is not the case in KEYNOTE-689. Please clarify further why selection the process adopted in TA1017 was considered the best approach in this submission.

MSD response:

In TA1017, the selection of distributions from the EF state started with selecting the EF→death distribution first as it had the fewest events and was therefore associated with the greatest uncertainty. In the KEYNOTE-689 trial, in contrast to the KEYNOTE-671 trial underpinning TA1017, all three transitions from the EF health state (EF→L/SR, EF→IRP and EF→death) demonstrated a reasonable number of events (see Table 28 provided in response to B10) to inform these transitions and therefore the decision on which distribution to select first is less clear.

The first step in the selection process, statistical fit based on MSE, was explored for each of the three transitions. For both EF→L/SR and EF→IRP there is not a distribution under each approach that clearly provides the best-fit based on average and minimum MSE in both arms (see Table 21 [in response to B5] and Table 25, respectively). In contrast, for EF→death the generalized gamma distribution unambiguously demonstrates the best statistical fit in both the perioperative pembrolizumab + SOC and SOC arms (Table 56 in Appendix J1.1). Therefore, by starting with first selecting the distribution of EF→death, it allowed for alternative combinations of EF→L/SR and EF→IRP (where the choice was less clear) to be further explored with regards to visual fit, statistical fit, and clinical plausibility.

For completeness, the distribution selection process has been replicated in response to question B5 to demonstrate that if the selection process began with the distribution for cause-specific hazards for a different transition (specifically, EF→L/SR) as the first-step, despite the challenges with a selecting a suitable distribution at the first step under Approach #1, the same base case, and a similar set of finalist combinations, is reached.

Table 25. Summary of statistical fit under different distributions of the EF → IRP cause-specific hazards (CPS≥1 population)

Distribution for EF → IRP	Unique combinations of distributions for EF → L/SR and EF → death with this EF → IRP distribution	Average of MSEs vs. observed EFS across combinations with this EF → IRP distribution		Minimum of MSEs vs. observed EFS across combinations with this EF → IRP distribution		Rank based on average of MSEs (among all EF → IRP distributions under each approach)		Rank based on minimum of MSEs (among all EF → IRP distributions under each approach)	
		Perioperative pembrolizumab +SOC	SOC	Perioperative pembrolizumab +SOC	SOC	Perioperative pembrolizumab +SOC	SOC	Perioperative pembrolizumab +SOC	SOC
Under approach #1 (separately fitted)									
Exponential	49 (=7×7)	0.0010368	0.0033042	0.0003281	0.0018548	7	7	7	7
Weibull	49 (=7×7)	0.0005884	0.0022189	0.0001448	0.0011695	5	5	5	5
Gompertz	49 (=7×7)	0.0003237	0.0009635	0.0001183	0.0006207	1	1	2	2
Log-normal	49 (=7×7)	0.0005045	0.0019692	0.0001248	0.0009810	3	3	3	3
Log-logistic	49 (=7×7)	0.0005657	0.0020637	0.0001398	0.0010727	4	4	4	4
Generalized gamma	49 (=7×7)	0.0003435	0.0012050	0.0001127	0.0005357	2	2	1	1
Gamma	49 (=7×7)	0.0006107	0.0023969	0.0001505	0.0012740	6	6	6	6
Under approach #2 (jointly fitted, time-constant HR)									
Exponential	9 (=3×3)	0.0012606	0.0039013	0.0005541	0.0026791	3	3	3	3
Weibull	9 (=3×3)	0.0008077	0.0025369	0.0002893	0.0016287	2	2	2	2
Gompertz	9 (=3×3)	0.0003600	0.0012071	0.0001386	0.0007577	1	1	1	1
Under approach #3 (jointly fitted, time-varying HR)									
Exponential	9 (=3×3)	0.0001007	0.0042370	0.0000743	0.0031008	2	3	2	3
Weibull	9 (=3×3)	0.0001100	0.0030101	0.0000803	0.0021001	3	2	3	2
Gompertz	9 (=3×3)	0.0000935	0.0012431	0.0000715	0.0008214	1	1	1	1

Abbreviations: CPS, combined positive score; EF, event-free; EFS, event-free survival; HR, hazard ratio; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; MSE, mean squared error; PD-L1, programmed death-ligand 1; SOC, standard of care.

B9. The EAG's clinical experts generally agree with the assumption that at 5 years, the EFS hazard is considerably reduced, reflecting a potential functional cure around 5 years. The company state that in the base case the models for the transitions from the EF state replicate this behaviour in the hazard trend (shown in Figure 23), but that, *"This same profile is not seen across all the finalist combinations, such as those included in the scenario analysis"* and thus the application of the cure point is appropriate in these scenarios. Please can the company comment on the modelled hazards used within the scenario analyses and whether these models are expected to require the implementation of the cure point (see question B7)

MSD response:

To clarify, the CS states that, as the hazard profile differs across the finalist combinations (including those in the scenario analyses), under different distributions it may be appropriate to apply a cure assumption in order to capture the plateau in EFS and very low risk of recurrence after 5 years predicted by the clinical experts. The statement was intended to highlight that the hazards and predicted EFS, and therefore the need to apply a cure point, should be assessed for each combination individually – not that a cure should necessarily be applied within these specific scenarios.

The implied hazard rates of EFS failure for the two scenarios presented in the CS using Approach #1, Generalized gamma/Generalized gamma/Generalized gamma and Log-normal/Gompertz/Generalized gamma, are presented in Figure 14. Both scenarios demonstrate a hazard rate of EFS failure that steeply reduces in the first two to three years since the start of treatment. However, in scenario 1 (Approach #1: Generalized gamma/Generalized gamma/Generalized gamma), the implied hazard rate in the SOC arm remains almost twice as high as is seen in the base case or scenario 2, and therefore it may not reflect the 'very low' risk expected by clinical experts. Clinical expert opinion to the company and the EAG supports a very low EFS hazard at 5 years, which would be expected to apply to both arms. In addition, the modelled EFS curve for scenario 1 does not present the expected plateau in EFS for the SOC arm that would be expected if a cure point was captured. As such, it may be appropriate to apply a cure point in this scenario (Figure 15).

In contrast, in scenario 2 (Approach #1: Log-normal/Gompertz/Generalized gamma) the hazard rate of EFS failure demonstrates the expected decline in rate over the first couple of years but then more or less equalises between the perioperative pembrolizumab + SOC and SOC arms at ~3 years. In this case, there is little differential in hazard rate between the arms and therefore the application of a cure assumption may have less of an impact on model

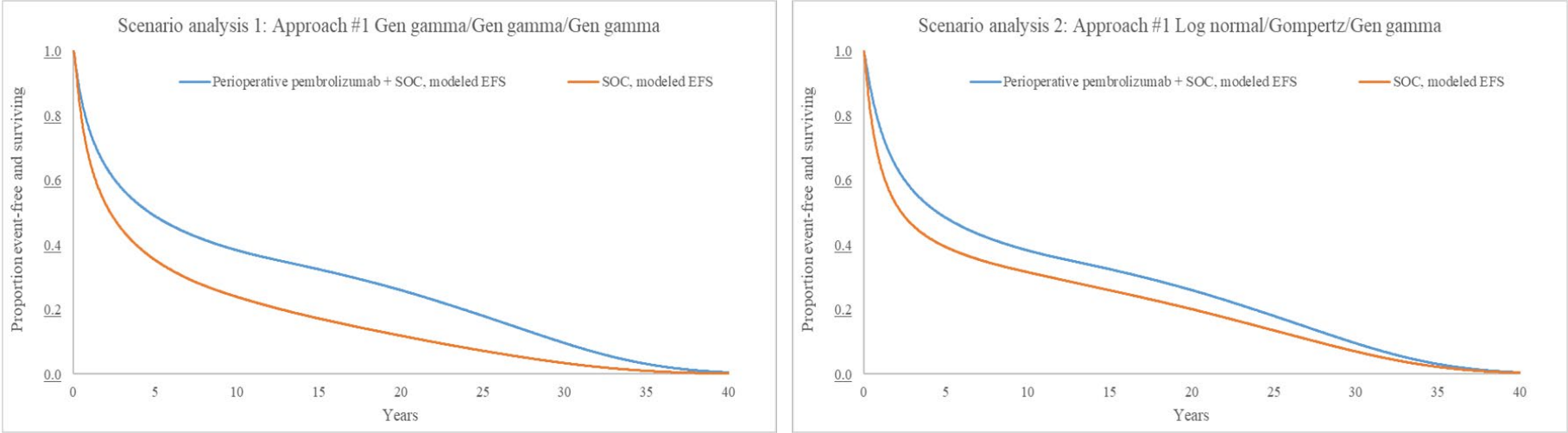
results. In addition, looking at the hazard rate of EFS failure in this scenario in more detail shows that the hazard rate in the perioperative pembrolizumab + SOC arm marginally exceeds the hazard rate in the SOC arm which lacks face validity (Figure 14). The application of a cure point in this scenario effectively equalises the hazards between arms which would address the face validity issue.

As demonstrated by the two scenarios selecting different combination of distributions under Approach #1, the curve selection results in a unique pattern of EFS hazard rate dependent on the parametric models selected. Therefore, the application of cure assumption should be assessed on case-by-case basis, to ensure the resulting hazard rate of EFS failure, and long-term predicted EFS, aligns with clinical expert expectations of real-world practice. Given the subjective nature of this assessment of the hazards, across all scenarios consideration of results both with and without cure can be informative to understand the impact of different assumptions on cost-effectiveness.

Figure 14. Implied hazard rate of EFS failure in company scenario analyses of alternative distributions presented in CS

Abbreviations: EFS, event-free survival; SOC, standard of care.

Figure 15. Long-term modelled EFS in company scenario analyses of alternative distributions presented in CS



Abbreviations: EFS, event-free survival; SOC, standard of care.

B10. In section 3.3.4 it is described that only █ patients experienced local or salvageable recurrence (L/SR) and then IRP as a subsequent recurrence event, of which only █ of which were on SoC. Therefore, the L/SR→IRP transition is only informed by these few patients. Please conduct a scenario analysis where the pooled sample sizes across both treatment arms are used to calculate these transitions.

A summary of the number of events informing each health state transition is presented in Table 28. To clarify, transitions from the L/SR state are informed by all patients who enter the L/SR health state – █ in the pembrolizumab + SOC arm and █ in the SOC arm. Therefore, whilst the number of patients who transitioned from L/SR to IRP was █ for perioperative pembrolizumab + SOC and █ for the SOC arm, respectively, the transition rates are estimated considering the risk of these patients transitioning to IRP in the context of the total sample size in each arm (i.e., █ and █, respectively). It is therefore more informative to consider the total sample size underpinning the analysis than the size of the subset of patients making the transition.

In addition, the transition probabilities from L/SR to IRP were varied within their 95% CIs as part of the deterministic sensitivity analysis presented in the CS and in the updated economic model Figure 22, demonstrating that changing the transition probability input value had only a small impact on the cost-effectiveness in favour of SOC.

A scenario where the pooled sample of patients in the L/SR health state (n=59) has been used to estimate transitions from the L/SR state has also been conducted to further explore the impact of uncertainty arising from the sample size (Table 26). The results of this scenario are presented in Table 27, demonstrating a small impact on the ICER in favour of the perioperative pembrolizumab + SOC arm.

Table 26. Transition probabilities from the L/SR state, using the pooled sample (CPS≥1 population)

	Log(rate)	SE
L/SR→IRP	█	█
L/SR→death	█	█

Abbreviations: IRP, incurable recurrence or progression; L/SR, local or salvageable recurrence; SE, standard error.

Table 27. Scenario analysis: Pooled transitions from L/SR

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)

Perioperative pembrolizumab + SOC						1.23	
SOC				-	-	-	-

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

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Table 28. Summary of health state transitions by treatment arm (CPS≥1 population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347	-	335	-	682	-
Health States Transition 1						
Number of EFS events	■	■	■	■	■	■
T1: Local/Salvageable Recurrence	■	■	■	■	■	■
T1: Incurable Recurrence/Progression	■	■	■	■	■	■
T1: Death	■	■	■	■	■	■
Number of Censored	■	■	■	■	■	■
Health States Transition 2						
T1: Local/Salvageable Recurrence	■	-	■	-	■	-
T2: Incurable Recurrence/Progression	■	■	■	■	■	■
T2: Death	■	■	■	■	■	■
T2: No further information	■	■	■	■	■	■
T1: Incurable Recurrence/Progression	■	-	■	-	■	-
T2: Death	■	■	■	■	■	■
T2: No further information	■	■	■	■	■	■
Health States Transition 3[†]						
T2: Incurable Recurrence/Progression	■	-	■	-	■	-
T3: Death	■	■	■	■	■	■
T3: No further information	■	■	■	■	■	■

Percent of participants in T2 and T3 health states are calculated as a percentage of the total in T1 and T2, respectively

Database Cutoff Date: 25JUL2024.

† T3 transitions represent subsequent transitions patients who had an IRP after a L/SR (i.e. transitioned from L/SR → IRP). They are not modelled separately, but are instead combined with T2 transitions from IRP to estimate transitions from the IRP.

B11. In Section 3.3.3 of the CS it is stated that “*The exponential distribution is commonly assumed when estimating transition probabilities starting from intermediate health states in a Markov model, as the hazard rate does not depend on time since entry into the health state.*” Please provide the rationale behind this statement. Were any alternatives considered such as using tunnel states to allow for non-constant transition risks, and if so why were these discounted?

A key limitation of Markov models is that they are ‘memoryless’, meaning that they cannot track individual patients through the model or therefore establish how long individual patients have been in any given health state (with the exception of the starting health state, in this case EF). This means that, in a Markov model, it is not possible to vary the probability of moving from an intermediate (i.e. non-starting) health state based on how long a patient has been in that health state (5). The exponential distribution assumes a constant hazard that does not vary over time and is therefore often used to estimate transition probabilities from intermediate health states.

To use alternative distributions which do allow for the transition probabilities to vary over time it would be necessary to adapt the model structure to track the time that patients spend in each health state. Whilst this could technically be achieved using tunnel states, given the structure of the current model where we have two intermediate health states (L/SR and IRP) and a short weekly cycle length, this approach would require thousands of tunnel states and significantly increase the computational burden of the model. Alternatively, this could also be achieved using VBA functionality, however this approach would also increase complexity and reduce transparency compared with assuming an exponential distribution.

There are two further reasons why the exponential distribution was considered appropriate in this instance:

- The cumulative incidence of transitions from L/SR and IRP observed in KEYNOTE-689 was well represented by the exponential distribution in both treatment arms (CS Figure 24, Figure 25, Figure 26). This is particularly applicable to transitions from the IRP state (CS Figure 26), where the data are relatively mature (approximately 70% of patients entering the IRP state had died by the end of follow up). It is therefore unlikely that use of alternative distributions would substantially improve the fit to the trial data, so the additional complexity was not considered necessary.
- Transitions from the L/SR state were based on a small number of patients in KEYNOTE-689 (see Table 28), therefore assuming non-constant hazards and using a

more complex distribution would increase the uncertainty and require further assumptions regarding what the long-term hazards would be for each transition.

B12. Please comment on the face validity of life-years accrued in the IRP state compared to previous STAs. For example TA661 (pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma [HNSCC]) reports survival estimates in excess of 0.8 years on SoC compared to [REDACTED] in the current submitted base case model.

Following clarification, the EAG advised that the statement “*survival estimates in excess of 0.8 years on SoC*” was informed by examining the results presented within the committee papers for TA661. They noted that all the life years reported within the EAG scenarios in the comparator arm are above 0.9 (range 0.949 to 1.271). In the ACD committee papers, the EAG reported life-years for the comparator arm between 0.987 and 1.412, whilst the company’s ACD response reports values between 0.96 and 1.41. The EAG therefore clarified that it would perhaps have been more accurate for the current clarification question to have said ‘*survival estimates in excess of 0.90 life years on SOC*’.

The [REDACTED] life years (LYs) figure quoted above corresponds to undiscounted LYs spent in the IRP state among all patients in the SOC arm, as estimated by the submitted base-case model. This number is calculated among all patients in the SOC arm (not specifically among the subset of patients in the SOC arm who enter the IRP state). To allow for an interpretable comparison with the quoted LY estimates for the TA661 comparator arm, the [REDACTED] figure needs to be divided by [REDACTED] (the cumulative proportion of patients in the SOC arm with an EF→IRP or L/SR→IRP transition by the end of the modelled time horizon) to obtain the undiscounted LYs spent within the IRP state per patient in the SOC arm who has entered the IRP state. The resulting number ([REDACTED] undiscounted LYs, or [REDACTED] discounted LYs calculated in a similar way) is comparable to the cited estimates from TA661.

B13. In the base case analysis, the proportion of time spent in the pre- and post-progression IRP states is derived from the ratio of the weighted average of mean progression-free survival (PFS) and mean OS (weighted according to the distribution of treatment received in KN-689), Appendix J2. The mean PFS and OS were derived from the application of hazard ratios (HRs) (from the network meta-analysis [NMA],

Appendix J4), to the exponential rates of the reference treatment (cetuximab + platinum +5-FU from KEYNOTE-048).

- a) Within the NMAs of OS and PFS it is acknowledged that the proportional hazards assumption was violated for some of the studies included within the analyses. Please confirm which studies this relates to. Please also confirm how this was assessed; in J.4.2.2 it is stated that log-cumulative hazard plots were used, was the proportional hazard assumption tested statistically and were Schoenfeld residual plots generated? Please provide the supporting evidence for the assessments of the proportional hazards.
- b) Please can the company clarify whether any treatment effect modifiers were included within the NMA of OS and PFS.
- c) Two first-line (1L) treatments (gemcitabine + paclitaxel and cisplatin + pemetrexed) could not be incorporated within the NMAs of OS and PFS and thus exponential rates were derived for these interventions directly via the fitting of exponentials to OS and PFS data. Please can the company elaborate why this approach was not implemented for all other treatments.
- d) In the model sheet 'Raw- 1L efficacy' rows 17 to 34, it appears the PFS HRs for 5-FU monotherapy, methotrexate monotherapy and cisplatin + paclitaxel were unavailable and thus assumed equal to other comparators, this is not discussed in J4. Please can the company provide the rationale for these assumptions?

MSD response

Responses to each part of the question are provided below.

- a) Log-cumulative hazard plots (Figure 16 and Figure 18), Schoenfeld residual plots, and Grambsch-Therneau tests (Figure 17 and Figure 19) suggested there may have been violations of the proportional hazards assumption for the comparisons of OS and PFS for pembrolizumab monotherapy versus the control arm in the CPS ≥ 1 subgroup of KEYNOTE-048, for PFS in Burtness et al., 2005, and for OS in Friesland et al., 2018 (CETMET).

- b) PD-L1 expression level was identified as a potential treatment effect modifier for pembrolizumab treatment. As such, the NMA was run for the CPS $\geq$ 1 subgroup specifically. The “CPS $\geq$ 1 network” included all trials from the total population networks but used data from the CPS $\geq$ 1 subgroups of patients in KEYNOTE-048. No other treatment effect modifiers were included.
- c) Data from the NMA were preferred where possible as NMA is considered a more comprehensive, robust approach to derive estimates of relative treatment effect than naïve comparison of data from individual trials. Note that gemcitabine + paclitaxel and cisplatin + pemetrexed have 0% market share in the model, therefore ultimately the exponential rates for all first-line treatments are derived by applying HRs derived from the NMA to the reference treatment.
- d) The three treatments mentioned by the EAG (5-FU monotherapy, methotrexate monotherapy and cisplatin + paclitaxel) did not have trial data available for PFS and therefore could not be included in the NMA or separately modelled by fitting an exponential directly to the Kaplan-Meier data. As such, they were assumed to be equivalent to similar chemotherapy regimens.

Figure 16. Log cumulative hazard plots for PFS



Figure 17. Schoenfeld residuals plots for PFS



Figure 18. Log cumulative hazard plots for OS



Figure 19. Schoenfeld residuals plots for OS



B14. 1L subsequent immunotherapies given at the IRP state have significantly higher OS estimates (■ to ■ weeks) compared to other non-immunotherapy subsequent treatments. These are given more frequently to patients in the SoC arm (■% when summing across both pembrolizumab and nivolumab) compared to the pembrolizumab arm (■ for the IO-eligible population and 0% for IO-ineligible). In the scenario analysis using the efficacy and market shares for treatments for relapsed/metastatic disease to estimate transitions from IRP to death, the risks of death are higher for the pembrolizumab arm (Table J2, Table 68) which might be expected given the lower usage of immunotherapies in the pembrolizumab arm. However, the weekly transition probability from IRP to death is lower with pembrolizumab when using the exponential curve fitted to the events observed in the trial (■ vs ■). Please comment on this logical inconsistency and whether this suggests that the scenario analysis is not a valid approach.

MSD response

In the scenario analysis using the efficacy and market shares for treatments for relapsed/metastatic disease to estimate transitions from IRP to death, the model conservatively assumes no ongoing benefit from perioperative pembrolizumab + SOC relative to SOC in the IRP state: Under this scenario, transition probabilities from IRP to death are assumed to be entirely dependent on the market shares and efficacy of subsequent treatments in the IRP state. In contrast, the base-case transition probabilities from IRP to death are fitted to observed time-to-event data from each arm of KEYNOTE-689 and would therefore capture any ongoing advantage of perioperative pembrolizumab + SOC relative to SOC in the IRP state. (For example, if IRP events that occur in the perioperative pembrolizumab + SOC arm tend to be less severe in some respect than IRP events in the SOC arm, survival in the IRP state may be better for patients in the perioperative pembrolizumab + SOC arm than those in the SOC arm, all else equal.) Such an advantage, if present, would counteract the impact of lower immunotherapy usage in the perioperative pembrolizumab + SOC arm, potentially resulting in a slightly lower transition probability from IRP to death in this arm compared to the SOC arm. The scenario analysis is therefore a conservative approach to estimating transitions from this health state.

Regardless, MSD maintains the position that the transition probabilities from the IRP state in the base case economic model are informed by fitting exponential models to patient-level data from KEYNOTE-689 which reduces the reliance on external data.

Utilities

B15. CS, p.123: Utility data from KEYNOTE-048 are considered unsuitable for use in the progressed IRP state due to the low proportion of patients in KEYNOTE-048 having recurrent disease rather than *de novo* metastatic disease. However, data from the EXTREME trial were considered suitable, even though this is also a trial in recurrent/ metastatic disease. Please give the proportion of patients in the EXTREME trial who had recurrent disease (as opposed to metastatic disease) at baseline and comment on why this trial is a more suitable source than KEYNOTE-048. In doing so please describe differences and similarities in their inclusion/exclusion criteria.

MSD response

Data on the reported proportions of patients with recurrent disease from KEYNOTE-048 and EXTREME are summarised in Table 29. To clarify, the statement included in section 3.4.3.2 on p123 of the CS inadvertently referred to the proportion of patients with *only LR* recurrence (27–32% of patients in KEYNOTE-048), whereas an additional 40–43% of patients had metastatic recurrence – consequently, only 26–32% of the trial population had *de novo* metastatic disease (6), and therefore the remainder could be assumed to have some form of recurrent disease (either LR or metastatic). The proportion with any form of recurrent disease in the EXTREME trial cannot be determined from the published literature (7), however 53–54% had *only LR* recurrence with the remainder reported as having ‘metastatic ± LR recurrence’ – it is therefore likely that the proportion with some form of recurrent disease is comparable to KEYNOTE-048, although the ratio of LR recurrence only to metastatic recurrence is higher in EXTREME.

Eligibility criteria between the two trials were very similar (Table 29), and baseline characteristics were broadly comparable (7, 8). However, KEYNOTE-048 required that patients had ‘adequately recovered from the toxicity and/or complications’ from any major surgery, whilst EXTREME specified that any major surgery must have taken place ≥4 weeks prior to study enrolment. Whilst baseline data on this are not reported, it is therefore plausible that recurrent patients in EXTREME started treatment earlier after major surgery and therefore had more associated morbidity than their KEYNOTE-048 counterparts which may account for the lower progressed utility in EXTREME.

The rationale for using the utility value from EXTREME for the post-progression health state was driven by face validity given the insights shared by clinical experts that HRQoL would be

expected to decrease on progression (9). This trend could not be captured using the data from KEYNOTE-048, as the post-progression utility from KEYNOTE-048 was higher than the pre-progression utility from KEYNOTE-689. The rationale for this is not fully clear, however potentially this could be due to differences in timing of recurrence between the trials, i.e. KEYNOTE-689 capturing earlier recurrences where patients have higher morbidity from recent surgery/RT vs KEYNOTE-048 enrolling patients with later recurrences who had a longer interval between any prior treatment and study enrolment. If the treatment interval is smaller in EXTREME vs KEYNOTE-048, this could also somewhat explain the difference observed between these two trials, however this information is not available from both studies and therefore this hypothesis cannot be verified.

MSD have acknowledged the uncertainty introduced by using external data to inform the IRP post-progression utility and therefore provided a scenario analysis (CS Table 61) assuming the same utility, sourced from KEYNOTE-689, for pre- and post-progression IRP. The impact on the ICER was negligible.

Table 29. Characteristics of KEYNOTE-048 vs EXTREME

	KEYNOTE-048(6, 8)	EXTREME(7)
% recurrent [†]	- Only LR recurrent (without metastases): 27–32% - Metastatic and recurrent: 40–43% - Metastatic only: 26–32% - Metastatic ± LR recurrence: 67–72%	- Only LR recurrent (without metastases): 53–54% - Metastatic and recurrent: NR - Metastatic only: NR - Metastatic ± LR recurrence: 46–47%
Eligibility criteria		
Age	≥18 years	≥18 years
Diagnosis	- Recurrent or metastatic HNSCC, ineligible for local therapy ≥1 lesion measurable per RECIST v1.1	- Recurrent or metastatic HNSCC, ineligible for local therapy ≥1 lesion bi-dimensionally measurable by CT or MRI
Fitness	- ECOG performance status 0–1 - Adequate organ function	- Karnofsky performance score ≥70 - Adequate haematologic, renal and hepatic function
Pathology	Known p16 expression for oropharyngeal cancers	Tumour tissue available for evaluation of EGFR expression
Key exclusion criteria	RT within previous 2 weeks, or not fully recovered from previous surgery	- Surgery or irradiation within previous 4 weeks - Previous systemic chemotherapy unless part of

	• Previous systemic chemotherapy unless part of multimodal treatment for LA disease completed ≥ 6 months previously • Nasopharyngeal carcinoma • Symptomatic CNS metastases • History of non-infectious pneumonitis requiring glucocorticoids • Active autoimmune disease	multimodal treatment for LA disease completed ≥ 6 months previously • Nasopharyngeal carcinoma • Other concomitant anticancer therapies

Abbreviations: CNS, central nervous system; CT, computed tomography; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; LA, locally advanced; LR, locoregional; MRI, magnetic resonance imaging.

† Ranges represent distribution across study arms of each trial, therefore may not sum to 100%.

B16. PRIORITY. Please can the company provide a more detailed description of how the utility for the post-progression IRP sub-state was derived from the EXTREME trial data and any possible limitations of this choice of approach. Some details are provided in TA172, however the number of patients and number of records appear not to be reported for the post-progression state. Additionally, this utility appears to be derived for the sub-group of patients with oral cavity cancer only. Please can the company that the estimate they used is based on this subgroup and comment on the appropriateness of this utility value for the IRP post-progression state.

MSD response

The EXTREME trial was not an MSD trial and therefore we do not have any further details regarding how the utility values were derived beyond what is stated in TA172/TA473. However, Table H7 in the original manufacturer's submission for TA172 (which targeted the full HNSCC population) reports the same utility values as in Table 8 in the manufacturer's submission for TA473 (which targeted the oral cavity subgroup). In addition, Table 8 in TA473 has a footnote stating: "*The utility scores for the oral cavity subgroup were assumed to be the same as those for all RM SCCHN tumour locations*" (10). MSD's interpretation is therefore that the utilities reported in TA172 represent the full HNSCC population of the EXTREME trial, and these were subsequently assumed to be applicable to the oral cavity subgroup for the purposes of TA473.

B17. CS, Section 3.4.3. The data suitable for the locally advanced (LA) and the progressed recurrence state are discussed in sections 3.4.3.1 and 3.4.3.2. However,

the latter appears to focus only on identifying data for patients who have progressed on first line treatment for recurrent/metastatic disease to inform the progressed ILR state. Please discuss the suitability of the data sources identified in the SLR as sources for the utility of the pre-progressed ILR state. In particular, please comment on why the pre-progression utilities from EXTREME are not suitable for the pre-progression IRP state. Please also comment on why the values from KEYNOTE-689 for this state were considered preferable to any of the literature-based estimates given that the estimate from KEYNOTE-689 for pre-progressed ILR is informed by a low number of observations. (n=■ patients and n=■ records).

MSD response

MSD's understanding is that the 'ILR' state referred to by the EAG relates to the IRP state used in the model. The NICE methods guide states that the preferred approach for incorporating HRQoL into the economic model is to collect health state measurements from patients relevant to the decision problem. Given it is the trial that the decision problem is based on, patients in the KEYNOTE-689 trial very closely reflected the decision problem (i.e. patients newly diagnosed with LA HNSCC who had a subsequent IRP) and it was therefore considered the best match to the relevant population when compared with the external studies identified as reporting utilities for recurrent or metastatic HNSCC (section 3.4.3.2). Consequently, it is the most representative source of utility data to populate the model health states.

All identified external studies (CS Table 34, Appendix F2.2-2.3 and Appendix F3) had some limitations, which are discussed in sections 3.4.3.1 and 3.4.3.2 of the CS and which related to alignment with the NICE reference case, the population and/or methods of elicitation or valuation; these apply to potential use in both the pre- and post-progression IRP states. The pre-progression utilities reported from the EXTREME trial in NICE TA172/473 (mapped to EQ-5D from EORTC-QLQ-C30) were 0.69 for stable response to cetuximab and 0.65 for stable response with standard treatment, which is averaged at 0.67 overall (10). Similarly, the 'progressive stage' utility from Parthan et al, 2009, which was mapped from EORTC-QLQ-C30, was 0.67 (11). These are highly comparable to the utility value for IRP pre-progression sourced directly from KEYNOTE-689. Singh et al reported an overall recurrent/metastatic utility value of 0.57, but methodological details are sparse (12). No other studies were sufficiently aligned with the NICE reference case.

MSD therefore consider that utilities derived from KEYNOTE-689 are the most appropriate to represent the IRP pre-progression health state, despite the modest sample size. The utility

value for IRP derived from this trial is comparable to external studies (10, 11) which gives confidence in the appropriateness of this value.

B18. Please comment on whether any of the literature-based utility values identified in the SLR are preferable to the utility value for the L/SR state from KEYNOTE-689 given that this value is informed by a low number of observations (n=█ patients, and n=█ records).

MSD response

Utility values identified in the SLR are presented in Appendix F2.2-2.3 and Appendix F3, and all had limitations which related to alignment with the NICE reference case, the population and/or methods of elicitation or valuation:

- De Almeida et al, 2014 (13) was a US study that surveyed 50 healthy subjects and clinical experts, rather than patients. Utilities for local recurrences ranged from 0.82–0.94, which lack face validity given the morbidity faced by HNSCC cancer, insights shared by UK clinicians, and the event-free utilities in KEYNOTE-689.
- The M-TAG utility study supporting NICE TA145 (14) surveyed 50 UK nursing staff using the EQ-5D. Health states relate to patients who were unresected, and does not report a utility for local recurrence (the utility for ‘post treatment, progressive or worsening disease’ was 0.129, which seems implausible)
- Parthan et al, 2009 (11) was a UK trial-based cost-effectiveness analysis of stage III-IV unresectable LA HNSCC that mapped EORTC-QLQ-C30 to EQ-5D, but it does not report a specific utility for local recurrence and the sample size is not reported; the reported utility for ‘progressive stage’ disease is 0.67
- Smith et al, 2017 (15) was a UK trial-based cost-effectiveness analysis of unresected LA HNSCC, but does not report a specific utility for local recurrence (it assumed that the utility for local recurrences was the same as for disease-free, i.e. 0.7)

Consequently, none of the literature sources provided utility data that could be considered more suitable than the L/SR utility derived from KEYNOTE-689. However, the values from Parthan 2009 and Smith 2017 were broadly similar to the L/SR value from KEYNOTE-689 (█) which gives confidence that the trial value is appropriate.

B19. Appendix K1: Why were only █ of the █ SoC patients expected to complete the EQ-5D-5L at baseline whereas █ of the █ pembrolizumab patients were

expected to complete EQ-5D-5L questionnaire at baseline. These seem to be quite different proportions (■■■% for SoC vs ■■■% for pembrolizumab), especially for a baseline measure. Please clarify the reasons patients were not expected to complete the EQ-5D-5L at baseline.

MSD response

The baseline PRO assessment is the PRO measurement obtained prior to the patient starting treatment. However, as per the KEYNOTE-689 trial design the two study arms had asymmetric treatment schedules because the modality of first treatment received, and therefore the schedule of visits, differed between arms. Specifically, in the pembrolizumab arm patients first received 2 cycles of neoadjuvant pembrolizumab, whereas in the SOC arm, the first treatment was surgery. As such, the definition of what constitutes the baseline assessment visit (as specified in the trial protocol) differed between the trial arms. The protocol-specified baseline PRO visit, as stated in the statistical analysis plan (SAP; see CSR section 9.7, SAP p21), was therefore:

- Pembrolizumab + SOC arm: day 1 of the first cycle of neoadjuvant pembrolizumab
- SOC arm: the last PRO assessment day prior to surgery

The proportion 'Expected to complete questionnaire' at the protocol-defined baseline study visit is informed by whether or not a baseline assessment was obtained for any PRO measure. Amongst patients included in the PRO analyses (PRO FAS analysis set: patients who had completed at least one PRO questionnaire [either EQ-5D-5L or EORTC-QLQ-C30] either at baseline or at a future study visit and have received treatment):

- Patients who had not completed either PRO measure (EQ-5D-5L or EORTC-QLQ-C30) at what should be their protocol-defined baseline study visit were recorded as 'Missing by design' for the baseline assessment and therefore were not considered 'Expected to complete questionnaire' for this study visit.
 - In the SOC group, there were 25 patients classed as 'Missing by design' for the baseline visit; as shown in CSR Table 14.2-51, all 25 were categorised as '...visit not scheduled' which indicates that no PRO data were collected prior to surgery and the baseline analysis window is before their last study visit (see response to B21). As baseline PRO study visits were not scheduled for these patients, PRO completions at baseline are not expected.
- For the EQ-5D-5L analysis, patients with an EORTC-QLQ-C30 questionnaire completed at the protocol-defined study baseline visit but no EQ-5D-5L questionnaire

were considered 'Expected to complete questionnaire' at baseline and then recorded as 'Not completed'.

This approach to PRO analyses is standard across trial protocols and is not unique to KEYNOTE-689. However, the asymmetric treatment schedules between arms in this instance may have contributed to differences in scheduling of the baseline PRO visits. For example, the pre-surgery visit (SOC arm) is less clearly defined than the neoadjuvant pembrolizumab administration visit and in some cases local implementation practices may have resulted in this visit not being scheduled for a few patients. By contrast, the neoadjuvant pembrolizumab administration visit must be scheduled for a patient to receive treatment. This asymmetry may have contributed to fewer patients completing a baseline PRO assessment in the SOC arm.

B20. PRIORITY Appendix K, Table 84: The footnote to this table describes how the number of patients expected to complete the PRO questionnaires excluded those who were 'missing by design'. Reasons for patients to be missing by design include disease progression and discontinuations due to adverse events.

- a) Please comment on what implications this has for the reliability of the utility estimates from KEYNOTE-689 for patients who are in a progressed state.
- b) Please comment on what implications this has for the reliability of the utility estimates from KEYNOTE-689 for the disutility of grade ≥ 3 adverse events (AEs).

MSD response

The KEYNOTE-689 protocol allowed collection of PROs both while patients were on study treatment and during post-treatment follow up, and patients who experienced disease progression or treatment discontinuation for adverse events remained eligible to complete questionnaires (see section 2 of Trial Protocol: Schedule of Activities [p18–41] included in the CSR document shared with the EAG). CS Appendix K (based on CSR Table 14.2-51) reports actual versus expected PRO completions within prespecified analysis windows; a visit with no assessment within its analysis window is labelled "missing by design." Where patients had already discontinued treatment (for progression or AEs, or for one of the other reasons listed in the CSR table) that reason is recorded alongside the "missing by design" flag, but discontinuation does not automatically imply PROs were not solicited or analysed. In short, the recorded discontinuation reason is additional contextual information and is not synonymous with the cause of a missing PRO assessment.

With regards to the implications for the specific utility values for progressed health states and for grade 3+ adverse events, it is unclear whether the reasons for non-completion of EQ-5D-5L in these health states are linked to HRQoL, and therefore it is unknown whether the HRQoL of patients who did not complete an EQ-5D-5L questionnaire differed to those who did. However, this issue is not unique to KEYNOTE-689 and is a recognised challenge within utility studies.

- a) EQ-5D-5L data were collected from [REDACTED] patients (yielding [REDACTED] observations) after progression or recurrence (see Table 32). As per the EFS analysis, 159 patients had a recurrence or progression event and therefore EQ-5D-5L data were collected from [REDACTED] of patients who entered a 'progressed' (i.e. L/SR or IRP) state.

If we were to assume that patients with poorer HRQoL were less likely to complete the PROs, this would suggest that the utility estimates for the L/SR and IRP health states derived from KEYNOTE-689 were overestimated. Applying lower utility values for these health states would result in a lower ICER; this would suggest that the base case cost-effectiveness estimates are conservative.

- b) EQ-5D-5L data were collected from [REDACTED] patients (yielding [REDACTED] observations) during a grade 3+ adverse events (see Table 32). This represents [REDACTED] of all EQ-5D-5L records collected in the EF health state [REDACTED].

If we were to assume that patients with more severe adverse events (and therefore poorer HRQoL) were less likely to complete the PROs, this would suggest that the utility estimates for the 'with grade 3+ AE' state were overestimated and therefore the disutility for grade 3+ adverse events was underestimated. Applying a larger disutility for adverse events may result in a slightly higher ICER, however the impact of adverse event disutility on the cost-effectiveness outcome in absolute terms is negligible, as demonstrated by varying the AE disutility within the deterministic sensitivity analysis (DSA).

B21. CS, page 120, Follow-up for PROs: A common reason for patients to be recorded as 'missing by design' in CSR Table 14.2-51, particularly in the post-adjuvant phase, appears to be 'completed treatment and visit not scheduled' or 'completed treatment and visit not reached'. Please clarify when this category was applied and how this related to the study schedule which required patients to complete the EQ-5D-5L, *"30 days ($\pm$ 14 days) from the last dose, and then every*

three months from last scan (± 7 days) for up to end of year 3 and every 12 months (± 14 days) in years 4 and 5,” as stated on CS, page 120.

MSD response

Patients included in the PRO FAS analysis population who did not have any PRO measure collected at a given protocol-specified study visit within the corresponding analysis window were classed as ‘Missing by design’ for that visit. The subcategories ‘Completed treatment and visit not scheduled’ and ‘Completed treatment and visit not reached’ refer to the patient’s treatment status (‘Completed’ vs ‘Discontinued’) and the reason why a PRO assessment was not completed for the corresponding study visit (‘visit not scheduled’ or ‘visit not reached’). Note that the recorded treatment status is additional contextual information and is not synonymous with the cause of a missing PRO assessment.

- If the patient did not discontinue treatment for some reason (such as death, adverse events, progression, loss to follow-up, non-compliance, trial withdrawal etc) which would categorise them in one of the other categories under ‘Missing by design’ and they completed the treatment, then they would be classed as ‘Completed treatment’.
- The reason why a PRO assessment was not completed for the corresponding study visit is determined based on the following:
 - ‘Visit not scheduled’: PRO data were not collected within the prespecified analysis window, and the analysis window is **before** the latest recorded study visit for that patient
 - ‘Visit not reached’: PRO data were not collected within the prespecified analysis window, and the analysis window is **after** the latest recorded study visit for that patient (i.e. the follow-up duration for that patient has not yet been long enough for them to have reached the corresponding study visit)

The protocol defined PRO data collection schedule and the corresponding mapping of study visits to analysis are provided in Table 4 and Table 5 of the SAP, which is included in the CSR shared with the EAG (see CSR section 9.7, SAP p21–23).

B22. PRIORITY In Section 3.4.1.1 it is stated that “*Summary statistics were computed based on multiple records per participant, which were treated as independent observations,*” and in Table 33 these are summarised including the number of records and the number of patients these correspond to. Please can the company provide an alternative analysis where the potential relationship between repeated measures of EQ-5D-5L is accounted for, for instance through the use of

mixed effect modelling. Please can these estimates be provided both as a pooled analysis (across arms) and for the separate arms. Please can the company present the associated uncertainty with these estimates also so that they can be incorporated within any probabilistic analyses. Please provide a scenario analysis in which these alternative estimates are incorporated into the cost-effectiveness model.

MSD response

Utilities estimated using a mixed-effects regression approach (random intercept linear mixed model [RILMM]) to account for repeated measures are presented in Table 30, shown both by treatment arm and pooled across arms. The models included independent variables for concurrent health status (EF during grade 3+ AE, EF without grade 3+ AE, L/SR, or IRP), with patient-level random intercepts to account for repeated measures.

The utility values from the mixed-effects regression in the pooled sample have been incorporated into the model as a new option in the dropdown menus for utility source in each health state. A scenario analysis was conducted in which utility in the EF, L/SR and IRP pre-progression states, as well as AE-related disutility, are based on this pooled mixed-effects regression analysis of KEYNOTE-689 data (note that for the IRP post-progression state this scenario analysis continues to use the base-case source of utility for post-progression, i.e., QLQ-C30 EXTREME trial [TA473] as this alternative method does not resolve this). This alternative method resulted in a small ICER increase compared with the base case analysis (Table 31).

However, note the descriptive means presented in the base case can already be viewed as if coming from a generalized estimating equations (GEE) regression model with an independence working correlation matrix. This ensures unbiased estimation of marginal means regardless of any true underlying subject-level correlation structure. For inference, the empirical sandwich standard error calculation is used which accounts for correlation of the estimators.

Because not all participants experience all health states at all time points, this results in data that fundamentally do not exist, rather than data which are simply missing. Consequently, there is no proper notion of a subject-level correlation matrix and no notion of subject-specific random effects that can be integrated over to properly estimate a marginal mean. Thus, a mixed model is not considered appropriate in this setting for estimating marginal population utility means, and therefore the summary utilities provided in the CS (i.e., the descriptive analyses) and used in the base case should be preferred for decision making purposes.

Table 30. Health state utilities derived from KEYNOTE-689, accounting for repeated measures

Health state	Pembrolizumab + SOC			SOC			Pooled		
	Patients, n	Records, n	RILMM Mean (SE)	Patients, n	Records, n	RILMM Mean (SE)	Patients, n	Records, n	RILMM Mean (SE)
EF (without grade 3+ AEs)	■	■	■	■	■	■	■	■	■
EF (with grade 3+ AEs)	■	■	■	■	■	■	■	■	■
L/SR	■	■	■	■	■	■	■	■	■
IRP	■	■	■	■	■	■	■	■	■
Disutility (grade 3+ AEs)	-	-	■	-	-	■	-	-	■

Abbreviations: AE: Adverse events; EF, event-free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; RILMM, random intercept linear mixed model; SE, standard error; SOC, standard of care.

Table 31. Scenario analysis on primary base case: Utilities estimated by accounting for repeated measures

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	■	■	■	■	■	1.22	■
SOC	■	■	■	-	-	-	-

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

B23. PRIORITY Please can the company also perform multiple imputation (incorporating potential explanatory variables and using at least 10 imputations) to account for missing utility data of patients. Please ensure that this analysis is conducted such that repeated measures are accounted for (as per the previous question). Comment on the plausibility of the imputed utility values and any significant differences to those used in the original cost-effectiveness model. Please provide these analyses reported as a pooled analysis (across) arms and for the separate arms. Please provide a scenario analysis in which these alternative estimates are incorporated into the cost effectiveness model.

MSD response

As shown in Appendix K, EQ-5D compliance was around 90% at most timepoints and therefore the majority of the missing utility data reflects the trial protocol design (i.e. data are “missing by design”: patients were not expected to complete the questionnaire as they did not have a scheduled PRO study visit within the corresponding analysis window). Under the trial’s estimand, the apparent “missingness” is therefore classed as undefined rather than missing. On the other hand, multiple imputation relies on the missing at random (MAR) assumption and implies that unobserved EQ-5D-5L values at these non-existent visits can be estimated from observed and selected covariates and the outcome. Given that missingness is structural (by design) rather than random, the MAR assumption is unlikely to hold and therefore multiple imputation would be potentially biased. Therefore, MSD do not consider it appropriate to conduct multiple imputation in this instance.

B24. PRIORITY Model sheet ‘RAW – Utilities’. The model provides trial-arm specific estimates of utilities from KEYNOTE-689 that are not summarised in the CS. Please comment on whether the disutility associated with AEs is consistent across the two trial arms when analysing each arm separately. Please also comment on whether the estimate of utilities for each health state (EFS without grade 3+ AEs, L/SR and IRP) are consistent between arms when analysing each arm separately. Please also clarify why treatment-specific utilities were included in the model but not presented as a scenario analysis in the CS.

MSD response

Trial-arm specific utilities from KEYNOTE-689 are provided in Table 32, along with the pooled utilities as per the CS. These suggest that, across all health states, the utilities are higher for patients in the pembrolizumab + SOC arm than for patients in the SOC arm. The estimated

disutility associated with grade 3+ adverse events is slightly larger with pembrolizumab + SOC compared with SOC alone but, despite this, the overall treatment-specific EF utility (with or without grade 3+ adverse events) remains higher in the pembrolizumab arm. Alternative utility estimates adjusted for repeated measures using a random intercept linear mixed model are also presented in Table 32. The same trend is observed in this analysis, although the difference between the two arms is slightly smaller.

It is unclear exactly why this pattern is observed, as there could be several contributing factors. Given the open-label design of the trial, it is possible that patients randomised to pembrolizumab + SOC were more likely to report a higher utility as a result of knowing they were receiving a potentially more effective treatment. Another factor could be that a smaller proportion of patients received adjuvant cisplatin in the pembrolizumab + SOC arm resulting in fewer all-grade chemotherapy-related adverse events.

Treatment-specific utilities were included in the model as they were initially explored as an option for inclusion in the submission. However, ultimately these were not presented as it was unclear what was driving differences between the arms and, in the L/SR and IRP states, estimates were derived based on a very small number of patients/records. In addition, using pooled utilities maximises the data available to inform the analysis and is consistent with recent appraisals of pembrolizumab, including in perioperative settings, where pooled utilities have consistently been used. In this case, use of pooled utilities is a more conservative approach.

Table 32. Treatment-specific utilities from KEYNOTE-689

Health state	Pembrolizumab + SOC				SOC				Pooled			
	Patients, n	Records, n	Mean (SE)	RILMM Mean (SE)	Patients, n	Records, n	Mean (SE)	RILMM Mean (SE)	Patients, n	Records, n	Mean (SE)	RILMM Mean (SE)
EF (with or without grade 3+ AEs)				-				-				-
EF (without grade 3+ AEs)												
EF (with grade 3+ AEs)												
L/SR												
IRP												
Disutility (grade 3+ AEs)	-	-			-	-						

Abbreviations: AE: Adverse events; EF, event-free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; RILMM, random intercept linear mixed model; SE, standard error; SOC, standard of care.

B25. Our clinical experts indicated that some Grade 2 AEs experienced by patients with LA HNSCC having surgery and adjuvant treatment may have a significant impact on HRQoL and would warrant inclusion in the model. Examples they gave were dry mouth, difficulty eating and swallowing, and exhaustion. Please identify any grade 2 AEs that differed significantly between trial arms and incorporate these in the economic analysis or explain why this is not a suitable approach.

MSD response

The model includes grade 3+ adverse events as these are events typically considered most likely to have a substantial impact on HRQoL and medical resource use. Adverse events (any grade) occurring in $\geq 10\%$ in either treatment arm are presented in Table 12 of Appendix D1.2, and specifically Grade 2+ adverse events occurring in $\geq 10\%$ in either treatment arm are shown in Table 33. The only Grade 2+ adverse event that differed by $\geq 10\%$ between arms was hypothyroidism. Drug-related adverse events (any grade) occurring in $\geq 5\%$ in either treatment arm are presented in Table 13 of Appendix D1.3; only hypothyroidism and stomatitis differed by $\geq 10\%$ between arms.

The adverse events mentioned by the EAG's clinical expert are likely to be related to the surgery, radiotherapy and cisplatin components of the treatment which applies to both arms, not specifically pembrolizumab, and therefore it is unsurprising that these do not differ between arms. It is also likely that the impact of some of these, particularly difficulty eating/swallowing and exhaustion, are already captured in the health state utilities as they may not be strictly considered adverse events.

The impact of adverse events on the cost-effectiveness estimates is negligible: excluding adverse event costs and disutilities from the current model increases the ICER by approximately £15. Therefore, whilst additional grade 2+ adverse events (e.g. hypothyroidism and stomatitis) could be included in the model, the costs and disutilities would most likely be less than their grade 3+ counterparts and the impact on the ICER would also be negligible. As such, it is not considered necessary to update the model to capture grade 2+ adverse events.

Table 33. Grade 2+ adverse events occurring in $\geq 10\%$ of patients

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
Stomatitis	64	17.7	80	25.4
Radiation skin injury	59	16.3	70	22.2
Weight decreased	50	13.9	34	10.8

Anaemia	46	12.7	42	13.3
Dysphagia	41	11.4	44	14
Constipation	34	9.4	21	6.7
Hypothyroidism	70	19.4	10	3.2
Nausea	34	9.4	29	9.2
Fatigue	38	10.5	18	5.7
Dry mouth	20	5.5	24	7.6
Diarrhoea	22	6.1	8	2.5
Lymphocyte count decreased	19	5.3	10	3.2
Insomnia	22	6.1	11	3.5
Vomiting	24	6.6	12	3.8
Dysgeusia	23	6.4	19	6
Alanine aminotransferase increased	12	3.3	10	3.2
Hypokalaemia	8	2.2	6	1.9
Hyponatraemia	6	1.7	3	1
Oral pain	26	7.2	15	4.8
Decreased appetite	18	5	17	5.4
Pyrexia	14	3.9	2	0.6
Neutrophil count decreased	19	5.3	19	6
Aspartate aminotransferase increased	10	2.8	5	1.6
White blood cell count decreased	21	5.8	13	4.1
Rash	12	3.3	1	0.3
Asthenia	16	4.4	14	4.4
Pruritus	3	0.8	2	0.6
Oral candidiasis	20	5.5	11	3.5

Resource use

B26. PRIORITY CS, Table 39. Please clarify if the unit costs for chemotherapy administration in Table 39 are unit costs for day case admissions or outpatient procedures. If the latter, please revise the model to use day case unit costs.

MSD response

Unit costs for drug administration are for outpatient procedures, sourced from the NHS Reference costs 2023/24. This approach is aligned with the methods used and accepted in previous NICE appraisals for pembrolizumab, including TA1092 (16).

MSD has previously consulted clinical experts in the field who advised that typical IV administration appointments would be held in the outpatient setting of the chemotherapy day

unit. A "day case" refers to a procedural unit in the hospital, either for short surgeries or medical procedures and this would not be the clinical environment for the administration of systemic therapies for cancer. However, activity data reported in the NHS Reference costs suggest that chemotherapy is delivered in both outpatient and day case settings (Table 34). To best reflect the potential variation across centres, MSD has updated the model to use the weighted average of the outpatient and day case costs.

Table 34. NHS Reference costs for IV administrations

Code	Outpatient procedures (OP)		Day cases (DC)		Weighted average OP/DC Cost
	Activity	Cost	Activity	Cost	
SB12Z	37,140	£152	177,223	£418	£372
SB13Z	20,312	£202	94,806	£528	£470
SB14Z	20,721	£352	136,844	£570	£541
SB15Z	47,292	£251	181,912	£426	£390
SB11Z	139,402	£247	49,002	£353	£275

Source: NHS Reference Costs 2023/24 (17).

B27. CS page 137 states, *"Other resources, such as dieticians and speech and language therapists, were not expected to differ by treatment and were therefore not included in the model."* If dieticians, and speech and language therapists are offered long-term, could use of these resources not vary according to OS? If so, they should be included in both arms to capture any differences. This may not be necessary if they are provided for a fixed period and the OS is similar across the relevant time frame. Please clarify if this is the case.

MSD response

Clinical experts at MSD's advisory board highlighted that allied health professionals, such as dieticians and speech and language therapists, are key members of the multidisciplinary team (MDT) supporting patients with HNSCC, particularly in the perioperative and adjuvant period as patients prepare for and recover from surgery and adjuvant treatment. The level and duration of support required is likely to vary between patients based on clinical need, however it is expected that most of the care would be provided in this initial perioperative phase and the resource costs would therefore be contained within the first few months to one year of the model (18).

The cost and resource use SLR did not identify any studies which provided information on the use of allied health professionals, and MSD have not identified any alternative sources which could reliably inform the typical frequency or duration of care provided by these teams in

clinical practice. Therefore, given the expected short-term impact, potential for lower resource use in the pembrolizumab arm in practice, and lack of reliable data, as a simplifying assumption these resources were not included in the EF state in the model. The impact of this assumption on the ICER is likely to be very small.

B28. CS, Table 42: Please clarify how the proportion having surgery has been calculated. The EAG would expect these figures to be [REDACTED]% for pembrolizumab and [REDACTED]% for SoC based on the data in CS, Table 9.

MSD response

The proportion of patients having surgery in each arm is calculated based on the 'all patients as treated' (APaT) analysis population, which consists of all randomised participants who received at least one dose of study intervention or surgery that is part of study treatment. This population was used to inform all model resource use inputs that were sourced from the trial, to account for the open-label nature of the KEYNOTE-689 trial and better reflect expected outcomes of patients receiving the respective treatment regimens. These figures are therefore calculated as [REDACTED] for pembrolizumab and [REDACTED] for SOC.

B29. CS Table 42: Please clarify why for radiotherapy unit costs, the weighted average of day case and regular day/night admission were taken. Why were outpatient costs not applied when these are far more frequent according to the National Costs Collection Data Publication 2023/24 (N=34,086 for regular day/night admissions, N=216 for day case N=274,065 for outpatient procedures). Moreover, the EAG located Wills 2023 (<https://link.springer.com/article/10.1007/s10198-023-01623-5>) where radiotherapy costs ranged between £81 to £2163 across different types of cancer. Please justify why such a discrepancy is found between the radiotherapy costs in the CS and the value from the literature.

MSD response

The calculation of cost per radiotherapy regimen followed the approach described in a prior NIHR Health Technology Assessment paper in LA HNSCC by Mehanna et al. (2017) (19). In this economic evaluation, unit costs of radiotherapy were based on the weighted average of day case and regular day/night admissions (see Table 57 in Mehanna et al., 2017).

B30. Table 44. Please clarify why only 80% of patients in the SoC arm require consultant visits and clinical nurse specialist visits, but 100% of patients in the pembrolizumab arm require these resources.

MSD response

This assumption was based on insights obtained from clinical experts (9, 20). They advised that ideally all patients would see a consultant after surgery, however in real world practice follow-up models vary between centres and currently only approximately 80% of patients receiving current SOC would regularly see an oncologist after surgery as not all patients receive adjuvant systemic therapy. They suggested that this figure would increase to 100% with pembrolizumab, as delivery of pembrolizumab requires oversight and follow-up by a consultant.

B31. CS, Table 49. Please provide dosing schedules for systemic treatments in the L/SR state similar to that provided in Table 49 for the ILR state or clarify if Table 49 covers both states.

MSD response

The dosing schedules provided in CS Table 49 apply to systemic treatments used in both the L/SR and IRP health states.

B32. CS, page 152 states “*As it is plausible that the trial subsequent treatment use disproportionately reflects early recurrences, a scenario assuming a treatment mix as per the SoC arm applied for recurrences after 18 months was conducted to explore the impact of higher pembrolizumab and cetuximab use in patients with later recurrence.*” Please clarify, why early recurrences may be disproportionately reflected in the trial?

MSD response

Data from the trial are inherently restricted by the duration of follow-up in the trial. That is, only patients who have a recurrence within the current trial follow-up at IA1 will be included in the subsequent treatment data. Therefore, the subsequent treatment data represent recurrences that occur early in the overall model time horizon.

However, the KEYNOTE-689 trial has a relatively long follow-up (median actual follow-up for the CPS $\geq$ 1 subgroup was 2.25 years) and clinical experts have indicated that the majority of recurrences in LA HNSCC occur in the first two years (9). This is supported by the pattern of

recurrences observed in the trial. Therefore, whilst the subsequent treatment data do represent earlier recurrences, in this case it is likely that earlier recurrences also comprise most recurrences of LA HNSCC. As such, the subsequent treatment data should be considered sufficiently representative of treatment patterns in practice. Scenario 16 in CS Table 61) is a conservative scenario that assumes a higher proportion of IO rechallenge in the pembrolizumab arm to explore the impact of any uncertainty around this.

B33. Clinical advice to the EAG was that clinical experts would not be likely to offer immunotherapy (IO) to patients with recurrent/metastatic disease if they had previously received adjuvant pembrolizumab. In contrast, the model allows patients in the pembrolizumab arm with an IRP recurrence occurring after 18 months to have immunotherapies as they are classed as IO-eligible; those with an IRP recurrence occurring before 18 months are classed as IO-ineligible. Please conduct a scenario analysis where all patients in the pembrolizumab arm are IO-ineligible for later recurrences.

MSD response

Advice to MSD was that IO rechallenge may be considered for later recurrences (≥ 18 months after initiation of neoadjuvant pembrolizumab [approximately 6 months after completing adjuvant therapy]), as is permitted in other tumour types where immunotherapy is available in both the early-stage (adjuvant) and recurrent/metastatic setting (9). However, as most recurrences of LA HNSCC occur within the first 2 years, it is expected that only a small proportion of patients would be eligible for IO rechallenge in practice. This is reflected in the very low use of IO rechallenge in the pembrolizumab + SOC arm of the KEYNOTE-689 trial.

Results for the requested scenario, using the updated company economic model as presented in Appendix B, are presented in Table 35; the impact on the ICER is negligible.

Table 35. Scenario analysis on primary base case: No IO rechallenge

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC						1.28	
SOC				-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; IO, immunotherapy; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care.

B34. The list of non-immunotherapy subsequent treatments in Table 52 and Table 53 appear to be much broader than those discussed in either of the cited guidelines (CS, refs 1 and 2). Homer et al. (CS, ref 1) describe cetuximab with platinum and 5FU as first-line palliative chemotherapy, with second-line options including carboplatin with paclitaxel or single-agent cetuximab, taxes or methotrexate. The list of treatments described by Machiels et al. (CS, ref 2) appears similar. Please provide a scenario analysis limiting subsequent treatments to those recommended in these clinical practice guidelines.

MSD response

The UK Head and Neck Cancer Guidelines (Homer et al. (18)) and EHNS-ESMO-ESTRO guidelines (Machiels et al. (21)) specifically recommend the following options for first-line palliative systemic therapy:

- Pembrolizumab monotherapy (KEYNOTE-048) – for patients with PD-L1 CPS $\geq$ 1 disease previously untreated for recurrent/metastatic HNSCC
- Nivolumab monotherapy (CheckMate-141) – for patients who have progressed during or within 6 months of platinum-based chemotherapy
- Cetuximab + platinum + 5-FU (EXTREME) – for patients with oral cavity tumours
 - However, note that the corresponding NICE recommendation and NHS Drugs list specifies ‘cetuximab in combination with platinum-based chemotherapy’, not explicitly restricting to the EXTREME regimen (10, 22).
 - The EHNS-ESMO-ESTRO guidelines also mention that the ‘TPeX’ regimen, which corresponds to cetuximab + cisplatin + docetaxel, can be considered as a treatment alternative to EXTREME (21) – this would also be covered under the NICE recommendation for cetuximab (10).

In relation to the EXTREME regimen, the UK guidelines also state that “*Simpler schedules of similar drugs may offer reduced toxicity and reduced duration of day-unit or in-patient stay, but have less evidence to support them (e.g. carboplatin and capecitabine)*”, indicating that single or dual agent platinum-based chemotherapy regimens may also be used. These treatments would have been standard of care prior to approval of the EXTREME regimen. It is therefore expected that a small proportion of patients in the SOC arm (e.g. those who are not fit enough, or are ineligible, for immunotherapy or cetuximab) would receive these therapies as first-line treatment at recurrence. In the pembrolizumab + SOC arm, patients have

fewer options on recurrence (assuming limited rechallenge with immunotherapy) and clinical expert advice to MSD was that there was variation in use of cetuximab across the UK, so a reasonable proportion of patients would be expected to get chemotherapy alone (9).

MSD therefore considers that, with the potential exception of methotrexate, the treatment mix included in the base case (CS Table 52) is reflective of the available, recommended treatment options in the UK.

In the second-line setting, the guidelines recommend:

- Nivolumab – for patients who had progressed after first-line platinum-based chemotherapy (e.g. the EXTREME regimen, platinum single or dual therapy)
- Carboplatin + paclitaxel
- Cetuximab + platinum-based chemotherapy – for patients who previously received pembrolizumab monotherapy (22)
- Taxanes (e.g. paclitaxel, docetaxel)
- Methotrexate
- Cetuximab monotherapy (however, this is not approved by NICE or routinely funded by NHS England (22)), therefore this is unlikely to be used in practice

MSD therefore considers that, with the potential exception of cetuximab monotherapy and cisplatin monotherapy, the treatment mix included in the base case (CS Table 53) is reflective of the available treatment options in the UK.

A scenario analysis redistributing the share of methotrexate in the first-line (Table 36) and cetuximab and cisplatin monotherapies in the second-line (Table 37) is therefore presented. The impact on the ICER is minimal (Table 38).

Table 36. Treatment mix in first-line IRP state – scenario analysis

First-line regimens in IRP state	% of patients, by perioperative treatment		
	Perioperative pembrolizumab + SOC		SOC
	IO eligible	IO-ineligible	
Pembrolizumab monotherapy	■	■	■
Pembrolizumab + chemotherapy [†]	■	■	■
Nivolumab	■	■	■
Cetuximab + platinum + 5-FU	■	■	■
Cisplatin + 5-FU	■	■	■

Carboplatin + 5-FU	■	■	■
Cetuximab + cisplatin + docetaxel	■	■	■
Cisplatin + paclitaxel	■	■	■
Gemcitabine + paclitaxel	■	■	■
Cetuximab + platinum + paclitaxel	■	■	■
Cetuximab + cisplatin	■	■	■
Cisplatin + pemetrexed	■	■	■
5-FU	■	■	■
Cisplatin	■	■	■
Methotrexate [‡]	■■■■■	■■■■■	■■■■■
No active treatment	■	■	■

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; PD-L1, programmed death-ligand 1; SOC, standard of care.

Source: KEYNOTE-689 (data cutoff date: 25-Jul-2024)

Note: The shares of first-line regimens in the IRP state were obtained from KEYNOTE-689 among patients who experienced IRP as their first EFS failure event. As a result of rounding, some columns may not sum to 100%.

† As pembrolizumab + chemotherapy is not reimbursed in the UK for this indication, the observed share of this regimen as first-line treatment in the IRP state in KEYNOTE-689 was redistributed to the other first-line regimens.

‡ It is unclear whether methotrexate would be given as a first-line treatment in the UK, therefore in this scenario the share has been redistributed to the remaining regimens.

Table 37. Treatment mix in second-line IRP state – scenario analysis

Second-line regimens in IRP state	% of patients, by treatment arm		
	Perioperative pembrolizumab + SOC		SOC
	IO eligible	IO-ineligible	
Pembrolizumab	■	■	■
Nivolumab	■	■	■
Cetuximab + platinum + 5-FU	■	■	■
Cisplatin + 5-FU	■	■	■
Carboplatin + 5-FU	■	■	■
Platinum + paclitaxel	■	■	■
Cetuximab + paclitaxel	■	■	■
Cetuximab + carboplatin + paclitaxel	■	■	■
Cetuximab [†]	■■■■■	■■■■■	■■■■■
Paclitaxel	■	■	■
Docetaxel	■	■	■
Cisplatin [†]	■■■■■	■■■■■	■■■■■
Methotrexate	■	■	■
No active treatment	■	■	■

Abbreviations: CPS, combined positive score; IRP, incurable recurrence/progression; PD-L1, programmed death-ligand 1; SOC, standard of care.

Source: KEYNOTE-689 (data cutoff date: 25-Jul-2024)

† May not be used as a second-line treatment in the UK, therefore in this scenario the share has been redistributed to the remaining regimens.

Table 38. Scenario analysis: Treatment mix adjusted to align with clinical guidelines

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	■	■	■	■	■	1.28	■
SOC	■	■	■	-	-	-	-

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

B35. Please clarify if the maximum number of pembrolizumab cycles (2 for neo-adjuvant and 15 for adjuvant treatments) offered in the clinical trial is specified as a restriction on treatment duration in draft the summary of product characteristics (SmPC).

MSD response

Please see the draft SmPC provided in response to C1. The draft wording in section 4.2 specifies the maximum number of doses of pembrolizumab which aligns with the clinical trial.

B36. CS, Page 149: Please clarify why the duration for second-line treatments for relapsed/metastatic disease (i.e. treatments for ILR post-progression) were based on mean durations for treatments given second-line in KEYNOTE-048, instead of using the data from Appendix O, Table 117, which appears to presents data for both 1st and 2nd subsequent line therapies for patients in the IRP state.

MSD response

KEYNOTE-048 data were used to populate the mean durations of second-line treatment regimens in the IRP state due to the longer available length of follow-up in this trial compared to KEYNOTE-689. Mean second-line treatment durations in the IRP state from KEYNOTE-689 were expected to be truncated in the first interim analysis (i.e., because follow-up may be insufficient to cover the entire duration of a patient's second-line treatment of IRP).

Moreover, because patients entered the KEYNOTE-048 trial in the first-line recurrent/metastatic HNSCC setting, second-line treatment in the IRP state corresponded with their next line of treatment after the study treatment. In contrast, patients entered KEYNOTE-689 in an early disease stage (resectable LA HNSCC), and second-line treatment in the IRP state is (at least) two lines after the study treatment; longer follow-up time would therefore be

needed to cover the full second-line treatment course in KEYNOTE-689 compared with KEYNOTE-048.

Technical model implementation queries

B37. The EAG is getting different sum values using the standard approach of half cycle correction (averaging each two subsequent cycles) when compared to the approach applied in the submitted model of taking half a cycle from the first one and adding half a cycle to the last one. Please amend the model to account for the standard approach.

MSD response

In “Trace_NeoAdjReg1” columns CV:DO, test calculations have been set up to compute half-cycle correction using an alternative formula that takes the average of consequent cycles. As shown in cell DQ10, we found these two different approaches to be equivalent. Of note, half-cycle correction is not applied to cost categories that are incurred at the beginning of a cycle, including neoadjuvant/adjuvant drug acquisition and administration costs (recurring costs starting from week 0), initial surgery and radiotherapy costs (applied at a specific time point from model entry), and AE-related costs in each model arm (applied as a lump-sum cost at week 0).

B38. PRIORITY The current model structure applies second-line (2L) subsequent treatment costs and post-progression IRP utility to the overall IRP cohort without accounting for patients who will not survive to reach the post-progressed IRP state. Please amend the model to account for PFS events which are deaths in the IRP state.

MSD response

The model accounts for the proportion of patients who do not receive 2L treatment in the IRP state via the market share of “No active treatment” in this setting (row 127 of “Market Shares” tab). The percentage of patients assigned to “No active treatment” is based on observed subsequent treatment usage in KEYNOTE-689. In the 2025 UK Advisory Board meeting for this submission, clinicians indicated that the percentages of patients receiving no 2L treatment in the IRP state (as observed in KEYNOTE-689) were in line with UK clinical practice (9).

B39. ‘Markov Traces’ sheet, columns BL and BM: These use the discounted treatment acquisition and administration costs from ‘Market Shares’ sheet columns

S71:T86. Please correct the model to account for these as undiscounted costs, and use the discounted costs in columns CH and CI instead.

MSD response:

Following the clarification call, the EAG has confirmed that the undiscounted and discounted costs are applied correctly in the model and therefore no changes have been to 'Markov Traces' columns BL and BM.

B40. Please calculate the discounted costs for 2L subsequent treatments in the same way as undertaken for 1L treatments ('Market Shares' sheet, rows 91 and 92), and adjust the model accordingly.

MSD response

For simplicity, 2L+ treatment costs for IRP were not subject to the same two-stage discounting process used for 1L treatments, given the shorter expected duration of 2L+ treatments. With the exception of 2L pembrolizumab (not used in the UK setting) and 2L nivolumab, treatment duration was expected to be between 1 and 5 months for all 2L+ treatment options; consequently, discounting the stream of 2L+ treatment costs (as was done for 1L treatment costs in the ToT_Advanced tab) would have provided minimal gains in precision, at the expense of greater model complexity. (Of note, 2L+ treatment costs are still discounted from the time of IRP entry to cycle 0 within the Markov trace tabs; however, the stream of 2L+ treatment costs was not discounted to the point of 2L treatment initiation when calculating the mean lump-sum cost of each 2L+ treatment regimen.)

B41. Model, 'Raw_ToT KM curves' sheet: Please explain why the intention to treat (ITT) population (row 55) was not used in the model base case to calculate the proportions undergoing initial surgery, adjuvant radiotherapy, or adjuvant cisplatin. Please amend the model to account for the ITT population instead.

MSD response

Please also see the response to B28. The APaT population was used to inform all model resource use inputs that were sourced from the KEYNOTE-689 trial, including:

- Proportion undergoing initial surgery
- Proportion undergoing adjuvant radiotherapy
- Proportion receiving adjuvant cisplatin

MSD maintain that this use of the APaT population (which is based on the treatments actually received by individual patients in the trial) is the most appropriate in order to account for the open-label nature of the KEYNOTE-689 trial and better reflect expected outcomes of patients receiving the respective treatment regimens. However, given the EAG's request for amending the model, deterministic and probabilistic scenario analyses in which these proportions are estimated based on the ITT population are presented in Table 39 and Table 40, respectively.

Table 39. Deterministic scenario analysis: Resource use based on ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC						1.28	
SOC				-	-	-	-

Table 40. Probabilistic scenario analysis: Resource use based on ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC						1.31	
SOC				-	-	-	-

B42. In cell K28 in the 'Source_Market_Shares' sheet, the total proportion sums to 103.6%. Also in L64 of the same sheet the sum is greater than 100%? Please clarify if these are calculation errors.

MSD response

Columns K:L in "Source_Market Shares" are used for an intermediate calculation step, which flows into the final calculation of market shares in columns G:I. Specifically, in columns K:L, market shares of excluded regimens are proportionally redistributed to all regimens listed in the table for a given setting. As a final step, in columns G:I, market shares are set to 0% for regimens that are listed in the table but not recommended for use in the UK. The resulting market shares sum to 100% and are used as in the model.

Section C: Textual clarification and additional points

C1. Appendix A1. Whilst we acknowledge that pembrolizumab does not yet have UK marketing authorisation for the indication under consideration in this appraisal, it would be helpful for the EAG to see the draft SmPC to inform its critique and this can be submitted as confidential material. Please provide the current draft SmPC for this indication.

MSD response:

The current draft SmPC has been provided as a separate commercial-in-confidential attachment to this response document. Please note that this SmPC is a draft version and the final version may differ based on possible further input/discussions with the Medicines and Healthcare products Regulatory Agency (MHRA).

C2. In Figure 18 of the CS, can the company clarify what censoring regime was used for the observed KEYNOTE-689 OS curve.

MSD response:

Observed OS in CS Figure 18 is based on the censoring rule used in the primary analysis of EFS, as applied in the model base case (i.e. censored at the date of last assessment, for patients who are censored with respect to both EFS and OS; censored at the last date known alive, for patients who are censored with respect to OS but not EFS).

C3. Appendix J1.5, Figure 14. Can the company clarify what is presented as the figure caption states “*Incremental EFS at 10 years for base case and scenario analysis*”, and the EAG is unclear why the data presented are described as ‘incremental.’

MSD response:

This figure presents the EFS curves predicted by the model with each combination of distributions applied in the base case and in the presented scenario analyses, by treatment arm. It was intended to illustrate the differences in predicted EFS treatment benefit with pembrolizumab + SOC vs SOC across the various scenarios (e.g. blue curves represent the curves in each arm of the base case analysis; other colours represent the four scenarios presented). For example, the figure shows that Approach #1 Gen gamma/Gen gamma/Gen gamma (purple curves) predicts a larger treatment benefit than the base case and that

Approach #1 Log-normal/Gompertz/Gen gamma (green curves) predicts a smaller treatment benefit than the base case.

C4. CS, Figures 6, 18: Can the company confirm whether the primary censoring rule for OS (censor at last known date alive) was used.

MSD response:

- Figure 6: Based on the primary censoring rule for OS (patients censored at last date known alive)
- Figure 18: See response to C2. Based on the primary censoring rule for EFS, as applied in the model base case (i.e. censored at the date of last assessment, for patients who are censored with respect to both EFS and OS; censored at the last date known alive, for patients who are censored with respect to OS but not EFS).

C5. CS, Section 2.8.1.2 and Appendices, Table 9, 10: please can the company confirm whether the primary censoring rule for OS (censor at last known date alive) was used when fitting the Cox PH models.

MSD response:

CS section 2.8.1.2, and Table 10 in the Appendices are based on the primary censoring rule for OS (patients censored at last date known alive). Table 9 in the Appendices refers to EFS and is based on the primary censoring rule for EFS (patients censored at date of last disease assessment).

C6. Appendices, Sections J.1.1, and J.3.1: please can the company confirm which censoring rule was used when evaluating the mean squared error (MSE) for the candidate models.

MSD response:

The censoring rule used when evaluating MSE is aligned with the censoring rule used in the analysis to which the distributions are fitted. As such, the primary censoring rule is used to calculate MSE when evaluating parametric distributions that have been fitted using the primary censoring rule. Likewise, the alternative censoring rule is used to calculate MSE when evaluating parametric distributions that have been fitted using the alternative censoring rule. Specifically:

- Section J1.1: Based on the primary censoring rule (as per trial primary censoring rule for EFS); EFS is censored at the date of last disease assessment

- Section J3.1: Based on the alternative censoring rule (as per trial primary censoring rule for OS); EFS is censored at the last date known alive

Appendix A: Summary of model updates

The updates in the revised economic model are summarised in Table 41, indicating which updates are applicable to the company base case. Additions are highlighted in red text in the model.

Table 41. Summary of updates to the company economic model

Summary	Description	Reference to corresponding CQ	Base case or scenario analysis
Survival curves			
Transition probabilities from the EF state (EF→L/SR, EF→IRP, EF→death)	Addition of a drop-down (Specifications, row 85) to allow for a scenario whereby the transition probabilities from EF state are based on observed cumulative incidence in the first 32 weeks of the model	B2	Scenario analysis
Transition probability from L/SR→IRP	The economic model has been updated with a drop-down to allow a scenario where the transition probability from L/SR→IRP is pooled across the two treatment arms	B10	Scenario analysis
Utilities			
Mixed-effects regression utilities	Addition of a drop-down to allow a scenario whereby the health-state utility values informed by KEYNOTE-689 (EF, L/SR and pre-progression IRP) and AE-related utility values are informed by a mixed-effects regression model, pooled between treatment arms	B22	Scenario analysis
Cost and resource use			
Resource use informed by the KEYNOTE-689 trial ITT population	Addition of a drop down (HCRU, row 14) to update resource use in the model using data from the KEYNOTE-689 trial (including initial surgery, adjuvant RT and adjuvant cisplatin use) to reflect the ITT population (previously based on APaT)	B41	Scenario analysis
IV administration costs	All administration costs (IV and oral) in the model have been updated from outpatient procedures (OP) to a weighted average between OP and day cases (DC)	B26	Base case
Market shares in 1L and 2L IRP state	Populated the user-specified market share tables for 1L and 2L	B34	Scenario analysis

	treatments in the IRP state with default values		
Miscellaneous			
Half cycle correction	Added test columns for an alternative half-cycle correction formula (Trace_NeoAdjReg1, columns CV:DQ)	B37	N/A

Abbreviations: AE, adverse event; CQ, clarification question; EF, event-free; IRP, incurable recurrence or progression; ITT, intention-to-treat; IV, intravenous; L/SR, local/salvageable recurrence

Appendix B: Updated model results

Updated model results are presented for the updated company base case, which includes the updated administration costs in the model (based on weighted outpatient procedures and day cases; see response to B26).

Base case results

Table 42. Primary base case deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	████	██	██	████	██	1.28	████
SOC	████	██	██	-	-	-	-

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

Sensitivity analyses

Table 43. Primary base case probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	████	██	██	████	██	1.31	████
SOC	████	██	██	-	-	-	-

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

Figure 20. PSA scatterplot at £30,000/QALY (primary base case)

█

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 21. Cost-effectiveness acceptability curve (primary base case)

█

Abbreviations: QALY, quality-adjusted life year; SOC, standard of care

Figure 22. Tornado diagram featuring top 10 individually influential parameters (primary base case)

Abbreviations: CI, confidence interval; EF, event free; HNSCC, head and neck squamous cell carcinoma; ICER, incremental cost-effectiveness ratio; IRP, incurable recurrence/progression; IV, intravenous; L/SR, local or salvageable recurrence; OS, overall survival; QALY, quality-adjusted life year.

Scenario analysis**Table 44. Scenario analyses on the primary base case**

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
-	Base case				████	1.28	████	
1	Distributions used to model transitions from EF (<i>EF</i> → <i>L/SR/IRP/ death</i>)	Approach #1, Gompertz/ Gompertz/ Gen gamma	Approach #1: Gen gamma/ Gen gamma/ Gen gamma (pessimistic incremental EFS and OS benefit)	Explore range of impact based on most and least incremental EFS and OS benefit of the 10 finalist curve combinations.	████	1.73	████	████
2			Approach #1: Log normal/ Gompertz/ Gen gamma (optimistic incremental EFS and OS benefit)		████	1.00	████	████
3			Scenario 1 + Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years	Explore the impact of applying a cure assumption to alternative distributions using Approach #1 to model transitions for EF, to ensure a modelled pattern of recurrence in line with clinical expert opinion.	████	1.49	████	████
4			Scenario 2 + Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years		████	1.09	████	████
5			Approach #2: Gompertz/ Gompertz/ Gompertz (proportional hazards)	Test impact of assuming proportional hazards Best-fitting combination under Approach #2.	████	1.38	████	████

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
6			Approach #3: Gompertz/ Gompertz/ Gompertz (time-varying proportional hazards)	Test impact of adopting a time-varying HR approach, given violation of proportional hazards for EF→L/SR. Best-fitting combination under Approach #3 (but not included in the final 10 combination of distributions).	■	1.54	■	■
7	Cure	No cure point applied	Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years	Reflect clinical expert opinion that patients are functionally cured at 5 years; similar to previous appraisals	■	1.26	■	■
8	Censoring of transitions from EF state	Censoring rule as per protocol for KEYNOTE-689 trial (last disease assessment, as per EFS analysis)	Alternative censoring rule (last known date alive, as per OS analysis) – Approach #1: Gompertz/Gompertz/Gen Gamma	Explore impact of different censoring rules applied for per protocol analyses of EFS and OS in trial. Base case selection for alternative censoring rule (see Appendix J3)	■	1.12	■	■
9			Alternative censoring rule (last known date alive, as per OS) – Approach #1: Gompertz/Gen Gamma/Gen Gamma	Explore impact of different censoring rules applied for per protocol analyses of EFS and OS in trial. Most optimistic for incremental EFS and OS benefit out of final combinations (see Appendix J3.4)	■	1.44	■	■

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
10	Transitions from IRP→death	Based on PLD from KEYNOTE-689	Based on efficacy (from NMA) and market shares of 1L treatments for R/M HNSCC	Explore impact of approach to modelling IRP transitions, and aligned with method in previous appraisals	■	1.25	■	■
11	IRP post-progression utility	EORTC-QLQ-C30 from EXTREME mapped to EQ-5D-3L, used in NICE TA172/TA473	As per pre-progression IRP utility in KEYNOTE-689 (assumes no HRQoL decrement on progression)	Consistent utility source across all health states	■	1.26	■	■
12	Pembrolizumab dosing (adjuvant)	200 mg Q3W for 1 dose, followed by 400 mg Q6W for up to 7 cycles	200 mg Q3W for up to 15 cycles	Reflect dosing in trial and possible variation in clinical practice	■	1.28	■	■
13	Vial sharing (for weight-based treatments)	Permitted	Not permitted	Explore variation in practice in the UK NHS	■	1.28	■	■
14	Mix of systemic treatment in L/SR state	Based on treatment patterns as observed for patients with L/SR in KEYNOTE-689	In L/SR setting, assume same treatment cost as per the 1L IRP setting	Explore impact of assuming more patients in L/SR are treated systemically, equal to patients in IRP	■	1.28	■	■
15	1L treatment for IRP (SOC arm)	SOC arm: Nivolumab share as per trial SOC arm	SOC arm: Nivolumab share in trial SOC arm redistributed to pembrolizumab	Clinical advice indicates that most patients on anti-PD-1 get pembrolizumab rather than nivolumab	■	1.28	■	■

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
16	1L treatment for IO-eligible patients in IRP (pembro arm)	IO-eligible (recurrences post-18 months): 1L treatment mix as per trial pembrolizumab arm	IO-eligible (recurrences post-18 months): 1L treatment mix as per trial SOC arm	Subsequent treatments in trial may disproportionately reflect early recurrences, and later recurrences may be more likely to receive further IO (as observed in SOC arm)	████	1.28	████	████
17	PD-L1 tests required to identify 1 CPS≥1 patient	Based on prevalence of CPS≥1 in KEYNOTE-689 (95.5%)	Based on prevalence of CPS≥1 in KEYNOTE-048 (72%)	Prevalence of CPS≥1 in the real-world population is unknown	████	1.28	████	████
18	Time horizon	Lifetime (40.1 years)	20 years	Understand impact of shorter time horizon (note: does not capture full lifetime costs and effects [████% still alive at 30 years])	████	1.05	████	████
19			30 years		████	1.25	████	████
20	Discount rate	3.5% for costs & effects	1.5% for costs and effects	As per NICE guidance	████	1.61	████	████
21	Apply relative dose intensity	Yes	No	Assuming 100% dose intensity	████	1.28	████	████
New scenarios in response to clarification questions								
22	Utility values informed by KEYNOTE-689	Descriptive utility values pooled across treatment arms	Regression-based utilities using a mixed-effects model pooled across treatment arms	In response to CQ B22	████	1.22	████	████
23	Transitions from EF state	Parametric distributions	Use observed cumulative incidence to model	In response to CQ B2	████	1.22	████	████

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
		fitted to full time horizon	transitions from EF state up to week 32					
24	Distributions used to model transitions from EF (<i>EF</i> → <i>L</i> / <i>SR</i> / <i>IRP</i> / <i>death</i>)	Approach #1 Gompertz/Gompertz/Generalized gamma	Approach #1: Gompertz/Gompertz/Gompertz	In response to CQ B5	■	1.13	■	■
25			Approach #1: Gompertz/Generalized Gamma/Gompertz		■	1.42	■	■
26	Transitions for L/SR state	Transition probabilities specific to each treatment arm	Transition probabilities pooled across treatment arms	In response to CQ B10	■	1.23	■	■
27	IO-rechallenge following perioperative pembrolizumab + SOC	IO-rechallenge possible after 18 months	No IO-rechallenge permitted	In response to CQ B32	■	1.28	■	■
28	Treatment mix in IRP	As per the use of subsequent therapies in the KEYNOTE-689 trial	Methotrexate redistributed in 1L and cetuximab and cisplatin monotherapies redistributed in 2L	In response to CQ B33	■	1.28	■	■
29	Source initial surgery, adjuvant RT and	KEYNOTE-689 APaT	KEYNOTE-689 ITT	In response to CQ B41	■	1.28	■	■

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
	adjuvant cisplatin use							

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SOC, standard of care.

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Single Technology Appraisal

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	THE SWALLOWS HEAD & NECK CANCER CHARITY
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Swallows is a UK-registered, patient-led charity and support group for people affected by head & neck cancers (patients, caregivers, family and friends). It offers peer-to-peer support, practical help, information, education, and advocacy. Support includes a 24/7 helpline/textline, monthly meetings, online resources, and support groups across the UK. The name “Swallows” refers partly to difficulties many head & neck cancer patients face with swallowing — a core challenge that unites many members. The Swallows receives income through donations, fundraising, and grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	NO

Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Swallows confirms that the evidence included in this NICE submission: • reflects genuine patient and caregiver experience • is not influenced by pharmaceutical or commercial interests • was collected independently through our peer-led national support network

Living with the condition

Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	What is it like to live with the condition? Head and neck cancer has a profound and often lifelong impact on people's physical abilities, emotional wellbeing, identity, and daily functioning. The condition affects fundamental human activities such as eating, drinking, swallowing, speaking, breathing, and social interaction. Patients consistently describe the experience as a <i>total life change</i>. Physical Impact Individuals experience a wide range of symptoms and long-term effects depending on tumour location and treatment, including: • Difficulty swallowing (dysphagia), which can cause choking episodes, fear of eating, malnutrition, and social avoidance. • Speech and communication difficulties, ranging from altered voice quality to complete loss of natural speech, particularly after surgery or laryngectomy. • Nutritional challenges, including reliance on modified diets, liquid supplements, PEG feeding, severe dry mouth, and loss of taste. • Long-term treatment effects such as fibrosis, trismus, neuropathic pain, altered sensation, hearing loss, lymphoedema, dental deterioration, and chronic fatigue. • Changes in appearance, including scarring, facial asymmetry, or the visible presence of a stoma or prosthesis, which can significantly affect body image and confidence. Many report that even years after treatment, late effects continue to worsen or remain unaddressed, affecting quality of life and independence. Emotional and Psychological Impact Patients commonly experience: • Persistent fear of recurrence or new primary cancers. • Anxiety, depression, and loss of identity, especially when speech or appearance is altered. • Social isolation, often linked to difficulties communicating or eating in public. • Feelings of abandonment once active treatment ends, due to limited long-term follow-up for late effects. The cumulative effect is a sense of uncertainty and vulnerability that permeates everyday life. Impact on Daily Living and Social Participation Head and neck cancer affects the ability to:

	• Return to work or maintain employment. • Eat socially or participate in family events. • Communicate easily, make phone calls, or engage in spontaneous conversation. • Carry out routine tasks without fatigue, discomfort, or fear of choking. Patients frequently describe the need to plan every aspect of their day around eating, communication, and energy levels. Many feel their world becomes smaller, with reduced social opportunities and increased dependence on others. What do caregivers experience when caring for someone with the condition? Caregivers often partners, family members, or close friends play a central role in supporting people with head and neck cancer. Their responsibilities can be extensive and emotionally demanding, and they frequently feel overlooked by the health system. Emotional Burden Caregivers report significant emotional strain due to: • Witnessing choking episodes, breathing difficulties, weight loss, or distressing treatment side effects. • Managing the patient's fear, anxiety, and changes in self-esteem. • Feeling helpless when communication is impaired or when the person refuses food out of fear of choking. • Constant worry about recurrence, infections, dehydration, or complications. Many experience chronic stress and emotional exhaustion, often without adequate psychological support. Practical and Physical Demands Carers often take responsibility for: • Preparing modified meals or managing PEG feeding and nutritional supplements. • Supporting communication, sometimes acting as the patient's "voice." • Managing stoma care, oral hygiene, medication schedules, and tracheostomy cleaning. • Attending appointments, advocating within the healthcare system, and coordinating care across multiple services.

	These tasks can be time-consuming and require skills that carers have not been formally trained to perform. Impact on Carers' Lives Caregivers frequently experience: • Sleep disruption, fatigue, and burnout due to continuous vigilance. • Reduced ability to work, financial strain, and loss of personal time. • Social isolation, as many feel unable to leave the patient alone for extended periods. • Grief and adjustment, especially when the patient undergoes visible changes or loses their natural voice. Many caregivers feel unrecognised and unsupported despite carrying substantial responsibility throughout the treatment and survivorship pathway. Summary Head and neck cancer profoundly affects both patients and carers. Patients face life-altering physical and psychological challenges, while caregivers take on demanding emotional, practical, and clinical responsibilities. Both groups report unmet needs in long-term support, management of late effects, communication, nutrition, mental health, and continuity of care.

7. What do patients or carers think of current treatments and care available on the NHS?	What do patients or caregivers think are the advantages of the current treatments? Patients and caregivers recognise several important advantages of the current NHS treatment pathway: 1. Treatments Are Potentially Curative Many patients are alive today because of timely surgery, radiotherapy, chemotherapy, immunotherapy, or combinations thereof. This is the most valued benefit. 2. High-Quality Expertise from MDTs Patients appreciate: • specialist surgeons • SLTs, dietitians, CNSs • radiographers and nurses • coordinated care during active treatment Where MDTs function well, patients feel safe, supported, and well-informed. 3. Radiotherapy and Surgical Advances Recent improvements such as: • IMRT • transoral robotic surgery • better reconstruction techniques have reduced toxicity and improved functional outcomes for some groups. 4. Access to PEG Feeding, Speech Valves, and Rehabilitation Although variable, many patients value: • early PEG placement for nutrition • voice restoration options after laryngectomy • swallowing therapy • psychological support where available 5. Dedicated CNS Support Where head and neck CNSs are available, patients value: • a consistent point of contact

- practical advice
- emotional reassurance
- help navigating complex pathways

What do patients or caregivers think are the disadvantages of the current treatments?

Patients and carers highlight significant disadvantages and burdens:

1. Severe Short- and Long-Term Side Effects

Treatment often leads to:

- dysphagia
- chronic dry mouth
- taste loss
- fibrosis
- pain
- trismus
- dental deterioration
- hearing loss
- breathing difficulties

These can have lifelong impact.

2. Long-Term Effects Are Under-Recognised

Patients commonly state that the most difficult challenges appear *after* treatment, yet:

- follow-up is inconsistent
- symptoms can worsen
- services for late effects are limited or unavailable

3. Loss of Voice or Major Changes to Communication

For laryngectomy patients or those with surgical impacts, losing their natural voice can feel devastating and isolating.

	4. Variability Across the UK The “postcode lottery” remains a major frustration, affecting: • access to SLT • dietetics • dental care • lymphoedema services • psychological support • prosthetics and laryngectomy supplies 5. Impact on Identity, Eating, Appearance, and Confidence Treatment alters basic bodily functions and can lead to: • embarrassment eating in public • social withdrawal • difficulty returning to work • loss of independence 6. Caregiver Burden Carers experience exhaustion, stress, and lack of training to manage PEGs, stomas, communication needs, or emergencies. Are there differences in opinion between patients and caregivers about the outcomes and experiences of treatment? Yes, there are some important differences: Patients • Focus more on loss of abilities (eating, speaking, swallowing, appearance, fatigue). • Experience greater emotional distress related to identity, independence, and physical changes. • Often under-report symptoms to avoid burdening carers or clinicians.

	Caregivers • Experience greater fear of emergencies (choking, aspiration, infections, airway issues). • Feel overwhelmed by practical responsibilities and healthcare navigation. • Are often more aware of functional decline or unsafe eating behaviours than patients themselves. • Report feeling excluded from clinical conversations or unsupported in their own right. Despite different perspectives, both groups strongly agree on: • the need for better long-term support • more consistent NHS access • improved communication across services What improvements do patients or caregivers want to see in the future? Across our groups, patients and carers consistently request: 1. Better Long-Term Follow-Up Particularly for: • dysphagia • trismus • fibrosis • lymphoedema • dental issues • PEG support • late effects care 2. Access to Specialist Dental Care A major unmet need. Patients want: • faster access • more dental clinicians trained in managing post-radiotherapy patients • removal of financial barriers

	• national consistency 3. More Speech & Language Therapy and Dietetic Support Including: • post-treatment swallowing rehabilitation • advice on safe eating • support with nutrition and supplements 4. More Psychological Support Patients and caregivers want: • trauma-informed counselling • mental health pathways tailored for communication impairments • family support • grief and adjustment support 5. Better Emergency Care Awareness Especially for people with: • laryngectomy • tracheostomy • complex swallowing needs Many report fear that emergency staff may not understand their altered airway. 6. Improved Coordination Between Services Patients want care that feels joined-up across: • oncology • SLT • dietetics • primary care • dentistry • rehabilitation • palliative care

	7. Greater Use of Digital and Remote Support Including apps, virtual check-ins, and access to support when travelling or unable to attend in person. 8. Inclusion of Third-Sector Organisations Patients want formal recognition of charities (like The Swallows) in providing real-world support during survivorship. What should we have asked the NHS about that we haven't? Patients and caregivers believe NICE should also consider: 1. Late Effects as a Distinct Phase of Care Treatment toxicity continues for years. Many feel late effects are “forgotten” within cancer pathways. 2. Experiences of People Living with a Laryngectomy They face unique risks and require specialised support that is not universally available. 3. Dental Access as a Critical Component of Cancer Care This issue is so severe that many say it impacts quality of life more than the original cancer treatment. 4. The Impact on Younger Patients and Working-Age Adults Returning to work, supporting families, and financial pressures are major concerns. 5. Inequalities in Access Particularly for: • rural areas • people with communication impairments • those from lower-income backgrounds • people without a strong advocate Additional Comments Patients and caregivers repeatedly express gratitude for NHS staff and the life-saving nature of treatment. However, they feel strongly that survivorship care is the weakest part of the pathway.

	Key concerns include: • lack of long-term, structured rehabilitation • lack of recognition of the complexity of head and neck cancer • insufficient emotional and psychological support • limited investment in services supporting communication, swallowing, and dental health • inconsistency in care across the UK The condition requires holistic, ongoing care, not just treatment. Patients want NICE to acknowledge the lifelong challenges and support the development of pathways that reflect the true lived experience of this population.

8. Is there an unmet need for patients with this condition?	Yes. There are substantial and persistent unmet needs for people living with head and neck cancer, across the entire care pathway from diagnosis through survivorship. These needs affect clinical outcomes, quality of life, safety, and long-term wellbeing. 1. Major Unmet Need in Long-Term Follow-Up and Management of Late Effects Late effects are often more debilitating than the original cancer treatment and can appear months or years later. Patients report inadequate access to: • swallowing rehabilitation • lymphoedema management • treatment for radiation-induced fibrosis • trismus therapy • dental care • pain management • specialist physiotherapy Many feel “abandoned” after active treatment ends, despite worsening or persistent symptoms. 2. Severe Unmet Need in Access to Specialist Dental Care during treatment, post treatment and in survivorship This is one of the biggest unmet needs raised by patients nationally: • long waiting times • lack of post-radiotherapy dental expertise • high costs • difficulty accessing NHS dentists at all Poor dental care puts patients at risk of osteoradionecrosis, infection, pain and deterioration in nutrition. 3. Unmet Psychological and Emotional Support Needs Both patients and carers report: • limited access to psychology or counselling • long waiting lists

Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	• lack of services that accommodate speech or swallowing difficulties • absence of trauma-informed and family-centred support This contributes to depression, anxiety, isolation, and declining mental health. 4. Insufficient Support for Communication Needs People with: • laryngectomies • tracheostomies • impaired speech often struggle to access: • communication aids • SLT follow-up • appropriate emergency care (especially altered airway awareness) This impacts safety, independence, and social participation. 5. Lack of Consistent Swallowing and Nutritional Support Patients report: • inconsistent access to SLTs and dietitians • insufficient follow-up to support safe swallowing • challenges with PEG maintenance • limited advice on long-term nutrition and supplements These gaps increase risk of malnutrition, aspiration, and avoidable hospital admissions. 6. Inequalities and Postcode Variation There are clear differences across the UK in: • late effects services • availability of dedicated CNSs

- access to lymphoedema clinics
- prosthetics and stoma supplies for laryngectomy patients
- allied health support

This variability creates unequal outcomes for patients based solely on geography.

7. Inadequate Support for Caregivers

Carers frequently experience:

- no formal training for PEG feeding or stoma care
- little psychological support
- lack of recognition within appointments or pathway planning
- financial and employment strain

Caregivers unmet needs directly affect patient safety and wellbeing.

8. Need for Better Integration Between Services

Patients experience fragmented care and poor coordination between:

- oncology
- SLT
- dietetics
- primary care
- dental services
- physiotherapy
- mental health services

This leads to delays, confusion, and unmet rehabilitation needs.

9. Recognition of Third-Sector Support as Essential

Charities like The Swallows meet a wide range of unmet needs emotional support, crisis support, survivorship guidance, and peer-to-peer advice yet third-sector support is not formally integrated into NHS pathways.

	Summary There is a significant unmet need in survivorship care, late-effects management, communication and swallowing rehabilitation, psychological support, dental access, and carer support. These gaps have a profound impact on patients' quality of life and long-term outcomes. Addressing them would lead to safer, more equitable, and more holistic care for people living with head and neck cancer.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and caregivers believe the technology offers several important advantages that directly address unmet needs in head and neck cancer care. Their views reflect themes gathered from support groups, surveys, and one-to-one conversations within The Swallows community. 1. Improved Quality of Life Patients feel the technology has the potential to: • reduce the severity of symptoms or treatment side effects • preserve or restore essential functions such as swallowing, speech, nutrition, or breathing • reduce pain, discomfort, or treatment burden • improve mental wellbeing and confidence Any intervention that helps maintain normal daily activities is seen as a major benefit. 2. More Effective or Targeted Treatment Patients appreciate technologies that: • offer better disease control • reduce the risk of recurrence • are more precise or personalised • minimise damage to healthy tissue Caregivers value anything that offers a clearer and safer pathway with fewer complications. 3. Reduction in Treatment Burden Patients and caregivers often highlight advantages such as: • fewer hospital visits • simpler treatment schedules • quicker recovery • fewer long-term effects This reduces stress for both patients and carers, especially those who travel long distances for care.

	4. Increased Independence Technologies that enable people to: • communicate more easily • eat and drink more safely • manage their symptoms at home • reduce reliance on caregivers ...are viewed as life-enhancing and empowering. 5. Improved Safety Caregivers particularly value technologies that: • reduce the risk of choking, aspiration, or airway emergencies • support better monitoring of symptoms • provide clearer guidance for home management This reduces anxiety and gives carers more confidence. 6. Better Support During Survivorship Patients appreciate innovations that: • provide long-term monitoring • support late-effects management • improve rehabilitation • connect them to support services Survivorship is a phase where patients feel most unsupported, so new tools or treatments that bridge this gap are highly valued. 7. Enhanced Communication With Healthcare Teams Technologies that improve communication whether through digital platforms, clearer information, or shared decision-making tools are valued because patients often feel overwhelmed or isolated.

	8. Reduced Inequalities in Access If the technology is easier to access, available closer to home, or reduces reliance on specialist centres, patients perceive this as a major advantage because current treatment availability varies significantly across the UK. Summary Patients and caregivers believe the technology is advantageous because it improves quality of life, enhances safety, reduces treatment burden, and supports long-term recovery areas where there are currently significant gaps in the NHS pathway. Any technology that helps patients speak, swallow, eat, breathe, communicate, or regain independence is viewed as transformative.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and caregivers recognise that, while the technology may offer important benefits, it also has potential disadvantages. These concerns were gathered through national support groups, online engagement, surveys, and one-to-one conversations and represent a broad range of lived experiences. 1. Side Effects or New Burdens Patients often worry that the technology might: • create complications that require additional appointments or interventions Caregivers fear increased responsibility managing technology at home. 2. Additional Appointments or Monitoring Some technologies require: • frequent hospital visits • blood tests, imaging, or check-ins • adherence to strict protocols Patients find this exhausting, especially those who travel long distances, and caregivers may struggle to balance work and caring responsibilities. 3. Uncertainty About Effectiveness Patients and caregivers express concern when: • technology not guaranteed to work • outcomes vary between deferent health professionals Hospital, GP, Dentist • the evidence is still evolving • they may undergo without certainty it will help This uncertainty creates anxiety at an already vulnerable time. 4. Increased Caregiver Responsibility Carers often highlight disadvantages such as: • need for additional care tasks

Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	• managing symptoms or side effects • learning new equipment or procedures • constant monitoring, especially if the patient is at risk of choking or airway issues Without training or support, this can be overwhelming. 6. Accessibility and Inequalities Patients are concerned that: • the technology may not be available in all NHS centres • access could depend on local funding decisions • some groups (e.g., rural patients, those with disabilities, people with communication difficulties) may have less access This raises fears of a “postcode lottery”. 7. Emotional Burden Some fear: • disappointment if the technology does not work • false hope • emotional strain of making a complex treatment decision • feeling pressured to try a new technology they do not fully understand Caregivers often feel an increased emotional weight trying to help patients navigate these decisions. 8. Complexity, Training or Usability Issues (if digital or device-based) Patients may struggle if the technology: • is difficult to use • requires digital skills they do not have • involves equipment they find uncomfortable or embarrassing • needs regular maintenance or technical troubleshooting

	Caregivers may become responsible for managing the technology on the patient's behalf.

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.	Yes. Patients with head and neck cancer are a highly diverse group with different needs depending on tumour site, treatment history, functional status, comorbidities, communication needs, and social context. Certain groups may benefit more or face barriers when using the technology.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. There are several important equality considerations for people affected by head and neck cancer. These relate both to the condition itself and to the technology being appraised. Many patient groups face additional barriers that may limit access, reduce benefit, or increase the risk of poorer outcomes unless addressed. These include language barriers, health literacy, and educational challenges, which can significantly affect understanding, decision-making, and safe use of the technology.

Other issues

13. Are there any other issues that you would like the committee to consider?	Yes. Patients, carers, and support-group leads have highlighted several additional issues that they feel the committee should consider when evaluating this condition and the technology. 1. Patients repeatedly report that they feel “abandoned” once active treatment ends. Survivorship and rehabilitation pathways are inconsistent and rarely meet the complexity of head and neck cancer needs. 2. Any technology that supports long-term recovery, monitoring, or self-management is therefore addressing a major gap. 3. Integration of Third-Sector Organisations Charities such as The Swallows provide: emotional support peer-to-peer lived experience crisis intervention survivorship guidance signposting digital support These services fill major gaps in NHS care. The committee should consider how the technology interacts with, supports, or relies upon third-sector provision.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Head and neck cancer has profound, lifelong impacts on eating, swallowing, speaking, breathing, appearance, mental health, and social participation, with many patients experiencing worsening late effects years after treatment. • Patients and caregivers value current NHS treatment, particularly the expertise of MDTs, but they face major gaps in long-term follow-up, late-effects management, dental access, psychological support, and coordinated survivorship care. • The technology addresses significant unmet needs, especially for those with severe functional impairment, communication difficulties, late effects, or limited access to specialist services. • Equality considerations are critical, including communication disability, language and literacy barriers, digital exclusion, socioeconomic disadvantage, and geographic variation in access across the UK • The committee should consider the major burden placed on caregiver, the importance of third-sector support, the lifelong nature of late effects, and the need for person-centred, accessible, and equitable implementation of any new technology.

Thank you for your time.

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Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Single Technology Appraisal

Pembrolizumab before surgery (neoadjuvant)then with radiotherapy after surgery (adjuvant)for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	██████
2. Name of organisation	Head and Neck Cancer UK(HANCUK)
3. Job title or position	Chair
4a. Brief description of the organisation (including who funds it). How many members does it have?	Registered charity (No 1175181). Patient led with considerable professional input aiming to improve outcomes for patients with Head and Neck Cancer by providing information, signposting support services and participating in research. Funded solely by Donations. Steering committee of 12 with hundreds of contacts.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links	No

Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Face to face, zoom and telephone discussions with patients responding to general call for input. (not specific to pembrolizumab)

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?	Difficulties eating, speaking and socialising. Depression and lack of self-confidence. Carers have to support and encourage with limited assistance and little or no medical background.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Could be much better
8. Is there an unmet need for patients with this condition?	Yes. There is very little professional support and no out of hours contact (except for one charity)

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	It is hoped that the shrinkage of tumours will prevent a recurrence

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects of pembrolizumab are well known, listlessness, pain, diarrhoea, dry mouth and many other occasional effects

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.	Depends on availability and access to treatment

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As above

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.	• Quality of life must be the over-riding consideration • Side effects and any proposals to mitigate should be taken into account • • •

Thank you for your time.

Patient organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

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Single Technology Appraisal

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on 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.

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- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Oxford University NHS Foundation Trust /British Association of Otorhinolaryngologists, Head and Neck Surgeons (ENT UK)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	Tertiary referral Hospital managing head and neck Cancer
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	I am not aware of any funding
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Professional organisation submission

Pembrolizumab before surgery (neoadjuvant)then with radiotherapy after surgery (adjuvant)for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve cure
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Long term disease specific survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. current treatment regimes for de-novo cancer have not evolved past surgery, RT/CRT

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Surgery or surgery and radiotherapy
9a. Are any clinical guidelines used in the	In the UK the most recent treatment guidelines are: Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition

Professional organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

treatment of the condition, and if so, which?	J Laryngol Otol 2024 Vol. 138 Issue S1 Pages S1-S224 DOI: 10.1017/S0022215123001615 https://www.ncbi.nlm.nih.gov/pubmed/38482835 There are also the NICE NG36 guidelines: Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	There would need to be increased PDL-1 testing to avoid delays in treatment. The time to surgery would be increased
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes
10a. How does healthcare resource use differ between the technology and current care?	There is a need for increased PDL-1 testing, There would be the need to administer IO
10b. In what clinical setting should the technology be	Surgically treatable head and neck cancer

Professional organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increased PDL-1 testing. Pathway reviews.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Potentially
11a. Do you expect the technology to increase length of life more than current care?	yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology

13. 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.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. 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?	

16. 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?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes. it is an evolution following on from IO used to treat palliative care
16b. Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival/ Disease specific survival. These have not be evaluated as yet
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA473?	
21. How do data on real-world experience	

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Increased pathological testing • Prolonging time to surgery • Appropriate end points • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Professional organisation submission

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

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Single Technology Appraisal

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Tuesday 6 January 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Please note that this statement template contains confidential information which must not be shared publicly. This information is provided solely as supporting evidence to assist in answering one of the questions.

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Part 1: Treating newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer and current treatment options

Table 1 About you, aim of treatment, place and use of pembrolizumab, sources of evidence and equality

1. Your name	Prof Chris Nutting
2. Name of organisation	Royal Marsden NHS Foundation Trust
3. Job title or position	Consultant Oncologist – Head and Neck Cancer Unit
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 newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer? ☒ A specialist in the clinical evidence base for newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer or pembrolizumab? ☒ Other (please specify): President, British Association of Head and Neck Oncologists
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Improve Overall Survival Improve Disease Free Survival Reduce local tumour recurrence
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	NA – Immunotherapy does not have a high response rate in the neo-adjuvant setting but does prolong EFS (progression, recurrence or death)
10. In your view, is there an unmet need for patients and healthcare professionals in newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer?	There is a major unmet need in patients with locally advanced head and neck cancer with no effective neoadjuvant therapies in this patient group for 20 years.
11. How is newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would pembrolizumab have on the current pathway of care?	Treatment for locally advanced head and neck cancer is with surgical resection and adjuvant radiotherapy (high risk cases) or chemoradiation (very high risk cases). This was the control arm in the Keynote 689 trial. Standard guidelines: final_bahno_standards_2020.pdf Head and neck cancers Topic NICE Practice/clinical care pathways are well defines across the UK. Addition of neo-adjuvant Pembrolizumab will require patients to have oncological treatment before surgery which will require pathway re-design, as patients currently receive oncology treatments in the post-operative period.

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant)then with radiotherapy after surgery (adjuvant)for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

12. Will pembrolizumab 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 pembrolizumab and current care? • In what clinical setting should pembrolizumab be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce pembrolizumab? (for example, for facilities, equipment, or training)	The protocol used 3-weekly Pembrolizumab 200mg fixed dose which is the same protocol used in the NHS for the same drug in the palliative (recurrent/metastatic) setting. Neoadjuvant pembrolizumab before surgery will require service redesign as currently patients do not receive oncology treatment prior to their surgery. Neoadjuvant pembrolizumab should be given in oncology centres specialising in head and neck cancer. Investment in additional capacity in oncology centres will be required.
13. Do you expect pembrolizumab to provide clinically meaningful benefits compared with current care? • Do you expect pembrolizumab to increase length of life more than current care? • Do you expect pembrolizumab to increase health-related quality of life more than current care?	The published data (Uppaluri R, et al. KEYNOTE-689 Investigators. Neoadjuvant and Adjuvant Pembrolizumab in Locally Advanced Head and Neck Cancer. N Engl J Med. 2025 Jul 3;393(1):37-50.) was a Phase 3 randomised clinical trial of 363 patients randomised to Soc vs neo-adjuvant and adjuvant pembrolizumab plus SoC. The trial reported that at the first interim analysis, with median follow-up 38.3 months. Event-free survival at 36 months was 59.8% in the pembrolizumab group and 45.9% in the control group (hazard ratio for progression, recurrence, or death, 0.66; 95% confidence interval [CI], 0.49 to 0.88; two-sided P=0.004) in the CPS-10 population; 58.2% and 44.9%, respectively (hazard ratio, 0.70; 95% CI, 0.55 to 0.89; twosided P=0.003), in the CPS-1 population; and 57.6% and 46.4%, respectively (hazard ratio, 0.73; 95% CI, 0.58 to 0.92; two-sided P=0.008), in the total population. This indicates that in the published data there was an improvement in EFS of 14% with reduction in progression, recurrence or death.

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

14. Are there any groups of people for whom pembrolizumab would be more or less effective (or appropriate) than the general population?	Patients with a CPS of 1 or more were included in the trial.
15. Will pembrolizumab 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)	Neo-adjuvant Pembrolizumab is not a toxic treatment. Treatment related adverse events were 42.9-44.6% in both arms of the trial. Neo-adjuvant Pembrolizumab will require medical treatment for 2 cycles over 6 weeks prior to the surgery and then adjuvant therapy for 12 cycles (36 weeks) after radiotherapy. This is significantly more treatment than current treatment schedules.
16. Will any rules (informal or formal) be used to start or stop treatment with pembrolizumab? Do these include any additional testing?	Treatment with pembrolizumab will continue for 12 cycles after radiotherapy unless there are disease related events (progression, recurrence, death). Follow up of this patient group is clinical and radiological.
17. Do you consider that the use of pembrolizumab will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the pembrolizumab or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No.
18. Do you consider pembrolizumab 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?	Neo-adjuvant and adjuvant pembrolizumab for locally advanced head and neck cancer is the largest change in management in this patient group for 20 years and in that sense is a step change.

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

- Is pembrolizumab a 'step-change' in the management of newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer ? - Does the use of pembrolizumab address any particular unmet need of the patient population?	The Keynote 689 trial shows a reduction in EFS (progression, recurrence, death). Overall Survival data is awaited. Tumours in the head and neck region (mouth, pharynx, larynx) have much greater consequences on eating, swallowing, breathing, and other basic physiological functions than tumours at other sites. The improvements in local tumour control are therefore more clinically important and valuable to patients than at other tumour sites.
19. How do any side effects or adverse effects of pembrolizumab affect the management of newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer and the patient's quality of life?	Neo-adjuvant Pembrolizumab is not a toxic treatment. Treatment related adverse events (G3 or more) were 42.9-44.6% in both arms of the trial. Lethargy is common during treatment as well as the risk of autoimmune side effects which can adversely effect QoL.
20. Do the clinical trials on pembrolizumab reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The standard arm of the Keynote 689 reflects both UK and International SoC. The Keynote 689 trial shows a reduction in EFS (progression, recurrence, death). Overall Survival data is awaited.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	The results are consistent with clinical practice.

Clinical expert statement

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

	Another trial of adjuvant immunotherapy with Nivolumab, (Bourhis et al. "NIVOPOSTOP (GORTEC 2018-01): A phase III randomized trial of adjuvant nivolumab added to radio-chemotherapy in patients with resected head and neck squamous cell carcinoma at high risk of relapse." (2025): LBA2-LBA2), also showed benefit of immunotherapy in this area and is about to be published.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer and this treatment? Please explain if you think any groups of people with newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	No.

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Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
Additional technical team questions	
24. Is the risk of death for people with head and neck squamous cell carcinoma (HNSCC) who survive after 5 years of diagnosis different to the general population's risk of death? If yes, please provide an estimate of the difference observed at 5 and 10 years post diagnosis	Not if matched for co-morbidity. However, these cancers of the oral cavity, pharynx, larynx and other sites are associated with smoking and alcohol use. These patients therefore have a higher rate of second cancers, cardiovascular, respiratory and liver disease than the general population in the years after treatment.
25. Table 19 from the EAG report (copied below, please note confidential data included in table) includes the event free survival and overall survival benefit of pembrolizumab versus standard of care. The first row includes the data from the interim-analysis of KEYNOTE-689. The subsequent rows shows the modelled results. - Please can you comment on the suitability of the results at 10 years and which of the models closely predicts the outcomes you would expect. - Do any models (1-10) over or underestimate the 10-year outcomes?	The model shows a [REDACTED] overall survival benefit which is approximately what the head and neck community hope to see from the trial follow up. This size of survival benefit would be sufficient to change clinical practice in head and neck cancer. The modelled numbers are too close together to select a preferred value.

Additional information from EAG report:

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Table 19 (from EAG report): Incremental EFS and OS benefit of pembrolizumab + SOC relative to SOC for the 10 candidate model combinations, (adapted from Table 65, CS Appendix J). (Confidential data included in table)

Model #	Approach # / EF → LR / EF → IRP / EF → Death	Predicted difference in EFS (Perioperative pembrolizumab + SOC vs. SOC)						Predicted difference in OS (Perioperative pembrolizumab + SOC vs. SOC)					
		1 yrs	2 yrs	3 yrs	4 yrs	4.5 yrs	10 yrs	1 yrs	2 yrs	3 yrs	4 yrs	4.5 yrs	10 yrs
NA	Observed, KEYNOTE-689*	13.2%	11.2%	13.3%	9.4%	11.5%	-						
1	1 / Log-normal / Gen gamma / Gen gamma	10.2%	11.9%	12.0%	11.8%	11.6%	10.0%						
2	1 / Gompertz / Gen gamma / Gen gamma	9.3%	11.4%	12.4%	13.1%	13.3%	13.5%						
3	1 / Gen gamma / Gen gamma / Gen gamma	9.2%	11.7%	12.7%	13.2%	13.4%	14.4%						
4	1 / Gompertz / Gompertz / Gen gamma	10.3%	11.2%	11.2%	11.2%	11.1%	10.4%						
5	1 / Log-logistic / Gen gamma / Gen gamma	10.1%	11.9%	12.3%	12.2%	12.2%	11.3%						
6	1 / Log-normal / Gompertz / Gen gamma	11.2%	11.7%	10.8%	9.9%	9.4%	6.7%						
7	1 / Weibull / Gen gamma / Gen gamma	10.1%	11.9%	12.3%	12.3%	12.3%	11.9%						
8	1 / Gamma / Gen gamma / Gen gamma	10.1%	12.0%	12.3%	12.3%	12.3%	11.9%						
9	1 / Gen gamma / Gompertz / Gen gamma	10.2%	11.5%	11.5%	11.3%	11.2%	11.7%						
10	1 / Log-logistic / Gompertz / Gen gamma	11.1%	11.7%	11.0%	10.3%	10.0%	8.4%						

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The Keynote 689 trial of neoadjuvant pembrolizumab is published and shows a reduction in Event-free-survival (progression, recurrence, death).

The standard arm of the Keynote 689 reflects both UK and International SoC

Neo-adjuvant and adjuvant pembrolizumab for locally advanced head and neck cancer is the largest change in management in this patient group for 20 years and is a step change.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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Single Technology Appraisal

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Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Tuesday 6 January 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Please note that this statement template contains confidential information which must not be shared publicly. This information is provided solely as supporting evidence to assist in answering one of the questions.

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer and current treatment options

Table 1 About you, aim of treatment, place and use of pembrolizumab, sources of evidence and equality

1. Your name	Will Ince
2. Name of organisation	Cambridge University NHS trust
3. Job title or position	Consultant 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 newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer? ☒ A specialist in the clinical evidence base for newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer or pembrolizumab? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

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7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	For newly diagnosed, resectable, locally advanced squamous cell head and neck cancer, the evidence suggests we are able to give treatment with curative intent, i.e., therapy designed to eradicate disease and deliver long-term remission rather than simply slow progression. This is reflected in standard-care pathways described in national guidance, where locally advanced disease is typically managed with definitive local therapy (surgery and radiotherapy) with escalation using systemic therapy (Cisplatin) in higher-risk situations, to remove or destroy the cancer and reduce the risk of recurrence.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	‘Treatment response’ is a broad term and should not be conflated with survival benefit. In my opinion, a treatment response is clinically significant in the metastatic if it produces a clear and measurable reduction in tumour burden of at least 30% in maximal diameter on cross-sectional imaging, consistent with a RECIST partial response, or an equivalent reduction in overall tumour volume. In the perioperative setting, as reflected in KEYNOTE-689, a clinically meaningful response may also be defined pathologically, with substantial tumour regression in the resection specimen, particularly major pathological response ($\leq 10\%$ viable invasive tumour), which indicates true biological anti-tumour activity. In resectable, locally advanced squamous cell head and neck cancer, such responses are clinically significant because they maintain or improve resectability and are associated with a materially reduced risk of recurrence, as captured by improvements in event-free survival.
10. In your view, is there an unmet need for patients and healthcare professionals in newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer?	There remains a clear and clinically important unmet need for both patients and healthcare professionals in newly diagnosed, resectable, locally advanced squamous cell carcinoma of the head and neck, and this is reflected in outcome data from contemporary series. Despite optimal standard management with surgery followed by risk-adapted radiotherapy or chemoradiotherapy, approximately 40–50% of patients with stage III–IV disease will experience disease recurrence, either locoregionally or at distant sites, within five years, and the majority of those who relapse will die of their disease. Five-year overall survival for resected, locally advanced disease has historically

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	remained in the region of 50% despite decades of treatment intensification, indicating that current multimodality approaches fail to cure a substantial proportion of patients. From the patient perspective, there is an unmet need to improve cure rates without disproportionately increasing long-term morbidity. Curative treatment frequently results in significant and durable functional impairment, with up to half of patients experiencing long-term swallowing dysfunction, speech difficulties, or feeding-tube dependence following surgery and adjuvant (chemo)radiotherapy. Conventional intensification strategies using cytotoxic chemotherapy modestly improve disease control but at the cost of increased acute and late toxicity. From the clinician and health-system perspective, there is a further unmet need for earlier and more effective systemic disease control. Current pathways rely largely on post-operative pathological features to guide escalation of therapy, yet distant metastases still occur in around 20–30% of high-risk patients, implying the presence of occult micrometastatic disease at diagnosis that is not adequately addressed by local therapy alone. There is therefore a clear need for treatments that can be safely integrated into curative pathways to reduce recurrence risk and improve long-term outcomes beyond what is achievable with existing standard care.
11. How is newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In the NHS, “newly diagnosed, resectable, locally advanced” squamous cell carcinoma of the head and neck (LA-HNSCC) is managed with curative intent using a multidisciplinary pathway. For most sites that are clearly resectable (particularly oral cavity, and selected larynx/hypopharynx), the standard approach is primary surgery with appropriate neck management (selective/modified radical neck dissection as indicated), followed by pathology-directed adjuvant radiotherapy (RT) or adjuvant chemoradiotherapy (CRT) when adverse features are present. In parallel, for some anatomically resectable tumours where function preservation is a key aim (classically larynx and parts of the pharynx, and many oropharyngeal cancers), definitive (chemo)radiotherapy with surgery reserved for salvage remains widely used. This “either surgery + risk-adapted adjuvant therapy” versus “primary (chemo)radiotherapy” choice is often the most important branch point in the pathway and depends on site, stage, predicted functional outcomes, and local expertise. Clinical guidelines used in NHS practice include NICE guidance on cancers of the upper aerodigestive tract and UK National Multidisciplinary Guidelines which are widely referenced by MDTs for staging, treatment selection and follow-up.

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What impact would pembrolizumab have on the current pathway of care?	The pathway of care is well defined (urgent referral, diagnostic work-up, staging, MDT decision, definitive treatment, rehabilitation, surveillance), but there is meaningful variation across the NHS in how “resectable locally advanced” cases are routed. The main areas of variation are: (1) the balance between primary surgery versus primary (chemo)radiotherapy for borderline or function-critical disease (especially oropharynx/larynx/hypopharynx), (2) thresholds and interpretation for “high-risk” pathological features that trigger adjuvant cisplatin-based CRT rather than RT alone, and (3) capacity and access issues (surgical reconstruction capacity, RT planning capacity, dental/SLT support), which can influence sequencing and timing. If perioperative pembrolizumab is adopted (as per KEYNOTE-689), it would add an immunotherapy component before surgery and continue after surgery alongside risk-adapted standard adjuvant therapy, rather than replacing surgery/RT/CRT. Practically, this would (a) introduce a neoadjuvant “window” of pembrolizumab prior to planned resection, (b) extend systemic treatment time post-operatively with adjuvant pembrolizumab, and (c) require MDT integration of immunotherapy logistics and toxicity management (immune-related adverse event recognition, steroid pathways, coordination with surgical timing and adjuvant RT starts). In KEYNOTE-689, the regimen improved event-free outcomes and increased major pathological response rates, and also appeared to reduce the proportion of patients with high-risk pathological features and the proportion requiring adjuvant high-dose cisplatin—an effect that, if reproduced in routine practice, could shift some patients away from the most toxic postoperative CRT intensification while preserving curative intent.
12. Will pembrolizumab 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 pembrolizumab and current care? - In what clinical setting should pembrolizumab be used? (for	Pembrolizumab is already established in NHS clinical practice for head and neck squamous cell carcinoma in the recurrent or metastatic setting, where it is used as first-line systemic therapy in patients with PD-L1–expressing disease. Its use in that context is well embedded within existing NHS secondary care oncology services. I have some concerns about the utility of the biomarker for patient selection outlined at the end of this section It is not currently part of routine NHS care for newly diagnosed, resectable, locally advanced disease when given in the perioperative setting (that is, before surgery and continued after surgery alongside radiotherapy with or without cisplatin). Use in this way would represent a change to the

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example, primary or secondary care, specialist clinic) • What investment is needed to introduce pembrolizumab? (for example, for facilities, equipment, or training)	current curative-intent pathway rather than a continuation of existing practice, and would be dependent on future NICE commissioning decisions. Compared with current standard care, which consists of surgery followed by risk-adapted adjuvant radiotherapy or chemoradiotherapy, a perioperative pembrolizumab strategy introduces additional systemic anti-cancer therapy activity both before and after surgery. This results in increased use of PDL1 testing, oncology day-unit capacity, pharmacy preparation services, pre-treatment assessments, routine blood monitoring, and outpatient oncology review appointments. There is also a requirement for structured pathways to recognise and manage immune-related adverse events, including access to acute oncology services and timely involvement of other medical specialties such as endocrinology, respiratory medicine, gastroenterology, dermatology and rheumatology. These needs differ from those associated with conventional cytotoxic chemotherapy and radiotherapy. That said, perioperative pembrolizumab may alter downstream resource use. By reducing the frequency of high-risk pathological features at surgery, it may reduce the proportion of patients requiring the most intensive adjuvant treatment (in particular high-dose cisplatin-based chemoradiotherapy), which is associated with significant toxicity, inpatient admissions, and long-term morbidity. The net impact on NHS resources would therefore depend on real-world toxicity rates, treatment compliance, and the balance between additional immunotherapy activity and potential reductions in downstream treatment intensity. If adopted for this indication, pembrolizumab would be delivered entirely within secondary care specialist oncology services. Treatment decisions would be made within the specialist head and neck multidisciplinary team, with close coordination between surgical, medical oncology and radiation oncology teams. Administration would take place in established systemic anti-cancer therapy units within cancer centres or accredited satellite units. Ongoing monitoring and management of toxicity would be overseen by oncology teams with support from acute oncology services, particularly given the

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	potential for immune-related adverse events to arise before surgery, after surgery, or during adjuvant radiotherapy. The introduction of perioperative pembrolizumab would not require major new physical infrastructure, as NHS cancer centres already deliver immunotherapy routinely. However, additional investment would likely be needed in day-unit capacity, pharmacy services, and staffing to accommodate increased treatment volume. Workforce training is an important requirement. This includes education for oncology nurses, pharmacists, surgeons, anaesthetists and acute oncology teams in recognising and managing immune-related toxicity, understanding perioperative timing considerations, and applying steroid and immunosuppression protocols safely in the curative setting. From a pathway perspective, systems would need to ensure timely reflex PD-L1 testing and reporting early in the diagnostic process and units access to timely PDL-1 testing is anecdotally very variable, integration of oncology reviews into pre-operative planning, and clear protocols governing treatment interruptions around surgery and radiotherapy. Governance arrangements, electronic prescribing systems, consent processes and outcome monitoring would also need to be updated to reflect the new treatment pathway. PD-L1 is a relatively poor biomarker for patient selection in the perioperative, curative-intent setting of resectable, locally advanced head and neck squamous cell carcinoma. While PD-L1 expression has prognostic and predictive value in the recurrent or metastatic setting, its utility is substantially weaker earlier in the disease course for several biological and practical reasons. PD-L1 expression is biologically dynamic rather than fixed. In newly diagnosed disease, PD-L1 levels can change over time and in response to inflammation, biopsy, surgery, radiotherapy and systemic treatment. A single pre-treatment biopsy may therefore not accurately reflect the immunological state of the tumour at the time when pembrolizumab is exerting its effect, particularly when treatment is delivered both before and after surgery.

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	PD-L1 assessment is subject to significant spatial heterogeneity. Head and neck tumours often show marked intra-tumoural and inter-tumoural variation in PD-L1 expression, and small diagnostic biopsies may misclassify tumours that have mixed PD-L1–positive and PD-L1–negative regions. This limitation is particularly relevant in resectable disease, where the surgical specimen frequently demonstrates broader immune heterogeneity than was apparent on biopsy. The mechanism of benefit in the perioperative setting is not limited to direct tumour PD-L1 expression. In this context, pembrolizumab may act through priming and expansion of systemic anti-tumour immune responses, including effects on micrometastatic disease and immune memory. These mechanisms are not fully captured by PD-L1 expression on the primary tumour alone and help explain why benefit is observed across PD-L1 subgroups in perioperative immunotherapy trials. It is an imperfect predictive biomarker even in advanced disease, where responses are still seen in PD-L1–negative tumours and non-response is common in PD-L1–positive tumours. This limitation becomes more pronounced in curative-intent populations with different tumour biology, lower disease burden, and longer natural history, reducing the discriminatory power of PD-L1 for individual patient benefit. Finally, from an NHS pathway perspective, strict reliance on PD-L1 as a gatekeeping biomarker risks excluding patients who may derive meaningful absolute benefit, particularly those with high-risk pathological features and substantial baseline recurrence risk. In a setting where the goal is cure rather than palliation, and where treatment is delivered within a defined perioperative window, a broader eligibility approach is clinically more appropriate than narrow biomarker restriction based on PD-L1 alone.
13. Do you expect pembrolizumab to provide clinically meaningful benefits compared with current care? Do you expect pembrolizumab to increase length of life more than current care?	Yes. Based on KEYNOTE-689, perioperative pembrolizumab is expected to provide clinically meaningful benefit compared with current care, principally by reducing the risk of recurrence (event-free survival) and, with longer follow up, improving overall survival in a population treated with curative intent. In the interim analysis (median follow up around 4.5 years), the observed absolute difference between arms was approximately 11.5% for event-free survival and ■■■ for overall survival. These

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Do you expect pembrolizumab to increase health-related quality of life more than current care?	are clinically important effect sizes in a curative setting where standard multimodality therapy still leaves a substantial residual recurrence risk. I also expect a modest improvement in health-related quality of life at a population level, primarily through fewer recurrences (avoiding salvage surgery, re-irradiation, and palliative systemic therapy) and potentially fewer patients requiring the most intensive adjuvant treatment. Any quality of life gain must be balanced against immune-related adverse events and the additional treatment visits associated with perioperative immunotherapy.
14. Are there any groups of people for whom pembrolizumab would be more or less effective (or appropriate) than the general population?	Yes. In my opinion, there are groups in whom pembrolizumab is likely to be more effective and/or more appropriate, and groups in whom benefit is less certain or use may be inappropriate. More likely to benefit: Patients with higher baseline risk of recurrence (for example bulky nodal disease, extranodal extension, multiple involved nodes, T4 primary disease or other adverse pathological features) are likely to gain greater absolute benefit, because their underlying event rate with current care is higher. Less likely to benefit (or smaller absolute benefit): Some HPV-associated oropharyngeal cancers have relatively favourable outcomes with established therapy; absolute incremental benefit may be smaller and needs careful consideration against added toxicity and pathway complexity. Less appropriate: Patients with active autoimmune disease requiring systemic immunosuppression, those on substantial baseline corticosteroids or other immunosuppressants, and patients with prior severe immune-related adverse events are at increased risk of harm. Patients in whom any delay to surgery or adjuvant radiotherapy would be clinically unsafe (for example very aggressive local disease or service circumstances where additional pre-operative therapy would risk breaching time-critical pathways) may be less suitable for neoadjuvant dosing.
15. Will pembrolizumab be easier or more difficult to use for patients or healthcare professionals than	Pembrolizumab will be more complex to deliver than current care for both patients and healthcare professionals because it adds systemic therapy visits pre-operatively and post-operatively, plus

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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)	monitoring for immune-related toxicity. This increases outpatient assessments, day-unit capacity requirements, pharmacy workload, and the need for clear acute oncology escalation pathways. For patients, the main practical implications are additional hospital attendances, blood tests and symptom monitoring, and the need for prompt reporting of new symptoms (rash, diarrhoea, breathlessness, fatigue, endocrine symptoms). Many patients will find the potential for improved cure rates acceptable, but the extra appointments and the uncertainty around immune-related events should be discussed clearly at consent. For professionals, the key practical issues are: integration with surgical timing, ensuring that adjuvant radiotherapy starts within clinically appropriate timeframes, and coordinated management of immune-related toxicities across oncology, surgery, anaesthetics and acute medicine. Conversely, if perioperative pembrolizumab reduces the proportion requiring high-dose cisplatin-based adjuvant chemoradiotherapy, this may reduce some chemotherapy-related toxicity, unplanned admissions and supportive care burden in a subset.
16. Will any rules (informal or formal) be used to start or stop treatment with pembrolizumab? Do these include any additional testing?	Starting rules should reflect trial entry criteria: confirmed resectable, locally advanced squamous cell carcinoma of the head and neck appropriate for curative-intent surgery; adequate performance status and organ function; and absence of major contraindications such as uncontrolled autoimmune disease requiring systemic immunosuppression. Depending on the final marketing authorisation and NICE recommendation, [REDACTED] I note the ITT population in the trial were all comers rather than [REDACTED]. Stopping and holding rules should follow established immunotherapy toxicity guidance, with treatment interruption for clinically significant immune-related adverse events (typically grade 2 events not resolving with supportive care, and all grade 3 or higher events), and permanent discontinuation for life-threatening immune toxicities (for example myocarditis, severe pneumonitis, severe neurological immune toxicity) or recurrent severe toxicity on rechallenge. Additional testing: routine baseline and on-treatment blood monitoring (full blood count, renal and liver function, thyroid function) is required. In symptomatic patients, additional investigations (for

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	example cortisol/ACTH, HbA1c/glucose, inflammatory markers, imaging, pulmonary function tests) should be triggered promptly through agreed pathways.
17. Do you consider that the use of pembrolizumab will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the pembrolizumab or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. There are substantial benefits that are often not fully captured by generic QALY instruments in this disease area. Avoidance of recurrence has large downstream effects that are not always well measured, including reduced need for salvage surgery or re-irradiation, reduced feeding-tube dependence after salvage, reduced tracheostomy rates, and reduced carer burden. Patients value avoiding repeated procedures, prolonged rehabilitation, and the psychological impact of recurrence, which may not be fully reflected in standard utility instruments. If perioperative pembrolizumab reduces the need for the most intensive adjuvant chemoradiotherapy in a subset, there may be benefits in acute toxicity and late functional outcomes (swallowing, speech, xerostomia) that are difficult to fully capture, particularly over long horizons.
18. Do you consider pembrolizumab 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 pembrolizumab a 'step-change' in the management of newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer ?	Yes. In my opinion, perioperative pembrolizumab is innovative and represents a potential step-change in the curative management of resectable, locally advanced head and neck cancer. This has excited the community. Historically, attempts to improve cure rates in this setting have relied on intensifying surgery, radiotherapy, or adding cytotoxic chemotherapy, with limited survival gains and substantial toxicity. Introducing effective immunotherapy earlier, integrated around surgery and adjuvant treatment, directly addresses the unmet need of reducing recurrence risk without simply escalating conventional toxicity. If implemented well, this approach can improve long-term outcomes while maintaining standard definitive local therapies, and may shift some patients away from the highest-toxicity postoperative intensification.

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Does the use of pembrolizumab address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of pembrolizumab affect the management of newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer and the patient's quality of life?	Pembrolizumab introduces immune-related adverse events that differ from the toxicity profile of radiotherapy and cisplatin. These can affect multiple organ systems (skin, gastrointestinal, endocrine, liver, lung, joints) and may occur pre-operatively, post-operatively, or during adjuvant radiotherapy. From a management perspective, this requires proactive patient education, low thresholds for investigation, and rapid access to acute oncology advice. Some events (for example hypothyroidism) may be manageable with long-term replacement therapy and limited impact on quality of life; others (for example pneumonitis, colitis) can be serious and may require hospital admission and high-dose steroids, which can temporarily worsen quality of life and complicate perioperative care. Overall, in experienced NHS centres with established immunotherapy pathways, these risks are manageable, but they must be balanced against potential improvements in cure and the avoidance of recurrence-related morbidity.
20. Do the clinical trials on pembrolizumab reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Overall, the trial pathways are broadly consistent with UK practice for resectable, locally advanced disease treated with curative intent, including surgery with appropriate neck management followed by risk-adapted adjuvant radiotherapy with or without cisplatin. The multidisciplinary decision-making model aligns well with UK head and neck MDT practice. Potential differences include variation in cisplatin eligibility and dosing, radiotherapy techniques and fractionation across centres, and real-world waiting times that can influence time to surgery and time to start of adjuvant radiotherapy. These differences do not invalidate the findings but emphasise the importance of implementing pembrolizumab without delaying definitive local therapy. The most important outcomes are event-free survival (captures recurrence and death, and is clinically meaningful in curative-intent settings), overall survival (clinically definitive but currently immature), and patient-centred functional outcomes (swallowing, speech, feeding-tube dependence). Pathological response measures (major pathological response and pathological

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Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	complete response) provide supportive biological evidence but should be considered surrogate endpoints; they are not, by themselves, sufficient unless linked to long-term event reduction. Safety, including immune-related adverse events and any impact on surgical complications and radiotherapy delivery, is also critical.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes. There is relevant supportive evidence from multiple neoadjuvant (“window-of-opportunity”) immunotherapy studies in resectable head and neck cancer demonstrating measurable pathological regression after short-course PD-1 blockade and suggesting that pathological response may correlate with longer-term outcomes. While these studies are smaller and not definitive for effectiveness, they support biological plausibility and feasibility of perioperative immunotherapy. In addition, extensive real-world experience with pembrolizumab in recurrent/metastatic head and neck cancer provides confidence in the practical management of immune-related toxicity within NHS services, although this does not substitute for curative-intent perioperative efficacy data.
22. How do data on real-world experience compare with the trial data?	For head and neck cancer, real-world outcomes with pembrolizumab in the recurrent/metastatic setting are broadly consistent with trial expectations, particularly in PD-L1–expressing disease, supporting generalisability of efficacy and a well-characterised safety profile. For the specific perioperative indication, real-world data are necessarily limited at present. In my view, the main determinant of whether real-world effectiveness matches trial effectiveness will be successful pathway integration, specifically avoiding delays to surgery and avoiding delays to the start of adjuvant radiotherapy. Centres with established immunotherapy governance and acute oncology support should be able to deliver outcomes close to those observed in trials.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer and this treatment? Please explain if you think any groups of	Potential equality issues include differential access to specialist head and neck MDTs, systemic therapy delivery units, and timely PD-L1 testing. Patients in remote regions may face greater travel burden for pre-operative and post-operative infusions, which could differentially affect people with lower socioeconomic status, limited mobility, or caring responsibilities. People with disabilities (for example severe baseline swallowing impairment, communication difficulties, or significant comorbidity) may be disadvantaged if pathways are not adapted to provide accessible information and rapid support for toxicity monitoring.

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people with newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Language barriers and health literacy may affect early reporting of immune-related symptoms, so services should ensure accessible written information and interpreter support. These issues are not unique to pembrolizumab but may be accentuated by the added number of contacts and the need for prompt symptom reporting.

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More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
Additional technical team questions	
24. Is the risk of death for people with head and neck squamous cell carcinoma (HNSCC) who survive after 5 years of diagnosis different to the general population's risk of death? If yes, please provide an estimate of the difference observed at 5 and 10 years post diagnosis	Yes. In my opinion, the risk of death for people who survive 5 years after diagnosis of locally advanced HNSCC remains higher than the general population. This is driven by: an ongoing risk of late recurrence in a minority; an elevated risk of second primary cancers (particularly aerodigestive tract and lung) in people with tobacco and alcohol exposure; and competing mortality from cardiovascular and respiratory disease, which is more common in this population and may be exacerbated by prior treatment. At a population level, I would expect excess mortality to persist at both 5 and 10 years post-diagnosis. A pragmatic estimate is that all-cause mortality risk remains meaningfully higher than age-matched general population risk (for example on the order of 20–50% higher), with the greatest excess in patients with continued smoking or significant comorbidity.
25. Table 19 from the EAG report (copied below, please note confidential data included in table) includes the event free survival and overall survival benefit of pembrolizumab versus standard of care. The first row includes the data from the interim-analysis of KEYNOTE-689. The subsequent rows shows the modelled results.	In my view, the 10-year modelled differences should be clinically plausible relative to the observed interim data at approximately 4.5 years. The observed absolute differences at 4.5 years are 11.5% for event-free survival and ■■■ for overall survival. Over time, recurrence hazards typically fall and the event-free survival curve tends to flatten; I would expect the incremental benefit at 10 years to be broadly similar to, or somewhat smaller than, the 4–5 year benefit, rather than increasing substantially. On that basis, models that predict 10-year EFS differences in the range of about 10–12% and OS differences around ■■■ appear most clinically plausible (for example Models 1, 4, 8, 9, and 10, noting that 10 is at the lower end).

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- Please can you comment on the suitability of the results at 10 years and which of the models closely predicts the outcomes you would expect. - Do any models (1-10) over or underestimate the 10-year outcomes?	Models 2 and 3 predict 10-year EFS differences of 13.5–14.4% and OS differences of ██████. In my opinion, these likely overestimate long-term benefit because they imply that the incremental separation continues to widen well beyond the period when most recurrences occur. Model 7 predicts substantially lower 10-year differences (EFS 6.7%, OS ██████ and underestimates benefit if the treatment effect is durable in a proportion of patients which is likely. Overall, I consider Models 1, 4 and 9 as closest to expected 10-year outcomes, with Models 2 and 3 likely optimistic and Model 7 likely pessimistic.

Additional information from EAG report:

Table 19 (from EAG report): Incremental EFS and OS benefit of pembrolizumab + SOC relative to SOC for the 10 candidate model combinations, (adapted from Table 65, CS Appendix J). (████████ included in table)

Model #	Approach # / EF → LR / EF → IRP / EF → Death	Predicted difference in EFS (Perioperative pembrolizumab + SOC vs. SOC)						Predicted difference in OS (Perioperative pembrolizumab + SOC vs. SOC)					
		1 yrs	2 yrs	3 yrs	4 yrs	4.5 yrs	10 yrs	1 yrs	2 yrs	3 yrs	4 yrs	4.5 yrs	10 yrs
NA	Observed, KEYNOTE-689*	13.2%	11.2%	13.3%	9.4%	11.5%	-	████	████	████	████	████	████
1	1 / Log-normal / Gen gamma / Gen gamma	10.2%	11.9%	12.0%	11.8%	11.6%	10.0%	████	████	████	████	████	████
2	1 / Gompertz / Gen gamma / Gen gamma	9.3%	11.4%	12.4%	13.1%	13.3%	13.5%	████	████	████	████	████	████
3	1 / Gen gamma / Gen gamma / Gen gamma	9.2%	11.7%	12.7%	13.2%	13.4%	14.4%	████	████	████	████	████	████
4	1 / Gompertz / Gompertz / Gen gamma	10.3%	11.2%	11.2%	11.2%	11.1%	10.4%	████	████	████	████	████	████
5	1 / Log-logistic / Gen gamma / Gen gamma	10.1%	11.9%	12.3%	12.2%	12.2%	11.3%	████	████	████	████	████	████
6	1 / Log-normal / Gompertz / Gen gamma	11.2%	11.7%	10.8%	9.9%	9.4%	6.7%	████	████	████	████	████	████
7	1 / Weibull / Gen gamma / Gen gamma	10.1%	11.9%	12.3%	12.3%	12.3%	11.9%	████	████	████	████	████	████
8	1 / Gamma / Gen gamma / Gen gamma	10.1%	12.0%	12.3%	12.3%	12.3%	11.9%	████	████	████	████	████	████

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9	1 / Gen gamma / Gompertz / Gen gamma	10.2%	11.5%	11.5%	11.3%	11.2%	11.7%						
10	1 / Log-logistic / Gompertz / Gen gamma	11.1%	11.7%	11.0%	10.3%	10.0%	8.4%						

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Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Perioperative pembrolizumab is expected to provide clinically meaningful benefit by reducing recurrence risk in resectable, locally advanced HNSCC treated with curative intent.

Interim KEYNOTE-689 results show clinically important absolute improvements at around 4.5 years.

Implementation in the NHS is feasible within established systemic therapy services but requires careful pathway integration to avoid delaying surgery or adjuvant radiotherapy.

Biomarkers in head and neck Benefit is likely greatest in PD-L1–expressing and higher-risk disease; patient selection and immunotherapy-toxicity governance are essential in a curative pathway.

Long-term modelling should be conservative; 10-year gains should not substantially exceed interim observed separation given the typical time course of recurrence.

Thank you for your time.

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Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]



University of
Sheffield

Division of
Population
Health

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]. A Single Technology Appraisal

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Rider on responsibility for report

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Contributions of authors

Sarah Davis acted as project lead. Emily Pulsford critiqued the company's search strategy. Christopher Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Jessica Forsyth critiqued the statistical aspects of the submission. Andrew Metry and Sarah Davis critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

AE	Adverse Event
AEOSI	Adverse Events of Special Interest
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
APaT	All Participants as Treated
BICR	Blinded Independent Central Review
BIPR	Blinded Independent Pathological Review
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CPS	Combined Positive Score
CRT	Chemoradiotherapy
CS	Company submission
CT	Computed tomography
CSR	Clinical Study Report
DCO	Data cut-off
DFS	Disease-free survival
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free survival
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module
EQ-5D-5L	EuroQol 5-Dimensions 5-Level
EUCTR	European Union Clinical Trials Register
EXTREME	Cetuximab plus platinum-based chemotherapy regimen

HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
IA1	First interim analysis
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRP	Incurable recurrence/progression
ITT	Intention-to-treat
IV	Intravenous
LA	Locally advanced
L/SR	Local or salvageable recurrence
mPR	Major pathological response
N/A	Not applicable
NMA	Network meta-analysis
NR	Not reached
OS	Overall survival
PAS	Patient Access Scheme
pCR	Pathological complete response
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient-reported outcome
PAS	Patient access scheme
QxW	Every x weeks
QALY	Quality-adjusted life year
R/M	Recurrent or metastatic
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk
RT	Radiotherapy
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SOC	Standard of care

TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TPS	Tumour proportion score
VAS	Visual analogue scale

1 Executive summary

This External Assessment Group (EAG) report assesses pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for the treatment of newly diagnosed resectable, locally advanced (LA), head and neck squamous cell cancer (HNSCC) in adults. The company submission (CS) states that pembrolizumab would be given as neoadjuvant treatment and adjuvant treatment in addition to the current standard of care (SOC) treatment, which it describes as being surgical resection followed by radiotherapy (RT) with or without concomitant platinum-based chemotherapy. The key study informing the CS is the KEYNOTE-689 trial which compares pembrolizumab with SOC to SOC alone. This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). The results presented in the EAG report include the patient access scheme (PAS) price for pembrolizumab but the list prices for comparator technologies and other technologies given as subsequent treatments. For the EAG analyses presented in the confidential appendix to this report, confidential prices have been used that reflect the commercial agreements for pembrolizumab, nivolumab and cetuximab.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in Sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of National Institute for Health and Care Excellence (NICE).

1.1 Overview of EAG's key issues

Most of the key issues identified by the EAG relate to the choice of extrapolation models used to estimate transitions from the event-free (EF) health state, which in turn impacts overall survival (OS), and the application of the cure assumption. The choice of models was also dependent on assessing the visual fit of the various model combinations to the data available from KEYNOTE-689, but this was subject to additional uncertainty due to the high degree of censoring in the OS data beyond 3 years.

There was also some uncertainty related to the rate of transitions from the local or salvageable recurrence (L/SR) and incurable recurrence/progression (IRP) states due to low numbers of events informing some of these transitions. The EAG also identified an issue with the company's estimates of resource use, which used data from the 'all patients as treated' (APaT) population instead of the 'intention to treat' (ITT) population.

Table 1 Summary of key issues

ID 6477	Summary of issue	Impact on results	Report sections
1	Uncertainty in the long-term extrapolation of OS due to data only being available from the first interim analysis of KEYNOTE-689	Unknown but has the potential to be important based on company scenario analyses.	4.2.6.7
2	Company's choice of extrapolation models to inform event free survival (EFS) and OS	Small	4.2.6.7
3	Uncertainty in the application of the cure assumption	Small but varies depending on the models selected	4.2.6.7
4	Uncertainty in transitions for patients leaving the L/SR and IRP state	Moderate	4.2.6.7
5	Resource use calculated based on the APaT population instead of the ITT population	Moderate	4.2.9.11

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- an alternative set of curves informing the transitions out of the EF state to avoid using the Gompertz curves which exhibited effective plateaus
- transitions from the L/SR and IRP states calculated by pooling data across both arms of KEYNOTE-689
- resource use for surgery and adjuvant therapy informed by the ITT population instead of the APaT population from KEYNOTE-689
- updated prices used for generic drugs
- corrected intravenous (IV) administration costs for adjuvant pembrolizumab
- corrected calculation of resource use frequency for the L/SR and IRP health states

However, the EAG notes that none of these changes individually had a large impact on the ICER.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing OS relative to SOC, with additional years spent in the EF health state which has a higher health-related quality of life (HRQoL) than the post-recurrence/post-progression states
- Marginally reducing the time spent in post-recurrence/post-progression states
- Increasing the adverse event burden of adjuvant treatment which has only a small impact on the QALYs

Overall, the technology is modelled to affect costs by:

- Increasing drug acquisition costs and administration costs during adjuvant treatment and during neoadjuvant treatment to a lesser extent
- Reducing drug acquisition costs for subsequent treatments given to patients who have experienced an IRP, and to a lesser extent reducing subsequent treatment costs to those experiencing an L/SR
- Reducing costs for surgery and adjuvant radiotherapy
- Increasing disease management costs during additional time spent in the EF state, although these are partially offset by reduced disease management costs for patients who experience a recurrence or progression
- Increasing costs required for programmed death-ligand 1 (PD-L1) testing to identify patients with a combined positive score (CPS) of ≥ 1 .

The modelling assumptions that have the greatest effect on the ICER are:

- Applying the most pessimistic choice of curves to extrapolate EFS and OS from within the 10 finalist curve combinations identified by the company
- Applying the least pessimistic choice of curves to extrapolate EFS and OS from within the 10 finalist curve combinations identified by the company
- Applying the alternative censoring for EFS to align with the censoring for OS
- Using the ITT population to define the proportions having initial surgery, adjuvant radiotherapy and adjuvant cisplatin use
- Applying transitions from the L/SR and IRP states calculated by pooling data across both arms of KEYNOTE-689

- Whether long-term survival is capped using general population mortality without any adjustment to reflect an increased risk of death for patients with HNSCC

1.3 EAG's key issues

The key issues related to the clinical effectiveness and cost-effectiveness of pembrolizumab with SOC compared to SOC are summarised below as issues 1 to 5.

Issue 1 Uncertainty in the long-term extrapolation of OS due to data only being available from the first interim analysis of KEYNOTE-689

Report section	4.2.6.7
Description of issue and why the EAG has identified it as important	There is uncertainty in the OS outcomes of this patient group within the KEYNOTE-689 trial due to the high degree of censoring at approximately 3 years within the data available from the first interim analysis (IA1). This therefore results in uncertainty when assessing the visual fit of the OS model estimates to the observed OS data and thus model selection.
What alternative approach has the EAG suggested?	No alternative approach is suggested as this issue is caused by the duration of trial follow-up available from KEYNOTE-689 at the time of the CS.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is uncertain as it depends whether data from any later data cut-offs (DCOs), when they become available, are in line with the long-term extrapolations made based on the current DCO (July 2024). However, the company's scenario analyses using plausible alternative extrapolation models fitted to the current DCO suggest that uncertainty in the long-term extrapolation of outcomes is the most important factor driving uncertainty in the cost-effectiveness estimates.
Could any additional evidence or analyses be provided to resolve this key issue?	The CS states that additional evidence may be available in the next 12 months, although the exact timing of the next database lock is uncertain as this is an event-driven study. Additional analyses incorporating evidence from this later DCO, when it becomes available, may help to reduce uncertainty.

Issue 2 Company's choice of extrapolation models to inform EFS and OS

Report section	4.2.6.7
Description of issue and why the EAG has identified it as important	The company's preferred set of models to extrapolate transitions out of the EF state (Gompertz/Gompertz/generalised gamma for EF→LSR/EF→IRP/EF→death) included Gompertz curves which exhibited effective plateaus, for the EF→L/SR and EF→IRP survival function for both arms.
What alternative approach has the EAG suggested?	The EAG preferred to identify an alternative set of models that did not include these Gompertz distributions. It selected the log-normal/generalised gamma/generalised gamma combination of curves as a plausible alternative.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER of using the EAG's preferred curve selection was small (decreased the company's base case ICER from £[REDACTED] to £[REDACTED] per QALY gained).
Could any additional evidence or analyses be provided to resolve this key issue?	The company could revisit its fitting of these curves, in conjunction with exploration of alternative approaches to incorporate a cure assumption (as per Issue 3) to explore this further.

Issue 3 Uncertainty in the application of the cure assumption

Report section	4.2.6.7
Description of issue and why the EAG has identified it as important	The company chose not to explicitly model a cure assumption in its base case as it considered its preferred set of extrapolation models already exhibited behaviour consistent with a cure assumption, likely due to the plateauing behaviour of the Gompertz distributions used, as outlined in Issue 2. However, it explored applying a cure assumption in scenario analyses which involved reducing the hazards of leaving the EF state by 95% instantaneously at year 5.
What alternative approach has the EAG suggested?	The EAG considered that the company should have used a more sophisticated approach to assess whether a cure assumption was plausible within this population such as fitting parametric mixture-cure models to the EFS individual patient data (IPD) and assessing whether a non-zero cure fraction is consistently predicted across different models. The EAG did this analysis and identified that most models predicted similar cure fractions which supports the plausibility of a cure-like behaviour, though the time at which any structural cure assumption should be introduced within the model is still subject to uncertainty.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER of implementing the cure assumption using the company's simplistic approach is fairly minimal when using either the company or the EAG's preferred set of extrapolation models (increased the EAG's base case ICER from £[REDACTED] to £[REDACTED]). However, the impact of applying the cure assumption in some of the company scenario analyses was more considerable due to the alternative model hazard behaviours.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could explore a more sophisticated approach to implementing the cure assumption, that does not result in a discontinuous hazard for EFS and OS. The EAG also notes that additional data from a later DCO of KEYNOTE-689, when it becomes available, may help reduce uncertainty regarding whether it is appropriate to apply a cure assumption and what form it should take.

Issue 4 Uncertainty in transitions for patients leaving the L/SR and IRP state

Report section	4.2.6.7
Description of issue and why the EAG has identified it as important	The transitions out of the L/SR states were informed by a low number of events which meant that they were subject to considerable uncertainty. Despite the low number of events available, the company fitted separate curves to each arm. Additionally, the two approaches explored by the company to estimate the transition probability of IRPàDeath provided contradictory results.
What alternative approach has the EAG suggested?	The EAG preferred to pool the data across both arms for transitions out of the L/SR state. It also applied the same approach to transitions out of the IRP state.
What is the expected effect on the cost-effectiveness estimates?	The company's scenario analysis which pooled data for transitions out of the L/SR state had a moderate impact on the ICER, decreasing it from £[REDACTED] to £[REDACTED]. The EAG's exploratory analysis in which it also pooled events across both arms for transitions out of the IRP state had a similar impact on the ICER decreasing it from £[REDACTED] to £[REDACTED].
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG does not consider that any additional analyses could be conducted to reduce the uncertainty further whilst using data from the IA1 DCO. It is possible that additional data obtained from a later DCO, should one become available, could reduce the uncertainty in these transitions.

Issue 5 Resource use calculated based on the APaT population instead of the ITT population

Report section	4.2.9.11
Description of issue and why the EAG has identified it as important	The company chose to use the APaT population to estimate resource use. However, this meant that patients in the SOC arm who did not receive surgery were excluded from the eligible population when calculating the proportion receiving surgery, radiotherapy or chemotherapy. However, patients in the pembrolizumab with SOC arm who received neoadjuvant pembrolizumab but did not go on to have surgery were included in the eligible population for the pembrolizumab with SOC arm.
What alternative approach has the EAG suggested?	The EAG prefers to use the ITT population to calculate resource use as this estimates the proportion receiving surgery, radiotherapy and chemotherapy within the population randomised to each arm.
What is the expected effect on the cost-effectiveness estimates?	The company provided a scenario analysis using the ITT population and this had a moderate impact on the ICER, increasing it by *% from £***** to £*****.
Could any additional evidence or analyses be provided to resolve this key issue?	No additional analyses are required.

1.4 Secondary issues identified by the EAG

The EAG identified two additional secondary issues described below.

Issue 6 Model structure restricted to only allowing time-invariant transitions out of the L/SR and IRP states

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The company has chosen to use a state-transition model structure that does not allow for time-varying transition probabilities for patients leaving the L/SR and IRP states. The company's rationale for this is that incorporating time-varying transition probabilities from these intermediate states would require a large number of tunnel states, or additional visual basic coding, that would increase the complexity of the model and reduce its transparency. However, this restriction to time-invariant transition probabilities meant that only exponential distributions could be employed to model transitions out of these intermediate states.
What alternative approach has the EAG suggested?	The EAG acknowledges that incorporating time-varying transition probabilities for these intermediate states would significantly increase the complexity of the model. The company's model structure limits the EAG's ability to explore alternative approaches, hence it is noted as a significant limitation.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER cannot be quantified when restricting the analysis to the company's current model structure.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could explore an alternative model structure which includes tunnel states or other means of allowing time-varying hazards for transition out of the intermediate states. However, the EAG acknowledges that this would require substantial additional work and would not address the uncertainty related to the low number of events informing transitions out of the L/SR state.

Issue 7 Long-term survival is capped using general population mortality without any adjustment to reflect an increased risk of death for patients with HNSCC

Report section	4.2.6.7 and 4.2.6.8
Description of issue and why the EAG has identified it as important	The company has used general population all-cause mortality rates to cap OS in the long-term. The company applied a standardised mortality ratio (SMR) of 1 to the general population mortality risks. Therefore, the company's approach does not reflect any increased risk of mortality in the population with HNSCC who survive long enough for the general population mortality risks to apply. No justification for this SMR was provided in the CS.
What alternative approach has the EAG suggested?	Although the EAG was unable to conduct a systematic literature review (SLR) in the time available, the EAG identified literature suggesting that HNSCC patients who survive the first 5 years after diagnosis remain at increased risk of death relative to the general population. They explored SMRs varying from 1.6 to 2.7 in scenario analyses.
What is the expected effect on the cost-effectiveness estimates?	Applying an SMR of 1.6 increased the EAG's base case ICER from £[REDACTED] to £[REDACTED] and applying an SMR of 2.7 increased it further to £[REDACTED].
Could any additional evidence or analyses be provided to resolve this key issue?	The company could provide an SLR examining whether long-term survivors with HNSCC have an increased risk of mortality relative to the general population to identify the most appropriate SMR to apply in the model.

1.5 Company's modelling errors identified by the EAG

The EAG identified two errors within the company's model. The first is related to the calculation of the administration costs for IV pembrolizumab, whereby the company incorrectly calculated the proportion of patients having pembrolizumab with cisplatin, which impacted on the ratio of attendances for IV administration that were costed as simple versus complex IV administration. The second error relates to an incorrect calculation to convert resource use reported in TA490, which used a 4-weekly cycle length, to the estimates required for the weekly cycle length applied in the company's model. These corrections had minimal impact on the ICER.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 provides the results from the EAG's exploratory analyses where each analysis shows the individual changes to the company's base case ICER. The largest changes in the ICER are seen when adopting the ITT population to calculate resource use in the adjuvant setting and when the same transitions are assumed from the L/SR and IRP states for both arms.

When including all the changes preferred by the EAG, the deterministic ICER increases to £[REDACTED] compared to the company's base case ICER of £[REDACTED] per QALY gained.

Table 2: Summary of EAG's preferred assumptions and ICER

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Company base case – post-clarification (Deterministic)					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG exploratory analysis 1: Updating acquisition prices					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG exploratory analysis 2: Correcting IV admin costs for adjuvant pembrolizumab					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG exploratory analysis 3: Correcting frequency of resource use for later stages					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG exploratory analysis 4: Using Log normal / generalised gamma / generalised gamma to model EFS					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG exploratory analysis 5: Adopting the ITT population for informing resource use					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG exploratory analysis 6: Assuming the same transitions from the L/SR and IRP states for both arms					
Pembrolizumab with SOC	████	██████	1.22	██████	██████
SOC	████	██████	-	-	
EAG base case applying analyses 1-6 (Deterministic)					
Pembrolizumab with SOC	████	██████	1.21	██████	██████
SOC	████	██████	-	-	
EAG base case applying analyses 1-6 (Probabilistic)					
Pembrolizumab with SOC	████	██████	1.20	██████	██████
SOC	████	██████	-	-	

Abbreviations: EFS, event-free survival; ICER, incremental net monetary benefit; IV, intravenous; ITT, intention-to-treat; QALYs, quality-adjusted life years; SOC, standard care

1.7 Outline of confidential comparator or subsequent treatment prices

The PAS discount is applied to pembrolizumab within the model regardless of whether it is used first-line or as a subsequent treatment. Confidential prices for treatments used as subsequent line therapies are included in the EAG analyses presented in the confidential appendix to this report. See Section 5.4 for further details.

2 Background

This report critiques the company submission (CS) for pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer. The CS states that pembrolizumab would be given in addition to the current standard of care (SOC) treatment, which it describes as being surgical resection followed by radiotherapy (RT) with or without concomitant platinum-based chemotherapy.

2.1 Critique of the company's description of underlying health problem

Overall, the External Assessment Group (EAG) considers the company's description of the underlying health problem in the CS to be broadly appropriate,¹ and a brief summary of the underlying health problem is provided here for context. Squamous cell carcinoma (SCC) is the most common form of head and neck cancer making up over 90% of all head and neck cancers.² It originates in the squamous cells found in the epithelium of the mucosal lining of the upper aerodigestive tract.² The main locations for SCC in the head and neck are therefore the oral cavity, the throat (pharynx), which is divided into the nasopharynx, oropharynx and hypopharynx, and the larynx (voice box).² Head and neck cancer occurring in other structures within the head and neck (e.g., the salivary glands, sinuses, muscles or nerves) are much less common than SCC of the head and neck.² Risks factors for developing HNSCC include tobacco use, alcohol consumption and infection with the human papillomavirus (HPV).² HPV is more commonly associated with oropharyngeal cancer and HPV positive oropharyngeal cancer is associated with more favourable outcomes.³ The CS reports that head and neck cancer is the 8th most common form of cancer in the UK with 9,997 diagnoses of cancers of the oral cavity, oropharynx, larynx, and hypopharynx in 2022.⁴ Head and neck cancer is staged using the tumour, node and metastasis (TNM) classification system (see CS, Figure 2).^{1, 5} The CS is focused on the population of patients with locally advanced HNSCC.¹ This includes patients with a low grade primary tumour (T1 or T2) but nodal involvement (N>0) and patients with higher grades of tumour (T3 or T4) irrespective of nodal involvement. The locally advanced population is distinct from patients with early-stage disease without nodal involvement (T1/T2 with N0) and patients with metastatic disease (M1). The CS notes that long-term survival depends on both the origin site of the cancer as well as the stage of the disease at diagnosis.¹ The CS states that the survival prognosis for locally advanced HNSCC is 69% at 5 years.⁶ It also describes the 10-year survival rate of patients with advanced HNSCC as being as low as 10%, but the EAG notes that study cited is for a cohort with unresectable HNSCC,⁷ whereas the focus of the CS is patients with resectable disease.¹ Recurrence for patients with locally advanced disease is described as being common, occurring in around half of patients,⁸ with recurrence usually occurring in the first 2 years.⁹ Later in the CS, when discussing the extrapolation of trial outcomes (CS, Section

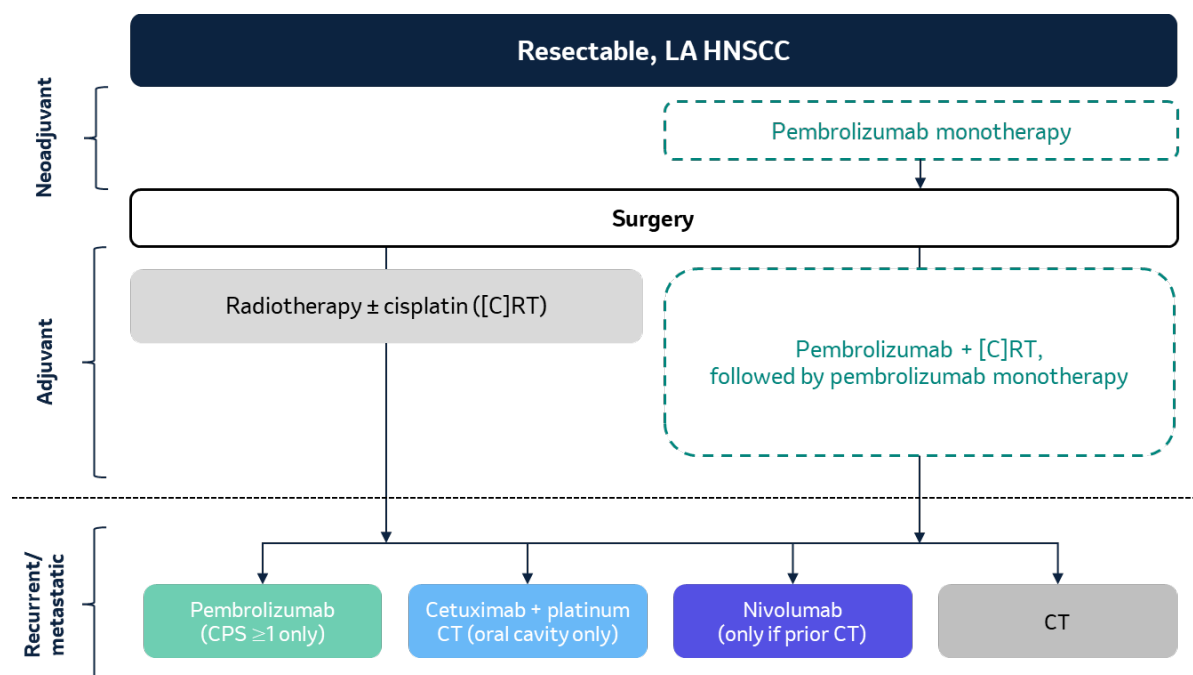
3.3.2.3), the company states that patients who have not experienced disease recurrence 5 years after treatment would be considered functionally cured, based on clinical expert opinion.¹

Common symptoms of HNSCC include a lump in the neck or a sore in the mouth or throat that does not heal, a change in the quality of the voice (e.g. hoarseness), or difficulty/pain when swallowing.¹⁰ Severe pain at diagnosis is predictive of lower survival.¹¹ Both the disease and the treatments offered to manage it can have considerable impact on HRQoL as they can impact on the patient's ability to speak, swallow, breath, smell and taste.¹² The CS notes that head and neck cancer is associated with a suicide rate that is three times higher than observed in the general population and that is the second highest rate among all cancer types.¹³ Fear of recurrence has also been demonstrated to contribute to poor HRQoL, particularly in patients experiencing ongoing pain.¹⁴

2.2 Critique of the company's overview of current service provision

Overall, the EAG considers the company's overview of current service provision in the CS to be broadly appropriate,¹ and a brief summary is provided here for context. The company's summary of the current treatment pathway for resectable LA HNSCC is shown in Figure 1. This figure also indicates the company's proposed positioning within the current treatment pathway. The CS states that the treatment pathway for LA HNSCC is primarily determined by whether the disease is considered resectable i.e., whether it is suitable for surgery to remove the tumour and lymph node dissection. Given that the proposed indication for pembrolizumab is for patients with resectable LA HNSCC, the company's description of the current treatment pathway focuses on this population. The CS states that the current standard of care (SOC) treatment is surgery followed by radiotherapy (RT) which may be given with or without concomitant cisplatin. This combination of RT and chemotherapy, in this case cisplatin, is sometimes referred to as chemoradiotherapy (CRT). Figure 1 does not describe any alternative chemotherapy agents being used in combination with radiotherapy as adjuvant treatment in this group. The CS notes TA145 which recommends cetuximab in combination with radiotherapy in patients with LA HNSCC for whom platinum-based chemotherapy is contraindicated. However, the CS describes cetuximab with radiotherapy as being used only for patients with unresectable LA HNSCC in current clinical practice. The EAG's clinical advisors agreed that cetuximab with radiotherapy is not used as an adjuvant treatment in patients with resectable LA HNSCC in current UK clinical practice.

Figure 1 The place of perioperative pembrolizumab in the UK treatment pathway for LA HNSCC (reproduced from CS, Figure 3)



Abbreviations: CPS, combined positive score; CT, chemotherapy. Dotted lines indicated the proposed positioning of perioperative pembrolizumab.

For patients who experience recurrent / metastatic disease, the CS describes three NICE recommended treatment options. These are:

- Nivolumab for patients who have progressed within 6 months of having platinum-based chemotherapy (TA736),
- Cetuximab in combination with platinum-based chemotherapy for patients whose disease started in the oral cavity (TA473), and
- Pembrolizumab monotherapy for patients who have a programmed death ligand 1 (PD-L1) combined positive score (CPS) of 1 or more (TA661).

Figure 1 also shows a fourth option of chemotherapy, although no further details are given on the relevant chemotherapy regimens. It is therefore unclear from the CS what treatments are offered to patients who are not eligible for any of the three treatments recommended by NICE for recurrent/metastatic disease. However, the EAG notes that the comparator treatment in TA473 was platinum-based chemotherapy (cisplatin/carboplatin with fluorouracil), and this was considered to

represent the current SOC at the time. The EAG therefore believes that this would remain the SOC for patients with cancer not originating in the oral cavity, who are also ineligible for both pembrolizumab and nivolumab, but who are suitable for platinum-based chemotherapy. In its response to clarification question B34,¹⁵ the company indicates the regimen of cetuximab with cisplatin and docetaxel would be considered as an alternative under TA473, as it combines cetuximab with platinum-based chemotherapy; however, the EAG disagrees as this combination was not appraised within TA473. In TA736, where the relevant population was patients who had progressed on platinum-based chemotherapy, docetaxel was considered the most relevant comparator, with methotrexate used in patients unsuitable for taxanes. The EAG's clinical experts stated that cetuximab with cisplatin and docetaxel was not part of their standard of care, with single agent docetaxel favoured after failure of platinum-based therapies, due to lower toxicity. Therefore, the EAG considers docetaxel to be most relevant treatment for recurrent/ metastatic HNSCC in patients unsuitable for both platinum-based chemotherapy and immunotherapy. Therefore, the fourth option of chemotherapy shown as 'CT' in Figure 1 would be platinum-based chemotherapy or docetaxel in those not eligible for platinum-based chemotherapy.

The company does not describe second or third-line treatment options for recurrent/metastatic HNSCC within its description of the current treatment pathway (CS, Section 1.3). The EHNS-ESMO-ESTRO Clinical Practice Guidelines state, "*taxanes with or without cetuximab and/or methotrexate are frequently used after platinum failure.*"¹⁶ The Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines describe carboplatin and paclitaxel as a possible second-line treatment for recurrent/metastatic disease, before going on to state that further options include single-agent cetuximab, taxanes or methotrexate.¹⁷ However, none of these later line options are recommended by NICE. In its response to clarification question B34, the company also highlighted that some of the first-line options could be used second-line in eligible patients. For example nivolumab for those previously progressed on platinum, and cetuximab with platinum-based chemotherapy in those previously progressed on pembrolizumab monotherapy.

The EAG asked its clinical experts about how earlier treatments lines would affect later treatment choices. They explained that rechallenging patients who had progressed on neoadjuvant/adjuvant pembrolizumab with a later line programmed cell death protein 1 (PD-1) inhibitor immunotherapy (e.g., pembrolizumab/nivolumab) would not be expected to be effective, particularly if the recurrence was within 6 months, and palliative chemotherapy is likely to be favoured over rechallenge. Although they also noted that this judgement was difficult to make in the absence of data on response rates in patients being rechallenged. When asked about rechallenging patients who had progressed after platinum-based adjuvant chemotherapy, they stated that they may rechallenge patients with platinum-based

chemotherapy if recurrence occurred more than 6 months after adjuvant therapy and other options were not available, such as enrolment in a clinical trial of a cancer vaccine.

2.3 Critique of the company's definition of decision problem

A summary of the company's adherence to the decision problem set out in the NICE scope is provided in Table 3. The EAG's critique of the company's deviations from the NICE scope are discussed in Section 2.3.

2.3.1. Population

The patient population considered in the CS is: "*Adults with newly diagnosed, nonmetastatic, resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC), [REDACTED]*." The EAG notes that this population is narrower than the population defined in the NICE scope due to the addition of the requirement for patients to have [REDACTED]. The EAG considers this to be a reasonable adjustment as it aligns the population addressed in the CS with the company's anticipated marketing authorisation.

The company also provides additional information on eligibility according to tumour location, disease stage and p16 status (positive p16 status indicates the tumour is likely caused by HPV). The EAG notes that these criteria define a population in-keeping with the population recruited to KEYNOTE-689 trial, and therefore specifying these additional criteria aligns the population with the evidence base presented in the submission, as KEYNOTE-689 is the key trial which compares pembrolizumab with SOC to SOC alone. However, it is unclear to the EAG if the marketing authorisation will be restricted in this manner and whether the committee is therefore being asked to consider a population that is narrower than the marketing authorisation.

In its discussion of relevant comparators, the company states, "*to be eligible for perioperative pembrolizumab (in the trial and in clinical practice), key criteria are that patients must have a resectable tumour, be planned for surgery, and be fit enough to undergo this surgery followed by adjuvant radiotherapy (RT) ± chemotherapy.*" Therefore, the population addressed in the CS is further refined to require that patients are considered suitable not only for surgery, but also for adjuvant radiotherapy with or without chemotherapy.

2.3.2. Intervention

The CS states that the anticipated marketing authorisation for this indication is:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The intervention is up to 17 cycles of intravenous (IV) pembrolizumab (200 mg) every 3 weeks (Q3W), which is administered across three distinct phases. The first phase is 2 cycles of neoadjuvant pembrolizumab given prior to surgical resection of the tumour. This is followed by post-operative pembrolizumab given for 3 cycles, concomitantly with either radiotherapy or chemoradiotherapy using cisplatin as the chemotherapy agent. This second phase is started after adequate recovery from surgery. This is then followed by a third stage of up to 12 cycles of pembrolizumab as monotherapy, giving a total maximum of 17 cycles. The second and third phases are referred to as adjuvant treatment, although adjuvant radiotherapy/chemotherapy only occur during phase 2. There is also the possibility for pembrolizumab to be administered as 400 mg every 6 weeks (Q6W) as an alternative to 200 mg Q3W. In the economic modelling this is assumed to occur after the 2 neoadjuvant cycles and the first adjuvant cycle have been administered, such that the remaining 14 Q3W adjuvant cycles of pembrolizumab are offered as 7 Q6W cycles of pembrolizumab (see Section 4.2.3). The dosages used in the radiotherapy/chemoradiotherapy component of treatment reflect those used in the current SOC and are therefore detailed below under comparators.

In the KEYNOTE-689 trial, pembrolizumab was stopped prior to completion of the 17 cycles if patients experienced confirmed disease progression or unacceptable toxic effects.¹⁸ The total number of cycles for 3-weekly 200 mg pembrolizumab specified in the draft SmPC is

[REDACTED].¹⁹ The draft SmPC also specifies [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].¹⁹ The

draft SmPC specifies that

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

2.3.3 Comparator

The CS describes the relevant comparator as being, “*surgical resection followed by radiotherapy with or without concomitant platinum-based chemotherapy.*” The EAG agrees that this comparator represents established care for this population in the absence of pembrolizumab. Although the company’s description of the comparator in CS, Table 1, does not specify that the platinum-based chemotherapy is cisplatin, the EAG’s clinical advisors stated that other forms of platinum-based chemotherapy (e.g., carboplatin) are not commonly used, and the current SOC consists of radiotherapy with or without concomitant cisplatin. In the KEYNOTE-689 trial, the dosage of cisplatin for those having chemoradiotherapy was 100 mg/m² by IV on day 1 of each 3-week cycle for three cycles. In CS, Section 3.2.3.1, it is mentioned that some centres offer weekly cisplatin at a dose of 40 mg/m²; however, the company’s clinical experts advised that many centres offer the Q3W dosing and this was considered generalisable to UK clinical practice. The EAG’s clinical experts advised that many centres use weekly cisplatin due to the shorter administration time, however, 3 weekly cisplatin was also considered a reasonable option as regimens that lower the burden of attendance on the patient are often preferred. Therefore, the Q3W dosing of cisplatin used in the KEYNOTE-689 appears to be reasonably reflective of current clinical practice.

In the KEYNOTE-689 trial, chemotherapy was only offered to patients classified as high-risk based on the following criteria: “*the presence of positive margins (<1mm in the primary resection specimen) or positive extranodal extension (ENE; defined as an extension of SCC from within a lymph node through the fibrous capsule and into the surrounding connective tissue).*” The EAG’s clinical experts were satisfied that these criteria reflect those used in current clinical practice to select patients for chemoradiotherapy instead of radiotherapy alone. However, they noted that some patients who are classified as being high-risk based on pathological criteria would not be considered fit enough to receive chemotherapy and would instead receive radiotherapy alone.

The dosages of radiotherapy used in the KEYNOTE-689 trial were as follows: 2 Gray (Gy) per day in 30 fractions (total of 60 Gy) for low-risk patients, 33 fractions (total of 66 Gy) for high-risk patients, and 35 fractions (total of 70 Gy) for patients with gross residual disease. The EAG’s clinical experts considered that these dosages were consistent with current clinical practice.

The CS notes that cetuximab with radiotherapy was also included in the NICE scope as a comparator treatment. However, the company argued that this treatment was only relevant for patients with unresectable disease (see Table 3) and it was therefore excluded as a comparator in the company’s clinical effectiveness review and economic model. The EAG’s clinical advisors agreed that cetuximab with radiotherapy is not used as an adjuvant treatment in current clinical practice, and therefore it is not a relevant comparator in a population with resectable disease.

2.3.4 Outcomes

The CS addresses the majority of the outcomes identified in the NICE scope (see Table 3). The notable omissions were progression-free survival (PFS) and disease-free survival (DFS). However, the company explained that event-free survival (EFS) is the relevant outcome when evaluating a treatment given in a neoadjuvant/adjuvant setting. The EAG agree with this position on the basis that patients are not disease-free in the neoadjuvant setting meaning that this outcome cannot be assessed from the point of randomisation. Similarly, PFS suggests that patients have ongoing disease, and the aim of treatment is to prevent progression. However, patients having surgery may be disease-free following surgery meaning that PFS is not a relevant outcome for all patients post-surgery. The primary trial outcome in KEYNOTE-689 of EFS (see, Table 8) is defined in such a way as to capture both progression events prior to surgery in the neoadjuvant phase, and disease recurrence and/or progression events post-surgery. Overall survival (OS) is included in the CS as it was reported as a key secondary outcome in KEYNOTE-689.

Response times were included in the NICE scope, but were also not addressed in the CS because this outcome was also not considered relevant in the neoadjuvant/adjuvant setting. The EAG agreed with this and notes that major pathological response (mPR) and pathological complete response (pCR), assessed by blinded independent pathological review (BIPR) of the surgically resected specimens from the primary tumour site and neck lymph nodes (see Table 8) were reported in the CS as key secondary outcomes from KEYNOTE-689.

HRQoL outcomes addressed in the CS included outcomes from the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 (QLQ-C30) and the EuroQol 5-Dimensions 5-Level (EQ-5D-5L) questionnaire. For the EORTC QLQ-C30, the CS reports outcomes for both the global health status and the physical functioning scale. Section 2 of the CS, which reports clinical effectiveness outcomes, only reports outcomes for the VAS component of the EQ-5D-5L. However, utility scores derived from the EQ-5D-5L questionnaire are used to inform the economic analysis. Although not included in the company's summary of outcomes (CS, Table 1), the CS also reports outcomes for the swallowing scale, speech symptom score and the pain symptom score of the EORTC Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N35).

Adverse events (AEs) from KEYNOTE-689 were reported in the CS, and further details on adverse events of special interest (AEOSIs) were provided in the company's clarification response (question A25).¹⁵ AEs were presented for the all-comer population according to treatment received rather than

according to the treatment group allocated at randomisation. This differed from the approach used for effectiveness outcomes whereby patients were analysed according to the treatment allocated at randomisation.

2.3.5 Subgroups

The only subgroup pre-specified in the scope was subgroups based on PD-L1 combined positive score (CPS). However, additional subgroup analyses that were pre-specified in the KEYNOTE-689 protocol are also presented in the CS (see Table 3).

The EAG notes that the KEYNOTE-689 trial recruited patients irrespective of PD-L1 status. However, the CS focuses on the population with PD-L1 CPS ≥ 1 . Although this was a pre-specified population for analysis in the KEYNOTE-689 trial, randomisation was not stratified by this specific PD-L1 cut-off and instead PD-L1 tumour proportion score (TPS) ($\geq 50\%$ vs. $<50\%$) was used as a stratification factor. The PD-L1 CPS ≥ 1 subgroup comprised 95.5% of the ‘all comers’ overall trial population. For the majority of study outcomes, subgroup analyses are presented within this PD-L1 CPS ≥ 1 subgroup. Results, including subgroup analyses are also presented for the ‘all comers’ overall trial population of KEYNOTE-689 in the appendices to the CS. No subgroup analyses were presented in the economic analysis.

2.3.6 Special considerations

Although no special considerations related to equity or equality are indicated with the company’s description of the decision problem (CS, Table 1), the company does describe a number of socioeconomic, sex-based, and racial/ethnic disparities in head and neck cancer in the UK in CS, Section 1.4. These are discussed further in Section 5.3.3 of the EAG report.

Table 3 Summary of decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated, newly diagnosed, resectable, locally advanced squamous cell head and neck cancer	Adults with newly diagnosed, nonmetastatic, resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC), [REDACTED] Specifically, patients with: - stage III oropharyngeal p16-positive disease with tumour size T4 and node stage N0 to N2, or - stage III or IVA oropharyngeal p16-negative disease, or - stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status. Rationale: Additional details provided to align with the anticipated UK marketing authorisation and the pivotal KEYNOTE-689 trial that forms the evidence base for this submission.	The company's population is narrower than the population specified in the NICE scope in that it is restricted to patients with [REDACTED]. The EAG understands that this is in line with the anticipated marketing authorisation and therefore considers this to be an appropriate restriction. The additional information on eligibility according to tumour location, disease stage and p16 status defines a population in-keeping with the population recruited to KEYNOTE-689 trial and therefore matches the population addressed in the CS. However, it is unclear to the EAG if the marketing authorisation will be restricted in this manner.
Intervention	Pembrolizumab before surgery (neoadjuvant) then with radiotherapy (with or without cisplatin) after surgery (adjuvant)	Aligned with the NICE scope, specifically: <i>Neoadjuvant therapy</i>: pembrolizumab monotherapy <i>Adjuvant therapy following surgical resection</i>: pembrolizumab in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy. Rationale: Additional clarity provided to align with the anticipated UK marketing authorisation and the pivotal KEYNOTE-689 trial that forms the evidence base for this submission.	It should be noted that the indication covers usage of pembrolizumab across multiple treatment phase (neoadjuvant, adjuvant therapy with RT/CRT, then monotherapy). The CS does not provide any evidence related to the usage of pembrolizumab for isolated phases of treatment.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Comparator(s)	For neoadjuvant (before surgery) or adjuvant (after surgery) head and neck cancer: - Established clinical management without pembrolizumab including but not limited to: - Radiotherapy with or without chemotherapy For locally advanced head and neck cancer: - Cetuximab in combination with radiotherapy	Established clinical management without pembrolizumab, consisting of: Surgical resection followed by radiotherapy with or without concomitant platinum-based chemotherapy Rationale: Management of LA HNSCC is guided first by considering whether the tumour is surgically resectable. Surgical resection is typically the recommended primary treatment for tumours of the oral cavity and larynx, whilst for oropharyngeal and hypopharyngeal tumours, surgery is usually reserved for larger (higher T stage) or more aggressive tumours. A tumour may be considered unresectable if it is too large or if surgery would be associated with unacceptable risk of severe or irreversible functional deficits (e.g. loss of ability to speak or swallow). Patient fitness for surgery is also a consideration, as well as the patient's preference for surgical versus non-surgical management.^{16, 17} As the reasons affecting the choice of surgery versus organ-sparing approaches are complex and multifactorial (and result in differences in trial design and endpoint definition), it is not possible to compare the efficacy of surgical and non-surgical treatment pathways. This therefore results in two distinct populations: resectable (patients planned for primary/definitive surgery), and non-resectable (patients planned for primary/definitive [chemo]radiotherapy). The KEYNOTE-689 study recruited patients with resectable, newly diagnosed, locally advanced nonmetastatic HNSCC. Pembrolizumab was given as a perioperative intervention. To be eligible for perioperative pembrolizumab (in the trial	The EAG's clinical advisors agreed that comparators for this population would be those treatments that are suitable for patients with resectable disease. They agreed that patients with resectable disease would be offered surgical resection followed by RT with or without concomitant platinum-based chemotherapy. The EAG's clinical advisors also agreed that cetuximab in combination with RT was used only in patients who did not have resectable disease and was not used as an adjuvant therapy in patients with resectable disease.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		and in clinical practice), key criteria are that patients must have a resectable tumour, be planned for surgery, and be fit enough to undergo this surgery followed by adjuvant radiotherapy (RT) ± chemotherapy. As such, any treatments which are intended for patients not undergoing surgery (i.e. for the non-resectable population) are not appropriate comparators for the population under consideration in the current decision problem. Further details are provided below. Established clinical management without pembrolizumab: • Current SOC for patients with untreated, resectable, LA HNSCC is surgery followed by adjuvant RT with or without platinum-based chemotherapy. As surgery is a key component of the SOC management regimen, as well as the pembrolizumab regimen, this should be specified in the definition of the comparator. MSD considers that the final scope comparator is therefore “Surgical resection followed by radiotherapy with or without concomitant platinum-based chemotherapy” and this is the only relevant comparator for the purposes of this submission. • For clarity, ‘Radiotherapy (with or without chemotherapy)’ in either the neoadjuvant setting or as definitive/primary treatment would not be an appropriate comparator, as neoadjuvant RT is not used in clinical practice, and primary/definitive (i.e. with curative intent) RT is not relevant to a resectable population. The wording of the comparator definition should specify that RT (with or without chemotherapy) is given following surgery (i.e. in the adjuvant setting) only, as specified above.	

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		MSD does not consider Cetuximab in combination with radiotherapy for locally advanced head and neck cancer to be a relevant comparator for the KEYNOTE-689 trial population: • The evidence base for cetuximab in combination with RT (for the patients specified in NICE TA145) consists of the Bonner trial, which excluded patients who had undergone surgery for HNSCC.²⁰ The trial did not include a surgery component and cetuximab + RT was therefore used as the definitive/primary treatment option, as an alternative to RT alone, in a non-resectable population; it was not positioned in the adjuvant setting for resected patients, and therefore cetuximab + RT is intended to treat a different population than that covered by the current decision problem. • Further, the Bonner trial enrolled patients with predominantly oropharyngeal tumours (~60%), with the remainder having laryngeal (~25%) or hypopharyngeal (~15%) tumours; no patients with oral cavity disease were included.²⁰ By contrast, the KEYNOTE-689 trial was comprised primarily of patients with oral cavity (~60%) or laryngeal (~20%) tumours, with oropharyngeal tumours representing only ~10% of the trial population. This discrepancy is consistent with the different treatment guidelines for the various anatomical sites and reflects how tumour site is an important factor contributing to the choice of treatment pathway. In addition, there was a higher proportion of T4 tumours (larger, more advanced) in the KEYNOTE-689 trial (~50%) than in the Bonner trial (~30%). This, too, is consistent with	

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		treatment guidelines relating to suitability for surgical resection (i.e. larger pharyngeal tumours are more likely to be resected [and thus eligible for inclusion in the KEYNOTE-689 trial]). These observations further highlight the distinction between the resectable versus non-resectable populations. • Related to this, anatomical site and tumour T stage, along with HPV/p16 status for oropharyngeal cancer, are important prognostic factors in LA HNSCC.^{16, 17} Consequently, the fundamental discrepancy in the composition of the two trial populations (driven by the initial clinical decision regarding whether the tumour should be surgically resected) in terms of anatomical site and T stage means that the trial results cannot be compared. • Additionally, the NICE TA145 recommendation restricts reimbursement of cetuximab + RT to patients whose Karnofsky performance-status score is 90% or greater and for whom all forms of platinum-based chemoradiotherapy are contraindicated (e.g. due to comorbidities).²¹ This therefore corresponds to a very small subgroup of the non-resectable LA HNSCC population. • Accordingly, clinical expert feedback to MSD has indicated that cetuximab + RT is very rarely used in the locally advanced HNSCC setting and in practice is reserved only for patients who do not undergo surgical resection and who have renal impairment. They also noted that there is RCT evidence that cetuximab + RT is associated with poorer survival outcomes compared with definitive/primary platinum-based chemoradiotherapy, which contributes to the very low	

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		usage in the UK (e.g. the RTOG 1016 and De-ESCALaTE HPV trials.^{22, 23} Therefore, given the differences in the target patient population, treatment pathway, and very low level of use in the UK clinical practice, cetuximab in combination with RT is not an appropriate comparator for this appraisal.	
Outcomes	The outcome measures to be considered include: - overall survival - event-free survival - progression-free survival - disease-free survival - Major pathological response - Pathological complete response - response times - adverse effects of treatment - health-related quality of life	- Event-free survival - Overall survival - Major pathological response - Pathological complete response - Health-related quality of life (EORTC QLQ-C30, EQ-5D-5L) - Adverse events Rationale: The KEYNOTE-689 study recruited patients with resectable newly diagnosed, locally advanced nonmetastatic HNSCC. Pembrolizumab was given as a perioperative intervention. The primary endpoint of the study was event-free survival (EFS), and overall survival (OS) was a key secondary endpoint. MSD does not consider the following outcomes to be relevant in this setting: - Progression-free survival: This was not an endpoint measured in the KEYNOTE-689 trial as it is not a relevant outcome for cancer in the early-stage (neoadjuvant/adjuvant) setting.	The EAG considers that the CS addresses relevant outcomes that are likely to predict benefits to patients and cost-effectiveness. The EAG's clinical experts noted that OS was probably more important to patients than EFS, although both endpoints are relevant.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		• Disease-free survival: This was not an endpoint measured in the KEYNOTE-689 trial. In the perioperative setting, event-free survival (EFS) is the appropriate endpoint for assessing efficacy versus the comparator. • Response times: This was not an endpoint measured in the KEYNOTE-689 trial as it is not a relevant outcome for cancer in the early-stage (neoadjuvant/adjuvant) setting.	
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 commercial schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Cost-effectiveness analysis, aligned with the NICE reference case	The EAG agrees that the cost-effectiveness analysis aligns with the NICE reference case and the requirements specified in the NICE scope. A more detailed assessment of alignment with the NICE reference case is presented in Table 17. It notes that there is a Patient Access Scheme (PAS) price for pembrolizumab which is applied in the company's base case analysis regardless of whether pembrolizumab is used first-line or as a subsequent treatment. The company's economic analysis uses prices for relevant generic products that form part of the comparator treatments or subsequent treatments included in the analysis. However, list prices are used for any treatments falling within the comparator or subsequent treatments that have confidential prices that reflect commercial

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
			agreements. See Section 5.4 for further details.
Subgroups	If the evidence allows subgroups will be considered based on: • PD-L1 combined positive score	• Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx) • Tumour Stage (III vs. IVA) • PD-L1 status (combined positive score [CPS]) • Age category (<65 vs. ≥65 years) • Sex (female vs. male) • Race (white vs. all others) • Smoking status (never vs. former vs. current) • Geographical regions (North America vs. European Union vs. Rest of the World) Rationale: Other subgroup analyses pre-specified in the KEYNOTE-689 clinical trial protocol have also been included.	The EAG notes that the CS focuses on the population with PD-L1 CPS ≥ 1. This was a pre-specified population for analysis. However, randomisation was not stratified by this factor and instead PD-L1 TPS ≥ 50% vs. TPS<50%) was used as a stratification factor. Subgroup analyses are presented for the majority of outcome (EFS, OS, mPR, cPR) within the PD-L1 CPS ≥ 1 population.
Special considerations including issues related to equity or equality	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.	N/A	Although no special considerations are indicated with the company's description of the decision problem (CS, Table 1), the company does describe a number of socioeconomic, sex-based, and racial/ethnic disparities in head and neck cancer in CS, Section 1.4. The disparities related to incidence, stage at diagnosis and mortality rates. However, the EAG considers that these disparities are unlikely to be impacted by whether or not this technology is

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
			reimbursed for this indication (see Section 5.3.3).

Abbreviations: cPR, complete pathological response; CPS, combined positive score; CRT, chemoradiotherapy; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-Dimensions 5-Level; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; LA, locally advanced; mPR, major pathological response; N/A, not applicable; OS, overall survival; PAS, patient access scheme; PD-L1, programmed death-ligand 1; QLQ-C30, quality of life questionnaire core-30; RT, radiotherapy; SOC, standard of care; TPS, tumour proportion score

3 Clinical effectiveness

This section presents a summary and critique of the clinical effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Sections 3.4 to 3.5 critique any indirect comparisons presented by the company. Section 3.6 covers additional work done by the EAG.

3.1 Critique of the methods of review

The clinical evidence contained in the CS is comprised of:

- A systematic literature review (SLR) of clinical evidence on the efficacy and safety of pembrolizumab as neoadjuvant therapy and pembrolizumab in combination with SOC radiotherapy with/without cisplatin as post-surgical adjuvant therapy in treatment-naïve participants with newly diagnosed Stage III/IVA, resectable, LA HNSCC;
- Summary and results for the KEYNOTE-689 trial.

In order to identify clinical trials reporting on the efficacy, safety and health-related quality of life outcomes of surgery with neoadjuvant and/or adjuvant treatments in newly diagnosed patients with resectable LA-HNSCC, systematic searches of the following databases were conducted in March 2025: Embase, MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily) and the Cochrane Central Register of Controlled Trials (CENTRAL).

Supplementary search methods included searching the trial registers ClinicalTrials.gov and the European Union Clinical Trials Register (EUCTR). Clarification was sought as to whether the World Health Organisation International Clinical Trials Registry Platform (ICTRP) was also searched. The company stated in response to clarification question A1 that this platform was not searched because ICTRP records largely come from ClinicalTrials.gov and the EUCTR so there is considerable overlap in coverage. The EAG agrees that the risk of missing relevant trial records is minimal, although it is not zero.

Conference proceedings of relevant organisations from 2021 to 2025 were also searched, along with the Northern Light database of Northern Light Life Sciences Conference Abstracts between 2010 to 2025. Additionally, the bibliographies of identified SLRs and network meta-analyses were searched. This process was not clearly reported in the CS, but the company's response to clarification question A3 confirmed that hand searching was performed of the bibliographies of

relevant systematic reviews and meta-analyses that had been identified at the abstract screening stage.

The overall strategy is an acceptable balance of specificity and sensitivity. The population has been quite narrowly defined, increasing specificity, but the search only includes two concepts overall (population and study design). Interventions and comparators have not been searched for, resulting in a more sensitive search (reflected in the high number of results that were retrieved and screened) that is adequate in retrieving relevant studies to meet the objectives of the clinical SLR.

The EAG had no major concerns regarding the conduct of the clinical effectiveness review. CS Appendix B.1.1.2¹ reports that, for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers, but it was unclear whether the selection of an item by a single reviewer made it eligible for consideration at full-text stage. However, this was clarified in response to a question by the EAG which confirmed that any discrepancies were resolved by discussion or by a third independent reviewer, if necessary (clarification response, A12).¹⁵ The EAG considers independent study selection by two or more reviewers, as conducted here, to be best practice in systematic reviewing. The results of the study selection process were detailed, as required, by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (CS Appendix B, Figure 1).¹

The clinical effectiveness review presented in the CS identified for inclusion 85 reports covering 49 studies (CS, Appendix B, p.14, Figure 1 and Table 7).¹ However, only evidence from one trial was presented in the clinical effectiveness section of the CS: KEYNOTE-689. Following a request for clarification from the EAG, the company confirmed that the SLR and search were conducted using a *“broader scope than that of the decision problem’ and that these results (n=49) were then further restricted to only those studies that specifically reported results of treatment using neoadjuvant and adjuvant pembrolizumab in the indication of interest.”* As a result, 48 studies were excluded for the following reasons: that they did not specifically report results of treatment using neoadjuvant and adjuvant pembrolizumab in the indication of interest; and the CS did not conduct an indirect treatment comparison (clarification response, A11).¹⁵ The EAG believes that no relevant published Phase III trials of neoadjuvant and adjuvant pembrolizumab in HNSCC patients have been omitted from the CS that could have provided additional data on safety and efficacy.

KEYNOTE-689 is an international Phase III, multi-centre, active-controlled, open-label study randomised controlled trial (RCT). One unpublished clinical study report (CSR)²⁴ and 1 conference abstract²⁵ relating to this trial were identified by the SLR (CS, Appendix B, Table 7).¹ The principal

publication for the trial¹⁸ was cited in the CS only in relation to the treatment pathway (CS, Section 1.3.2., p.35).¹ The EAG requested clarification from the company regarding the omission of the key publication from the clinical effectiveness review (but cited elsewhere in the submission). The company confirmed that the paper was published (July 2025) after the searches were conducted (31st March 2025) and that the company submission occurred within 6 months of these search and so inclusion of more recent publications was not required, and that it did not contain any data different from the CSR. As a result, there was “*no need*” for its inclusion (clarification response A9).¹⁵ A published protocol was also available but not cited in the CS ([NCT03765918](#)).²⁶ In the absence of referencing, the EAG requested clarification on the source of clinical data reported in the CS; the company confirmed that all data reported in the CS for KEYNOTE-689 were extracted exclusively from the CSR²⁴ (clarification response A10).¹⁵

Data extracted from the included studies are presented in Sections 2.2-2.8 of the CS.¹ Details of the data extraction process are reported in CS Appendix B.1.1.3.¹ The process was undertaken independently by two reviewers, and any discrepancies were resolved by consensus or by discussion with by a third independent reviewer, if necessary. The EAG considers complete independent data extraction by two or more reviewers, as conducted here, to be best practice in systematic reviewing.

CS Appendix B.1.14¹ reports that the quality assessment process was undertaken independently by two reviewers, and any discrepancies were resolved by consensus or by discussion with by a third independent reviewer, if necessary. The EAG considers independent risk of bias/quality assessment by two or more reviewers, with referral to a third if necessary, as conducted here, to be best practice in systematic reviewing. However, differences between the company and EAG in the quality assessment of the principal included trial are reported in Section 3.2.4.

The EAG agrees with the CS (Section 2.9)¹ that a meta-analysis is not appropriate given that only a single relevant trial was identified (KEYNOTE-689), and no other relevant trial has been missed. The KEYNOTE-689 trial is ongoing and is estimated to complete in September 2026. The CS argues that an indirect treatment comparison comparing pembrolizumab with therapies other than SOC (radiotherapy ± cisplatin) is not necessary because KEYNOTE-689 provided direct evidence for the treatment comparison of relevance to this appraisal (CS, Section 2.10).¹ This assessment is discussed in detail in Section 3.5.

3.2 Critique of the methods of KEYNOTE-689

3.2.1 Characteristics and study design of the KEYNOTE-689 trial

KEYNOTE-689 an international Phase III, multi-centre, active-controlled, open-label study RCT with an unspecified planned follow-up period. The trial was conducted in 192 centres across North and South America, Europe and Asia. There were six UK centres (patients n=19, CS, Appendix L4, p.235¹) ([NCT03765918](#)²⁶). Details of study location, treatments, trial inclusion and exclusion criteria, permitted and prohibited concomitant medications and relevant outcomes are reported in Table 4. The primary completion date was 25th July 2024, and the estimated completion date is listed as 10th September 2026 ([NCT03765918](#)). The full eligibility criteria of the KEYNOTE-689 study are listed in Table 4. The KEYNOTE-689 trial enrolled patients aged ≥ 18 years with a new clinical diagnosis of non-metastatic, resectable LA HNSCC. Eligible patients also had to have tumour stage III or IVA/B and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1. Patients were randomly assigned in a 1:1 ratio. The intervention arm treatment consisted of pembrolizumab (200 mg intravenously [IV] every three weeks [Q3W] for two cycles) as neoadjuvant therapy prior to surgery, followed by either pembrolizumab (200 mg IV Q3W for 15 cycles) plus SOC radiotherapy (RT) with cisplatin (100 mg/m² IV Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients, or pembrolizumab (200 mg IV Q3W for 15 cycles) plus SOC RT without cisplatin as adjuvant therapy following surgery for low-risk patients. The comparator arm treatment consisted of SOC RT with cisplatin (100 mg/m² IV Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients, or SOC RT without cisplatin as adjuvant therapy following surgery for low-risk patients. The criteria for post-surgery risk categorisation are described in Table 4.

Table 4 Summary of the trial design of KEYNOTE-689 (adapted from CS, Section 2.3.1, Table 5¹)

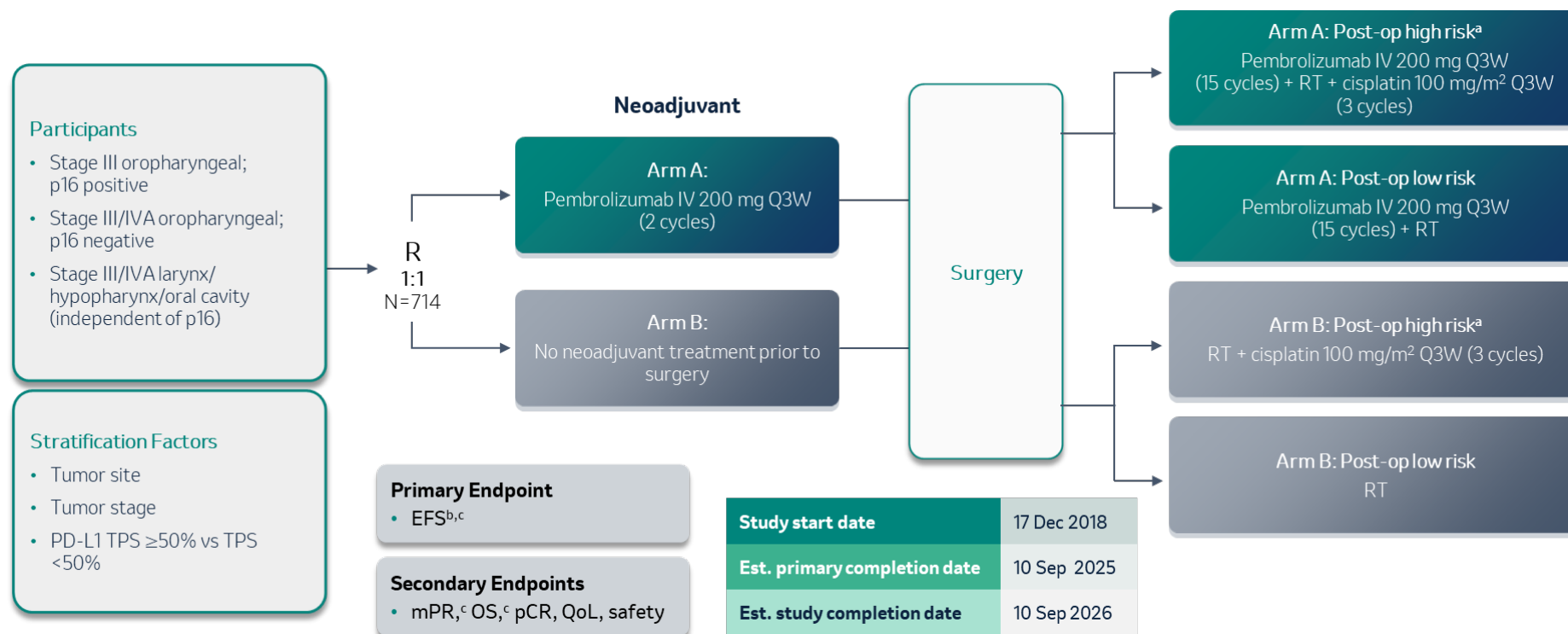
Study name	KEYNOTE-689
Trial design	Phase III, randomised, active-controlled, multicenter, open-label study.
Eligibility criteria for participants	Eligible participants were 18 years of age or older and had newly diagnosed, nonmetastatic, resectable locally advanced HNSCC with either: • Stage III oropharyngeal p16-positive disease with tumour size T4 and node stage N0 to N2, or • Stage III or IVA oropharyngeal p16-negative disease, or • Stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status. Participants had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability), were eligible for primary surgery, and provided newly obtained tumour tissue for programmed death-ligand 1 (PD-L1) and human papillomavirus (HPV) analysis.
Settings and locations where the data were collected	Multinational trial with locations in: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Ireland, Israel, Japan, Poland, Portugal, Russian Federation, South Korea, Spain, Switzerland, Taiwan, United Kingdom, Ukraine, United States.
Trial drugs	• Pembrolizumab (200 mg IV every three weeks [Q3W] for two cycles) as neoadjuvant therapy prior to surgery, followed by either pembrolizumab (200 mg IV Q3W for 15 cycles) plus standard-of-care radiotherapy with cisplatin (100 mg/m² IV Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients or pembrolizumab (200 mg IV Q3W for 15 cycles) plus standard-of-care radiotherapy without cisplatin as adjuvant therapy following surgery for low-risk patients; or • No neoadjuvant therapy prior to surgery, followed by either standard-of-care radiotherapy with cisplatin (100 mg/m² IV Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients or standard-of-care radiotherapy without cisplatin as adjuvant therapy following surgery for low-risk patients. (Participants were categorised as high risk if extranodal extension and/or positive margins (<1 mm in the primary resection specimen) of resection were assessed to be present and were categorised as low risk if these pathological features were absent.)
Primary outcomes	The primary end point is event-free survival assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumours, version 1.1.
Other outcomes used in the economic model/specified in	Key secondary end points are major pathological response (mPR), ($\leq 10\%$ residual viable invasive squamous-cell carcinoma) assessed by blinded independent pathological review and overall survival. Other secondary end points include pathological complete response

Study name	KEYNOTE-689
the scope	as assessed by blinded independent pathological review and safety and side-effect profile.
Pre-planned subgroups	• Primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx) • Tumour Stage (III vs. IVA) • PD-L1 status (TPS $\geq$ 50% versus TPS<50%) • Age category (<65 vs. $\geq$65 years) • Sex (female vs. male) • Race (white vs. all others) • Smoking status (never vs. former vs. current) Geographical regions (North America vs. European Union vs. Rest of the World)
Duration of study	Study period: December 2018 to September 2026

Abbreviations: HPV: human papillomavirus; IV: intravenous; PD-L1: programmed death ligand 1; Q3W: every 3 weeks; TPS: tumour proportion score

A diagram summarising the design of KEYNOTE-689 is reproduced in Figure 2.

Figure 2 Summary diagram of the KEYNOTE-689 study (reproduced from CS, Section 2.3.1, Figure 4¹)



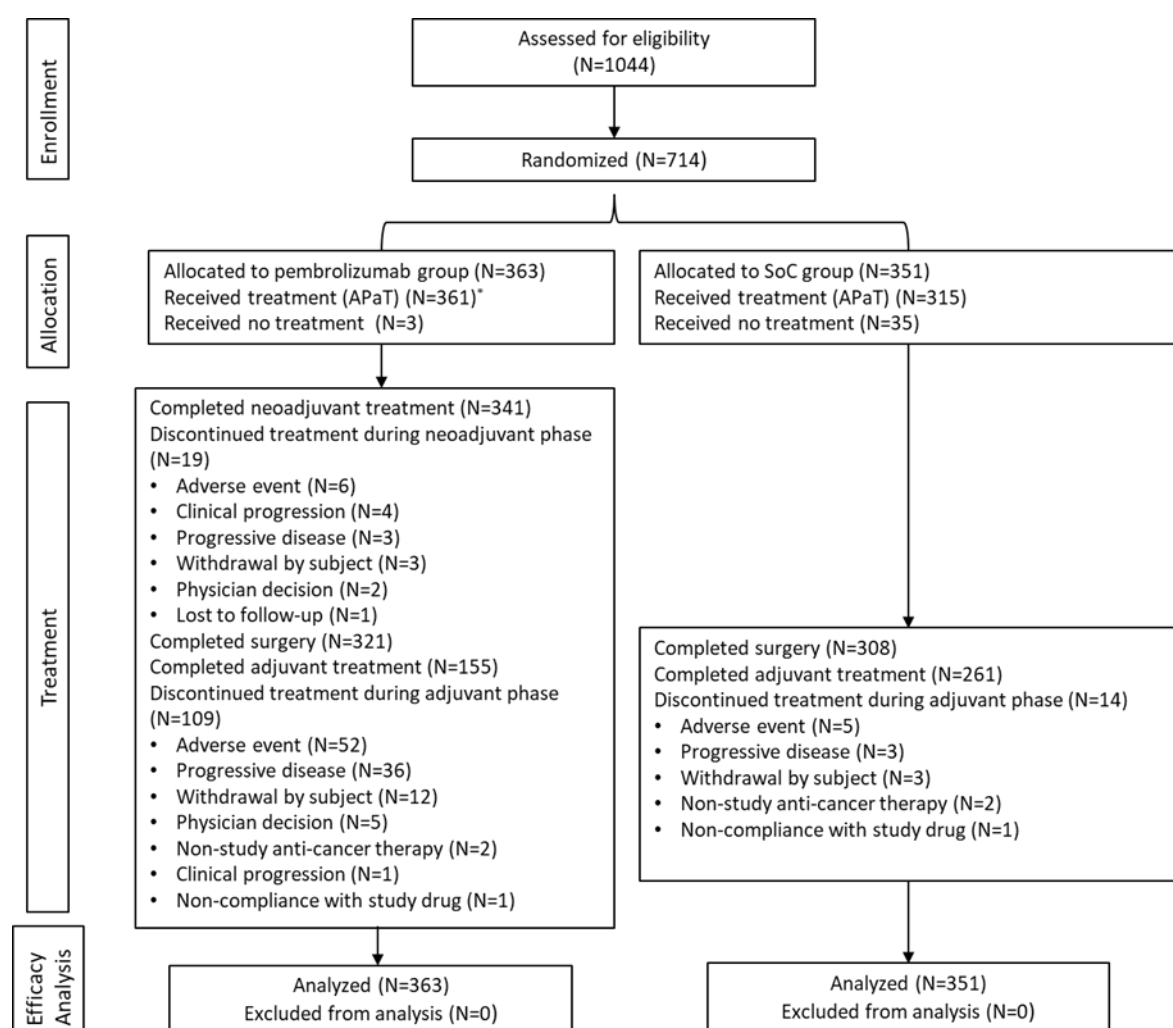
EFS: event-free survival; mPR: major pathological response; OS: overall survival; pCR: pathological complete response; PD-L1 TPS: programmed death ligand 1 total positive score; Q3W: every 3 weeks; QoL: quality of life; RT: radiotherapy

^aHigh-risk definition: Positive margins (< 1 mm in the primary resection specimen), positive extranodal extension. ^bEFS: time from the date of randomization to the date of first record of any of the following events: radiographic disease progression; local or distant recurrence, as assessed with imaging or biopsy as indicated; or death due to any cause. ^cAnalysis populations will include CPS cut-offs of CPS ≥ 10 , CPS ≥ 1 , and all participants

3.2.2 Participant flow and analysis populations: KEYNOTE-689

In KEYNOTE-689, overall, 1044 patients with a new clinical diagnosis of nonmetastatic, resectable LA HNSCC were enrolled, and 714 patients satisfied the eligibility criteria and were randomised: 363 were allocated to pembrolizumab and 351 to SOC. The disposition and flow of participants is detailed in Figure 3 ('all comer' population). In the pembrolizumab arm (n=363), three patients received no treatment; 341 completed neoadjuvant treatment; 321 completed surgery, [REDACTED] started adjuvant treatment and 155 completed adjuvant treatment. In the SOC arm (n=351), 315 patients received treatment ('All patients as Treated' [APaT]); 308 completed surgery; [REDACTED] of the 'all comer' population started adjuvant treatment, and 261 completed adjuvant treatment. The CS (Section 2.6.1.1 and Table 11¹) reported that the median actual follow-up was [REDACTED] in the pembrolizumab arm and [REDACTED] in the SOC arm.

Figure 3 **Consort Diagram Disposition of Participants (all comer) of KEYNOTE-689**
(reproduced from CS, Appendix N.2, Figure 27¹)



*The total number of participants allocated to receive treatment (All Patients as Treated [APaT]) includes 1 additional participant from the SoC group who had mistakenly received 2 neoadjuvant cycles of pembrolizumab, who underwent surgery, and who subsequently was discontinued from study treatment without receiving any adjuvant treatment.

The EAG notes that, while the KEYNOTE-689 trial included all adult patients with a new clinical diagnosis of nonmetastatic, resectable LA HNSCC (the ‘all comer’ trial population, represented in Figure 3), the CS focused on participants with PD-L1 CPS_≥1

(CS, Section 1.1 and Table 1 and Section 1.3.3).¹ The CS notes (Section 2.6¹) that patients with CPS _≥1 comprised 95.5% of the ‘all comer’ overall trial population and the proportion of patients with CPS _≥1 was balanced between the two trial arms (95.6% in the pembrolizumab + SOC arm and 95.4% in the SOC arm). Sixteen patients in each arm did not satisfy the PD-L1 CPS_≥1 criterion, reducing the randomised numbers from 363 to 347 in the pembrolizumab + SOC arm, and from 351 to

335 in the SOC arm. Given that these were the focus of the efficacy section of the CS, only the data on this slightly narrower population are presented here (Table 5) and for the efficacy findings. The equivalent data for the ‘all comer’ populations were reported in the Appendix of the CS¹, but are not reproduced here. However, the safety findings for the ‘all comer’ population were reported in the CS (Section 2.11¹) and are presented below.

In the pembrolizumab + SOC arm, the disposition of the PD-L1 CPS $\geq$ 1 population was as follows: 347 participants were randomised; 347 started neoadjuvant treatment (11 participants were randomised but not treated); 347 started surgery (11 discontinued the trial before surgery and 11 continued to adjuvant treatment without surgery); 347 participants were therefore potentially eligible for adjuvant treatment following the surgery stage (including 11 participants who did not receive surgery but continued to adjuvant treatment, and 347 who discontinued from surgery). Of the 347 participants eligible to start adjuvant treatment, 11 discontinued between having surgery and starting adjuvant treatment; 347 participants therefore started adjuvant treatment, and 347 completed adjuvant treatment. However, only 347 of the 264 patients who started adjuvant treatment received pembrolizumab (clarification response, Table 7).¹⁵ In the SOC arm, 335 patients started adjuvant treatment and 335 completed adjuvant treatment, but adjuvant treatment in the SOC arm was of a shorter duration.

Table 5 Disposition of participants in KEYNOTE-689 (participants with PD-L1 CPS $\geq$ 1, ITT population) (modified from CS, Section 2.6.1.1, Table 9, with additions from clarification response A14¹⁵)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	
Status for Neoadjuvant Study Treatment						
Started	347		335		682	
Completed	347	100%	335	100%	682	100%
Discontinued	11	3%	11	3%	22	3%
Adverse Event	11	3%	11	3%	22	3%
Clinical Progression	11	3%	11	3%	22	3%
Lost To Follow-Up	11	3%	11	3%	22	3%
Physician Decision	11	3%	11	3%	22	3%
Associated with COVID-19	11	3%	11	3%	22	3%
Progressive Disease	11	3%	11	3%	22	3%
Withdrawal By Subject	11	3%	11	3%	22	3%
Status Not Recorded	11	3%	11	3%	22	3%

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Status for In-study Surgery						
Did not receive surgery	■		■		■	
Continued to adjuvant Treatment stage without Surgery ^a	■	■	■	■	■	■
Discontinued Treatment Prior to Surgery ^b	■	■	■	■	■	■
Randomized but Not Treated ^c	■	■	■	■	■	■
Started surgery	■		■		■	
Completed surgery	■	■	■	■	■	■
Discontinued	■	■	■	■	■	■
Tumour Found To Be Surgically Unresectable	■	■	■	■	■	■
Status for Adjuvant Study Treatment						
Discontinued in the phase between surgery and adjuvant treatment	■	■	■	■	■	■
Progressive Disease	■	■	■	■	■	■
Adjuvant Treatment without Surgery ^a	■	■	■	■	■	■
Started	■		■		■	
Completed	■	■	■	■	■	■
Discontinued	■	■	■	■	■	■
Adverse Event	■	■	■	■	■	■
Associated with COVID-19	■	■	■	■	■	■
Clinical Progression	■	■	■	■	■	■
Non-Compliance With Study Drug	■	■	■	■	■	■
Non-Study Anti-Cancer Therapy	■	■	■	■	■	■
Physician Decision	■	■	■	■	■	■
Associated with COVID-19	■	■	■	■	■	■
Progressive Disease	■	■	■	■	■	■
Withdrawal By Subject	■	■	■	■	■	■
Participants Ongoing	■	■	■	■	■	■
Status for Study Treatment (Overall)						
Started	■		■		■	
Completed	■	■	■	■	■	■
Discontinued	■	■	■	■	■	■
Adverse Event	■	■	■	■	■	■
Associated with COVID-19	■	■	■	■	■	■
Status for Study Treatment (Overall)						
Clinical Progression	■	■	■	■	■	■
Lost To Follow-Up	■	■	■	■	■	■
Non-Compliance With Study Drug	■	■	■	■	■	■
Non-Study Anti-Cancer Therapy	■	■	■	■	■	■

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Physician Decision	█	█	█	█	█	█
Associated with COVID-19	█	█	█	█	█	█
Progressive Disease	█	█	█	█	█	█
Withdrawal By Subject	█	█	█	█	█	█
Participants Ongoing	█	█	█	█	█	█
Status for Trial						
Discontinued	█	█	█	█	█	█
Death	█	█	█	█	█	█
Associated with COVID-19	█	█	█	█	█	█
Lost To Follow-Up	█	█	█	█	█	█
Withdrawal By Subject	█	█	█	█	█	█
COVID-19 association unspecified, Subsequently died	█	█	█	█	█	█
Participants Ongoing	█	█	█	█	█	█
If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation. ^a SoC participants in this category were eligible to receive radiation ± cisplatin. Pembrolizumab participants were eligible to receive pembrolizumab ± radiation ± cisplatin. Reasons for not receiving surgery: Adverse event; physician decision; withdrawal by subject; tumour found to be surgically unresectable. ^b Participants in this group received at least one dose of pembrolizumab and discontinued treatment before surgery. Reasons given for trial discontinuation: Adverse events; lost to follow-up; physician decision; progressive disease; withdrawal by subject; non-study anti-cancer therapy. ^c Participants in this group did not continue to any phase of treatment (including surgery) following randomisation. Database Cut-off Date: 25JUL2024						

The EAG notes that the most common reason for discontinuation between surgery and adjuvant treatment in the pembrolizumab + SOC arm was progressive disease (█ participants) compared to █ in the SOC arm (Table 5). In response to a request from the EAG, the company clarified that a possible reason for this disparity was the greater frequency of scans in the pembrolizumab + SOC arm compared with the SOC arm, which led to ‘an increased likelihood of capturing more events in the pembrolizumab arm’ (clarification response, questions A16 and A17).¹⁵

3.2.3 Baseline characteristics, endpoints and analysis sets

Baseline characteristics: KEYNOTE-689

The demographic and baseline characteristics of those patients randomised in KEYNOTE-689 and satisfying the PD-L1 CPS $\geq$ 1 criterion are presented in Table 6. The two arms were generally well-balanced at baseline across most variables, including prognostic factors such as age, tumour site and stage, HPV status and race.^{16, 17, 27, 28} The median age was 60 years (range 29-82 years) in the pembrolizumab arm and 61 years (22–87 years) in the SOC arm. Most participants were male and white. Most participants across both groups had an overall cancer staging at baseline of IVA (74.6% in the pembrolizumab arm vs 73.4% in the SOC arm), with the primary tumour site being the oral cavity (60.5% vs 61.2%, respectively). The pembrolizumab arm had more patients with an ECOG PS score of 1 (rather than 0) compared with the SOC arm (46.1% vs 40.0%). Clinical advice to the EAG confirmed that the characteristics of the trial participants in KEYNOTE-689 were largely similar to the population in clinical practice in England, with the exception that there might be more patients in clinical practice who were HPV positive, and fewer patients with oropharynx as the primary site as most of these patients would be considered inoperable and treated with definitive CRT. Baseline data for the ‘all comer’ population were provided in the CS, Appendix Section N.¹

Table 6 KEYNOTE-689 study participant baseline characteristics – participants with PD-L1 CPS $\geq$ 1, ITT population (reproduced from CS, Section 2.3.2, Table 6¹)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	
Sex						
Male	272	(78.4)	265	(79.1)	537	(78.7)
Female	75	(21.6)	70	(20.9)	145	(21.3)
Age (Years)						
< 65	237	(68.3)	220	(65.7)	457	(67.0)
$\geq$ 65	110	(31.7)	115	(34.3)	225	(33.0)
Mean	59.5		60.4		59.9	
SD	10.0		10.0		10.0	
Median	60.0		61.0		60.0	
Range	29 to 82		22 to 87		22 to 87	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.3)	1	(0.1)
Asian	47	(13.5)	42	(12.5)	89	(13.0)
Black Or African American	8	(2.3)	9	(2.7)	17	(2.5)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Multiple	9	(2.6)	16	(4.8)	25	(3.7)
American Indian Or Alaska Native, Black Or African American, White	2	(0.6)	2	(0.6)	4	(0.6)
American Indian Or Alaska Native, White	1	(0.3)	7	(2.1)	8	(1.2)
Black Or African American, White	4	(1.2)	6	(1.8)	10	(1.5)
Native Hawaiian Or Other Pacific Islander, Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander, White	0	(0.0)	1	(0.3)	1	(0.1)
White, Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	1	(0.3)	2	(0.3)
White	273	(78.7)	260	(77.6)	533	(78.2)
Missing	9	(2.6)	6	(1.8)	15	(2.2)
Ethnicity						
Hispanic Or Latino	54	(15.6)	43	(12.8)	97	(14.2)
Not Hispanic Or Latino	285	(82.1)	285	(85.1)	570	(83.6)
Not Reported	4	(1.2)	4	(1.2)	8	(1.2)
Unknown	0	(0.0)	2	(0.6)	2	(0.3)
Missing	4	(1.2)	1	(0.3)	5	(0.7)
Region						
North America	63	(18.2)	48	(14.3)	111	(16.3)
European Union	134	(38.6)	139	(41.5)	273	(40.0)
Rest of World	150	(43.2)	148	(44.2)	298	(43.7)
PD-L1 Status by TPS Score						
TPS <50%	244	(70.3)	228	(68.1)	472	(69.2)
TPS ≥50%	103	(29.7)	107	(31.9)	210	(30.8)
Primary Tumour Site						
Oropharynx	34	(9.8)	37	(11.0)	71	(10.4)
Oral Cavity	210	(60.5)	205	(61.2)	415	(60.9)
Larynx	77	(22.2)	67	(20.0)	144	(21.1)
Hypopharynx	26	(7.5)	25	(7.5)	51	(7.5)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
ECOG PS						
0	187	(53.9)	201	(60.0)	388	(56.9)
1	160	(46.1)	134	(40.0)	294	(43.1)
HPV Status						
Positive	11	(3.2)	14	(4.2)	25	(3.7)
Negative	336	(96.8)	320	(95.5)	656	(96.2)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Unknown	0	(0.0)	1	(0.3)	1	(0.1)
Overall Cancer Staging at Baseline						
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
██████	█	████	█	████	█	████
Cancer T Staging at Baseline						
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
██████	█	████	█	████	█	████
Cancer N Staging at Baseline						
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
████	█	████	█	████	█	████
██████	█	████	█	████	█	████
Cancer M Staging at Baseline						
████	█	████	█	████	█	████
██████	█	████	█	████	█	████
Smoking Status						
██████████	█	████	█	████	█	████
██████████	█	████	█	████	█	████
██████████	█	████	█	████	█	████
██████	█	████	█	████	█	████
Cigarette use (packs per year)						
██████████████	█	████	█	████	█	████
██████	█	████	█	████	█	████
████	█	████	█	████	█	████
██████	█	████	█	████	█	████
Alcohol use						
████	█	████	█	████	█	████
████	█	████	█	████	█	████

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)

SD=Standard deviation.

European Union category in this table includes European Economic Area, United Kingdom and Switzerland.

Database Cut-off Date: 25JUL2024.

The EAG notes that there was a

(Table 7). Clinical advice to the EAG on risk profiles confirmed that the risk categorisations applied, and their impact on treatment choices, were similar to UK clinical practice. The EAG notes that no evidence was provided to indicate whether the differences in risk profile were related to exposure to neoadjuvant pembrolizumab. A smaller proportion of high risk of patients in the pembrolizumab arm received cisplatin () compared with the SOC arm () (see clarification response, question A18).¹⁵

Table 7 Summary of Post-Surgical Risk Categorisation by Treatment Group, Participants With CPS $\geq$ 1, (ITT Population) (reproduced from CS, Section 2.6.1.1, Table 10¹ and clarification response, question A18¹⁵).

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	
Risk Category by Central Assessment						
HIGH RISK						
LOW RISK						
Missing						
Number of participants who received cisplatin						
HIGH RISK						
LOW RISK						
Post-surgical pathological risk categorisation of participants as either high or low risk was completed based on central (BIPR) pathological assessment of the surgically resected specimens from the primary tumour site and neck lymph nodes. Database Cut-off Date: 25JUL2024						

Study endpoints: KEYNOTE-689

Primary and secondary endpoints for KEYNOTE-689 are summarised in Table 8. Following clinical advice, the EAG accepts that these represent reasonable clinical endpoints (with OS being the most relevant endpoint). The EAG notes that the original protocol listed mPR and EFS as the

primary efficacy endpoints (original protocol, Section 10.4.1.1, p.130¹⁸), but this was changed in September 2023 and mPR was demoted to a secondary endpoint (final protocol, p.3).

Table 8 KEYNOTE-689 study endpoints (modified from CS, Section 2.4.1, Table 7¹)

Endpoint(s)
Primary
• Event-free survival (EFS) defined as the time from the date of randomisation to the date of first record of any of the following events: ○ radiographic disease progression, ○ radiographic disease progression during the neoadjuvant phase that precludes surgery, ○ local or distant disease progression or recurrence as assessed with imaging or biopsy as indicated, ○ death due to any cause (a secondary primary malignancy is not considered an EFS event)
Secondary
• Overall survival (OS) defined as the time from the date of randomisation to the date of death due to any cause
• Major pathological response (mPR) defined as having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumour specimen and all sampled regional lymph nodes
• Pathological complete response (pCR) – having no residual invasive squamous cell carcinoma within the resected primary tumour specimen and all sampled regional lymph nodes
• European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ)-C30, and swallowing, speech and pain symptoms using the EORTC Head and Neck– Specific QoL questionnaire (EORTC QLQ-H&N35) ○ EORTC QLQ C30- global health status/QoL scale (items 29 and 30) ○ EORTC QLQ-C30 physical functioning scale (items 1-5) ○ EORTC QLQ-H&N35 swallowing scale (items 35-38), speech scale (items 46, 53-54), and pain scale (items 31-34)
• Adverse events (AEs) • Study drug discontinuations due to AEs

Analysis sets: KEYNOTE-689

The trial and analyses in the CS (Section 2.4.2.1 to 2.4.2.3¹) included the following population sets described in Table 9.

Table 9 KEYNOTE-689 analysis sets (modified from CS, Section 2.4.1-2.4.3¹)

Analysis set	Details
Efficacy	The Intention-to-treat (ITT) population was the primary population for efficacy analyses in this study, defined as all randomised participants. Participants were included in the treatment group to which they are randomised.
Safety	Safety analyses were conducted in the All Participants as Treated (APaT) population, defined as all randomised participants who received at least one dose of study intervention or surgery that is part of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This was the treatment group to which they are randomised except for participants who take incorrect study treatment for the entire treatment period; such participants were included in the treatment group corresponding to the study treatment actually received. Analyses of laboratory or vital sign measurements included only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis assessed change from baseline, a baseline measurement was also required.
PRO	The Patient Reported Outcome (PRO) analyses were based on the PRO Full Analysis Set (FAS) population, defined as all randomised participants who have at least one PRO assessment available for the specific endpoint and have received treatment. Participants were analysed in the treatment group to which they are randomised.

3.2.4 Quality assessment of the KEYNOTE-689 trial

The CS reported risk of bias assessments in Appendix B.3 (Table 8).¹ The appraisal of the quality of relevant clinical trials was conducted using the Cochrane Risk of Bias tool (Version 2).²⁹ The EAG confirms that this is an acceptable tool for risk of bias assessment. The assessments of both the company and the EAG are based on information in the CSR and protocol.

The CS and EAG judgements for the KEYNOTE-689 trial are presented in Table 10. The CS judged the KEYNOTE-689 trial to be at low risk of bias (CS, Appendix B.3).¹ The EAG agreed with the company's judgements of 'Low risk of bias' regarding the randomisation process, management of

missing data (and the application of an appropriate ITT analysis) and the absence of selective reporting.

However, the EAG questioned the company's judgement regarding deviations and the measurement of some outcomes (which also affected the 'missing outcome data'). The company confirmed that, while the recorded deviations were unlikely to be clinically important, the judgement could be revised to 'Some concerns' 'to explicitly acknowledge these deviations if necessary' (clarification response, question A22).¹⁵

The appraisal did not specify which outcomes were being assessed (e.g., primary and/or key secondary endpoints only). In its clarification response to question A24, the company confirmed that, as a result of the open-label nature of the trial, 'some subjective endpoints (e.g., PROs and safety outcomes) could theoretically be affected by the open-label design', but judged that this had 'probably not' affected 'the outcome' because these were not 'part of the hypothesis-testing hierarchy.'¹⁵ However, the EAG judged this item to have 'Some concerns' because the appraisal was not only limited to outcomes that used objective measures.

The overall risk of bias was therefore assessed by the EAG to be 'Some concerns', given that at two of the five categories were judged to have 'Some concerns'.

Table 10 Cochrane risk of bias assessment tool (Version 2) results for KEYNOTE-689 (modified from CS, Appendix B.3, Table 8¹)

Category	Item	CS Assessment	EAG Assessment
Rando misatio n process	1.1 Was allocation sequence random?	Y	Y
	1.2 Was allocation concealed?	Y	Y
	Support for judgement for 1.1 & 1.2 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Treatment allocation/rand omisation occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS).	Treatment allocation/randomisation occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS).
	1.3 Did baseline differences between groups suggest a problem?	N	N
	Support for judgement for 1.3 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Similar baseline characteristics	Similar baseline characteristics
	Assessor's Judgement	Low-risk	Low-risk

Deviations from intended interventions	2.1 Were participants aware of assigned intervention?	Y	Y
	2.2 Were carers aware of assigned intervention?	Y	Y
	Support for judgement for 2.1 & 2.2 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Open-label	Open-label
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from intended intervention?	N	Y
	Support for judgement for 2.3 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	No deviations reported	The EAG notes that 
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	PN

	Support for judgement for 2.4 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	Small numbers and application of ITT analyses.
	2.5 If Y/PY/NI to 2.4: Were these deviations balanced between groups?	NA	N
	Support for judgement for 2.5 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y

	Support for judgement for 2.6 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Intention-to-treat analysis	Intention-to-treat analysis
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	NA

	Support for judgement for 2.7 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	--
	Assessor's Judgement	Some concerns (clarification response, A22) ¹⁵	Some concerns
Missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	PY
	Support for judgement for 3.1 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Outcome available for all/nearly all patients	Outcome available for nearly all patients. Clarity is lacking on disposition of some patients (Clarification Response A22 ¹⁵), and some quality of life / PRO outcome data from patients who were 'discontinued' due to an adverse event are 'missing by design' (CSR, 14.2.4) ²⁴
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
	Support for judgement for 3.2 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	--

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its value?	NA	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
	Support for judgement for 3.3 & 3.4 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	--
	Assessor's Judgement	Low-risk	Some concerns
Measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	N
	Support for judgement for 4.1 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Kaplan-Meier and RECIST	Kaplan-Meier and RECIST
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN

	Support for judgement for 4.2 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	The same outcome measurement methods were used in both arms at similar timepoints.	The same outcome measurement methods were used in both arms at similar timepoints for the efficacy endpoints.
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PY	PY
	Support for judgement for 4.3 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Open-label	Open-label
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	PY
	Support for judgement for 4.4 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	Open label

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	PY
	Support for judgement for 4.4 & 4.5 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	PROs and some safety outcomes might have been affected by outcome assessors' knowledge of intervention received.
	Assessor's Judgement	Low-risk	Some concerns for certain outcomes
Selecti on of the reporte d result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y	Y
	Support for judgement for 5.1 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	Data analysed in accordance to pre-specified analysis in protocol	Data analysed in accordance to pre-specified analysis in protocol, but the EAG notes that mPS was demoted from a primary to a secondary endpoint in a protocol change. ¹⁸

	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N
	Support for judgement for 5.2 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	--
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N
	Support for judgement for 5.3 (quotes from paper, reviewer's judgement, rationale, and/or no information available)	--	--
	Assessor's Judgement	Low-risk	Low-risk
Overall	Assessor's Overall Judgement	Low-risk	Some concerns

Abbreviations: ITT: Intention to Treat; N: No; NA: Not applicable; PN: Probably No; PY: Probably Yes; Y: Yes.

3.3 Critique of the results of the trials of the technology of interest

The CS reports the latest available results from the KEYNOTE-689 study from the first interim analysis (IA1) with a database cut-off date of 25th July 2024.¹ The interim analysis was planned after 207 events of disease progression, disease recurrence, or death in the CPS-10 population and 9 months after the last participant underwent randomisation.¹⁸ The clinical efficacy sections of the CS (Section 2.2 to 2.8¹) only reported the results for the subgroup of participants with PD-L1 CPS ≥ 1 ; the efficacy results for the entire “all comer” overall KEYNOTE-689 participant population were reported in the CS, Appendix N, but are not reported here. PD-L1 status, measured using tumour proportion score (TPS), was a stratification factor at randomisation to ensure that the treatment groups were balanced with respect to this potential effect modifier. The CS reported safety results for the ‘all comer’ APaT (All Participants as Treated) population (Section 2.11).¹

3.3.1 Primary endpoint: Event free survival (EFS) in KEYNOTE-689

The primary efficacy endpoint was EFS by Blinded Independent Central Review (BICR). The definition of EFS assessed by RECIST 1.1 was described in Table 8 and the findings for the primary efficacy endpoint are reported in Table 11. The CS reports a statistically significant improvement in EFS per RECIST 1.1 as assessed by BICR for participants in the pembrolizumab + SOC arm compared with the SOC arm (Hazard Ratio [HR]: 0.70; 95% Confidence Interval [CI]: 0.55, 0.89; $p=0.00140$). This represents a 30% reduction in the risk of an EFS event in the pembrolizumab + SOC group versus the SOC group. Median EFS was reported to be 59.7 months in the pembrolizumab + SOC group compared with 29.6 months in the SOC group. The CS (Section 2.6.1.2¹) also reports that this improvement was ‘clinically meaningful’, but no definition of what constituted ‘clinically meaningful’ was given. The EAG therefore requested clarification of this terminology. The company responded that “‘Clinically meaningful’ in these instances refers to ‘the results being impactful as it relates to the clinical state or outcome. No specific quantitative thresholds etc. were considered’ (clarification response A21).¹⁵ The EAG therefore notes that this term is not based on a validated threshold, such as a Minimally Clinically Important Difference (MCID). The EAG notes that the incidence of local progressive disease (PD)/recurrence was 10.7% in the pembrolizumab + SOC group vs 11.0% in the SOC group, while distant PD was 6.9% in the pembrolizumab + SOC group vs 15.2% in the SOC group.

Table 11 Analysis of Event-Free Survival by BICR per RECIST 1.1 in KEYNOTE-689 (Participants with CPS≥1, ITT Population) (reproduced from CS, Section 2.6.1.2, Table 12¹)

	Pembrolizumab	SOC
	(N=347)	(N=335)
Number of Events (%)	128 (36.9)	156 (46.6)
Death	63 (18.2)	62 (18.5)
Distant PD	24 (6.9)	51 (15.2)
Local And Distant PD	4 (1.2)	6 (1.8)
Local PD/Recurrence	37 (10.7)	37 (11.0)
Number of Censored (%)	219 (63.1)	179 (53.4)
Last assessment showing no progression	216 (62.2)	168 (50.1)
Randomization	3 (0.9)	11 (3.3)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
[Q1, Q3]	[11.9, NR]	[6.9, NR]
Person-months		
Event Rate / 100 Person-months		
vs SOC		
Hazard Ratio (95% CI) ^b	0.70 (0.55, 0.89)	
p-value ^c	0.00140	
EFS Rate at month 6 (%) (95% CI)		
EFS Rate at month 12 (%) (95% CI)		
EFS Rate at month 24 (%) (95% CI)		
EFS Rate at month 36 (%) (95% CI)	58.2 (51.9, 64.0)	44.9 (38.4, 51.2)
EFS Rate at month 48 (%) (95% CI)		

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

b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

c One-sided p-value based on log-rank test stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

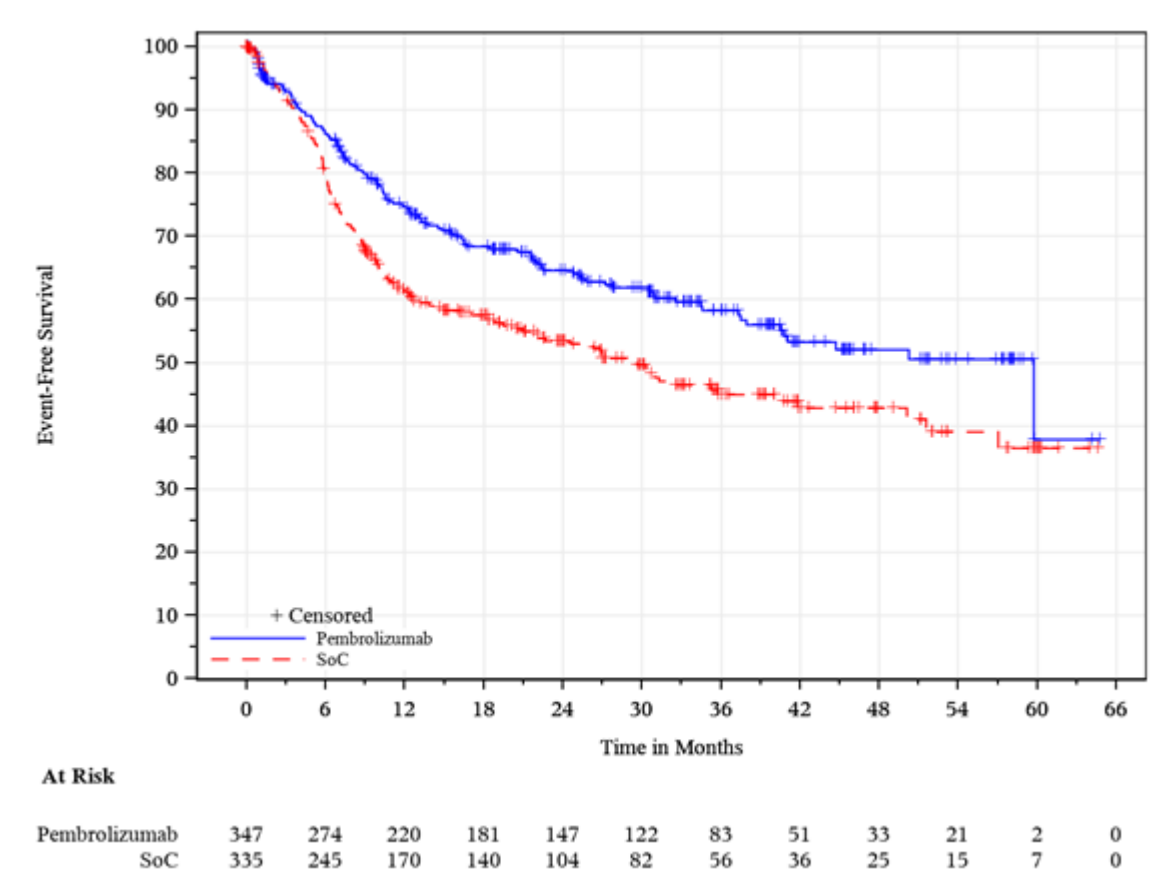
Abbreviations: NR = Not reached; PD: Progressive disease.

Primary censoring rule.

Database Cut-off Date: 25JUL2024

The EFS rate at 6, 12, 24, 36 and 48 months was also reported to be higher in the pembrolizumab + SOC group than in the SOC group at all (Table 11). These data are also presented in the Kaplan-Meier plot for EFS (Figure 4).

Figure 4 Kaplan-Meier Plot of Event-Free Survival by BICR per RECIST 1.1 in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.6.1.2, Figure 5¹)



Primary censoring rule.

Database Cut-off Date: 25JUL2024

3.3.2 Secondary endpoints

Overall Survival (OS)

The CS reported a number of secondary endpoints from the KEYNOTE-689 trial. OS was a secondary outcome in the KEYNOTE-689 trial. Clinical advice to the EAG indicated that OS was the most important clinical outcome. The findings for the secondary efficacy endpoint of OS in patients with baseline PD-L1 CPS $\geq$ 1 are reported in Table 12 and Figure 5 based on the IA1 data cut-off of 25th July 2024. The CS (Section 2.6.1.3) reports that, as per the prespecified multiplicity strategy, OS was not

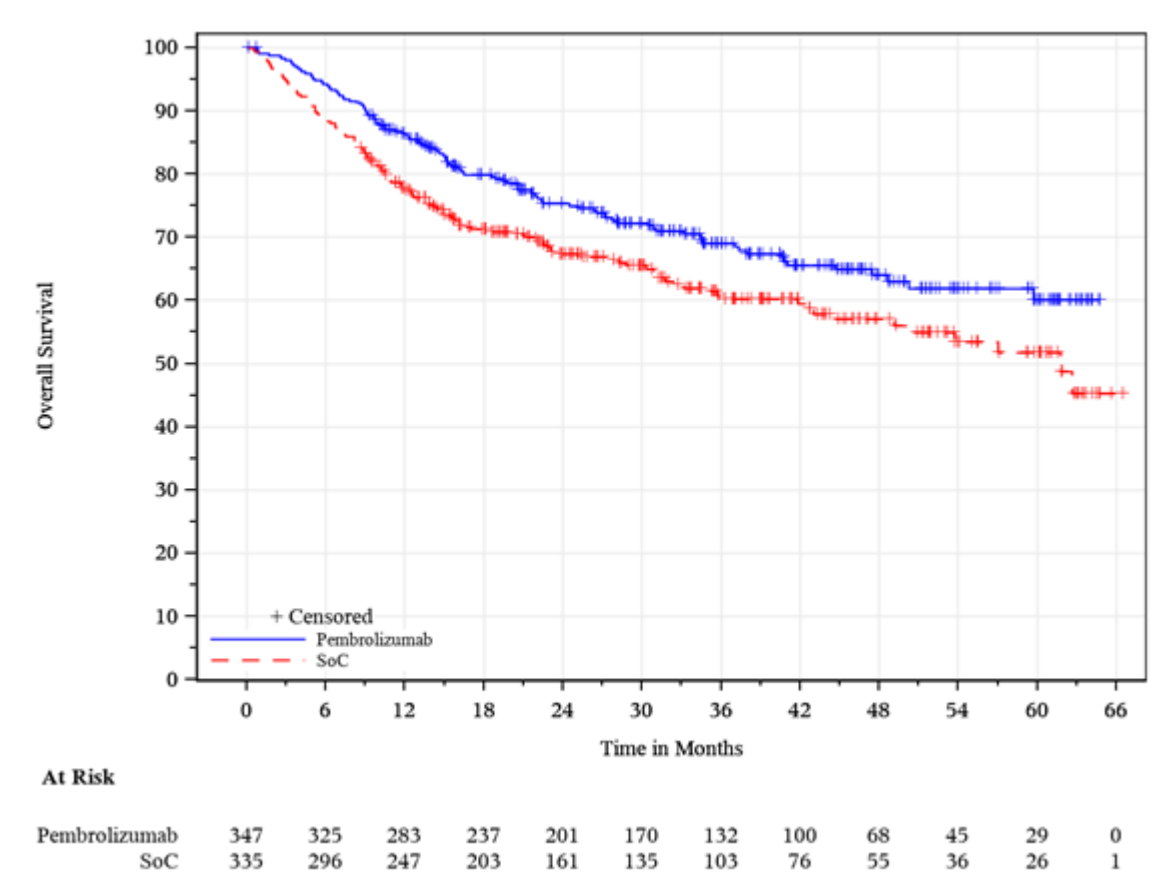
formally tested in the CPS $\geq$ 1 population at IA1 due to the lack of statistical significance of OS within the CPS $\geq$ 10 population.¹ The median actual follow-up time was 117.4 weeks, and the OS HR estimate statistically significantly favoured pembrolizumab + SOC group versus SoC (HR:0.72; 95% CI: 0.56, 0.94; nominal p=0.00666). Median OS was not reached in the pembrolizumab + SOC group compared with a median OS of 61.8 months in the SOC group.

Table 12 Analysis of Overall Survival in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.6.1.3, Table 13¹)

	Pembrolizumab	SOC
	(N=347)	(N=335)
Number of Events (%)	106 (30.5)	128 (38.2)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
[Q1, Q3]	[24.5, NR]	[14.2, NR]
Person-months	██████████	██████████
Event Rate / 100 Person-months	████	████
vs SOC		
Hazard Ratio (95% CI) ^b	0.72 (0.56, 0.94)	
p-value ^c	0.00666	
OS Rate at month 6 (%) (95% CI)	████████████████████	████████████████████
OS Rate at month 12 (%) (95% CI)	████████████████████	████████████████████
OS Rate at month 24 (%) (95% CI)	████████████████████	████████████████████
OS Rate at month 36 (%) (95% CI)	69.0 (63.3, 74.0)	60.2 (54.1, 65.8)
OS Rate at month 48 (%) (95% CI)	████████████████████	████████████████████
OS Rate at month 60 (%) (95% CI)	████████████████████	████████████████████

a From product-limit (Kaplan-Meier) method for censored data.
b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
c One-sided p-value based on log-rank test stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
NR = Not reached.
Database Cut-off Date: 25JUL2024

Figure 5 **Kaplan-Meier Plot of Overall Survival in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.6.1.3, Figure 6¹)**



Database Cut-off Date: 25JUL2024.

Major Pathological Response (mPR)

The secondary efficacy endpoint mPR was assessed by Blinded Independent Pathologist Review (BIPR). The EAG notes that the original protocol listed mPR and EFS as the primary efficacy endpoints (original protocol, Section 10.4.1.1, p.130¹⁸), but this was changed in September 2023 and mPR was demoted to a secondary endpoint (final protocol, p.3¹⁸). The definition of mPR was described Table 8

and the findings for this secondary efficacy endpoint are reported in Table 13. The CS reports a statistically significant improvement in mPR as assessed by BIPR for participants in the pembrolizumab + SOC group (9.8%) compared with the SOC group (0%) with a difference in response rates of 9.8% (95% CI: 7.0%, 13.3%; $p < 0.00001$). The CS also states that this finding was below a p-value boundary of 0.0005.¹

Table 13 Analysis of Major Pathological Response (mPR) Based on BIPR Assessment in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.6.1.4, Table 14¹)

Treatment	N	Number of mPR	mPR Rate (%) (95% CI)	Difference in % vs. SOC	
				Estimate (95% CI) ^a	p-Value ^b
Pembrolizumab	347	34	9.8 (6.9, 13.4)	9.8 (7.0, 13.3)	<0.00001
SOC	335	0	0.0 (0.0, 1.1)		

^a Based on Miettinen & Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
^b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
mPR = Major Pathological Response. BIPR = Blinded independent pathologist review. Database Cut-off Date: 25JUL2024.

Pathological Complete Response (pCR)

The secondary efficacy endpoint pCR was assessed by BIPR. The definition of pCR was described previously in Table 8 and the findings for this secondary efficacy endpoint are reported in Table 14. The CS reports a statistically significant improvement in pCR as assessed by BIPR for participants in the pembrolizumab + SOC group (3.2%) compared with the SOC group (0%) with a difference in response rates of 3.1% (95% CI: 1.6%, 5.6%; $p = \blacksquare$).

Table 14 Analysis of Pathological Complete Response (pCR) Based on BIPR Assessment in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.6.1.5, Table 15¹)

Treatment	N	Number of pCR	pCR Rate (%) (95% CI)	Difference in % vs. SOC	
				Estimate (95% CI) ^a	p-Value ^b
Pembrolizumab	347	11	3.2 (1.6, 5.6)	3.1 (1.6, 5.6)	$\blacksquare$
SOC	335	0	0.0 (0.0, 1.1)		

^a Based on Miettinen & Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
^b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
pCR = Pathological Complete Response. BIPR = Blinded independent pathologist review.
Database Cut-off Date: 25JUL2024.

HRQoL outcomes

The KEYNOTE-689 trial measured HRQoL using both disease-specific (EORTC QLQ-C30 and EORTC QLQ-H&N35) and generic measures (EQ-5D-5L), and reported analyses of the change from baseline to post-adjuvant CRT/RT in Weeks 25 and 51. The CS¹ (Section 2.6.1.6) reports findings using the EORTC QLQ-C30 Global Health and Physical Functioning Scales, as well as and the swallowing, speech and pain symptom scales of the more-specific EORTC QLQ-H&N35:

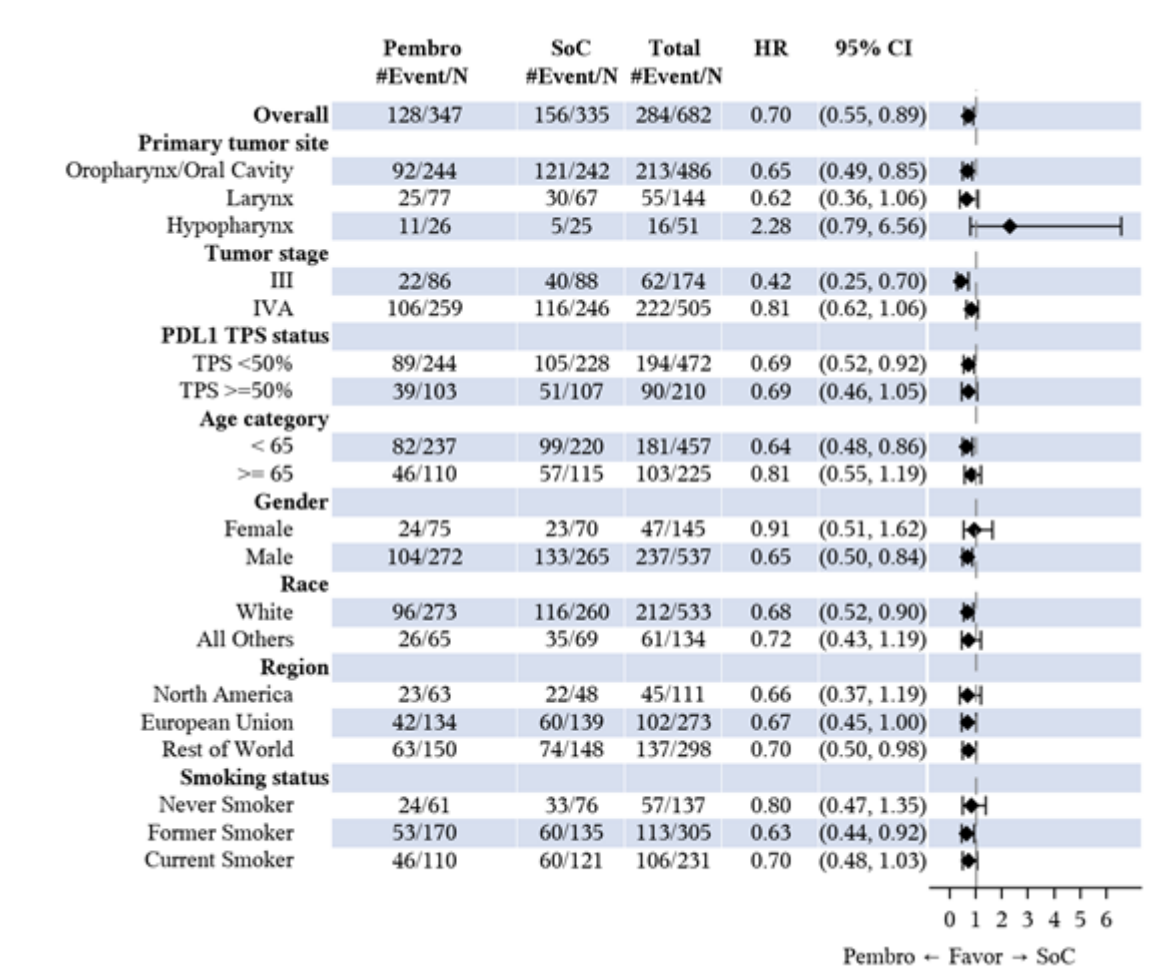
EQ-5D 5L VAS scores in the pembrolizumab + SOC group and the SOC group were also reported in the CS¹ (Section 2.6.1.7): these

Utility scores based on EQ-5D-5L responses are not reported in the clinical effectiveness section of the CS, but were used to inform the economic analysis as discussed in Section 4.2.8.

3.3.3 Subgroup analyses

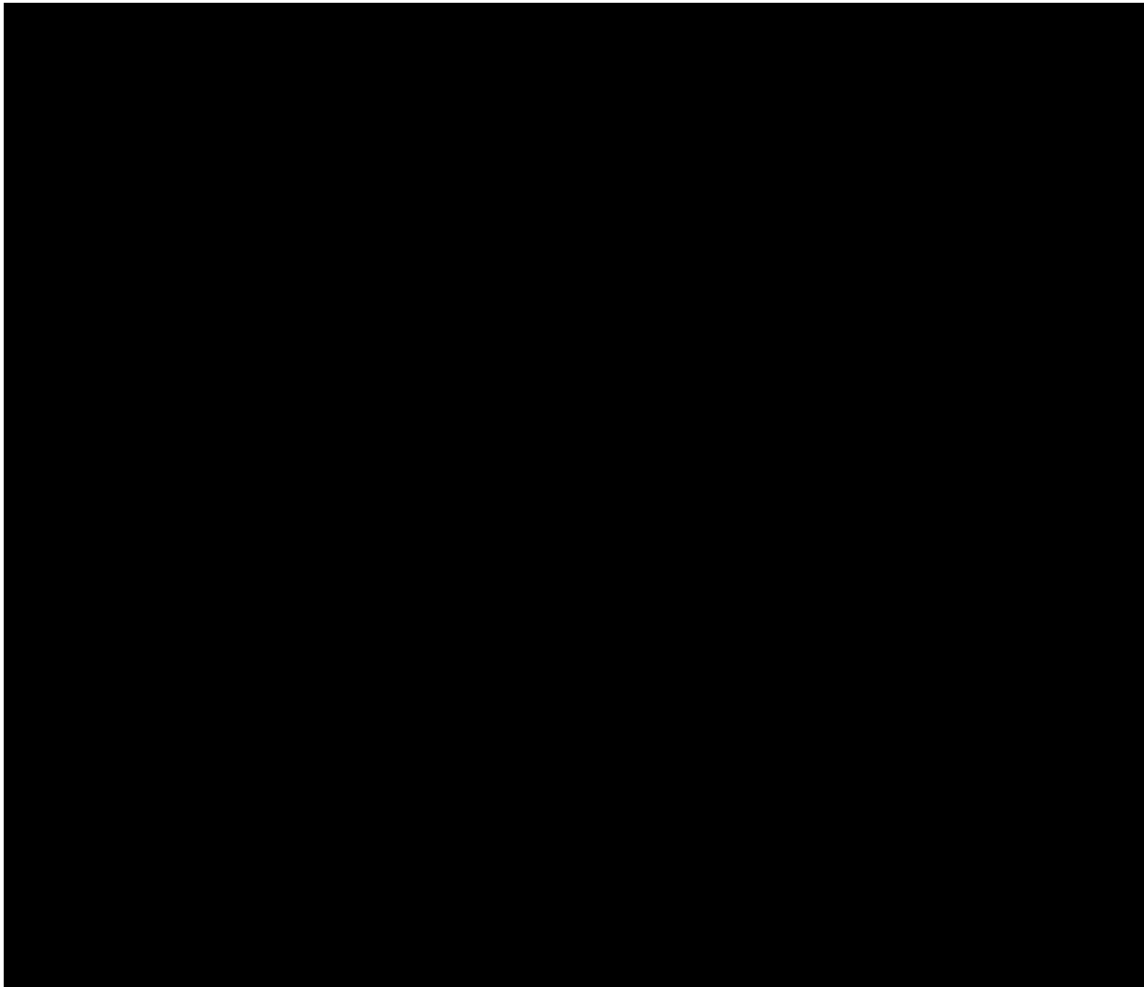
The subgroup analyses of the primary and secondary efficacy endpoints of KEYNOTE-689 (EFS, OS, mPR and pCR) are reported in the CS Section 2.8.¹ The subgroups were pre-specified in the study protocol and analysis plan. The results of these analyses are presented in Figure 6, Figure 7, Figure 8 and Figure 9. The benefit of pembrolizumab + SOC over SOC appears to be consistent across all prespecified subgroups and efficacy endpoints, although small sample sizes in some subgroups (principally primary tumour site: hypopharynx) resulted in wide CIs; the results of those analyses should therefore be interpreted with caution.

Figure 6 Forest Plot of EFS Hazard Ratio by Subgroup Factors in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.8.1.1, Figure 13)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed. European Union category in this graph includes European Economic Area, United Kingdom and Switzerland. Database Cut-off Date: 25JUL2024

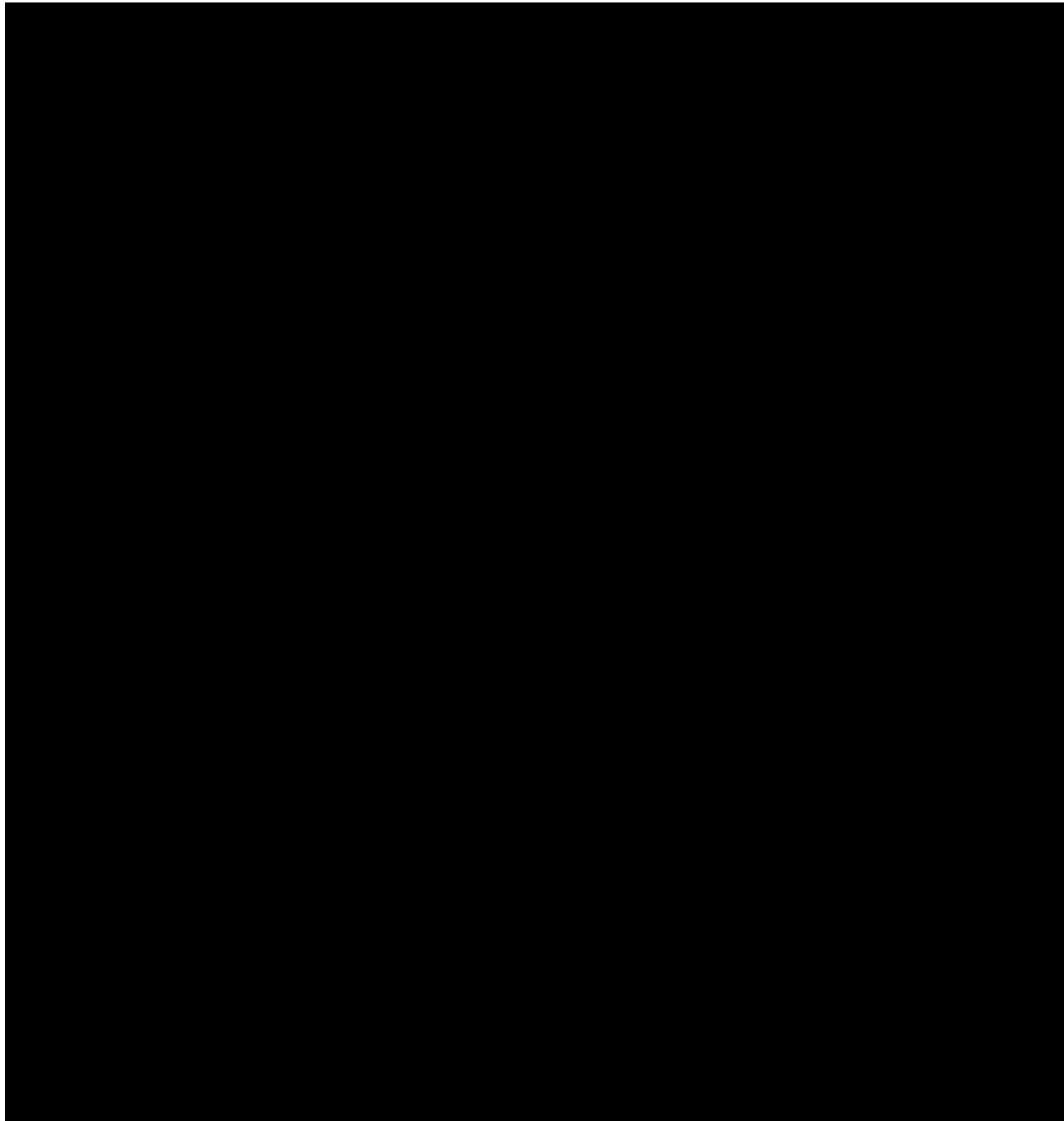
Figure 7 Forest Plot of OS Hazard Ratio by Subgroup Factors in KEYNOTE-689
(Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.8.1.2, Figure 14)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed.

European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.
Database Cut-off Date: 25JUL2024

Figure 8 Forest Plot of Difference in mPR Rate by Subgroup Factors in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.8.1.3, Figure 15)

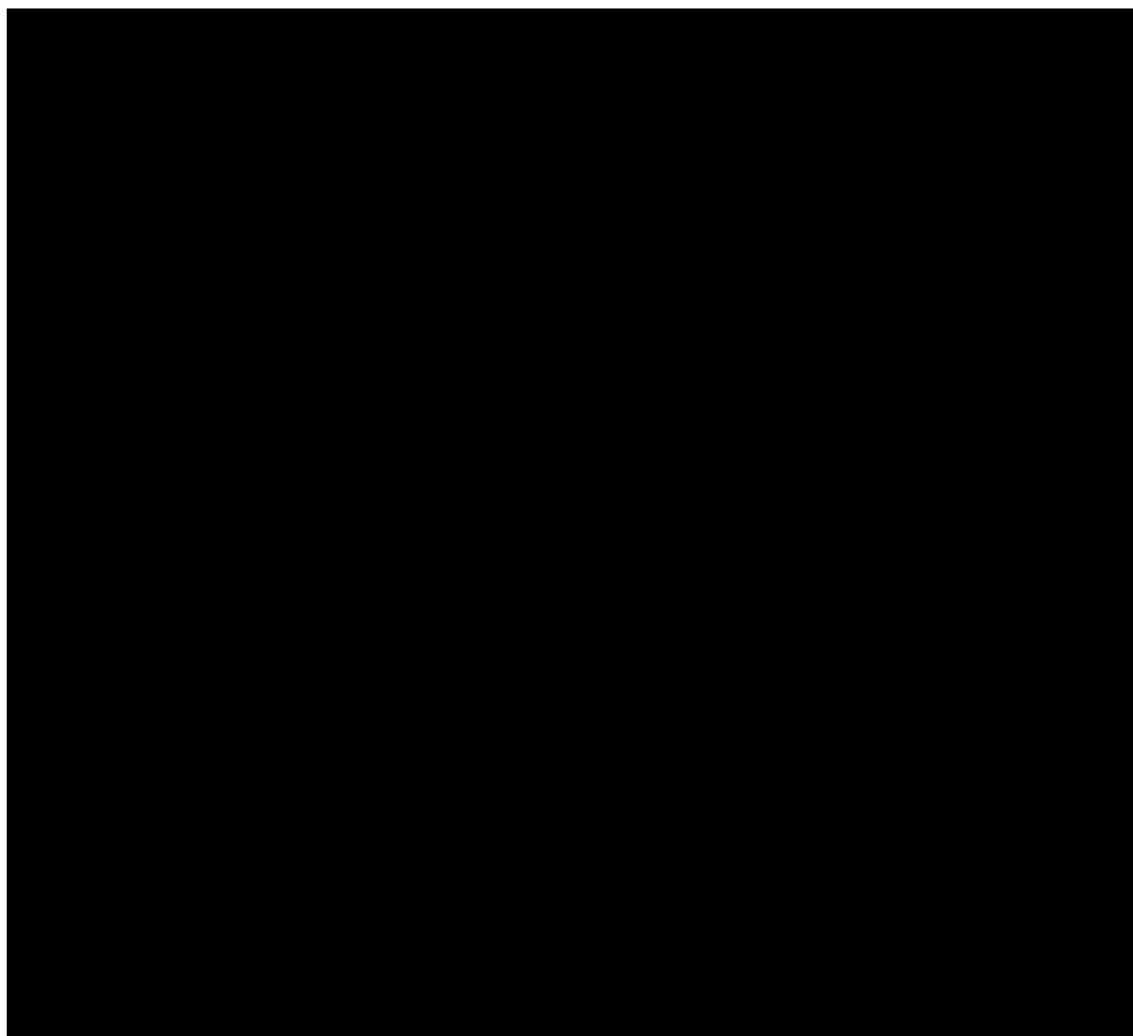


For overall population, analysis is based on Miettinen and Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Miettinen and Nurminen method. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed.

European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.

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Figure 9 Forest Plot of Difference in Pathological Complete Response Rate by Subgroup Factors in KEYNOTE-689 (Participants with CPS $\geq$ 1, ITT Population) (reproduced from CS, Section 2.8.1.4, Figure 16)



For overall population, analysis is based on Miettinen and Nurminen method stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Miettinen and Nurminen method. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed.

European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.

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3.3.4 Safety

The incidence and types of AEs for the ‘all comer’ APaT population (n=361 in the pembrolizumab + SOC group and n=315 in the SOC group) in KEYNOTE-689 are reported in Table 15. The CS reports AE data in Section 2.11 and Appendix D.¹ The incidence of AEs overall, including drug-related AEs, AEs leading to death, and Grade 3 to 5 AEs in the pembrolizumab + SOC group was similar to the SOC group. However, the incidence of the following types of AE was higher in the pembrolizumab + SOC group than the SOC group: SAEs (49.6% vs 36.8%, respectively); drug-related SAEs (19.1% vs 10.5%),

the most common being colitis, stomatitis, immune-mediated hepatitis and pneumonitis; drug discontinuation due to an AE (24.4% vs 14.3%), the most common being decrease in neutrophil count, pneumonitis and colitis; as well as drug discontinuation due to the following: a drug-related AE (17.7% vs 12.4%); a SAE (13.0% vs 3.5%) and a drug-related SAE (7.5% vs 2.5%).

Table 15 Adverse event summary for KEYNOTE-689 (all comer overall population, APaT population) (reproduced from CS, Section 2.11, Table 23¹).

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	348	(96.4)	305	(96.8)
with no adverse event	13	(3.6)	10	(3.2)
with drug-related ^a adverse events	294	(81.4)	258	(81.9)
with toxicity grade 3-5 adverse events	275	(76.2)	233	(74.0)
with toxicity grade 3-5 drug-related adverse events	161	(44.6)	135	(42.9)
with serious adverse events	179	(49.6)	116	(36.8)
with serious drug-related adverse events	69	(19.1)	33	(10.5)
who died	25	(6.9)	24	(7.6)
who died due to a drug-related adverse event	4	(1.1)	1	(0.3)
discontinued drug due to an adverse event	88	(24.4)	45	(14.3)
discontinued drug due to a drug-related adverse event	64	(17.7)	39	(12.4)
discontinued drug due to a serious adverse event	47	(13.0)	11	(3.5)
discontinued drug due to a serious drug-related adverse event	27	(7.5)	8	(2.5)
^a Determined by the investigator to be related to the drug. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Grades are based on NCI CTCAE version 4.03. Database Cut-off Date: 25JUL2024.				

The EAG requested clarification from the company regarding details of the following reported AEOSIs: drug-related AEs with toxicity Grade 3-5 (9.4% for pembrolizumab + SOC group vs 0% in the SOC group) and those leading to discontinuation (7.8% for pembrolizumab + SOC group vs 0% in SOC group) (CS, Appendix D.1.1 and Table 11¹). The company clarified

[REDACTED]

[REDACTED]

[REDACTED] (clarification response,

question A25).¹⁵ The most common AEOSIs (>5%) when considering events of any grade were:

hypothyroidism (24.7% for pembrolizumab + SOC group vs 5.4% in SOC group); hyperthyroidism (8.9% for pembrolizumab + SOC group vs 3.2% in SOC group) and pneumonitis (5.5% for pembrolizumab + SOC group vs 0% in SOC group) (clarification response, question A25).¹⁵

The EAG notes that the AE profile is likely to be affected by longer treatment duration in the pembrolizumab + SOC group (drug exposure, mean [SD] study days on therapy: pembrolizumab + SOC group 8.0 (5.1) days compared with 2.7 (1.2) days in the SOC group (CS, Appendix N.3.1, Table 100).¹ [REDACTED] (clarification response, question A19)¹⁵

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The EAG agrees with the company that an indirect treatment comparison comparing pembrolizumab with therapies other than SOC (radiotherapy ± cisplatin) was not necessary because KEYNOTE-689 provides direct evidence for the treatment comparison of most relevance to this appraisal.

3.5 Critique of the indirect comparison or multiple treatment comparison

No indirect comparison was provided in the CS, as per Section 3.4.

3.6 Additional work on clinical effectiveness done by the EAG

No additional analysis of clinical effectiveness data was conducted by the EAG.

3.7 Conclusions of the clinical-effectiveness section

The EAG had no major concerns regarding the conduct of the clinical effectiveness review. The pivotal trial evidence was provided by KEYNOTE-689, which is an international Phase III, multi-centre, active-controlled, open-label study RCT. The trial was conducted in 192 centres across North and South America, Europe and Asia. There were six UK centres (patients n=19). KEYNOTE-689 is ongoing and is estimated to complete in September 2026. The EAG accepts that no other relevant trial evidence was missed.

The EAG notes that, while the KEYNOTE-689 trial included all adult patients with a new clinical diagnosis of nonmetastatic, resectable LA HNSCC, in accordance with the NICE decision problem,

the CS focuses on a narrower population of participants with PD-L1 CPS $\geq$ 1,

██████████ The EAG considers that this was a reasonable adjustment. Participants with CPS $\geq$ 1 comprised 95.5% of the ‘all comer’ overall KEYNOTE-689 population and the proportion of patients with CPS $\geq$ 1 was balanced between the two trial arms (95.6% in the pembrolizumab + SOC arm and 95.4% in the SOC arm). Clinical advice to the EAG confirmed that the characteristics of the trial participants in KEYNOTE-689 were largely similar to the population in clinical practice in England, with the exception that there might be more patients in clinical practice who were HPV positive, and fewer patients with oropharynx as the primary site as most of these patients would be considered inoperable and treated with definitive CRT.

The primary endpoint was event-free survival (EFS) per RECIST 1.1 as assessed by BICR. The secondary endpoints were OS, and mPR and pCR as assessed by BIPR. The CS reports a statistically significant improvement in EFS for participants in the pembrolizumab + SOC arm compared with the SOC arm (HR: 0.70; 95% CI: 0.55, 0.89; $p=0.00140$). Median EFS was reported to be 59.7 months in the pembrolizumab + SOC group compared with 29.6 months in the SOC group. For OS, HR estimate statistically significantly favoured pembrolizumab + SOC group versus SOC (HR:0.72; 95% CI: 0.56, 0.94; nominal $p=0.00666$). Median OS was not reached in the pembrolizumab + SOC group compared with a median OS of 61.8 months in the SOC group. The CS reports a statistically significant improvement in mPR for participants in the pembrolizumab + SOC group (9.8%) compared with the SOC group (0%) with a difference in response rates of 9.8% (95% CI: 7.0%, 13.3%; $p<0.00001$), and a statistically significant improvement in pCR for participants in the pembrolizumab + SOC group (3.2%) compared with the SOC group (0%) with a difference in response rates of 3.1% (95% CI: 1.6%, 5.6%; ██████████). Following clinical advice, the EAG accepts that these represent reasonable clinical endpoints (with OS being the most relevant endpoint).

The benefits of pembrolizumab + SOC over SOC for all primary and secondary endpoints appears to be consistent across all prespecified subgroups and efficacy endpoints, although small sample sizes in some subgroups (principally primary tumour site: hypopharynx) resulted in wide CIs; the results of those analyses should therefore be interpreted with caution.

The incidence of AEs overall, including drug-related AEs, AEs leading to death, and Grade 3 to 5 AEs in the pembrolizumab + SOC group were similar to the SOC group. However, the incidence of the following types of AE were higher in the pembrolizumab + SOC group than the SOC group: SAEs; drug-related SAEs; drug discontinuation due to an AE; and drug discontinuation due to the following: a drug-related AEs, SAEs or drug-related SAEs. The EAG notes that the AE profile is likely to be affected by longer treatment duration in the pembrolizumab + SOC group.

The EAG judged the overall risk of bias of KEYNOTE-689 to have ‘Some concerns’. This was because the trial was judged to be at low risk of bias for the categories of randomisation, missing outcome data and data selection, but judged to have ‘Some concerns’ for the two categories covering deviations and the measurement of some outcomes (which also affected the ‘missing outcome data’).

The EAG agrees with the company that an indirect treatment comparison comparing pembrolizumab with therapies other than SOC (radiotherapy $\pm$ cisplatin) was not necessary because KEYNOTE-689 provided direct evidence for the treatment comparison of most relevance to this appraisal.

4 Cost effectiveness

4.1 Critique of the review of cost-effectiveness evidence

4.1.1 Search strategy

The search strategies for the economic evaluation SLRs were performed in April 2025. Publications related to cost-effectiveness and cost and healthcare resource use were searched for using one set of search strings (reported in CS Appendix E) and then screened for inclusion in the relevant review. HRQoL studies and health state utility values studies were searched for separately (reported in CS Appendix F).

The eligibility criteria reported in CS Appendix E1.2 indicates that a broader population was searched for (locally advanced HNSCC patients with unresectable status or unknown resectability status), although a core scope (to match the population of the KEYNOTE-689 trial, including the requirement for patients to have resected/resectable disease) was prioritised during screening. If no studies from the core scope were identified, then studies matching the broader scope were included.

A comprehensive range of databases were searched: Embase; MEDLINE, including MEDLINE In Process; and EconLit. Although the CS reports that NHS EED, DARE, International HTA database and Tufts CEA registry were also searched, search strategies were not reported. The company's response to clarification question A8 provided these, along with updated PRISMA diagrams incorporating the number of search results from these databases. Database searching was supplemented by searching a comprehensive set of relevant conference proceedings and HTA websites for the years 2021-2025 to retrieve relevant results not indexed by Embase.

The search reported in Appendix E, Table 22 was a simultaneous search of MEDLINE and Embase conducted on Embase.com. During the clarification round, the EAG queried this approach because it may be subject to potential issues with the platform mapping the two distinct controlled vocabularies used for MEDLINE and Embase in an unpredictable manner. The company's response to clarification question A4 that the Embase.com platform does effectively handle mapping MeSH terms from imported MEDLINE records to the Emtree subject headings used for Embase. The EAG is unable to access Embase.com to assess this more fully, although it accepts that the risk of missing studies through imperfect subject heading mapping is low.

CS Appendix, E Section E1.1 and Appendix F, Section F1.1 mention that filters were used to ensure the search matched the relevant review question. The company's response to clarification question A6 confirms that the sources for these filters were the Scottish Intercollegiate Guideline Network (SIGN)

and Canada's Drug Agency (CDA-AMC), and that they had been modified for use in the searches to align with the objective of the SLRs. The EAG considers it best practice to use validated search filters without modification for most reliable results, and to justify reasonable modifications where they have been made.

Overall, the searches for the economic evaluation SLRs have been effectively conducted to identify relevant studies of cost-effectiveness, HRQoL, health state utility valuation studies and cost and healthcare resource use.

4.1.2 Identified studies

CS Appendix E reports the results of the economic SLR. Three studies were identified for the core scope (including only resectable patients with LA HNSCC), and a further 10 studies were identified for the broader scope (including LA HNSCC patients regardless of resectability).

None of the three 'core scope' studies were conducted in the UK, whereas three 'broader scope' studies were UK-specific. Out of the three UK studies, two studies relate to the appraisal of cetuximab in addition to radiotherapy versus radiotherapy alone for LA HNSCC in NICE and SMC,^{21,30} whereas the third was a cost-utility analysis of docetaxel as induction chemotherapy followed by chemoradiation.³¹

4.1.3 Interpretation of the review

None of the included studies in either scope were UK studies relevant to the current decision problem, thus the company developed a *de novo* economic model (outlined in Section 4.2.2).

4.2 Critique of the submitted economic evaluation

Section 4.2 provides a summary and critique of the methods of the economic evaluation submitted by the company, with results summarised in Section 5.1. Unless otherwise stated, it reflects the version submitted following the clarification request. The EAG's exploratory analyses to explore areas of uncertainty identified in the company's analysis are summarised in Section 5.2.

4.2.1 NICE reference case checklist

Table 16 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 2.

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
The decision problem	The scope developed by NICE	The EAG is satisfied that the decision problem in the CS is generally aligned with the scope and any deviations are reasonable. See Table 3 for details.
Comparator	As listed in the scope developed by NICE	Although the company excluded cetuximab in combination with radiotherapy as a comparator, the EAG considered this to be reasonable on the basis of advice from its clinical experts that this treatment regimen is only used in patients with unresectable disease. See Table 3 for details.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The company's economic analysis includes outcomes for patients. Caregiver effects are not included. The EAG considers that this is reasonable
Perspective on costs	NHS and Personal Social Services	All relevant costs have been included, consistent with the reference case
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	A cost-utility analysis is presented, consistent with the reference case. Fully incremental analysis is not required as there is only one relevant comparator in the analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A life-time horizon (up to 100 years of age) is taken. This is considered consistent with the NICE reference case
Synthesis of evidence on health effects	Based on systematic review	A systematic review was undertaken but this identified only one relevant trial meaning that a synthesis of health effects was not required
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health benefits are measured in QALYs; the EQ-5D-5L measurements from the key trial are the primary source of utilities in the economic analysis
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	The primary source of utilities is EQ-5D-5L measured in patients in the KEYNOTE-689
Source of preference data for valuation of changes	Representative sample of the UK population	The EQ-5D-5L responses were mapped onto the UK EQ-5D-3L

Element of health technology assessment	Reference case	EAG comment on company's submission
in health-related quality of life		value set using an appropriate crosswalk algorithm ³²
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	No QALY weighting has been applied based on the company's assessment of the lifetime QALY shortfall
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Relevant measures of resource use and unit costs consistent with the NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The discount rate is consistent with NICE reference case

Abbreviations: EAG, evidence appraisal group; NHS, national health service; QALY, quality adjusted life year

4.2.2 Population

The modelled population considered by the company for this STA is adults with untreated, newly diagnosed, resectable, LA HNSCC who have PD-L1 CPS $\geq$ 1. This is

[REDACTED]

The modelled population is narrower than the NICE final scope, which includes people with PD-L1 CPS $\geq$ 1 only as a subgroup but the EAG does not consider this to be unreasonable as the pre-specified analysis of KEYNOTE-689 and clinical data used in the economic model used to estimate cost-effectiveness reflect this subgroup.

Baseline characteristics of the modelled population are reflective of the 'all comer' cohort of KEYNOTE-689, which is the key trial used for this STA. Table 24 of the CS presents these characteristics including BSA, and glomerular filtration rate (GFR). BSA was used for calculating the doses of cisplatin, 5-FU, cetuximab, gemcitabine, paclitaxel, pemetrexed, and methotrexate, whereas GFR was used to calculate the dose of carboplatin.

4.2.3 Interventions and comparators

The intervention considered for the economic analysis is perioperative pembrolizumab in addition to SOC. Pembrolizumab, which is an IV infusion, is delivered as a monotherapy 200 mg every three weeks (Q3W) in the neoadjuvant setting for a maximum of two cycles. Conditional on eligibility, this is followed by surgical resection which is the first step of the SOC arm.

After surgery, patients receive pembrolizumab in addition to SOC, which comprises radiotherapy with or without cisplatin. In KEYNOTE-689, pembrolizumab 200 mg IV was given for a maximum of 15 three-week cycles postoperatively. Cisplatin 100 mg/m² is given to patients with high-risk pathological features following surgery for a maximum of three three-week cycles, whereas radiotherapy is given to patients regardless of the patient's classification as having high or low risk pathological features.

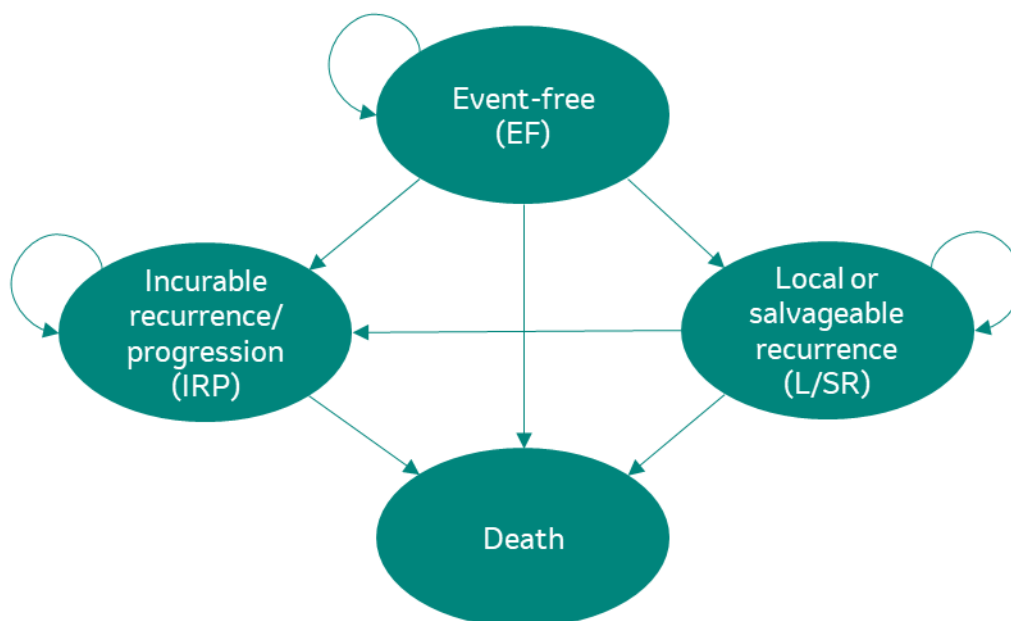
In the adjuvant setting, pembrolizumab can be given as a 400 mg IV Q6W as an alternative to the Q3W dosing schedule. Of note, the CS base case uses the three-week regimen only for the first cycle adjuvant cycle which is followed by seven cycles of 400 mg Q6W. This was assumed due to service capacity constraints, where the initial two doses were spaced at three weeks to reflect "*closer patient monitoring as they reinitiate treatment with pembrolizumab after surgery, and to prevent delivering a higher total dose of pembrolizumab over the full treatment schedule than is specified in the protocol.*" The dosing regimen assumed in the model provides a total dose which is in line with the total pembrolizumab dose received in KEYNOTE-689. The EAG's clinical experts agreed that the six weekly pembrolizumab dosing is preferred in clinical practice.

Radiotherapy dosing depended on the patient's risk level. Low-risk patients received 2 Gy per day in 30 fractions (total of 60 Gy) compared to 33 fractions (total of 66 Gy) for high-risk patients, and 35 fractions (total of 70 Gy) for patients with gross residual disease.

4.2.4 Model structure

A *de novo* state transition model was developed in Microsoft Excel® to assess the cost-effectiveness of perioperative pembrolizumab + SOC compared with SOC alone. The model structure developed by the company aims to simulate the disease pathway after diagnosis of resectable stage III-IVa LA HNSCC, in that patients can remain event-free, experience either a local/salvageable or incurable recurrence or die. Thus, the health states included in the model are event-free (EF), local or salvageable recurrence (L/SR), incurable recurrence/progression (IRP) and death. Figure 10 presents the model schematic. Although the company describes it's submitted as a Markov model, time-varying transition probabilities are allowed for transitions out of the EF state. However, the Markovian assumption of constant hazards over time is applied to transitions from the intermediate states (L/SR and IRP).

Figure 10 **Model structure (reproduced from CS, Figure 17)**



All patients enter the model in the EF health state following diagnosis and remain in this state until recurrence of disease or death. Recurrence of disease in the model is defined as either local or salvageable recurrence (where subsequent treatment, if any, is given with curative intent) or incurable recurrence (whereby cancer has spread to a distant organ/site and treatment is given with palliative intent). Transitions from the EF health state to the L/SR state, IRP state and death are informed by analyses of individual patient data (IPD) from KEYNOTE-689 (as discussed in Section 4.2.6).

In the L/SR health state, a proportion of patients receive salvage surgery or radiotherapy and remain in this health state if their disease does not progress further, or they die (transition to the death state). If the disease progresses, patients transition to the IRP health state. Transitions from the L/SR health state to the IRP health state and death are informed by analyses of IPD from KEYNOTE-689 (as discussed in Section 4.2.6).

Patients who transition to the IRP health state remain in this state until death. The IRP state consists of two sub-states which the CS does not explicitly mention: pre-progression IRP and post-progression IRP. This structure enables the costs and HRQoL implications of metastatic HNSCC to be more accurately captured and is reflective of the health states that would typically be included in metastatic oncology modelling; however, these sub-states were not independently modelled (i.e., using separate transition probabilities).

The pre-progression IRP state represents patients who have a confirmed IRP recurrence; all patients who transition to the IRP health state enter the pre-progression sub-state and a proportion of patients are assumed to receive first-line systemic therapy for metastatic HNSCC. The post-progression IRP state represents patients who have progressed on first-line therapy; a proportion of these patients are assumed to receive second-line systemic therapy for metastatic HNSCC.

The expected proportion of time spent pre- versus post-progression within the IRP state was estimated using the ratio of mean PFS and OS of first-line treatments for recurrent/metastatic HNSCC. This is based on the treatments received in the pembrolizumab + SOC and SOC arms in the KEYNOTE-689 trial, which are provided in Table 52 of the CS and the details of the approach are outlined in CS Appendix J2. The mean PFS and OS (in weeks) were determined according to the following steps for each arm:

- 1) A reference treatment, cetuximab + platinum + 5-FU (the comparator from KEYNOTE-048, a Phase 3 RCT of pembrolizumab ± chemotherapy versus cetuximab + chemotherapy in patients with incurable untreated R/M HNSCC) was chosen and the weekly exponential rates of OS and PFS were evaluated for the CPS $\geq$ 1, untreated population using the reported median survival.
- 2) For the other first-line treatments, HRs identified from a SLR for recurrent/metastatic HNSCC with CPS $\geq$ 1 were synthesised and HRs corresponding to the treatment versus the reference treatment were estimated within a fixed effect NMA (see Appendix J4 and Table 67 of CS Appendix J2). Two treatment regimens, gemcitabine + paclitaxel and cisplatin + pemetrexed, could not be connected within the NMA and thus the exponential rates were evaluated directly as a function of the reported median OS and PFS without applying HRs, see Table 66 in CS Appendix J2. The treatments 5-FU monotherapy, methotrexate monotherapy and cisplatin + paclitaxel did not have OS or PFS data available for synthesis and instead the efficacy was assumed to be equal to that of similar chemotherapy regimens (for e.g., cisplatin + paclitaxel was assumed the same as cisplatin monotherapy).
- 3) The estimated HRs for each treatment regimen were applied to the OS and PFS exponential rates of the reference treatment, and the subsequent mean OS and PFS evaluated for that treatment regimen.
- 4) The overall mean OS and PFS (averaging over all first-line treatments) was calculated as a weighted average, according to the market shares of first-line treatments for recurrent/metastatic HNSCC (see Table 52 of the CS).
- 5) The ratio of the overall mean PFS and overall mean OS was subsequently evaluated. The ratio of PFS:OS therefore represents the proportion of time within the IRP state that a patient spends in the pre-progression IRP sub-state, while 1 - (PFS/OS) represents the remaining proportion of time spent in the post-progression IRP sub-state.

The ratio of mean PFS:OS was then calculated for each model arm, and this ratio was used to determine the relative weight given to the pre-progression IRP versus post-progression IRP values for utility values (Section 4.2.8) and disease management costs (Section 4.2.9) as these factors differ between the two sub-states. In the company's base case analysis, these estimated PFS and OS ratios do not inform the estimated time to death for the IRP state, which is instead based on parametric survival models fitted to the KEYNOTE-689 trial (Section 4.2.6.4).

The company assumed a model cycle length of one week with half-cycle correction applied. The model time horizon was set to 40.1 years (lifetime), as the mean age in KEYNOTE-689 at baseline was 59.9 years. The perspective of the analysis was based on the UK NHS, with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.

4.2.4.1 EAG Critique of the model structure

The EAG considers the company's model structure to be generally appropriate. However, some concerns were identified regarding how the health states were defined and parameterised. The distinction between L/SR and IRP states seems subjective and dependant on the investigator's notes. Moreover, the presence of such two intermediary states within a transition-based model made it challenging to apply a time-varying hazard of transitioning out of these two states. The company stated that including the potential for time-varying hazards of transitioning out of the intermediate L/SR and IRP states using either tunnel states or visual basic coding would increase complexity and reduce transparency in the model compared with assuming an exponential distribution (clarification response, B11). Hence, the company chose to apply a Markovian assumption for these states and explored only exponential fits for these transitions (see Section 4.2.6).

The EAG notes that there are some limitations to the approach underpinning the estimate of the pre-versus post-progression time ratio within the IRP state. Firstly, the NMAs used within the estimation of the ratio of mean PFS and OS for first-line treatments of recurrent/metastatic HNSCC were reliant on the proportional hazards (PH) assumption. The PH assumption was tested using log cumulative hazard plots and there was suggestion that the PH assumption did not hold for all studies within the network. In response to clarification question B13, the company provided Schoenfeld residual plots and applied Grambsch-Therneau tests to assess the PH assumption. The company states that there may have been potential violations of the PH assumption for both OS and PFS in the KEYNOTE-048 trial,³³ for PFS in Burtness *et al.*,³⁴ and for OS in Friesland *et al.*³⁵

Secondly, although the population within the NMAs was restricted to CPS $\geq$ 1, no additional effect modifiers were discussed or included within the NMAs which may result in biased estimates within the evaluation of the mean PFS and OS.

Thirdly, the reference treatment to which the synthesised HRs are applied was approximated via an exponential fit which assumes constant hazards and is potentially a large simplification of the true observed behaviour and projection of PFS and OS for this treatment. However, the EAG acknowledges that this approach is pragmatic and allows for the incorporation of data from multiple sources in the instance that this ratio could not be estimated using the KEYNOTE-689 data alone.

4.2.5 Summary of evidence sources used to inform the company's model parameters

Table 17 summarises the evidence sources used to inform the parameters of the company's base case model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 17: Summary of evidence sources used to inform the model parameters for the company's base case

Parameter type	Pembrolizumab + SOC	SOC
Patient characteristics	Average baseline characteristics (age, gender, BSA, and weight) across both arms of KEYNOTE-689 taken from the 'all comer' population.	
EFS	Survival models fitted independently to time-to-event data for each type of EFS event (EFS à L/SR; EFS à IRP; EFS à death) in each arm of KEYNOTE-689	
OS	Survival models fitted independently to time-to-event data for time to death from each state (EFS à death; L/SR à death; IRP à death) in each arm of KEYNOTE-689	
Time on treatment (ToT)	Treatment usage for each component of treatment (neoadjuvant pembrolizumab, surgery, radiotherapy, chemotherapy, adjuvant pembrolizumab) as reported for each trial arm in KEYNOTE-689 (PD-L1 CPS ≥ 1 subgroup, APaT population)	
AE frequencies	Grade ≥ 3 AEs that occurred with a frequency of ≥ 5% in either treatment arm as reported for each trial arm in KEYNOTE-689 (APaT population)	
AE costs	NHS Cost Collection for hospital admissions and outpatient visits for non-hospitalised patients; proportion hospitalised, duration of AEs and episodes per patient estimated from KEYNOTE-689 (APaT population, pooled across arms).	
AE disutilities	Disutility for Grade ≥ 3 AEs estimated by comparing utility pooled across trial arms for patients in the EF state with and without grade ≥ 3 AE in KEYNOTE-689 (all comer population)	
EFS utility	Utilities based on EQ-5D-5L responses mapped to the EQ-5D-3L UK preference set for patients who are recurrence/progression free; pooled across both arms of KEYNOTE-689 (all comer population)	
L/SR utility	As for EFS, but pooled across patients with local / salvageable recurrence.	
Pre-progression IRP utility	As for EFS, but pooled across patients with incurable recurrence / progression.	
Post-progression IRP utility	EORTC-QLQ-C30 from EXTREME study mapped to EQ-5D-3L, as reported in NICE TA172/TA473.	
Drug costs	PAS price for pembrolizumab; Other drugs price as for SOC	eMIT/BNF prices
Drug administration costs	NHS Cost Collection for administration of chemotherapy, weighted average of outpatient procedure and day cases	

Parameter type	Pembrolizumab + SOC	SOC
Surgery / radiotherapy costs	Usage based on KEYNOTE-689 (APaT population); NHS Cost Collection	
Health state costs	Resource use based on clinical guidelines and clinical expert opinion combined with NHS Cost Collection. Resource use differs by treatment for EF state only.	
Subsequent therapies in L/SR	Surgery and radiotherapy based on usage in KEYNOTE-689 (APaT population). ToT and treatment mix for systemic treatments based on KEYNOTE-689 (PD-L1 CPS ≥ 1 population).	
Subsequent therapies in IRP – first-line	SLR and NMA of first-line treatments for recurrent/metastatic disease used to inform ToT. Mix of treatments based on KEYNOTE-689 (PD-L1 CPS ≥ 1 population).	
Subsequent therapies in IRP – second-line	ToT based on KEYNOTE-048. Treatment mix based on KEYNOTE-689 (PD-L1 CPS ≥ 1 population).	

Abbreviations: AE, adverse event; APaT, all patients as treated; EFS, event free survival; eMIT, electronic market information tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D-3L, EuroQol 5-dimension 3-level questionnaire; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; IRP, incurable recurrence or progression; L/SR, local or salvageable recurrence; OS, overall survival; PAS, patient access scheme; PD-L1 CPS, programmed death-ligand combined positive score; SOC, standard of care; ToT, time on treatment

4.2.6 Treatment efficacy within the model

The company used IPD from KEYNOTE-689 to estimate transitions from the EF, L/SR and IRP states for both the pembrolizumab + SOC and SOC arms.

A multistate modelling approach, accounting for competing risks was implemented for the transitions from the EF state, as described by Williams *et al.*,^{36, 37} whereas exponential (time-invariant) rates were applied for the transitions from the L/SR and IRP states. The approaches used for the transitions for each state are summarised in Table 18 and discussed in Section 3.3 of the CS. The approach is discussed in the following subsections and additional discussion of the application of a cure assumption is given thereafter.

Table 18: Summary of approaches used to estimate transition probabilities from each health state, (adapted from Table 26, CS).

Transitions	Estimation approach	Data source
EFàL/SR EFàIRP EFàDeath	Parametric multistate modelling approach. Three approaches trialled including: 1) standard parametric model fits to each EF state transition (independently fit to each arm) 2) PH model fits (with constant HR) 3) piecewise PH model fitting with two HRs (one applied prior to 1 year post randomisation, and one applied thereafter).	Patient-level data from KEYNOTE-689 trial. Transition probabilities to death were constrained using national life tables to define the minimum probability of death.*
L/SRàIRP L/SRàDeath	Exponential rates of transitions originating from L/SR estimated using KEYNOTE-689 data. Independently fit to data for each arm.	
IRPàDeath	Exponential rates of transitions originating from IRP estimated using KEYNOTE-689 data. Independently fit to data for each arm. These data included patients who experienced IRP as a first event as well as patients who experienced IRP as the second event (i.e., via the L/SR state).	

EF, event free; L/SR, local/salvageable recurrence; IRP, incurable recurrence/progression; PH, proportional hazards; HR, hazard ratio

* Transition probabilities for each transition to death were constrained to be at least as high as all-cause mortality, estimated using age and sex distributions of the cohort within each cycle. National lifetables for the United Kingdom between 2021 and 2023 from the Office for National Statistics were used.

4.2.6.1 Censoring rules applied in the estimation of transition probabilities

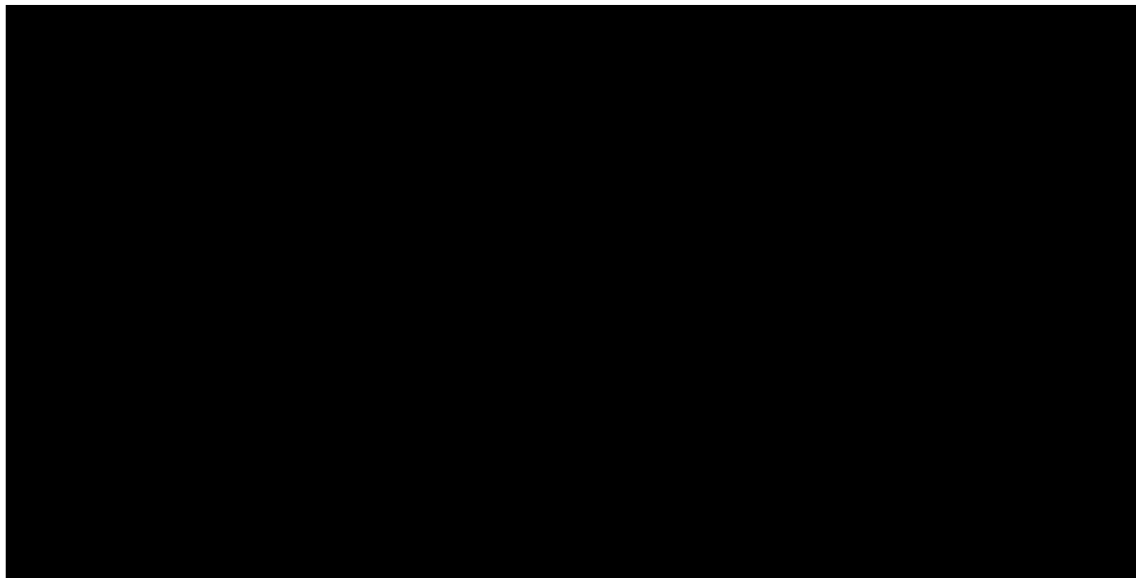
The primary censoring rules for EFS and OS differed in the KEYNOTE-689 analyses. Censoring for EFS was such that patients were censored at the date of last assessment, whereas for OS, patients were censored at the date they were last known to be alive. Therefore, the censoring times under the OS rule were consistently greater than or equal to those in the primary censoring case. According to the primary censoring criteria of KEYNOTE-689, ■■■ and ■■■ patients in the all-comer population were censored in the 25-Jul-2024 DCO Kaplan-Meier analysis of OS and EFS respectively. On average, the date of last disease assessment was ■■■ days before the last date the patient was known to be alive.

Due to the structural linking of EFS and OS within the company's model, the censoring of EFS and OS needed to be aligned. In the company's base case, the censoring according to EFS was employed, and thus OS was re-censored to align with this. OS therefore was censored according to the last disease assessment for patients who are censored according to both EFS and OS, and the last date known alive

for patients who are only censored according to OS. The impact of re-censoring EFS and OS to align the censoring rules is shown in Figure 11 and Figure 12.

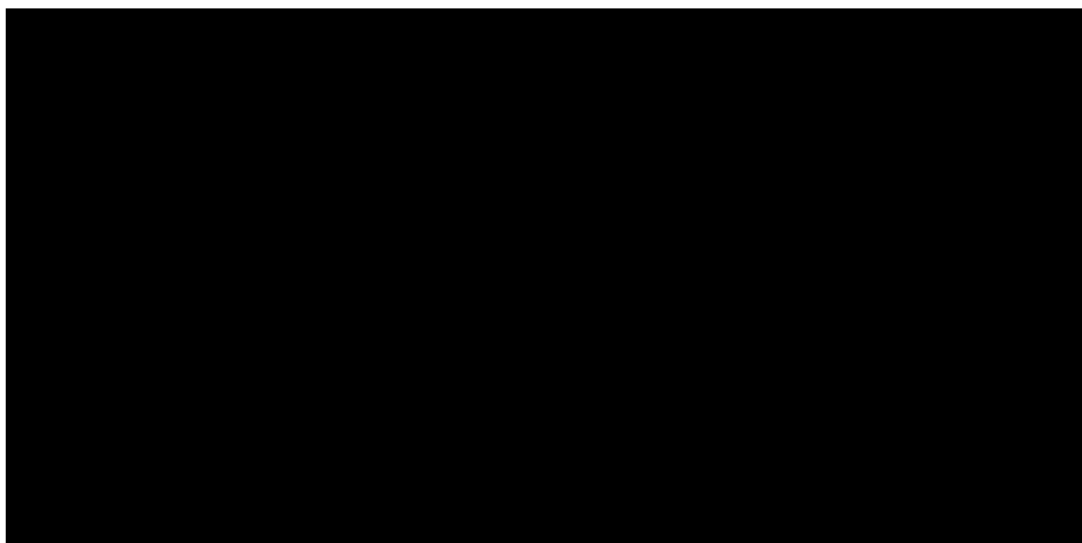
The company selected to use the EFS censoring regime within their base case as EFS was the primary outcome of KEYNOTE-689 and this reflects how patients are followed up in clinical practice.

Figure 11: Comparison of EFS under the primary and alternative censoring rules, (figure generated by the EAG using the company's model).



Abbreviations EFS, event free survival; SOC, standard of care

Figure 12: Comparison of OS under the primary and alternative censoring rules, (figure generated by the EAG from the company's model).



Abbreviations OS, overall survival; SOC, standard of care

4.2.6.2 Transitions from the EF state

Within the company's submitted model, there are three transitions from the EF state (EFàL/SR, EFàIRP and EFàDeath). Transition probabilities were estimated according to a parametric multistate modelling approach described by Williams *et al.*^{36, 37} using individual patient data from the KEYNOTE-689 trial. Standard parametric models independently fitted to each treatment arm, PH models with a "time-constant treatment effect" and PH models with a "time-varying treatment effect" were used to estimate cause-specific hazards for each transition for the pembrolizumab + SOC and SOC arms. The transition probabilities within each weekly cycle were evaluated as a function of the three cause-specific hazards by calculating the proportion of the joint hazard of any EFS event attributing to each event type and then converting onto the probability scale, as outlined in the following section.

Estimation of cause-specific hazards and transition probabilities

To calculate the cause-specific hazards with respect to time for each failure type, the individual patient data were first re-censored to account for the competing event types. For each failure type, the two competing failure types were considered censoring events.³⁸ For example if re-censoring the IPD for EFàL/SR, the competing failure types (EFàIRP and EFàDeath) were treated as censoring events. Parametric models were fit to each of the re-censored datasets. The model fitting was performed using the *flexsurvreg* package in R.³⁹

For each transition type, thirteen models, were fit to the re-censored data. These models spanned three approaches and included:

- Approach 1: Independently fitting standard parametric survival models (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma distributions) to the pembrolizumab + SOC and SOC arms. The same model choice for both arms was assumed.
- Approach 2: Jointly fitting PH models with a time-constant treatment effect. This was restricted to the exponential, Weibull and Gompertz models within the PH class. For this approach, a single, constant HR was assumed to apply indefinitely.
- Approach 3: Jointly fitting PH models with a time-varying treatment effect. As in Approach 2, the three PH models were fitted. Instead of assuming a single constant HR, two HRs were assumed within the model, one corresponding to the model at times less than 1 year, and another for the period from 1 year onwards. The 1-year cut-point was chosen as it corresponds with the maximum duration of adjuvant pembrolizumab.

When implementing Approaches 2 and 3, the PH assumption was initially assessed through the statistical assessment of Schoenfeld residual plots, but following the clarification response, cumulative log-hazard plots were also provided. In the CS the company stated that the PH assumption did not hold for EFàL/SR ($p=0.0351$) and that this was supported by the residuals displaying a non-horizontal trend. The PH assumption could not be formally rejected for EFàIRP ($p=0.4414$) and EFàDeath ($p=0.0558$). The company clarified that because the PH assumption did not hold for one of the three transitions, combinations of models under Approach 2 were excluded; however, the models under Approach 2 were retained for scenario analyses to ensure completeness.

As both Approach 2 and Approach 3 are reliant on the PH assumption within regions of the data set, and this was demonstrated not to hold for all transitions, the EAG does not expand on these methods further; results for these approaches can be found in Section 3.3 of the CS and CS Appendix J. Additionally, the final 10 candidate models (see Section 4.2.6.5) identified by the company included only models using Approach 1 and thus the EAG considers it is appropriate to focus on this approach within this report.

Estimation of transition probabilities

Following the fitting of the models outlined in Approaches 1-3, the cause-specific hazards for each of the transitions were used to calculate the transition probabilities from the EF state according to the following steps:⁴⁰

1. For each cause of failure, denoted k , the average cause-specific hazard from week $t - 1$ to week t , $(\bar{h}_k(t))$, was calculated as

$$\bar{h}_k(t) = H_k(t) - H_k(t - 1),$$

Where $H_k(t)$ is the cumulative hazard of cause k from the parametric model fitted to the re-censored individual patient data for cause k at time t .

2. The average hazard for any EF failure event (of any type) between week $t - 1$ and week t was evaluated as the sum of the cause-specific hazards for all event types ($\bar{h}_{EFS}(t)$). The probability of any EF failure event occurring was thus given as

$$1 - e^{-\bar{h}_{EFS}(t)}$$

3. The transition probability for cause k was subsequently calculated by multiplying the relative contribution of cause k by the probability of an EF failure event.

$$\frac{\bar{h}_k(t)}{\bar{h}_{EFS}(t)} (1 - e^{-\bar{h}_{EFS}(t)})$$

To account for background mortality, the transition probability from EF→Death was constrained to be the maximum value of the model-derived probability of transition to death and the age- and sex-matched background mortality for that cycle. Background mortality rates were derived from the Office for National Statistics (ONS) United Kingdom life tables 2021-2023.⁴¹ A standardised mortality rate (SMR) of 1.0 was assumed.

The model selection for each transition type from the EF state is further discussed in Section 4.2.6.5.

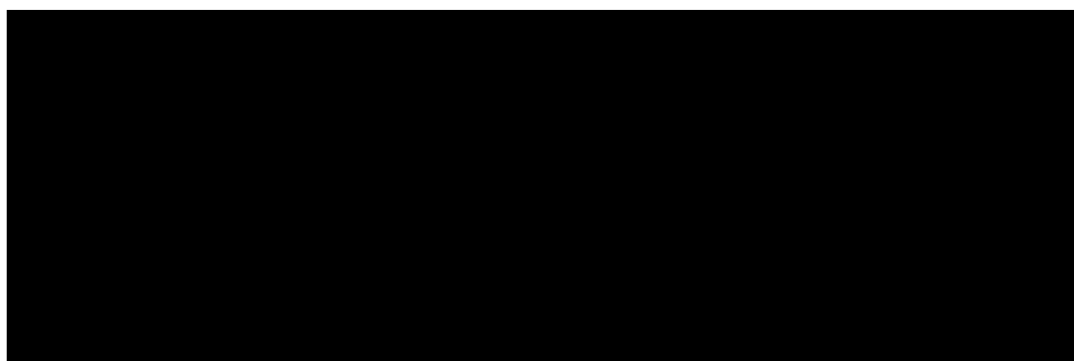
4.2.6.3 Transitions from the L/SR state

The cost-effectiveness model is a Markov model and therefore transition probabilities from intermediate states cannot, by design, be dependent on the amount of time spent in the intermediate state. Therefore, exponential models, with constant hazards, were chosen to model the cause-specific hazards of the L/SR→IRP and L/SR→Death transitions. This choice appears to have been made based on the selection of the Markov structure as opposed to clinical input regarding the plausibility of constant hazards of event within intermediate states.

As for the transitions from the EF state, IPD from the KEYNOTE-689 trial were used. The PD-L1 CPS≥1 population was used and there were ■ patients (■ in the pembrolizumab + SOC arm, ■ in the SOC arm) who experienced L/SR as their first EFS failure event.

There were ■ (■ in the pembrolizumab + SOC arm and ■ in the SOC arm) patients who first experienced L/SR and subsequently IRP as a recurrence event. To estimate the cause-specific hazards for the L/SR→IRP transition, patients were censored at the earliest of the death date, or date last known to be alive, and an exponential model fit to the re-censored individual patient data. The cumulative incidences predicted by the model and the observed data are shown in Figure 13.

Figure 13: Observed versus predicted cumulative incidence for the L/SRàIRP transition (reproduced from Figure 24, CS).

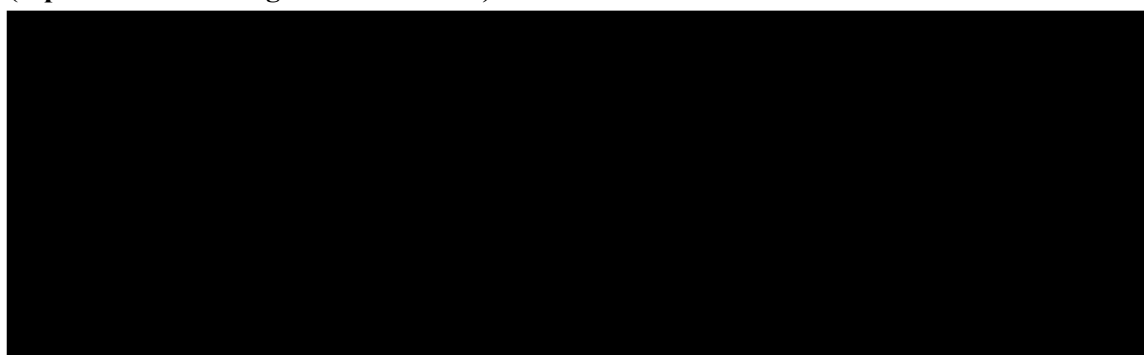


Abbreviations: IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence, SOC, standard of care

There were ■ (■ in the pembrolizumab + SOC arm and ■ in the SOC arm) patients who experienced death following an L/SR event. Patients were censored at the earliest of the last date known to be alive or the date that the patient experienced an IRP recurrence, and an exponential model was fit to the re-censored patient data.

As for the EFàDeath transition, the transition probability for L/SRàDeath was constrained as the maximum of the model-derived probability of transitioning to death or the age- and sex-matched background mortality for that cycle. The cumulative incidences predicted by the model and the observed data are shown in Figure 14.

Figure 14: Observed versus predicted cumulative incidence for the L/SRàDeath transition, (reproduced from Figure 25 of the CS).



Abbreviations: IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence, SOC, standard of care

The transition probabilities were subsequently calculated using the cause-specific hazards for each of the transitions from the L/SR state using the approach outlined in Section 4.2.6.2. Note that the

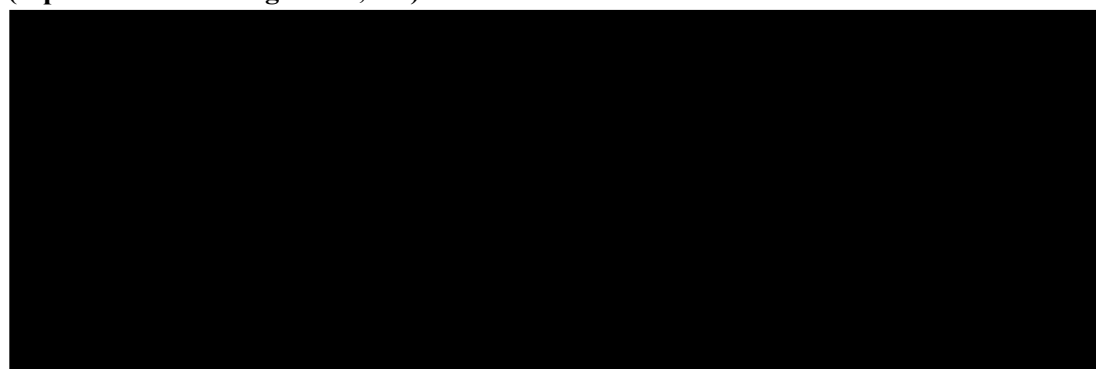
transition probabilities are time-invariant, as the model structure does not allow for time-varying transition rates in the intermediate health states.

4.2.6.4 Transitions from the IRP states

Following the approach used to model transitions from the L/SR intermediate health state (Section 4.2.6.3), exponential models were fit to the KEYNOTE-689 IPD and were used to estimate the cause-specific hazard of the IRP→death transition.

There were ■■■ patients (■■■ in the perioperative pembrolizumab + SOC arm and ■■■ in the SOC arm) who experienced IRP as their first EFS failure event and ■■■ patients (■■■ in the perioperative pembrolizumab + SOC arm and ■■■ in the SOC arm) who experienced L/SR followed by IRP as a subsequent recurrence event. Of the patients who experienced IRP as their first EFS failure event, ■■■ patients (■■■ in the perioperative pembrolizumab + SOC arm and ■■■ in the SOC arm) experienced death as a subsequent event. Of the patients who experienced IRP as their second EFS failure event, ■■■ patients (■■■ in the perioperative pembrolizumab + SOC arm and ■■■ in the SOC arm) experienced death as a subsequent event. These data, from patients who experienced L/SR followed by IRP and those who experience IRP as their first event, were pooled and exponential models were fit to the time from IRP health state entry to death or censoring (due to end of data or loss of follow-up) for each arm. The transition probabilities were subsequently derived from the exponential model rates. As for the EF→Death and L/SR→Death transitions, the probability of IRP→Death was constrained as the maximum of the model-derived probability of transition to death or the age- and sex-matched background mortality for that cycle. The observed cumulative incidences and the model predicted cumulative incidence curves are shown in Figure 15.

Figure 15: Observed versus predicted cumulative incidence for the IRP→Death transition, (reproduced from Figure 26, CS).



Abbreviations: IRP, incurable recurrence/progression; SOC, standard of care

The company also considered a sensitivity analysis to assess the impact of varying the exponential rate of the IRPàDeath transition within the 95% CI of the exponential rate.

4.2.6.5 Selection of base case models

The CS states that assessing model fit is more challenging in the context of a multistate model as opposed to the context of simpler partitioned survival models. The proportions of individuals experiencing an event are determined by combinations of survival models as opposed to a single survival model.³⁸ Thus there is a significantly higher number of potential model combinations that must be assessed.

As exponential models were chosen to model events from intermediate states (L/SRàIRP, L/SRàDeath and IRPàDeath), only the combination of models for EFàL/SR, EFàIRP and EFàDeath needed to be considered during model selection. In accordance with TSD 14, the company chose to use the same functions for the pembrolizumab + SOC and SOC arms.⁴² Under the three approaches outlined in Section 4.2.6.2, with 13 (7 + 3 + 3) candidate model choices for each transition, there was a total of 397 possible combinations of models for the transitions from the EF state. Of these, 343 (7×7×7) combinations corresponded to the models fitted according to Approach 1.

The choice of models was informed by the following criteria:

- Statistical fit via the mean squared error (MSE) of the model EFS prediction relative to the observed EFS

The company states that the Akaike Information Criteria (AIC) “*is not a suitable measure of fit with observed data when modelling competing risks*” as per Williams *et al.*³⁶ The MSE of EFS was therefore used as an alternative measure to assess the fit of the predicted EFS curves from different combinations of models with the observed EFS curve. The MSE of EFS was calculated by evaluating the difference between the observed and modelled EFS at weekly intervals and weighted according to the numbers of patients at risk for each combination of models.

- Visual assessment of predicted EFS and observed EFS

Predicted EFS curves from different combinations of models for EFàL/SR, EFàIRP and EFàDeath were compared visually to the observed EFS Kaplan-Meier curve as per the approach by Williams *et al.*³⁶ In addition, cumulative incidence curves for each of the individual transitions were compared with the observed cumulative incidence curves from KEYNOTE-689.

- Clinical plausibility and external validity of model long-term EFS and OS extrapolations.

The company conducted a targeted literature review to identify real-world studies reporting long-term EFS and OS outcomes to inform clinical plausibility of the fitted models. The company did not identify any previous studies which implemented treatment strategies including neoadjuvant or perioperative treatment for resectable LA HNSCC. As a result, any identified studies reported DFS as opposed to EFS. There was therefore a discrepancy between the time of randomisation and thus the time for which patients are considered at risk. The company therefore did not identify any studies with comparable EFS data for external validation of the model extrapolations. The company also highlighted significant differences in trial populations, especially with regards to the anatomical site which can be a strong prognostic factor within LA HNSCC. Despite this, the company did use external studies with longer follow up (with potential caveats) to assess the predicted OS extrapolations for the SOC arm (see CS Appendix J1.4 for full details of studies). The company also sought expert opinion relating to the possibility of long-term trends in EFS such as an observed plateau. The company did not use expert-derived survival estimates to inform the model selection process. The company concluded that the follow-up period of the KEYNOTE-689 trial (approximately 5 years), was sufficient to allow for robust internal validation of candidate models via comparison of the EFS and OS model predictions and observed Kaplan-Meier curves from KEYNOTE-689.

Consideration of the hazard plots for the model combinations was primarily considered when assessing the applicability of the cure assumption (see Section 4.2.6.6) and not during the curve selection process.

Curve selection step 1: Priority transition model choice

The company's model selection process first aimed to prioritise the choice of model for the EFàDeath transition. For each choice of model for the EFàDeath transition, the minimum and average MSE was calculated across all other combinations of models for EFàL/SR and EFàIRP. To evaluate the minimum and average MSE for each model set, the following was performed.

1. Evaluate the MSE for each individual model combination (i.e., evaluate the MSE for all 397 model combinations).
2. Group the model combinations according to the choice of distribution for the EFàDeath transition. This results in 13 sets of models corresponding to the use of the exponential, Gompertz, Weibull, log-logistic, log-normal, generalised gamma, and gamma under Approach 1, the 3 time-constant PH models under Approach 2, and the 3 time-varying PH models under Approach 3.

3. For each set according to the choice of model for the EFàDeath transition, evaluate the minimum and average MSE of the set. This corresponded to the minimum/average MSE of 49 model combinations under Approach 1 for each EFàDeath model choice, three sets of 9 model combinations under Approach 2, and three sets of 9 model combinations under Approach 3.
4. Identify the model set with the lowest minimum and average MSE values to select the model for EFàDeath.

The company chose to prioritise the EFàDeath transition to initially refine the list of candidate models as assessment of the minimum and average MSEs for each model set resulted in a clearer choice of best distribution for the EFàDeath transition in both arms compared to the other two transitions. According to both the minimum and average MSE for each set, presented in Table 56 of CS Appendix J the generalised gamma distribution for the EFàDeath transition provided the best fit to EFS for both the pembrolizumab + SOC arm and SOC arm.

As highlighted in Section 4.2.6.2, the PH assumption was shown not to hold for the EFàIRP transition and thus the best fitting models for EFàDeath under Approaches 2 and 3 are not summarised within this report, though the company did explore these to fully assess the potential impact of these approaches on the cost-effectiveness estimates. The EAG does not believe the models under Approaches 2 and 3 are appropriate and therefore focuses on the candidate models under Approach 1 only.

Curve selection step 2: Selection of distributions for remaining transitions

Having selected the generalised gamma distribution for the EFàDeath transition, there were 49 candidate model combinations to consider for the remaining two transitions. The visual fit of predicted versus observed cumulative incidence curves was assessed for each candidate combination (see Figure 16, Figure 17 and Figure 18).

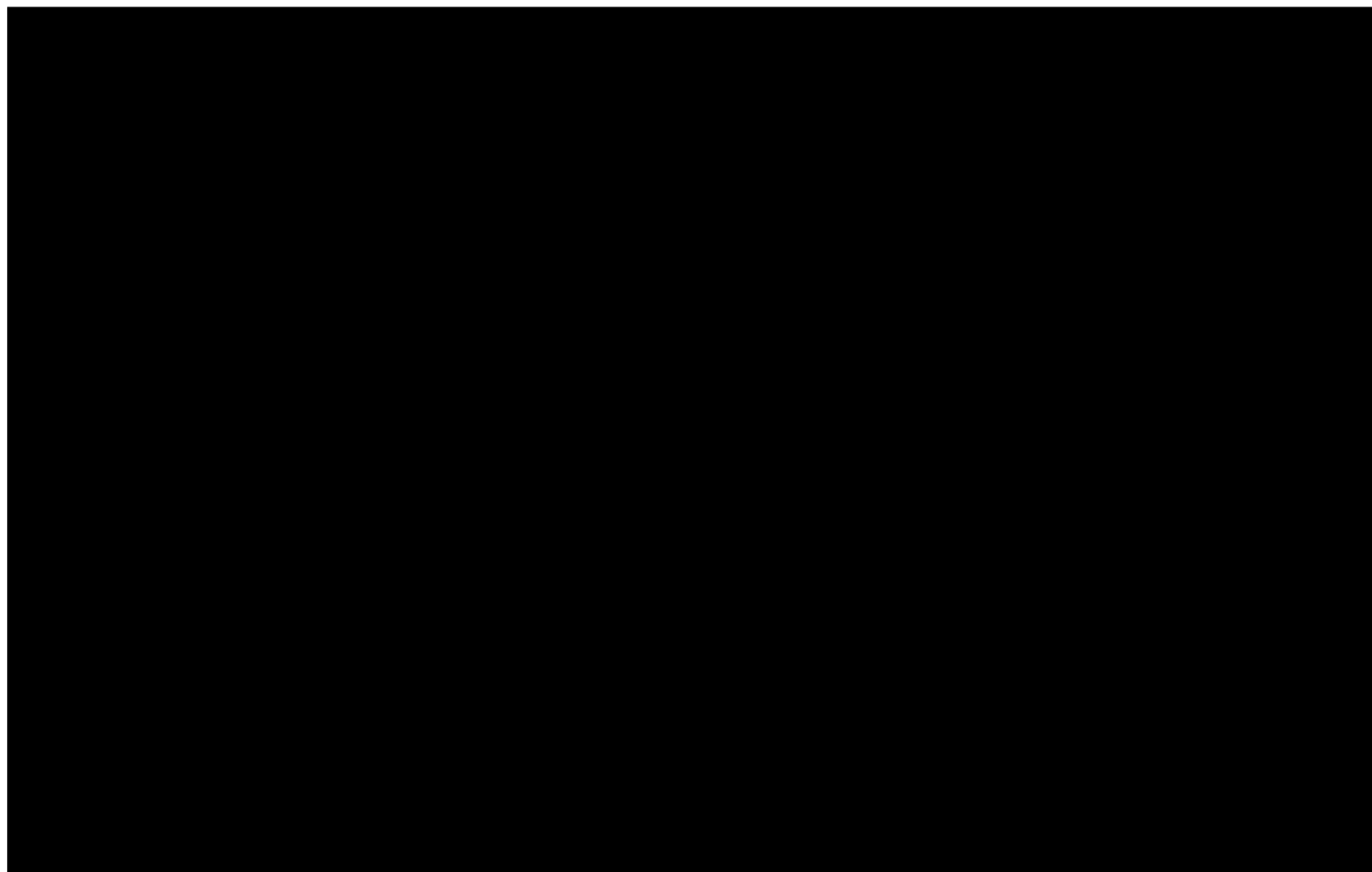
Within Figure 16, the colour family corresponds to one model fitted to the EFàL/SR cause-specific hazards, and the different shades correspond to the different models for EFàIRP (i.e., the red colour family corresponds to the seven models where the EFàL/SR transition is modelled by the exponential, and the different shades of red correspond to combinations where EFàIRP is modelled via the exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma and gamma distributions). Therefore, for each colour, there are seven curves corresponding to the different combinations of models under that choice of the EFàL/SR model. In Figure 17 and Figure 18, each colour family instead corresponds to the model choice for the EFàIRP state, and the different shades correspond to the different model choices for the EFàL/SR state (i.e., the red colour family corresponds

to the seven models where the EFàIRP transition is modelled by the exponential, and the different shades of red correspond to combinations where EFàL/SR is modelled via the exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma and gamma distributions).

For both arms, all combinations of models, except models which applied the exponential model to the EFàL/SR state, showed good visual fit of the cumulative incidence of EFàL/SR (see Figure 16). As shown in Figure 17, it was evident that models applying the Gompertz distribution for EFàIRP tended to produce the best visual fit of predicted versus observed cumulative incidence for EFàIRP. The company also identified the generalised gamma distribution as a candidate model choice for EFàIRP. There was little difference between the predicted and observed EFàDeath cumulative incidence under the candidate models; however, there was variability in the long-term projections of cumulative incidence between the models.

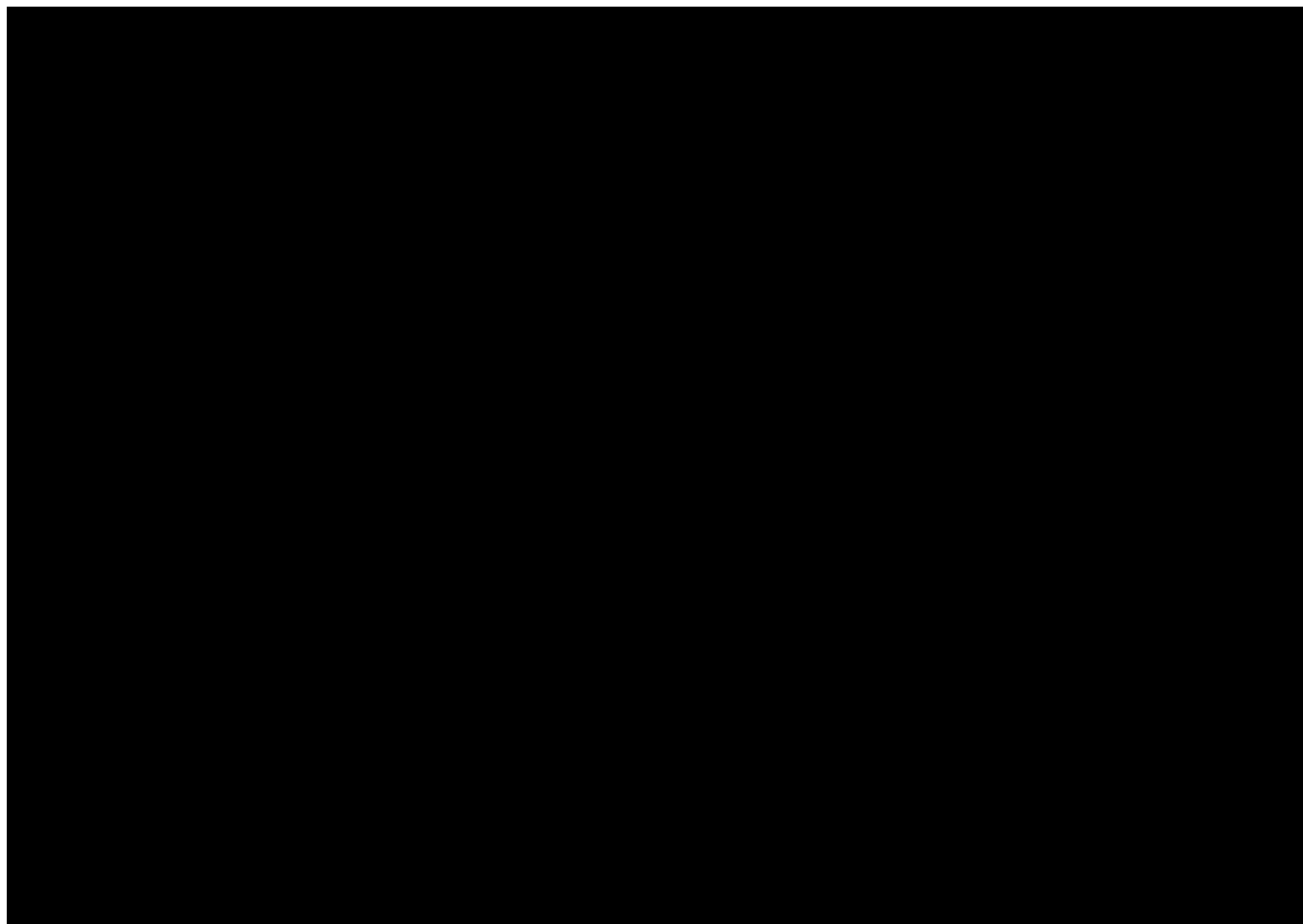
Following these visual assessments, the company identified 12 candidate models under Approach 1, which applied either the Gompertz or generalised gamma distribution for EFàIRP, the generalised gamma distribution for EFàDeath and excluded the exponential distribution for EFàL/SR.

Figure 16: Predicted versus observed cumulative incidence for EFàL/SR, (reproduced from Figure 7, CS, Appendix J).



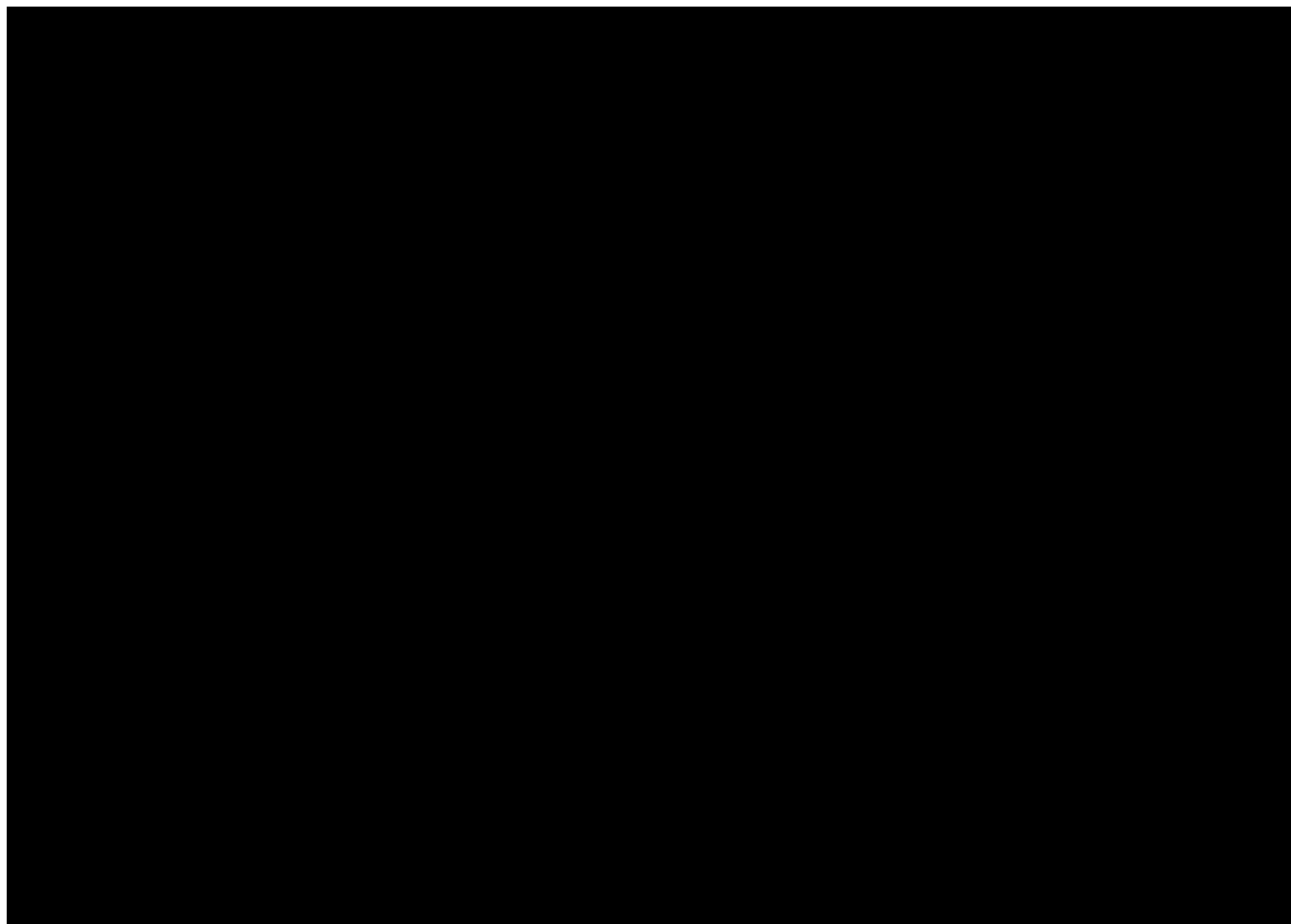
Abbreviations: EF, event-free; IRP, incurable disease/progression; L/SR, local recurrence

Figure 17: Predicted versus observed cumulative incidence for EFàIRP, (reproduced from Figure 8, CS, Appendix J).



Abbreviations: EF, event-free; IRP, incurable disease/progression; L/SR, local recurrence

Figure 18: Predicted versus observed cumulative incidence for EFàDeath, (reproduced from Figure 9, CS, Appendix J).



Abbreviations: EF, event-free; IRP, incurable disease/progression; L/SR, local recurrence

Curve selection step 3: Statistical assessment of candidate models

All model combinations following selection of the generalised gamma distribution for the EFàDeath transition were ranked according to their MSE of EFS for each arm. The MSE for each of the 12 candidate models all resided in the top half of the rankings for best statistical fit according to MSE (Table 58 and Table 61 in the CS Appendix J).

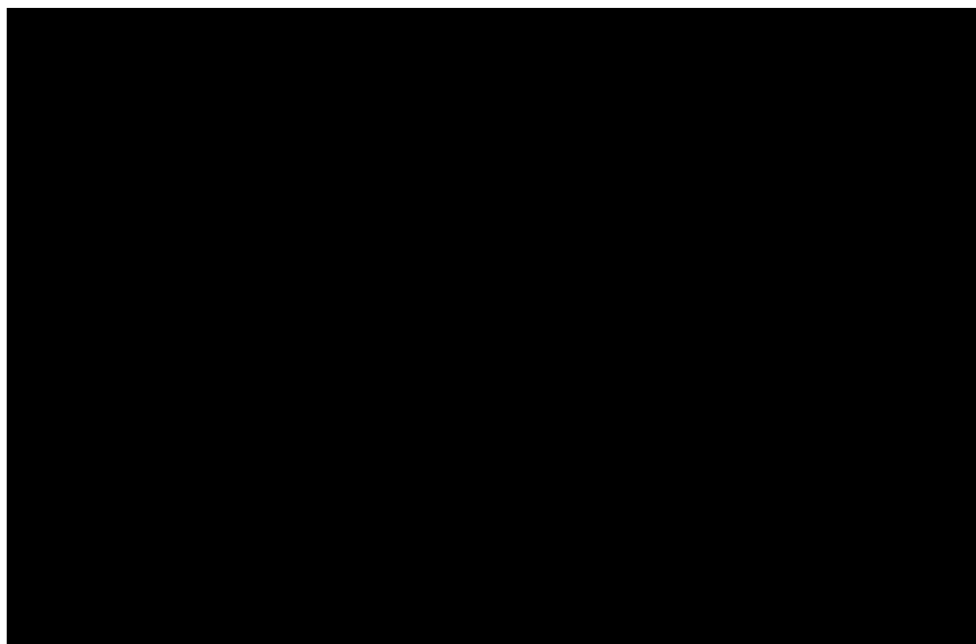
It was noted that the MSE for the SOC arm was generally higher than the MSE for the pembrolizumab + SOC arm, indicating a poorer fit, therefore the choice of model combination was driven by the ranking according to the SOC arm.

Two model combinations from the 12 candidate models (Weibull/ Gompertz/ generalised gamma and gamma/ Gompertz/ generalised gamma given as EFàL/SR / EFàIRP / EFàDeath respectively) were excluded from further analysis as they did not appear in the top 10 MSE ranked distributions in the SOC arm.

Curve selection step 4: Comparison of predicted versus observed EFS and OS

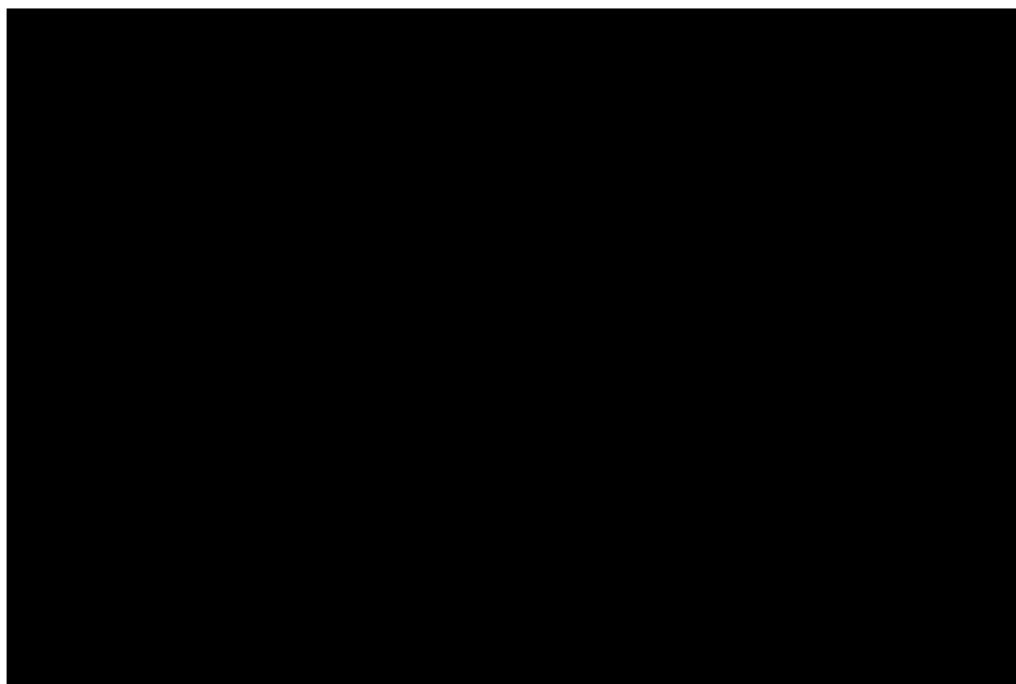
All 10 candidate model combinations provided good agreement to the observed OS from KEYNOTE-689 for the pembrolizumab + SOC and SOC arms, as presented in Figure 19 and Figure 20, respectively. In addition to the candidate model extrapolations for the SOC arm, longer-term data from three external studies are displayed. These three studies are not directly comparable to KEYNOTE-689, due to differences in population and thus present a large variability in long-term survival. The study reported by Leeman *et al.* predominantly included patients with oropharyngeal disease.⁴³ Of these patients 48% were HPV-positive which is associated with a better prognosis than HPV-independent disease. Burbure *et al.* and Chen *et al.* both report survival for hypopharyngeal patients who historically have worse outcomes compared with other tumour sites.^{44, 45} However, the company highlight in Section 3.3.2.3 of the CS that the candidate model projections fall within the range of these external studies which supports their selection as candidate models.

Figure 19: Candidate model extrapolations for OS and external validation for the pembrolizumab + SOC arm, (generated by the EAG using the company's model).



Abbreviations: OS, overall survival; SOC, standard of care

Figure 20: Candidate model extrapolations for OS and external validation for the SOC arm, (reproduced from Figure 18, CS).



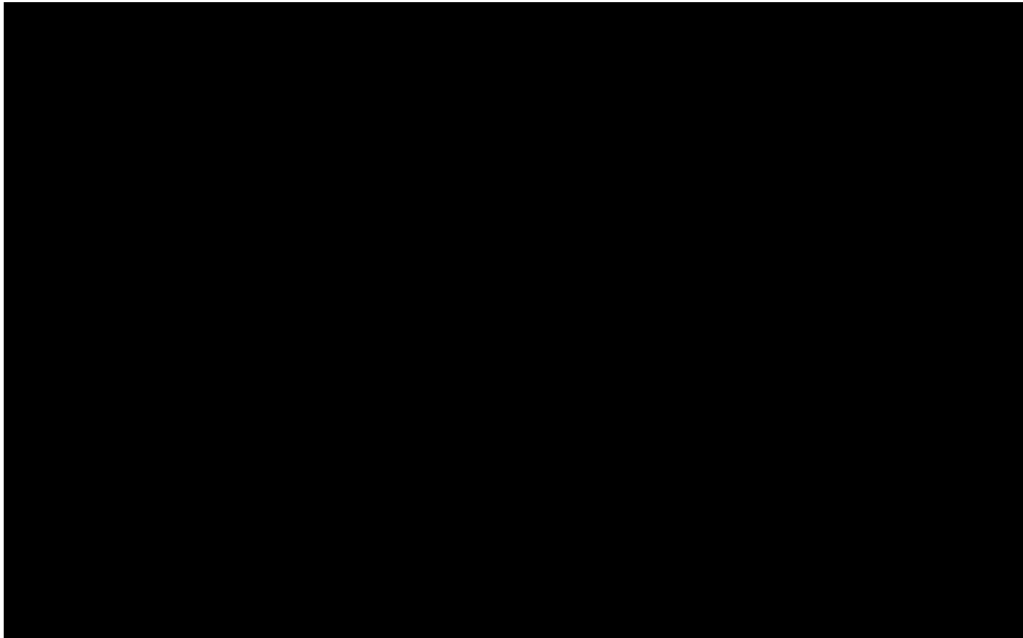
Abbreviations: EF, event free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; OS, overall survival; SOC, standard of care

Note that for all candidate models, the EF→Death transition is modelled using the generalised Gamma distribution.

Also note the fourth curve labelled as “Generalized gamma” corresponds to the Generalized gamma, Gompertz combination of models.

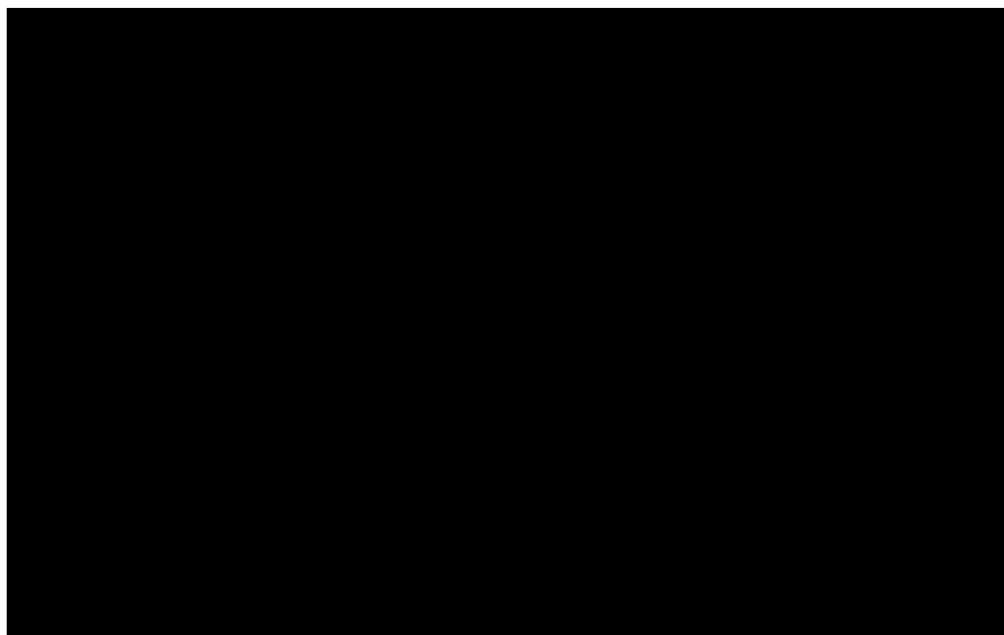
The predicted versus observed EFS for the pembrolizumab + SOC and SOC arms are presented in Figure 21 and Figure 22, respectively. All models demonstrate good agreement.

Figure 21: Candidate model extrapolations for EFS and external validation for the pembrolizumab + SOC arm, (generated by the EAG using the company's model).



Abbreviations: OS, overall survival; SOC, standard of care

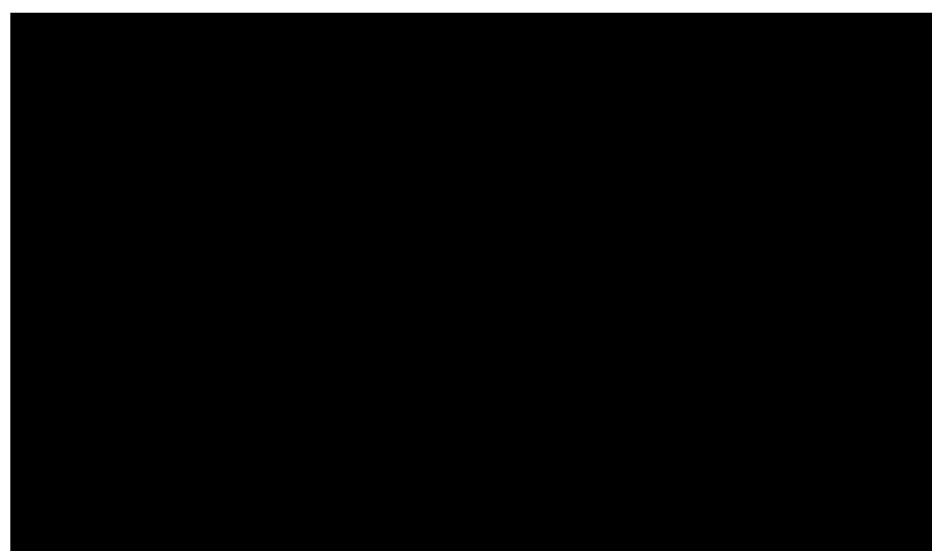
Figure 22: Candidate model extrapolations for EFS and external validation for the SOC arm, (generated by the EAG using the company's model).



Abbreviations: OS, overall survival; SOC, standard of care

The company also provided smoothed hazard plots for EFS and OS in the $CPS \geq 1$ population from the KEYNOTE-689 at the clarification stage (question B6), which are reproduced in Figure 23 and Figure 24, respectively. These were smoothed using a kernel-based approach, but the bandwidth of the kernel was not provided. The company also provided the corresponding predicted EFS and OS hazards for the 10 candidate models (Figure 25 and Figure 26, respectively). However, the hazard trends did not inform the company's choice of models for the base case and scenarios.

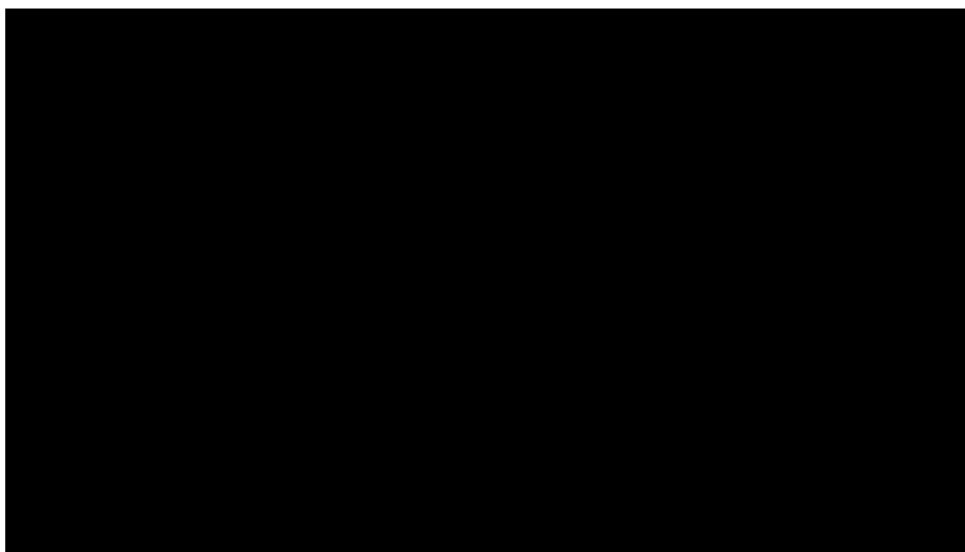
Figure 23: Smoothed hazard plots^a for EFS, (reproduced from clarification response B6).



Abbreviations: EFS, event-free survival; SOC, standard of care.

^aNote that the EAG believes the hazard presented corresponds to the monthly.

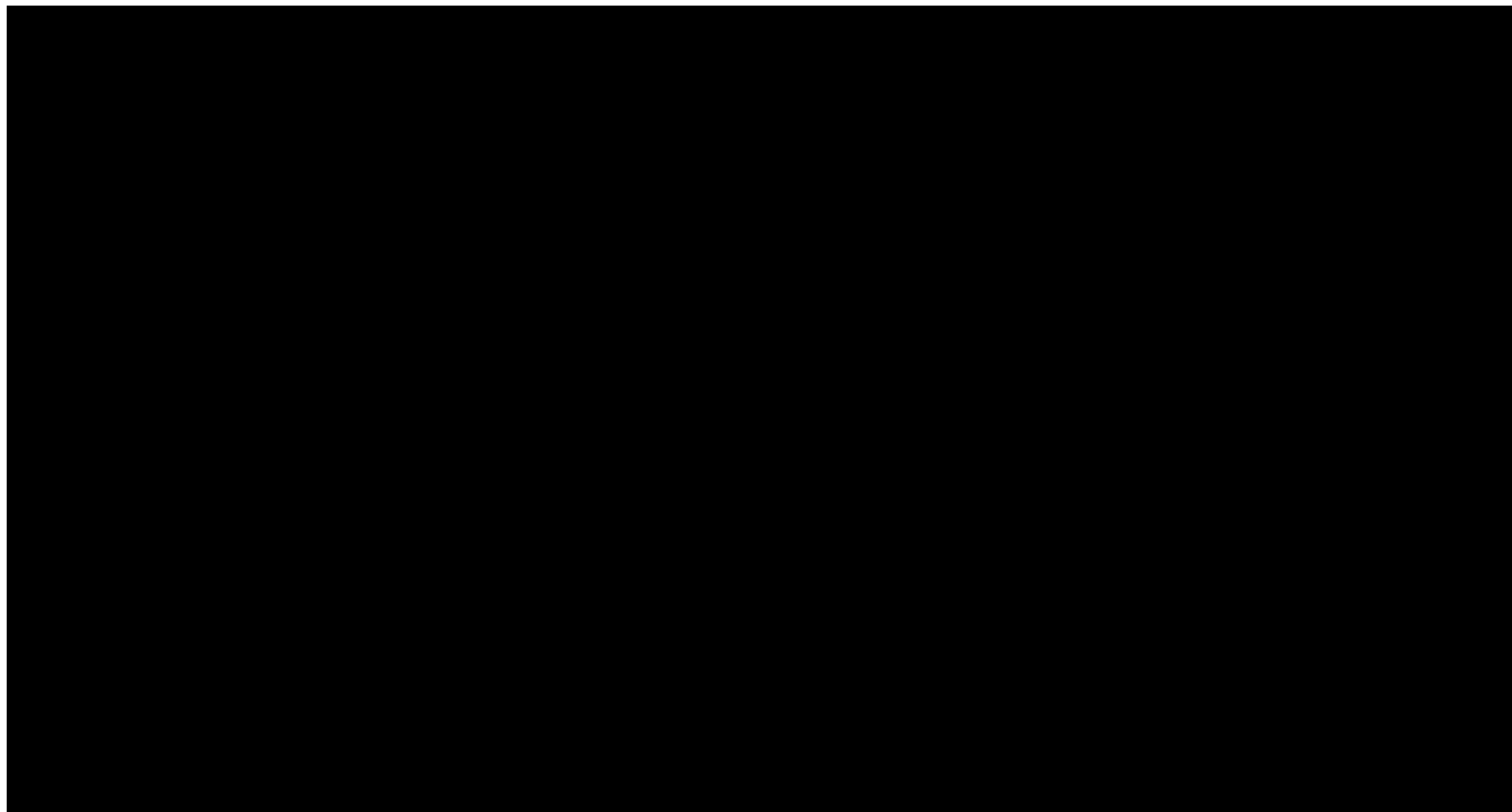
Figure 24: Smoothed hazard plots^a for OS. (Reproduced from clarification response B6).



Abbreviations: OS, overall survival; SOC, standard of care.

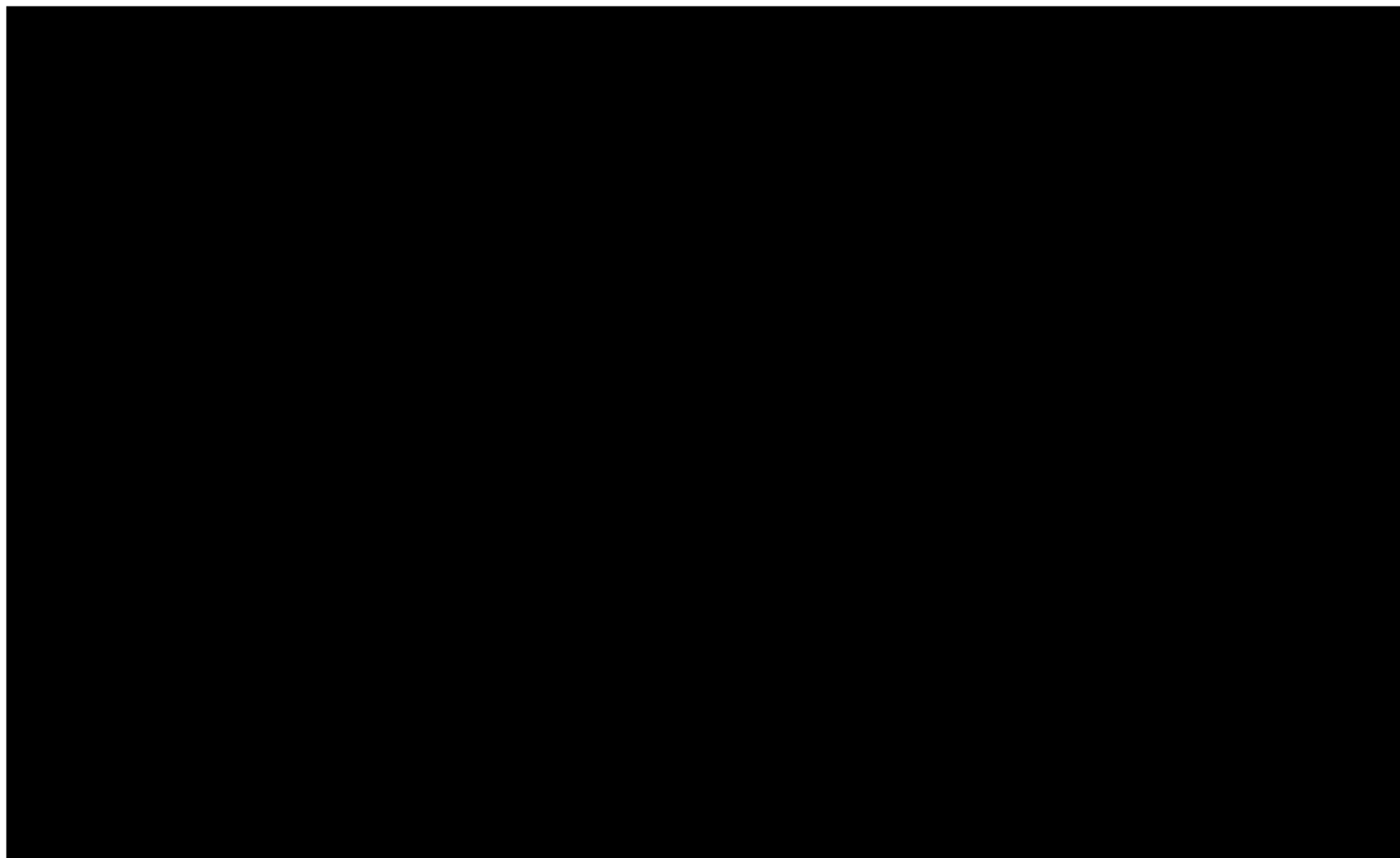
^aNote that the EAG believes the hazard presented corresponds to the monthly.

Figure 25: Predicted model hazard rates for EFS for the 10 candidate models, (generated by the EAG using the company's model).



Abbreviations: EFS, event-free survival; SOC, standard of care. Curves are described by specifying EF→L/SR then EF→IRP then EF→ death

Figure 26: Predicted model hazard rates for OS for the 10 candidate models, (generated by the EAG using the company's model).



Abbreviations: OS, overall survival; SOC, standard of care.

Curve selection step 5: Assessment of incremental EFS and OS benefit at 10 years

Finally, the incremental benefits between the pembrolizumab + SOC and SOC arms for EFS and OS were evaluated at 1, 2, 3, 4, 5 and 10 years, see Table 19. The incremental benefits at 1 to 5 years could be compared with the observed incremental benefits observed within the KEYNOTE-689 trial. All 10 candidate models resulted in close predictions of the observed incremental benefits for both EFS and OS, see Table 19.

At 10 years, the log-normal/Gompertz/generalised gamma distribution resulted in incremental benefits of 6.7 and 6.8 percentage points for EFS and OS respectively, which appeared to be an outlier compared to the 9 remaining distributions. It was highlighted by the company's clinical experts that patients who remain event-free at 5 years would be considered cured in both arms and a plateau in the EFS would be expected after 5 years. The log-normal/Gompertz/Generalised model choice does not show this behaviour, however, the company retained this distribution for use as a pessimistic scenario, as outlined in Section 4.2.6.6.

The company identified the generalised gamma/generalised gamma/generalised gamma model combination as having the largest incremental EFS benefit at 10-years and also retained this for a scenario analysis.

Table 19 Incremental EFS and OS benefit of pembrolizumab + SOC relative to SOC for the 10 candidate model combinations, (adapted from Table 65, CS Appendix J).

Approach # / EF → LR / EF → IRP / EF → Death	Predicted difference in EFS (Perioperative pembrolizumab + SOC vs. SOC)						Predicted difference in OS (Perioperative pembrolizumab + SOC vs. SOC)					
	1 yrs	2 yrs	3 yrs	4 yrs	4.5 yrs	10 yrs	1 yrs	2 yrs	3 yrs	4 yrs	4.5 yrs	10 yrs
Observed, KEYNOTE-689*	13.2%	11.2%	13.3%	9.4%	11.5%	-						
1 / Log-normal / Gen gamma / Gen gamma	10.2%	11.9%	12.0%	11.8%	11.6%	10.0%						
1 / Gompertz / Gen gamma / Gen gamma	9.3%	11.4%	12.4%	13.1%	13.3%	13.5%						
1 / Gen gamma / Gen gamma / Gen gamma	9.2%	11.7%	12.7%	13.2%	13.4%	14.4%						
1 / Gompertz / Gompertz / Gen gamma	10.3%	11.2%	11.2%	11.2%	11.1%	10.4%						
1 / Log-logistic / Gen gamma / Gen gamma	10.1%	11.9%	12.3%	12.2%	12.2%	11.3%						
1 / Log-normal / Gompertz / Gen gamma	11.2%	11.7%	10.8%	9.9%	9.4%	6.7%						
1 / Weibull / Gen gamma / Gen gamma	10.1%	11.9%	12.3%	12.3%	12.3%	11.9%						
1 / Gamma / Gen gamma / Gen gamma	10.1%	12.0%	12.3%	12.3%	12.3%	11.9%						
1 / Gen gamma / Gompertz / Gen gamma	10.2%	11.5%	11.5%	11.3%	11.2%	11.7%						
1 / Log-logistic / Gompertz / Gen gamma	11.1%	11.7%	11.0%	10.3%	10.0%	8.4%						

Abbreviations: CPS, combined positive score; EFS, event-free survival; HR, hazard ratio; IRP, incurable recurrence/progression; LR, local recurrence; OS, overall survival.

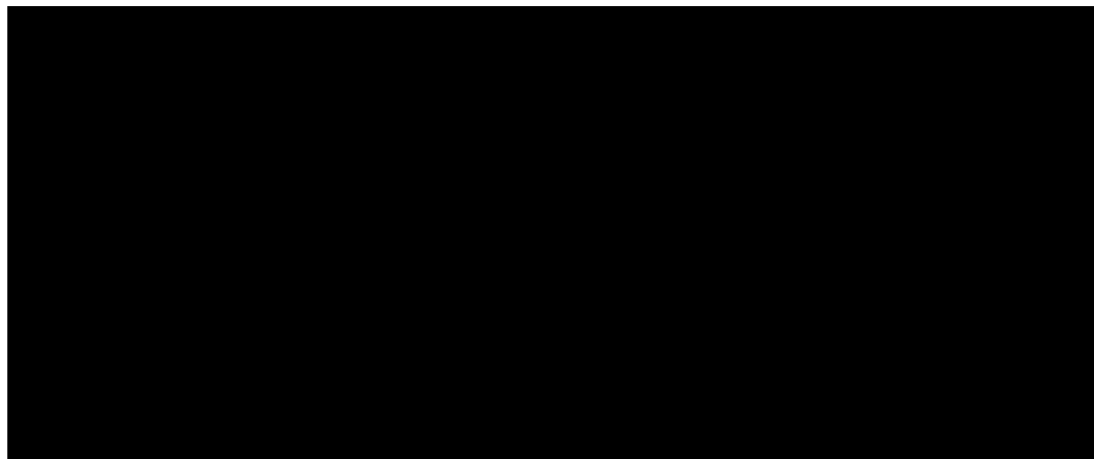
*Evaluated using the re-censored OS data under the EFS censoring rule

Selected base case model

Following the approach outlined in the previous sections, the company selected the Gompertz/Gompertz/generalised gamma model combination as their base case. This model choice was deemed to be the best-fitting model according to the assessment of MSE of EFS, visual assessment of cumulative incidence curves, comparison of observed versus predicted EFS and OS (see Figure 27 and Figure 28), a mid-range predicted incremental EFS and OS among the ten candidate models, and consistency with expert opinion regarding long-term plateauing of the EFS curve. Further to this, this combination of models ranked first for the SOC arm MSE analysis, see Table 61, CS Appendix J.

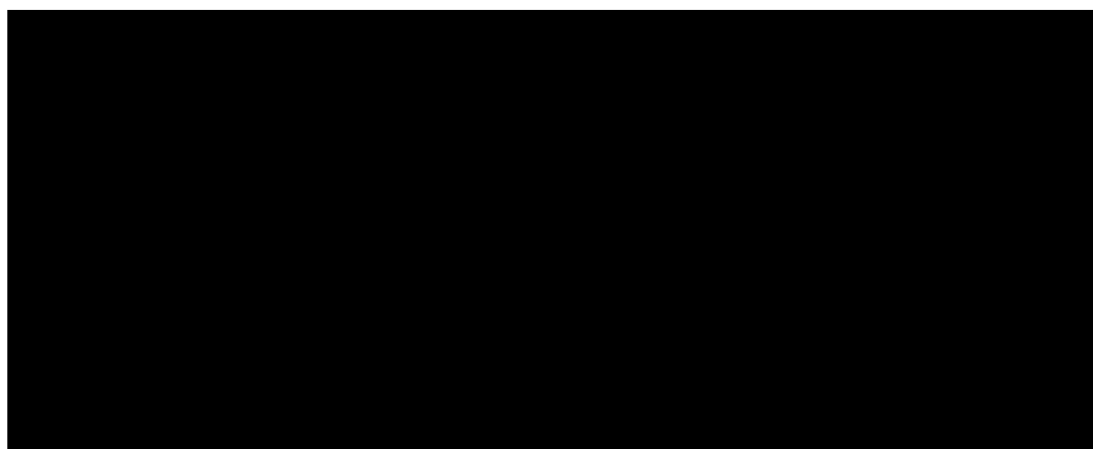
The selected base case model combination resulted in the capping of the EFàDeath, and L/SRàDeath transition probabilities to that of the background population (derived from age- and sex-matched lifetables) due to the model estimated transition probabilities dropping below the corresponding background probabilities. In the company's base case, the capping for EFàDeath at weeks 628 and 471 for pembrolizumab + SOC and SOC respectively, and for L/SRàDeath at week 2036 for the pembrolizumab + SOC arm only. Following these time points, the probability of death for the age-, sex-matched background population was used with an SMR=1.0.

Figure 27: Base case modelled and observed EFS over the model time horizon (CPS≥1 population), (reproduced from Figure 20, CS).



Abbreviations: CPS, combined positive score; EFS, event-free survival; SOC, standard of care

Figure 28: Base case modelled and observed OS over the model time horizon (CPS $\geq$ 1 population), (reproduced from Figure 21, CS).



Abbreviations: CPS, combined positive score; OS, overall survival; SOC, standard of care

4.2.6.6 Selection of scenario analyses

Alternative model choice for transitions from the EF state

As highlighted in the Section 4.2.6.5, out of the 10 candidate models the log-normal/Gompertz/generalised gamma model combination was selected as a pessimistic scenario as this model predicts the lowest incremental EFS and OS benefits at 10-years (Scenario SA2, CS, Table 61).

The generalised gamma/generalised gamma/generalised Gamma model provided the largest incremental benefit out of the 10 candidate models and was chosen as a complementary scenario analysis (Scenario SA1, CS, Table 61).

Additional model combinations under Approaches 2 and 3 were also included in scenario analyses conducted by the company (Scenarios SA5 and SA6 in CS, Table 61); however, these are not presented within this report due to the aforementioned reasons relating to the applicability of the PH assumption.

Alternative choice of priority transition in curve selection step 1

During the clarification stage, the EAG asked the company to conduct the curve selection process using a different priority transition within the first step of the curve selection process (see clarification response, question B5). The company stated that when EFàL/SR or EFàIRP was prioritised, different best fitting models for the priority transition were identified for the two arms.

However, the company did explore the selection of EFàL/SR as the priority transition, as discussed in the response to clarification question B5. The prioritisation of this transition followed the approach in

TA1017 where the transition with the fewest numbers of events was chosen as the candidate distribution.⁴⁶

The Gompertz distribution was selected as the most appropriate model for the EFàL/SR transition as this was ranked second best fitting according to minimum and average MSE for both the pembrolizumab + SOC and SOC arms (Table 21 of the clarification response). The best-fitting model differed for the pembrolizumab + SOC and SOC arms (generalised gamma and log-normal respectively); this is explored further in Section 4.2.6.7. The selection of the Gompertz model therefore reflected a pragmatic approach to balance the accuracy of the fit according to EFS and ensuring the same model was selected for both arms.

Despite prioritising EFàL/SR, the company resulted in the selection of the same base case scenario. Two additional candidate combinations were identified and explored in SA24 and SA25 in the clarification response.

Use of observed cumulative incidence curves up to 32 weeks

Despite the highly flexible nature of the employed approach, the EAG noted that the company's base case model combination provides a relatively poor fit to the cumulative incidence curve for the EFàIRP transition for the SOC arm (Figure 17). During the clarification stage the EAG requested the trial of more flexible models such as spline models in order to improve the fit for the cumulative incidence comparison (see clarification response, question B2).

In its response, the company stated that the inclusion of spline models within the curve selection process would have further complicated the selection of the base case. Additionally, the company stated that the inclusion of spline models could have led to over-fitting due to the approach currently employed already being flexible due to the combination of three model types.

The company also highlighted that the sharp increase observed in the cumulative incidence of EFàIRP in the SOC arm is likely to be an artefact due to the scheduling of the first CT/MRI of these patients at 12 weeks (± 7 days), (see Figure 17).

Despite the deviation between the observed and predicted cumulative incidence only occurring for a short period within the follow-up, the company provided a scenario whereby the observed cumulative incidence was used for all transitions up to 32 weeks, and the base case parametric distributions used thereafter. This approach therefore aimed to capture behaviours relating to the more nuanced shape of the EFàIRP cumulative incidence for the SOC arm. This scenario did however still utilise parametric

fits in the tail region which were derived from the entirety of the observed data, see SA23 in the clarification response for further details.

Consideration of cure

The company was advised by its clinical experts that the majority of recurrences within this population were likely to occur within the first two years. Any patients remaining event-free at 5 years following treatment would be considered functionally cured and discharged. It was highlighted that the risk of recurrence would not be zero. This was believed to apply to both the pembrolizumab + SOC and SOC arms.

The selected base case model choice appears to capture this plateau in EFS for both arms and also has low hazard rates for both arms implying a low risk of recurrence, thus reflecting the clinical expert opinion, see Figure 25. The company therefore believes that the potential for cure has already been captured by the base case model and concluded that including a further structural cure assumption in the base case model would potentially “overestimate and potentially double count” the likelihood of cure within the population.

The company did however also present a scenario analysis whereby a structural cure assumption was applied to the base case, with an instantaneous application of the cure assumption at 5 years applying a 95% risk reduction in the predicted probability of recurrence or death from the EF state (Scenario SA7, CS, Table 61).

In its response to clarification question B9, the company highlighted that the application of the cure assumption should be considered on a curve-specific basis, in that the behaviour of the EFS extrapolations at 5 years should be considered, as well as the hazard rates. Therefore, some distribution choices for the transitions from the EF state may result in models whereby the clinical expert opinion is not captured fully, and thus the cure assumption could be applied in these cases without the risk of overestimating the likelihood of the cure.

The company highlighted that for the pessimistic scenario analysis, whereby the incremental EFS and OS benefits are shown to be the least out of the 10 candidate models (log-normal/Gompertz/generalised gamma), the EFS hazard of both arms steeply decline, as expected, but then cross which lacks face validity (Figure 25). The application of the cure assumption mitigates this effect of hazards crossing and is explored as an additional scenario analysis (Scenario SA4, CS, Table 61).

For the optimistic scenario analysis (generalised Gamma/generalised gamma/generalised gamma), the hazard rates appear to be approximately twice the magnitude of those observed in the base case which may not reflect the clinical expert opinion received by the company (Figure 25). This combination of models also does not capture the plateau in EFS. Therefore, the company further explored the application of the cure assumption to this scenario as an additional analysis (Scenario SA3, CS, Table 61).

Alternative transition probability for IRPà Death

The company also presented a scenario analysis (Scenario SA10, CS, Table 61) where efficacy data from subsequent treatments used within the IRP state were used to estimate transitions from IRPà death instead of data from KEYNOTE-689 (details provided in Section 4.2.2 and CS Appendix J2).

The weekly hazard rate was evaluated by dividing 1 by the mean OS (evaluated as the weighted average according to market shares) for each arm independently. The alternative exponential hazard rates for the pembrolizumab + SOC and SOC arms used in the scenario analysis are presented in Table 68, CS Appendix J.

Alternative censoring

The primary censoring rules for EFS and OS differed in the KEYNOTE-689 analyses. As EFS and OS are structurally linked within the model, the impact of censoring according to the OS censoring regime, as opposed to that employed for EFS as in the base case, was assessed in a scenario analysis (Scenarios SA8 and SA9, CS, Table 61).

The EFS data were re-censored according to the OS censoring rule and the same approach to fit parametric models to each of the transitions from the EF state was applied, as outlined in CS Appendix J3. Models for each of the competing events were chosen using the same model selection process and transition probabilities for each of the transitions evaluated using the approaches outlined in Section 4.2.6.2.

The Gompertz distribution for EFàL/SR and EFàIRP and the generalised gamma distribution for EFàdeath were selected as the most clinically plausible combination of models for both arms. This, as for the base case, was based on evaluation of the MSE, visual fit of cumulative incidence functions, clinical plausibility assessed via incremental EFS and OS, and visual fit to EFS and OS curves (according to the alternative censoring regime) from KEYNOTE-689. Seven other finalist combinations of models were identified under the alternative censoring rule and were tested as scenario analyses, though only the results for the scenario analysis corresponding to the use of the Gompertz model for EFàL/SR and the generalised gamma for EFàIRP and EFàDeath were presented.

4.2.6.7 Critique of approach to include treatment effectiveness

The EAG believes that the overall approach to the selection of models within this multistate approach is pragmatic and captures a representative range of scenarios that reflect the potential uncertainty in long-term clinical effectiveness regarding EFS and OS given the current data available (IA1) and the restriction to the standard parametric models. There is uncertainty in the survival outcomes of this patient group within the KEYNOTE-689 trial due to the high degree of censoring at approximately 3 years. This therefore results in uncertainty when assessing the visual fit of the OS model estimates to the observed OS data and thus model selection.

The base case model combination selected by the company reflects clinical opinion from the EAG clinical experts including that: (i) it is not expected for OS to converge between 10-15 years; (ii) relapses following 5 years are rare and (iii) the majority of transitions from the EF state are to death as opposed to L/SR or IRP. Clinical experts also suggested that the observation that EF $\rightarrow$ IRP is lower in the pembrolizumab + SOC arm compared to the SOC is plausible due to the potential mechanism of action of the neoadjuvant and adjuvant use of pembrolizumab.

Additionally, from the EAG's own analyses, it is evident that the combination of models for the transitions from the EF state is highly multi-modal, with many model combinations presenting similar overall fits to the observed EFS and OS. However, the EAG notes some potential limitations to the methods employed.

Whilst the EAG appreciates that it may not be appropriate to use the AIC and BIC when selecting the individual models for each of the transition types, as per Williams *et al.*,³⁶ the use of the MSE to identify the best fitting combination of models for EFS is not necessarily validated within the literature. Therefore, this approach may have limitations and may not robustly identify the most applicable models. The EAG is generally content with the approach adopted but highlights that there may be limitations in this approach.

In curve selection step 1, the company uses the aggregate minimum and average MSE evaluated across all model combinations within each set to select the optimum model choice for the EF $\rightarrow$ Death transition (Section 4.2.6.5). The EAG notes that by adopting this approach and considering the minimum and average MSE to select the model for the EF $\rightarrow$ Death transition, some model combinations which provide adequate fits to the EFS and OS may have been excluded early within the curve selection process and thus not considered later in subsequent analyses. The full plausible range of model extrapolations may therefore not have been captured within the scenario analyses adopted by the company.

Within TSD 14 and TSD21 it is recommended that the hazard trend of candidate models should be considered when selecting a base case and scenario analyses.^{42, 47} The overall predicted hazards for EFS and OS should have been compared to the observed empirical hazards for EFS and OS and factored into the model selection process. On clarification, the company did provide the necessary figures to facilitate this comparison, but the figures provided by the company appeared to have been subject to heavy smoothing and the methods to produce the plots were unclear. However it was noted that all ten candidate models demonstrated [REDACTED] in the EFS hazard (Figure 25), but this behaviour was not evident in the smoothed EFS hazard (Figure 23). This, however, may be an artefact of the smoothing approach employed by the company, but as mentioned previously, the approach to generate the hazard plots was not described in sufficient detail. Despite this, the overall trend in the hazard, ignoring the [REDACTED], appears to align with the model predicted hazard trend.

The approach employed by the company relies on the assumption that there is no strong reason to assume different curve selections across the two arms. However, the two treatment arms do differ, for instance in the inclusion of a neoadjuvant component of the treatment regimen versus no neoadjuvant treatment, and a prolongation of the adjuvant treatment period, and thus there could be rationale for different models across the two arms, but this was not considered. Additionally, the selected base case and scenario analyses appear to provide a generally poorer fit to the observed data in the SOC arm which could reflect the need for different model choices for the two arms. However, both the clinical experts to the company and to the EAG supported the argument that if patients remained event-free until 5 years, they could be considered functionally cured, and thus the projected long-term EFS and OS behaviour is likely to be consistent across both arms. Additionally, the EAG highlights that the consideration of differing models across the arms would result in a greater number of potential model combinations to consider which would require more complex approaches for curve selection in order to retain robustness and clarity of the selection process.

More fundamentally, the use of the exponential model for transitions from the intermediate states is a limitation of this approach. The EAG highlights that alternative models could have better captured transitions from the intermediate states, though this would necessitate a semi-Markov model structure, allowing for time-varying hazards of transitioning out of the intermediate states. Further to this, there are very few events informing the L/SRàIRP transition, particularly in the SOC arm (Section 4.2.6.3). This low number of events could therefore lead to high uncertainty in the fit of the exponential providing unstable estimates of the exponential rate parameter. In response to the classification request (B10), the company explored the impact of pooling data across arms when estimating the rates for transitions out

of the L/SR state in a scenario analysis. The EAG preferred to incorporate these pooled estimates for transitions out of the L/SR state in its base case (see Section 5.2.2 and 5.2.3).

When the transition probabilities from IRP to Death were evaluated using the efficacy and market shares for treatments for relapsed/metastatic disease, the risk of death from the IRP state was found to be higher for the pembrolizumab + SOC arm, whereas in the company base case, where KEYNOTE-689 data was used, the risk of death from the IRP state was higher in the SOC arm. Clinical experts to the EAG stated that the case in which the risk of death from IRP is highest in the pembrolizumab + SOC arm could reflect the potentially reduced treatment options within this arm, but that there are little data to inform this. They also noted that it would be clinically plausible for pembrolizumab to improve survival for patients experiencing disease progression if the treatment results in recurrent disease that is less extensive. However, further long-term follow-up would be needed to demonstrate any such benefit. The company also highlighted that in the scenario analysis, a conservative approach is assumed whereby there is no ongoing benefit from perioperative pembrolizumab + SOC relative to SOC in the IRP state. Whereas, in the base case, where the transition probabilities were estimated using the KEYNOTE-689 trial data, these benefits would be captured. The company stated that this ongoing benefit could counteract the lack of available immunotherapy treatment options available to these patients at this later stage. The EAG therefore believes this to be an uncertain area of the model. To address this uncertainty the EAG explored the impact of pooling events across arms for transitions out of the IRP state. It combined this with pooling events out of the L/SR state in its EAG exploratory analyses (See Section 5.2.2) and incorporated this change in its base case (see Section 5.2.3). However, as it considered this to be an area of uncertainty, the EAG also explored removing this from its base case in its scenario analyses (see Section 5.2.4)

The company surmises that due to the shapes and magnitudes of the observed EFS hazard in the base case, the cure assumption should not be applied but should be considered for the two scenario curve combinations. The company states that the appropriateness of applying the cure assumption for a particular set of curves should be considered on a case-by-case basis. The EAG agrees with this but highlights that the company has not provided a set of definitive rules for making this judgement. Therefore, choice of whether to apply the cure assumption remains potentially subjective. The company also did not comment on the behaviour of the fitted Gompertz distributions which exhibit effective plateauing behaviour for EF to L/SR and EF to IRP for both arms. The EAG believes that any cure-like behaviour should be captured via an intentional structural assumption (i.e., via the cure assumption) as opposed to the use of these Gompertz distributions with effective plateauing behaviours. Therefore, the EAG's adoption of a base case model without explicit use of the Gompertz, further explores the

potential implications of this (see Section 4.2.6.8 for discussion of the EAG's preferred alternative model, with the impact on the cost-effectiveness results presented in Section 5.2.2).

The application of the cure assumption in the company's model occurs instantaneously at 5 years and imposes a risk reduction of 95% to the transitions from the EF state. Though the EAG's clinical advisors agree with this timepoint for a potential cure, this approach is somewhat simplistic and results in a discontinuous hazard for EFS and OS in both SA1 and SA2. The EAG notes that if cure was believed to be plausible within this population, approaches including dedicated cure methods could have been explored, for instance by fitting parametric mixture-cure models to the EFS IPD and assessing whether a non-zero cure fraction is consistently predicted across different models, the EAG has further explored this in Section 4.2.6.8, with the impact on the cost-effectiveness results presented in Section 5.2.2.

Additionally, a SMR equal to 1.0 is assumed within the model meaning no excess mortality was applied to the general population mortality to model background mortality for this appraisal's population. The EAG notes that the choice of this value does not appear to have been explored, nor does this choice appear to have been validated by clinical experts. Clinical experts highlighted that this population may be subject to other comorbidities following longer survival, and thus the impact of a non-unity SMR should have been explored. The EAG also explores this further in Section 4.2.6.8, with the impact on the cost-effectiveness results presented in Section 5.2.2.

Within the company's base case and the majority of scenario analyses, the EFS censoring regime was chosen. The EAG agrees with this decision, as the alternative censoring regime (used for OS within KEYNOTE-689) would result in the assumption that between the time of last-assessment and last known date alive, any patient who has not had a recurrence/progression at their last assessment, must remain progression-free until the date they are known to be alive. In some cases, this period between the last assessment and the last date known alive was considerable, hence this assumption may not hold. This is a fundamental feature and challenge associated with the KEYNOTE-689 trial design. The EAG is however content with the primary use of the EFS censoring rules and the subsequent exploration of the impact of censoring according to the OS censoring rules.

Finally, whilst the EFS data appears to have sufficient follow-up and events to enable some meaningful comparison of estimated EFS and observed EFS, the OS data is subject to a large degree of censoring beyond 3 years and is comparatively immature. Therefore, when comparing the estimated OS with the observed OS, there is a potentially high degree of uncertainty. The current data and analyses correspond to IA1 and the company states in the Section 2 summary of the CS that the KEYNOTE-689 trial is ongoing and may provide additional evidence in the next 12 months. Additional follow-up may impact

the final choices of model combinations for transitions from the EF state, though the EAG notes that the OS data is only used for visual assessment of estimated model fits to the observed data, unlike the EFS which is used when assessing the statistical fit of the curves. The high degree of censoring in the OS data, means that there is uncertainty regarding the survival outcomes of this patient group within the KEYNOTE-689 trial, and thus also a source of uncertainty within the cost-effectiveness assessment.

4.2.6.8 Additional work conducted by the EAG

To further supplement the evidence provided by the company and explore some areas of uncertainty in the modelling of the treatment efficacy, the EAG conducted several additional analyses which are outlined in the following sections.

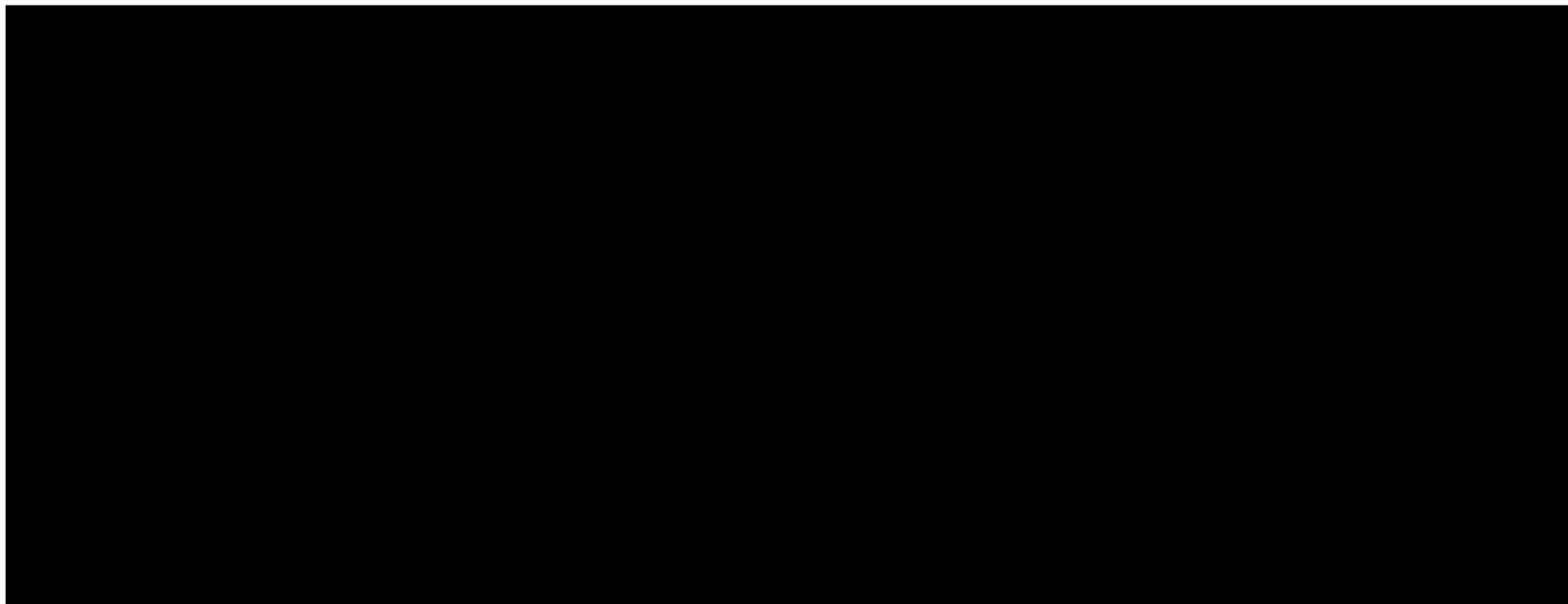
EAG base case model combination

The Gompertz distributions used to model EF→L/SR and EF→IRP exhibited effective plateaus for both the pembrolizumab + SOC and SOC arms, as discussed in 4.2.6.7. Following this, and as per Section 4.2.6.7, the EAG believes that any cure-like behaviour should be captured via an inherent structural assumption which implements cure within the model. The EAG has therefore identified an alternative combination of models for transitions from the EF state.

The EAG has selected the model combination which did not use a Gompertz model for either EF→L/SR or EF→IRP, with the lowest EFS MSE for the SOC arm from Table 61 of the CS, Appendix J. The SOC arm was prioritised when identifying this model combination due to the generally poorer fits observed for the SOC arm compared to the pembrolizumab + SOC arm. The log-normal/generalised gamma/generalised gamma was ranked first out of all model combinations under Approach 1 for the SOC arm and ranked fifth for the pembrolizumab + SOC arm (Table 58, CS Appendix J). This model combination was also identified in the company's initial identification of the 10 candidate models, as discussed in Section 4.2.6.5.

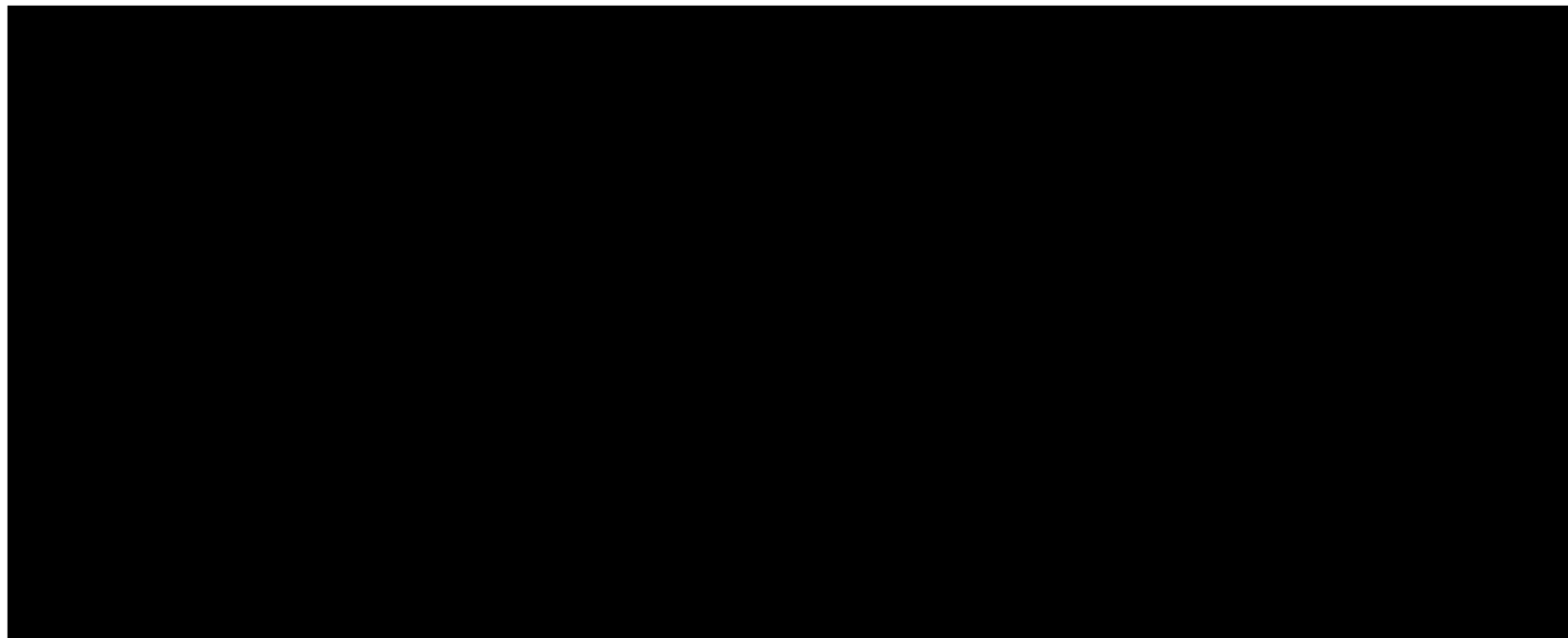
The predicted model fits to the EFS and OS appear to be plausible (see Figure 29 and Figure 30) and provide similar visual fits to the company base case model and the remaining 8 candidate models identified by the company (see Section 4.2.6.5). The fits to the cumulative incidences also appear to be adequate, though the poorer fitting for the SOC arm is noted for the EF→IRP state, as was the case in the company base case due to the artefacts introduced by the scheduling of patient follow-up following initial treatment, see Figure 31. Finally, the hazard plots for this alternative model combination exhibit the same behaviour of an initial increase, see Figure 26, followed by a decrease until background mortality is used to inform the death transitions due to the capping. The times at which the capping is applied for this combination of models, is the same as the company base case, outlined in Section 4.2.6.5.

Figure 29: Selected EAG base case model combination, predicted and observed EFS over the model time horizon (CPS $\geq$ 1 population), (generated by the EAG using the company's model)



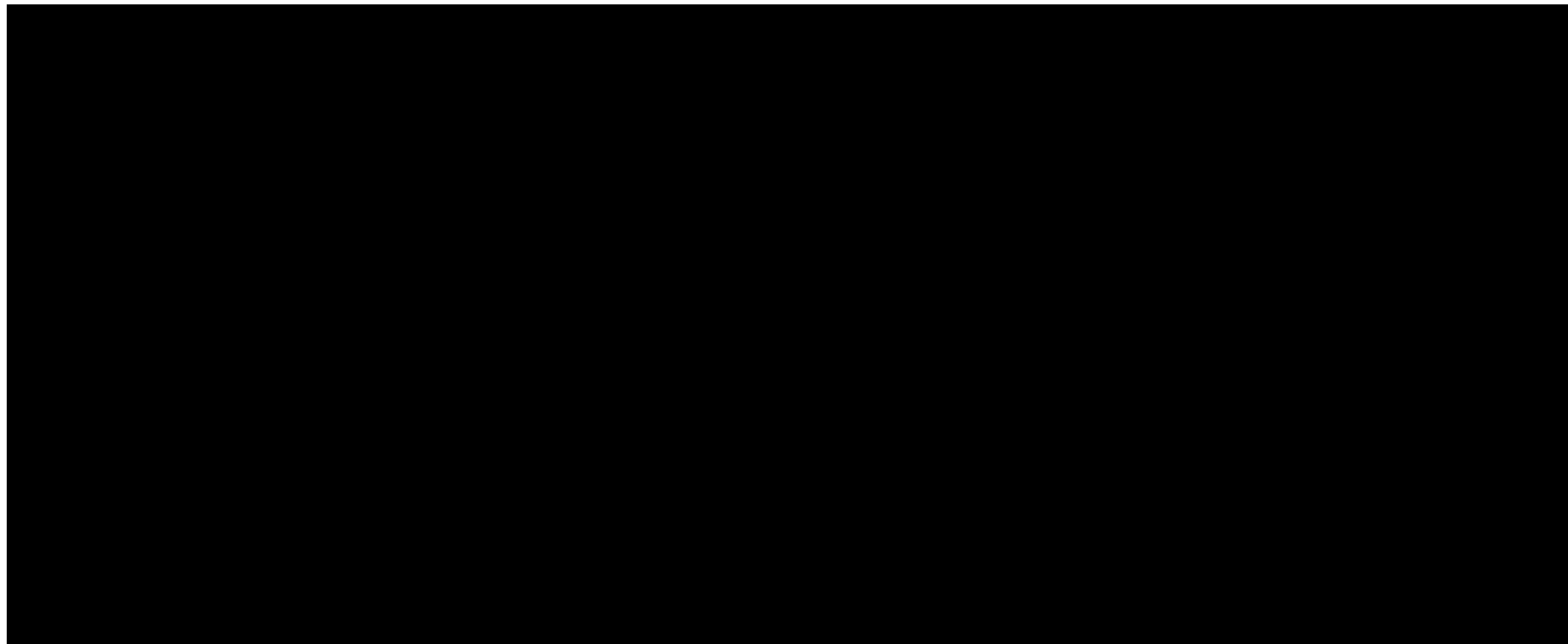
Abbreviations: EFS, event-free survival; CPS, CPS, combined positive score; EAG, external assessment group; SOC, standard of care

Figure 30: Selected EAG base case model combination, predicted and observed OS over the model time horizon (CPS $\geq$ 1 population), (generated by the EAG using the company's model)



Abbreviations: OS, overall survival; CPS, CPS, combined positive score; EAG, external assessment group; SOC, standard of care

Figure 31: Observed versus cumulative incidence curves, for the $CPS \geq 1$ population, pembrolizumab + SOC and SOC arms, EAG base case model combination, (generated by the EAG using the company's model)



Abbreviations: EF, event-free; L/SR, local/salvageable recurrence; IRP, incurable recurrence/progression; CPS, CPS, combined positive score; EAG, external assessment group; SOC, standard of care

Alternative curve selection for transitions from the EF state

Due to the large number of possible model combinations for transitions from the EF state and the possibility of missing additional plausible model combinations, the EAG explored alternative combinations of models for the three transitions. Firstly, the EAG considered the approach in the clarification response to questions B5/B8 where instead of prioritising EFàDeath, EFàL/SR was prioritised during the initial step of the curve selection process. Within its response, the company chose the Gompertz model for EFàL/SR as a pragmatic approach to balance statistical fit with selection of the same model for both arms. The generalised gamma distribution for EFàL/SR was ranked best for the pembrolizumab + SOC arm and the log-normal distribution ranked best for the SOC arm. These model choices were thus explored.

Following the company's approach for curve selection, the visual fits to the cumulative incidence curves when choosing the generalised gamma distribution for EFàL/SR for both arms were assessed. All models where the exponential was chosen for either EFàIRP or EFàDeath resulted in poor fits to the cumulative incidences and thus these were excluded, leaving 36 candidate combinations. From further visual assessment of the cumulative incidence curves for EFS and OS (under the primary EFS censoring regime), the EAG identified four additional potentially viable model combinations (in addition to those already previously identified by the company) whereby the Gompertz distribution was selected for EFàIRP and then the Weibull, Gompertz, log-normal and log-logistic models were chosen for EFàDeath.

This process was then repeated but instead using the log-normal distribution for EFàL/SR for both arms. This process resulted in an additional four candidate combinations which applied the Gompertz distribution for EFàIRP and the Weibull, Gompertz, log-normal, and log-logistic distributions for EFàDeath.

However, all eight of these alternative model combinations were reliant on EFàIRP being modelled via a Gompertz distribution exhibiting plateau-like behaviours (see Section 4.2.6.7). Therefore, these alternative model combinations were not explored further in the EAG's scenario analyses.

Consideration of the statistical plausibility of cure

The plausibility of cure was supported by both the company clinical experts and the EAG's clinical advisors. Both sources supported the notion that at 5 years there would likely be fewer recurrences and progressions of individual who remained event-free until this stage. To explore this further and the plausibility of the cure assumption, the EAG utilised the EFS KM estimates from the company model and re-constructed IPD for the pembrolizumab + SOC and SOC arms using the Guyot algorithm.⁴⁸ Mixture-cure models, using the seven parametric models (exponential, Weibull, Gompertz, log-logistic,

log-normal, gamma and generalised gamma), were fitted independently for the two arms using the *flexsurvcure* package in R which builds on the *flexsurv* package.³⁹ The estimated cure fractions are presented in Table 20, and the model fits for the pembrolizumab + SOC and SOC arms shown in Figure 32 and Figure 33 respectively.

Most mixture-cure models predicted similar cure fractions, though the Gompertz and generalised gamma mixture-cure models displayed highly uncertain estimates for the pembrolizumab + SOC arm. The cure fraction is mostly stable in these statistical estimates and therefore the EAG believes this may support the plausibility of cure-like behaviour within the EFS data as discussed by clinical experts to the company. The EAG has explored the impact of applying the cure assumption to the EAG's preferred base case scenario in its scenario analyses (see Section 5.2.4).

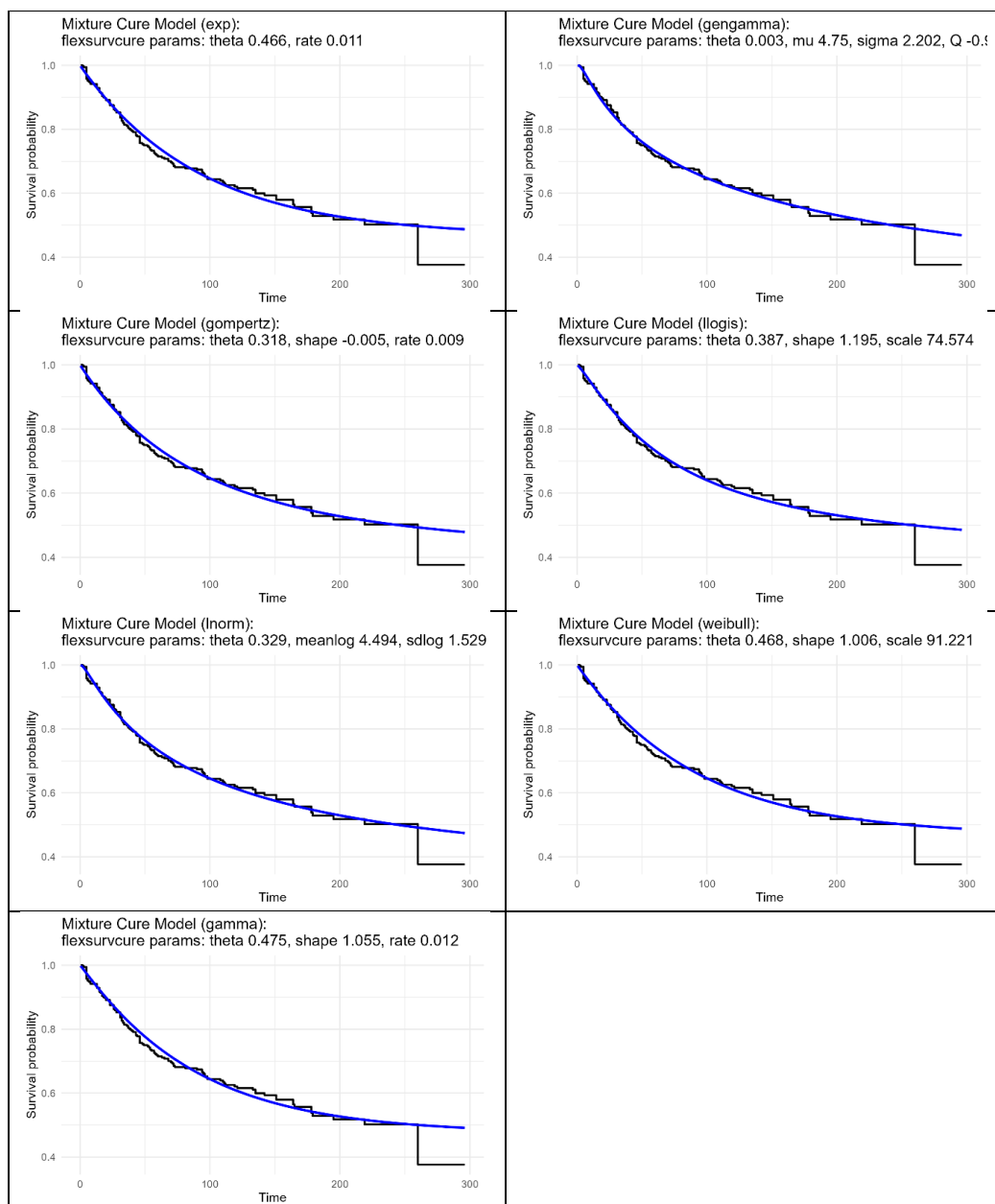
Table 20: Estimated cure fractions according to EAG fitting of mixture-cure models to reconstructed IPD for the pembrolizumab + SOC and SOC arms

	Cure fraction estimate (95% CI)	
Distribution	Pembrolizumab + SOC	SOC
Exponential		
Weibull		
Gompertz		
Log-logistic		
Log-normal		
Gamma		
Generalised gamma		

SOC, standard of care; CI, confidence interval

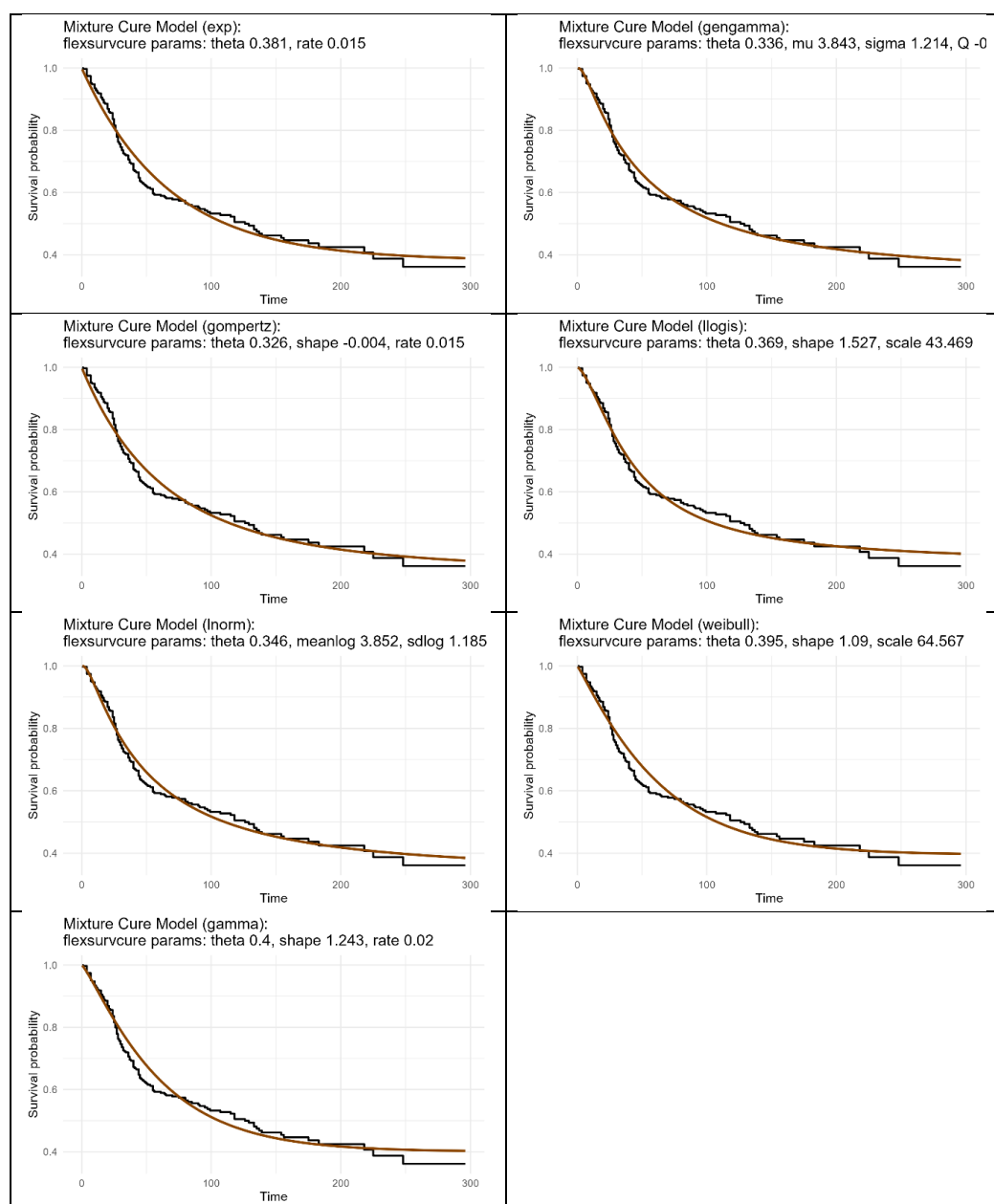
* The generalised gamma and Gompertz models did not appear to converge for the pembrolizumab + SOC arm.

Figure 32: Mixture-cure model fits to the reconstructed pembrolizumab + SOC IPD (Fitted by the EAG)



Note: all parameters reported in the figure are those fit on the natural (transformed) scale, theta corresponds to the cure fraction.

Figure 33: Mixture-cure model fits to the reconstructed SOC IPD (Fitted by the EAG)



Note: all parameters reported in the figure are those fit on the natural (transformed) scale, theta corresponds to the cure fraction.

SMR applied to background mortality

The CS presents no evidence that the background mortality for adults with untreated, newly diagnosed, resectable, LA HNSCC who have PD-L1 CPS $\geq$ 1 would be the same as general population mortality in patients who survive long enough for the general population mortality rates to apply. The EAG could not conduct a formal SLR to search for evidence on SMRs for this population, however it conducted hand searches on causes of mortality for long-term survivors of HNSCC. The EAG found considerable literature indicating that this population has significant burden due to baseline cardiovascular risk

factors in addition to a higher incidence of second primary malignancy.⁴⁹⁻⁵¹ Most notably of the identified articles was Du *et al.* which is a prospective cohort study where cases surviving five years post diagnosis were compared to age-matched, noncancer controls.⁵² Ten-year survival was examined by site, stage, p16, and treatment using Kaplan-Meier and Cox proportional hazard models with analyses adjusted for race, sex, age, insurance, and smoking status. Though this study does not explicitly report SMR values, hazard ratios (HR) for death versus general population controls were reported for the several subgroups which broadly represented the majority of the population of the KEYNOTE-689 RCT. These included patients who had radiation and surgery (HR=1.6), surgery and chemoradiotherapy (HR=1.9), stage III disease (HR=2.4), stage IV disease (HR=2.5), oral cavity tumour (HR=2.7), and larynx tumour (HR=2.0). Although a higher HR was identified for patients having hypopharynx tumour (HR=3.6) these were a small minority of patients in both the KEYNOTE-689 RCT and in the cohort study by Du *et al.* making the estimate from Du *et al.* both uncertain and less relevant to the KEYNOTE-689 population. Therefore, the EAG considered that the HR relevant to the KEYNOTE-689 population would likely lie in the range of 1.6 to 2.7. In the absence of better data sources to inform the most appropriate SMR value, the EAG conducted scenario analysis using these HR bounds as proxies for SMR values and applied it to the EAG preferred base case as discussed in Section 5.2.4.

4.2.7 Adverse events

The CS includes all-cause treatment-emergent adverse events (TEAE) of Grade 3 or higher that were reported by at least 5% of patients in either treatment arm of KEYNOTE-689 as presented in CS, Table 32. This was obtained from the all comer APaT population. The mean duration, mean number of episodes per patient, and percent resulting in hospitalisations for each AE was obtained via pooling across both trial arms of KEYNOTE-689. These data are used to estimate the QALY loss and costs associated with AEs per each treatment arm as explained in Section 4.2.8.2 and Section 4.2.9.4 respectively.

In response to clarification question B25, the company provided a table of Grade 2+ AEs occurring in $\geq 10\%$ of the trial population. There were some differences among the two arms (e.g., hypothyroidism occurred in 19.4% versus 3.2% of the pembrolizumab + SOC versus SOC arm). Clinical advice received by the EAG highlighted some of these AEs to be of significance on HRQoL; however, the EAG agrees with the company that the impact on cost-effectiveness estimates would be minimal.

4.2.8 Health-related quality of life

The company used data from KEYNOTE-689 and performed an SLR to identify external studies which reported appropriate health state utilities, the SLR is described in CS Appendix F. The identified studies are discussed in Section 4.2.8.3.

4.2.8.1 HRQoL data from KEYNOTE-689

Health state utility values are derived from EQ-5D-5L data from KEYNOTE-689 for the EF, L/SR, and pre-progression IRP health states, while such data were collected from few patients and were too limited to inform the post-progression IRP state as the company implies that this happened beyond the available follow-up data for most patients.

In KEYNOTE-689, EQ-5D-5L data were reported for the PRO FAS population (see Table 8 for definition). Data were collected both pre- and post-surgery. However, the baseline PRO visit was defined differently between the two treatment arms; for pembrolizumab +SOC it occurred on day 1 of the first cycle of neoadjuvant pembrolizumab whereas for SOC it was the last PRO assessment prior to surgery. This led to a higher proportion of patients being classified as ‘missing by design’ for baseline EQ-5D in the SOC arm as local implementation sometimes meant this pre-surgical PRO visit was not scheduled (see response to clarification question B19). Pre-surgical assessment of EQ-5D was scheduled to occur at weeks 1, 4 and 6 for the pembrolizumab + SOC arm. After surgery, EQ-5D-5L questionnaires coincided with radiotherapy ± cisplatin treatment prior to treatment administration on weeks 1 and 4 in both arms. Thirty days after completion of adjuvant radiotherapy ± cisplatin treatment, questionnaires were administered once, and then every three months up to end of year 3, and then annually in years 4 and 5 (CS, Section 3.4.1.1). As reported in CS Appendix K, compliance with the EQ-5D-5L questionnaires (defined as the proportion of patients expected to complete the questionnaire in any given visit, excluding those missing by design) exceeded █% in both treatment arms at all visits up to week 129. It is notable that missing by design includes death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, non-compliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, and unavailable translation). The EAG's understanding based on the company's response to clarification question B21 is that patients who had discontinued treatment were classified as missing by design, with the reason for treatment discontinuation reported for contextual information, and those who had not discontinued from treatment but who had not had PRO data reported in the expected time frame were also reported as missing by design with ‘completed treatment’ reported for context. The company's response to clarification question B20 further clarifies that whilst these patients could be marked as “missing by design” according to the trial protocol if PROs were not obtained, their

discontinuation did not automatically imply that PROs were not solicited or analysed; hence, estimates for the progressed state and the EF state with Grade 3+ AEs could be obtained. However, the EAG is concerned that excluding patients who were ‘missing by design’ from the calculation of compliance has the potential to overestimate data completeness.

The company base case uses descriptive utility values which were evaluated without explicitly accounting for repeated measures. Utilities were estimated by pooling across both arms as the company deemed that there was no clinically meaningful HRQoL difference between the two arms (see CS, Sections 2.6.1.6 and 2.6.1.7). Baseline measurements were excluded from the analysis. In clarification response B22, the company highlighted that the descriptive means could be viewed “*as if coming from a generalised estimating (GEE) regression model with an independence working correlation matrix*”. Although the company did not provide the GEE derived estimates at the clarification stage, they later provided these within their factual accuracy check and confidential information check response. When these estimates were compared with those used in the company base case, the point estimates were identical, but the standard error (SE) was larger in those derived using the GEE approach.

In accordance with NICE’s updated manual for health technology assessment, patient responses to the EQ-5D-5L questionnaire were mapped onto the UK EQ-5D-3L values set using the approach developed by Hernández Alava *et al.* ³²

The estimated utilities are presented in Table 33 of the CS. In response to clarification question B22, the company also presented a mixed-effects regression for the pooled sample, and for each treatment arm separately (see clarification response, Table 30). The estimated utilities differed slightly between the two methods. The mixed-effects approach however does not produce marginal estimates (i.e., reflecting the population average rather than being subject-specific) of the utility for each health state and thus the company highlighted that its original approach should be used within the decision-making context.

4.2.8.2 Adverse event related disutilities

AE-related disutilities were applied as a one-time QALY decrement in the first model cycle, calculated based on the proportion of patients in each treatment arm who experienced each AE, the mean duration of each AE, the mean number of episodes as mentioned in Section 4.2.7, and the mean estimated disutility for a Grade 3+ AE (██████). Mean disutility is calculated as the difference between the mean utility across patient-visits in the EF state with any Grade 3+ AE minus the mean utility in the EF state with no Grade 3+ AE. The resultant QALY decrements applied to each treatment arm in the CS base case are ██████ and ██████ for the perioperative pembrolizumab + SOC and SOC arms respectively.

4.2.8.3 HRQoL data from external sources

A SLR was conducted to identify alternative, external sources of utility values for the L/SR and IRP states. Details pertaining to the SLR are presented in CS Appendix F.

HRQoL data from external sources relevant to progressed/recurrent HNSCC

As explained in Section 4.2.8.1, EQ-5D data from KEYNOTE-689 could not inform the HRQoL associated with the post-progression IRP state; hence, external literature was consulted. Five utility estimates were identified within the SLR, which are summarised in Table 34 of the CS. Four of the identified sources were concluded by the company not to be appropriate due to the following reasons.

Utilities for the post-progression IRP state estimated in KEYNOTE-048, which were available to the company, appeared to be greater than those estimated for the IRP pre-progression state using KEYNOTE-689 (██████████). Clinical experts consulted by the company believed that they would ordinarily expect the utility of patients to decrease on progression; however, in this specific case the observation is plausible as patients with *de novo* metastatic disease are likely to have better HRQoL versus patients who have progressed from LA disease. However, due to the reduction in utility between pre- and post-progression, this study was not deemed to be informative for this health state.

Singh *et al.* report a patient preference study; however, this study was not specific to the post-progression status and limited description of the patient characteristics was provided.⁵³ Therefore, this study was not deemed useful.

The M-TAG utility study which informed TA145 was also identified, but these values were obtained from oncology nursing staff rather than HNSCC patients and thus are not aligned with the NICE reference case.⁵⁴ Additionally, the reported utility for post-progression was 0.129 which was described by the company as being “remarkably low” and may be considered to lack face validity.

An additional study, TAX-323/EORTC-24971 (Parthan *et al.*³¹), reported utility values collected via EORTC-QLQ-C30 which were mapped to the EQ-5D. However, the study population was patients with unresectable LA HNSCC. Therefore, the utility values for progressed disease from this study reflected patients who had progressed from LA HNSCC and therefore were not specific to patients who had progressed on treatment for incurable/metastatic disease.³¹

The company chose the EXTREME trial used to inform the utility values in NICE TA172 and its revision (TA473).⁵⁵ That appraisal assessed cetuximab for treating recurrent or metastatic HNSCC, where EQ-5D-3L utility values were obtained by mapping EORTC QLQ-C30 data collected from patients in the EXTREME trial. This study reported a value of 0.52 for the post-progression state. The

company concluded that this utility value was logically consistent with the utility data from KEYNOTE-689 and captures the limited treatment effect expected within this stage of the treatment pathway, so it is selected for the CS base case.

4.2.8.4 HRQoL data applied in the model

The EQ-5D-5L measurements collected in KEYNOTE-689 for the EF, L/SR, and pre-progression IRP were mapped back to the EQ-5D-3L version of the tool using the NICE DSU algorithm.³² A summary of the utility values used in the company's base case model is presented in Table 21.

Table 21 Summary of utility values for cost-effectiveness analysis (reproduced from CS, Table 36)

State	Utility, mean	SE	Reference in submission	Source and justification
EF (without AEs)	██████	██████	3.4.1	EQ-5D-3L values, mapped from EQ-5D-5L derived from patients directly relevant to the decision problem (from KEYNOTE-689) using UK value set, in line with the NICE reference case
L/SR	██████	██████		
IRP (pre-progression)	██████	██████		
IRP (post-progression)	0.52	0.209 [†]	3.4.3	EORTC-QLQ-C30 from EXTREME mapped to EQ-5D-3L, reported in NICE TA172/TA473 ⁵⁵ Alignment with NICE reference case and to ensure face validity with KEYNOTE-689 values
	██████	██████	3.4.1	Scenario analysis (assuming no HRQoL decrement on progression)
Grade 3+ AE	██████	██████	3.4.4	KEYNOTE-689, in line with the NICE reference case

Abbreviations: AE, adverse event; EF, event-free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; SE, standard error.

[†] Calculated based on 95% CI reported in ERG report.

The company's model also includes age-related utility decrements in the base case as derived from Health Survey for England 2014 data.⁵⁶ These were only applied after 2.6 years, based on the mean actual follow-up in KEYNOTE-689.

The utility value derived from the EXTREME trial was used for the IRP post-progression state in the base case and the company explored the impact of this choice by applying the same utility for both IRP

sub-states using the value derived for the pre-progression state using the KEYNOTE-689 data (Scenario SA11, CS, Table 61).

As the model does not explicitly track the occupancy of the pre-and post-progression IRP states separately, the utility for the IRP state was evaluated as a weighted average of the IRP pre- and post-progression utility values derived from KEYNOTE-689 and the EXTREME trial respectively. This average was weighted according to the expected proportion of time spent pre- versus post-progression, as summarised in Section 4.2.2 and CS Appendix J2.

4.2.8.5 Critique of approaches used to estimate utilities within the model

Overall, the EAG is fairly satisfied with the utility values used in the model, although it has some concerns regarding the proportion of HRQoL observations which were categorised as ‘missing by design’ and the potential impact of this on the trial-based utility estimates.

The point estimates of the descriptive utility values used within the base case, which do not explicitly account for repeated measures, are identical to those estimated via the GEE regression model. However, the SE of the utilities is smaller than when calculated using the GEE regression model which accounts for repeated measures. Therefore, there would be no impact to the deterministic base case if the alternative utility values were used, but the EAG notes that there is an underestimation of uncertainty in the probabilistic analyses. The EAG therefore considers the utilities used for the EF without Grade 3+ AEs, EF with Grade 3+ AEs, L/SR and IRP pre-progression states, using the KEYNOTE-689 to be appropriate but highlights that there may be an underestimation of uncertainty within the probabilistic analyses. However, the EAG notes that no methodological details of the GEE method used were provided. Additionally it does not appear that baseline utility or other covariates were included within the analysis.

The EAG also notes that, as discussed in the company’s response to clarification question B20, there are some states which may be affected by PROs being “missing by design” due to progression or AEs. However, the company highlighted that under the assumption progressed patients with poorer HRQoL are less likely to complete the PRO surveys, the company’s base case utility estimates for the progressed states would likely be overestimates, and thus the company base case provides a conservative estimate of cost-effectiveness.

Similarly, the company stated in its response to clarification question B20 that under the assumption that patients who are event-free who have more severe AEs are less likely to complete PRO surveys,

the utility associated with the EF with Grade 3+ AEs state is likely to be an overestimate. This may result in a higher QALY loss than is currently estimated, though the company noted that in the deterministic scenario analysis (DSA) the effect of changing the utility for this state appeared to have negligible impact on the ICER.

Additionally, when evaluating the utility values using the KEYNOTE-689 data, baseline values were excluded. The EAG highlights that there is therefore no adjustment for baseline utility within the analysis, though it is also apparent that due to the asymmetric treatment schedules, there were considerably more missing HRQoL assessments at baseline for the SOC arm versus the pembrolizumab + SOC arm, which may have presented a challenge have baseline utility been included within the utility analysis.

Due to the inability to evaluate the utility value for the IRP post-progression state using KEYNOTE-689, as discussed in Section 4.2.8.1, external data sources were explored to inform the choice of utility value. Ultimately the company chose to use utility data from the EXTREME trial reported in TA172/TA473. The EAG however notes some concerns and limitations with this approach as the methods employed to inform the evaluation of the utility value using the HRQoL data from the EXTREME trial are not reported and are not available to the company, making it harder for the EAG to assess the robustness of this estimate.

The EAG asked the company to clarify why external sources were not considered as an alternative to the estimates from KEYNOTE-689 for the pre-progression IRP state, given that these were also based on a low number of observations. The company responded that the values from the literature available from the Parthan study (0.67) and the EXTREME trial (0.67) were consistent with the values obtained from KEYNOTE-689 (██████) (clarification response B17). The value from Singh *et al.* was lower (0.57) but details regarding the methodology employed in this study were sparse. The company did not comment on the values from KEYNOTE-048 (██████) which were higher than the value from KEYNOTE-689 (██████), but the potential reasons for this discrepancy have been previously described for the post-progression IRP utility values. Given the consistency between the value from KEYNOTE-689 and two alternative published sources, and the fact that the KEYNOTE-689 trial provides a direct measure of utility in the population of interest, the EAG is satisfied with the company's rationale for not using alternative sources from the literature for the pre-progression IRP state.

4.2.9 Resources and costs

The company performed an SLR of cost and HCRU studies, and these were reported in Appendix G. This resulted in 10 publications reporting costs and 23 publications reporting HCRU. Resources used

mainly rely on data from KEYNOTE-689, expert elicitation, and published literature. Costs were obtained from publicly available sources which primarily included the British National Formulary (BNF) and NHS Cost Collection.^{57, 58}

The costs included in the economic model consist of drug acquisition costs, administration costs, initial surgery and adjuvant radiotherapy costs, disease management costs by health state including subsequent treatment costs, costs for managing AEs, PD-L1 testing costs, and terminal care costs incurred at the end of life. The details of each are given in the following subsections. All cost data were sourced from recent literature of the current cost year (such as NHS Cost Collection) except for terminal care costs which are inflated to 2024 prices using the ONS Health Consumer Price Index.⁵⁹ Typically, NHS Cost inflation indices from PSSRU are preferred, however the impact here would be negligible.

Vial sharing is assumed for all included IV treatments, and weight- and BSA- dependant dosing is calculated based on the average weight or BSA rather than method of moments.

There are no relevant confidential prices for comparator treatments; however, several treatments used as subsequent-line therapies have confidential prices, and these are discussed further in Section 5.4.

4.2.9.1 Drug acquisition costs in the neoadjuvant/adjuvant settings

Neoadjuvant pembrolizumab is given as a fixed 200 mg dose administered by IV infusion every three weeks (Q3W) for up to two cycles. In KEYNOTE-689, pembrolizumab was given after surgery as 200 mg every 3 weeks for 15 cycles. However, in the economic analysis, the company assumes that the patient receives one 200 mg dose at the start of adjuvant treatment, and then three weeks later, the patient is switched to 6-weekly treatment with 400 mg for 7 cycles to manage capacity. [REDACTED] of the perioperative pembrolizumab + SOC arm received adjuvant pembrolizumab reflecting [REDACTED] patients from the pembrolizumab arm with PD-L1 CPS $\geq$ 1 (N = 345) of KEYNOTE-689.

Both arms were able to receive adjuvant 100 mg/m² cisplatin administered by IV infusion Q3W for up to three cycles if the patient was classified as high risk. This is equivalent to a 180 mg dose based on a mean BSA of 1.8 as per KEYNOTE-689. Of the patients who received any study treatment, [REDACTED] ([REDACTED]/345) versus [REDACTED] ([REDACTED]/300) received adjuvant cisplatin from the pembrolizumab + SOC versus SOC arms of KEYNOTE-689 respectively.

A relative dose intensity of 100% is assumed for all treatments and the model uses the Kaplan-Meier estimates to capture time on treatment for each regimen as described in Section 4.2.9.3. Table 38 of the CS presents the unit drug costs for all regimens including subsequent therapies used in later stages. All

costs were sourced either from electronic Market Information Tool (eMIT) or the British National Formulary (BNF).^{57, 60}

The list price per 100 mg vial of pembrolizumab is £2,630.00. There is currently a Patient Access Scheme (PAS) discount in place for pembrolizumab which is accounted for the economic model. The NICE Committee should refer to Table 54 in Appendix I of the company submission for more information.

4.2.9.2 Drug administration costs

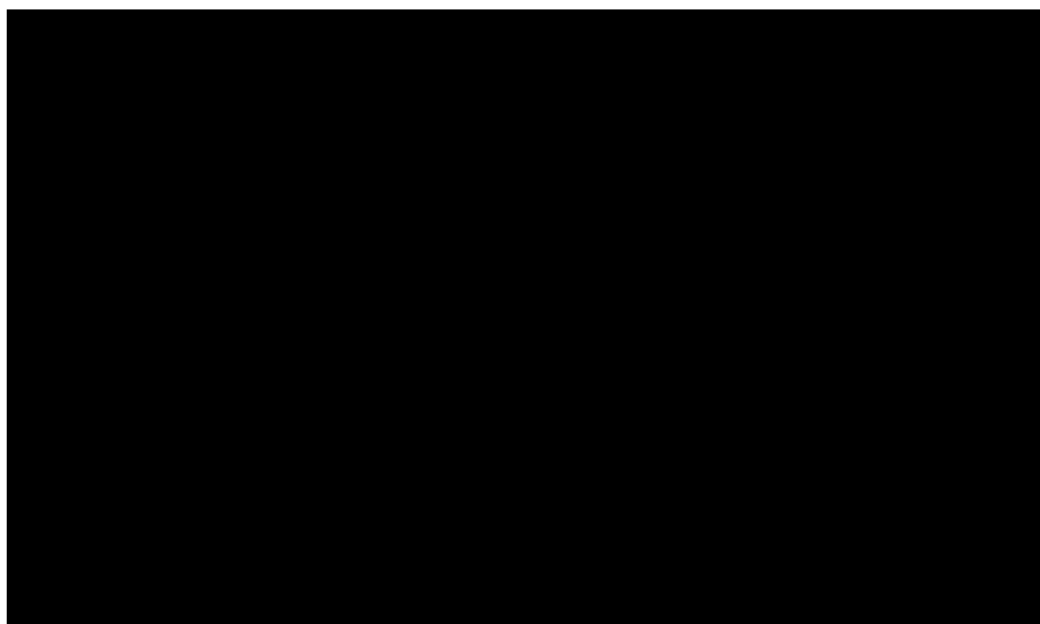
In response to clarification question B26, administration unit costs were updated to reflect the relative activity for outpatient versus day case chemotherapy. Administration costs for neoadjuvant pembrolizumab were based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS Cost Collection 2023-2024,⁵⁸ which is £372 as the weighted average between an outpatient procedure and day case. For adjuvant pembrolizumab, the first two cycles involved adjuvant cisplatin for [REDACTED] of the pembrolizumab + SOC arm as mentioned in Section 4.2.9.2, which was costed based on the more complex parenteral chemotherapy at first attendance (SB13Z) of £470; while patients not receiving concomitant cisplatin accrued the same administration costs as with neoadjuvant chemotherapy.

The third cycle of cisplatin in the pembrolizumab + SOC arm does not coincide with pembrolizumab administration and therefore is costed as a simple parenteral chemotherapy (£372). This is applied in the economic model by allocating one third of this cost (£124) for each cisplatin cycle.. For the SOC arm, the full cost (£372) was assigned for each cisplatin cycle.

4.2.9.3 Time on treatment

As explained in Section 4.2.9.1, perioperative pembrolizumab and adjuvant cisplatin both have a maximum number of cycles before discontinuation. Therefore, fully mature time-on-treatment (ToT) Kaplan-Meier estimates from KEYNOTE-689 were used directly in the model to estimate the proportion of the patient cohort for whom perioperative pembrolizumab and adjuvant cisplatin acquisition and administration costs are applicable. These are presented in Table 40 of the CS and replicated in Figure 34.

Figure 34: Time on adjuvant treatment observed in KEYNOTE-689



Additionally, as shown in Table 41 of the CS, the mean time from the start of treatment exposure to the first adjuvant dose was [REDACTED] and [REDACTED] weeks for the perioperative pembrolizumab + SOC and SOC arm, respectively. Therefore, the model applies the associated costs with adjuvant therapy at week 13 in the perioperative pembrolizumab + SOC arm and at week 7 in the SOC arm.

4.2.9.4 Adverse event management costs

The unit costs of treating AEs are given in Table 54 of the CS. Unit costs were derived from NHS Cost Collection 2023-2024.⁵⁸ AE management costs are applied as a single cost in the first model cycle, calculated based on the proportion of patients in each treatment arm who experienced each AE, as described in Section 4.2.7.

All AEs not requiring hospitalisation are assumed to have the same cost per episode (£159.94 which is the cost of an outpatient visit), whereas the other costs were AE-specific if it resulted in hospitalisation. The calculated total costs associated with AEs are £192.31 for the perioperative pembrolizumab + SOC arm versus £227.57 for the SOC arm.

4.2.9.5 Initial surgery and adjuvant radiotherapy costs

Surgery costs were sourced from NHS Cost Collection 2023-2024 code CA93A (£8,051.66).⁵⁸ In KEYNOTE-689, [REDACTED]% ([REDACTED]/345) versus [REDACTED]% ([REDACTED]/300) proceeded to surgery from the pembrolizumab + SOC versus SOC arms, respectively, and these estimates inform the costs for surgery in the model. This cost was applied in the pembrolizumab + SOC arm six weeks after entry into the model to account for time on neoadjuvant pembrolizumab, whereas for the SOC arm, this cost was applied upon model entry.

Radiotherapy costs comprise two parts; preparation one-off cost equal to £2,460 (NHS Cost Collection 2023-2024 code SC41Z), and costs of delivered radiotherapy fractions. As observed in KEYNOTE-689, the model uses five fractions/week for a mean of 6.4 weeks and the cost per fraction is £238 (NHS Cost Collection 2023-2024 code SC23Z). Therefore, estimated total radiotherapy cost is £10,095.39 and was applied after seven weeks from initial surgery. In KEYNOTE-689, █% (█/345) versus █% (█/300) received radiotherapy from the pembrolizumab + SOC versus SOC arms respectively - these figures inform the radiotherapy costs in the model.

4.2.9.6 Disease management costs

Disease management costs were applied in the model for each health state based on the estimated healthcare resource use in each state, and the unit costs associated with each resource. Unit costs and healthcare resource use frequencies for each health state were applied equally to the pembrolizumab + SOC and SOC arms. The unit costs of healthcare resources considered in the model are provided in CS, Table 43.

The company's estimates of the frequency of resource use and the proportion of patients incurring these resource are provided in Tables 44 and 45 of the CS. The weekly frequencies for the resources used in the EF state are informed by the company's clinical experts (N = 5) and included: consultant visits; clinical nurse specialist visits; blood tests and computed tomography (CT) scans. These differed by treatment arm to capture the additional resource use associated with delivering perioperative pembrolizumab. Other resources such as consultations with dieticians and speech and language therapists were not included as these were assumed equal between both arms. Frequencies are assumed the highest in the first year, then lower from year 2 to year 5, after which no resources are assumed, and the patient is discharged.

The resource use for disease management (i.e. excluding subsequent treatments described in Sections 4.2.9.7 and 4.2.9.8) is assumed to be the same for the L/SR and pre-progression IRP health states based on the company's clinical experts. These, together with resources for post-progression IRP, were sourced from TA490.⁶¹ TA490 based the resources used and the proportion of patients who received each resource item on Nash Smyth *et al.*; this is a UK study which reported treatment patterns and resource use in patients with repeatedly-treated metastatic HNSCC.⁶² In the absence of specific data, TA490 assumed for simplicity that each resource item was used once per cycle. Because the cycle length used in TA490 was four weeks, the current CS converts all the 4-week proportions of patients from TA490 to weekly proportions using the following equation:

$$P_{\text{weekly}} = 1 - \exp\left(\frac{\ln(1 - P_{\text{monthly}})}{\frac{365.25}{12}}\right)$$

Because the current model structure does not differentiate between pre- and post-progression IRP, a weighted average of resource use associated with pre- versus post-progression IRP, based on the estimated proportion of time spent progression-free within the IRP state was calculated to estimate disease management costs in the IRP state. The per-cycle disease management costs applied in the model are provided in Table 22.

Table 22: Disease management costs as applied in the CS model

Health state	Application in the model	Cost (£)
Event-free (Perioperative pembrolizumab + SOC)	Year 1	57.30
	Years 2 to 5	16.03
	Year 5 onwards	0.00
Event-free (SOC)	Year 1	24.53
	Years 2 to 5	12.99
	Year 5 onwards	0.00
Local / salvageable recurrence and pre-progression incurable recurrence		177.81
Post-progression incurable recurrence		107.39

4.2.9.7 Subsequent treatment costs following L/SR

Following L/SR, subsequent treatment costs include radiotherapy, salvage surgery or systemic therapies, and are applied as one-time costs once patients enter the state, as per the proportions of patients who received each of these therapies in the KEYNOTE-689 trial.

Unit costs for salvage surgery and radiotherapy are assumed to be the same as with initial surgery and adjuvant radiotherapy, except that the duration of radiotherapy was assumed half that of the adjuvant radiotherapy (i.e., 3.2 weeks) to account for increased morbidity following recurrence. Clinical advice received by the EAG indicates that the duration of retreatment radiotherapy is indeed shorter, however remains “very difficult” to quantify due to the variety of different regimens used in the UK.

Therefore, total costs for surgery and radiotherapy are estimated to be £8,051.66 and £6,277.62, respectively. These costs for surgery and radiotherapy are applied to ■■■■ (out of ■■ patients from both arms who experienced L/SR as their first EFS event, ■■ had surgery) and ■■■■ (out of ■■ patients

from both arms who experienced L/SR as their first EFS event, █████ had radiotherapy), respectively, in both modelled treatment arms.

Subsequent systemic therapies include: pembrolizumab monotherapy; nivolumab; cisplatin + 5-FU; cetuximab + cisplatin + docetaxel; cisplatin + paclitaxel, cetuximab + cisplatin and cisplatin alone. Data on mean ToT and proportions of patients receiving each treatment regimen were available from KEYNOTE-689 (CS, Table 47 and Table 48, respectively). Dosing schedules for L/SR were assumed the same as in the first-line IRP setting (CS, Table 49 and clarification response, question B31). Mean ToT and dosing schedules are used to calculate the total acquisition and administration costs per each treatment regimen. Pembrolizumab plus chemotherapy is not recommended by NICE; hence, the proportions of patients who had this treatment combination were redistributed among the other included regimens based on the market share of each.

Only █████ and █████ patients received systemic therapies with curative intent in the perioperative pembrolizumab + SOC and SOC arms of KEYNOTE-689, respectively, therefore █████ and █████ are assumed to receive no active treatment. The resultant total acquisition and administration costs for systemic therapy are provided in Table 22.

Table 23: Systemic therapy costs associated with the L/SR state

Weighted average costs (£)	Perioperative pembrolizumab + SOC	SOC
Drug acquisition	█████	█████
Drug administration	█████	█████

4.2.9.8 Subsequent treatment costs following IRP

The company included subsequent treatment costs associated with the IRP state, in first-line (pre-progression) and second-line (post-progression) settings, as a single cost on entry to the IRP health state. The dosing schedule for the first- and second-line treatment regimens with the relative dose intensity and sources for these data are provided in CS, Table 49. Drug acquisition costs for all subsequent treatments (CS, Table 38) were sourced from the BNF and eMIT.^{57, 60}

Updated administration costs (clarification response, Table 34) were sourced from NHS Cost Collection 2023-2024.⁵⁸ Activity codes SB12Z, SB13Z, SB14Z, SB15Z, or SB11Z were used dependent on the complexity, duration, and means of administration, IV or oral, of each subsequent treatment.

First-line subsequent treatment was assumed to continue until progression based on exponential PFS curves estimated for each first-line treatment regimen. These PFS curves were estimated based on an

exponential curve fit to median PFS estimated from the NMA conducted by the company and reported in Appendix J4. Table 50 of the CS provides the discontinuation rates for the three reference treatments of the NMA, with the HR used to calculate the rates for the rest of regimens. Some regimens or components of a regimen had a maximum treatment duration and could be stopped earlier. Mean ToT for second-line therapies was sourced from KEYNOTE-048 and provided in CS, Table 51.

In the company's base case, a two-stage discounting approach was adopted for first-line subsequent treatment costs. For the first stage, a total cost for a full course of first-line treatment was discounted as if it were initiated in cycle 0, this cost was then applied in the model on entry to the IRP health state and then in the second stage was discounted again to account for the delayed initiation (relative to cycle zero). Second-line treatment costs were only discounted via the second stage. The market share estimates applied in the CS base case, for both the pembrolizumab + SOC and SOC arms, are provided in Table 52 and 53 for the first- and second-line therapies, respectively. These were based on regimens used in KEYNOTE-689, including the following adjustments:

- The first-line treatment mix includes options that met three criteria: a) had relevant PFS and OS inputs available, (b) that are recommended by EHNS–ESMO–ESTRO clinical guidelines, and (c) may be used in the UK.
- The share of excluded options based on the above criteria was redistributed among the selected regimens in proportion to their observed usage as patients' first systemic treatment in the IRP state.
- Because pembrolizumab plus chemotherapy is not recommended by NICE, the proportion of patients who received this regimen were redistributed among the other included regimens based on the market share of each.
- Patients in the pembrolizumab + SOC arm were divided into two subgroups based on whether they would be eligible for rechallenge with an anti-PD-1 immunotherapy (i.e., pembrolizumab or nivolumab). Those who recurred within the first 18 months of model entry were assumed ineligible for further anti-PD-1 immunotherapies. The shares of these immunotherapies were redistributed among the selected regimens in proportion to their observed usage for the immunotherapy-ineligible population.

A weighted average of administration and acquisition costs, for a full course of each first- and second-line subsequent therapy, is applied on entry to the IRP health state. These costs are provided in Table 24.

Table 24: Systemic therapy costs associated with the IRP state

Weighted average costs (£)	perioperative pembrolizumab + SOC (IO-eligible)	perioperative pembrolizumab + SOC (IO-ineligible)	SOC
First-line subsequent therapies			
Drug acquisition (undiscounted)	██████████	██████████	██████████
Drug acquisition (discounted)	██████████	██████████	██████████
Drug administration (undiscounted)	██████████	██████████	██████████
Drug administration (discounted)	██████████	██████████	██████████
Second-line subsequent therapies			
Drug acquisition	██████████	██████████	██████████
Drug administration	██████████	██████████	██████████

4.2.9.9 PD-L1 testing costs

PD-L1 testing costs are sourced from NHS Cost Collection 2023-2024 code PATH02 (£36.20).⁵⁸ These are applied once in the economic model upon entry in the EF and IRP states. In the EF state, this is only applied to the pembrolizumab + SOC arm and the cost of 1.05 tests is used to reflect the expected number of PD-L1 tests needed to identify one patient with PD-L1 CPS ≥ 1 (i.e., $1.05 = 1 / 95.5\%$). In the IRP state, the cost of one test is applied to both arms upon entry to the state. The requirement for a repeat test even in patients were previously tested for PD-L1 at first-line is justified by the company on the basis of advice from clinical experts that it is possible for the disease pathology of recurrent tumours to differ to the primary tumour.

4.2.9.10 Terminal care costs

The CS includes a one-off end-of-life cost, applied upon transition to the death health state. This cost reflects the management costs associated with terminal care. A cost of £6,207.60 was sourced from Georgiou and Bardsley 2014⁶³ and inflated to its 2024 value (£8,498.27).

4.2.9.11 EAG critique

NICE informed the EAG of eMIT price updates for 5-FU, carboplatin, cisplatin, docetaxel, gemcitabine, methotrexate, paclitaxel, pemetrexed. These are reflected in the EAG cost-effectiveness analysis reported in Section 5.2.

The company's base case model uses the APaT population to inform all model resource use inputs sourced from KEYNOTE-689. This limits the sample size to patients who started neoadjuvant pembrolizumab in the pembrolizumab + SOC arm and patients who underwent surgery in the SOC arm. In response to clarification question B41, the company justified this approach over using the ITT

population (i.e., all patients randomised regardless of whether treatment was received) in order to account for, “the open-label nature of the KEYNOTE-689 trial and better reflect expected outcomes of patients receiving the respective treatment regimens”.

The EAG notes that in the pembrolizumab + SOC arm, number of patients is similar between the ITT and APaT PD-L1 CPS ≥ 1 populations (■■■■ versus ■■■■ respectively). This contrasts with the SOC arm where the APaT population comprises only ■■■■ patients compared to ■■■■ in the ITT population. The EAG considers that more patients would have been captured in the APaT population of the SOC arm had they had neoadjuvant therapy which is part of the positioning of pembrolizumab in the current appraisal. The population used makes a difference in the estimated proportions of patients undergoing initial surgery, adjuvant radiotherapy, and adjuvant cisplatin as shown in Table 25. This critique point is subsequently explored in the EAG’s exploratory analyses in Section 5.2.2, when the EAG has changed the company’s base case assumption from using the ITT instead of the APaT population. This change has also been included in the EAG’s preferred base case scenario (see Section 5.2.3).

Table 25: Differences in proportions receiving adjuvant treatment between the APaT and ITT populations

Population receiving regimens (n, %)	ApaT population (company’s base case)		ITT population	
	pembrolizumab + SOC (N=■■■■)	SOC (N=■■■■)	pembrolizumab + SOC (N=■■■■)	SOC (N=■■■■)
Initial surgery	■■■■	■■■■	■■■■	■■■■
Adjuvant radiotherapy	■■■■	■■■■	■■■■	■■■■
Adjuvant cisplatin	■■■■	■■■■	■■■■	■■■■

The EAG identified two calculation/implementation errors in the model. The first concerned administration costs assigned to adjuvant pembrolizumab. Based on ■■■■ receiving adjuvant cisplatin in the pembrolizumab + SOC arm, the model assigns to ■■■■ (1-■■■■) of patients starting adjuvant pembrolizumab the administration cost of simple IV chemotherapy, whereas the rest would be assigned the cost of delivering IV complex chemotherapy owing to the delivery of two chemotherapy regimens. However, the ■■■■ is reported as part of the whole arm population and not only those who received pembrolizumab. Hence, the breakdown should be ■■■■ (■■■■ minus ■■■■) receiving pembrolizumab alone versus ■■■■ receiving pembrolizumab with cisplatin. This equates to a ratio for simple IV delivery to complex IV delivery of ■■■■:■■■■ complex IV delivery instead of the ratio in the company’s base case of ■■■■:■■■■.

The second error was related to the frequency of resource use for the L/SR and IRP health states sourced from TA490. The EAG does not believe such a rate/probability conversion is necessary as these

resources are not one-off events. The EAG prefers simply to divide the resource use by the ratio of cycle lengths between the current appraisal and TA490 (i.e., if one resource was used once every 4 weeks in TA490, then this means its weekly use is 0.25). Both errors are subsequently explored in the EAG's exploratory analyses in Section 5.2.2.

Regarding the dosing schedule for adjuvant pembrolizumab, the EAG notes that this does not coincide with the SmPC for using pembrolizumab in this setting. The EAG considered it more likely that pembrolizumab 200 mg Q3W would be given alongside cisplatin for three cycles (instead of the first two in the CS base case), and then the 400 mg Q6W schedule would take over after this. However, the EAG found a negligible impact of this change on the cost-effectiveness estimates and has therefore not included it formally in its exploratory analyses.

The EAG considers that there is uncertainty regarding whether patients having pembrolizumab as neoadjuvant/adjuvant treatment would be rechallenged with an immunotherapy if they experience an IRP occurring at least 6 months after completing treatment with pembrolizumab. The company has provided two scenario analyses exploring this. The first scenario (company scenario 16) explores a higher usage of immunotherapy, matching that used in the SOC arm, which they argue may better reflect immunotherapy usage for later recurrences, which they claim may not be adequately captured in the KEYNOTE-689 follow-up. The second scenario (company scenario 27), provided in response to the clarification request (B33) explored a situation in which no rechallenge with immunotherapy was offered to patients having neoadjuvant/adjuvant pembrolizumab. Although both scenario analyses had minimal impact on the ICER, the EAG notes that these scenario analyses only impact the costs of subsequent treatments in the pembrolizumab with SOC arm. Therefore, they do not capture the full uncertainty, which includes whether rechallenge would be more or less successful than the mix of subsequent treatments offered in KEYNOTE-689, in which only small proportion of patients in the pembrolizumab with SOC arm received immunotherapy after IRP (■■■■% pembrolizumab for first-line treatment of IRP and ■■■■% nivolumab for second-line treatment of IRP). The EAG has explored the impact of assuming no immunotherapy rechallenge in its scenario analyses, presented in Section 5.2.4, although it notes the limitation that this only impacts subsequent treatment costs.

Finally, subsequent treatments used in the company's model included options not mentioned in clinical practice guidelines. In response to clarification question B34, the company provided a scenario analysis where methotrexate was excluded from first-line treatments given in the IRP health state, and cetuximab monotherapy and cisplatin monotherapy were excluded from second-line treatments in the IRP state. The EAG replicated applied these changes to the EAG's preferred base case as a scenario analysis, as described in Section 5.2.4.

4.2.10 Model validation steps taken by the company

The company reports using quality control procedures to verify the model programming. It also reports performing internal validation of EFS and OS by comparing outcomes predicted by the model to the KEYNOTE-689 data which was used to inform the model. However, it notes that this comparison was complicated by the use of different censoring rules for the EFS and OS survival analyses. It also reports using published OS estimates from other cohorts to perform external validation. However, it notes that there were several limitations with the external validation process.⁴³⁻⁴⁵ Firstly, the studies that were identified reported DFS for adjuvant treatments rather than EFS which is the relevant outcome for neoadjuvant treatments, as reported in KEYNOTE-689. Secondly, the external studies reporting OS varied in terms of the patient characteristics in their cohorts, with particular concerns regarding the distribution of anatomical sites for HNSCC,^{44, 45} and the proportion of HPV-positive HNSCC (see Section 4.2.6).⁴³ These studies were also adjuvant treatment studies meaning that OS was reported from the time of surgery, reflecting a different period of risk from KEYNOTE-689 where OS was reported from randomisation with a potential delay in surgery for the pembrolizumab arm to accommodate neoadjuvant treatment.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions, and Section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

All results presented in Section 5 are based on the updated version of the company's model submitted in response to the clarification process.

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

Table 26 and Table 27 present the central cost-effectiveness estimates from the deterministic and probabilistic models, respectively, comparing perioperative pembrolizumab + SOC with SOC. The probabilistic version of the model suggests that pembrolizumab + SOC is associated with an incremental gain of 1.31 QALYs and an incremental cost of [REDACTED], leading to an expected ICER of [REDACTED] per QALY gained. The deterministic version of the model suggests similar findings with a slightly higher ICER of [REDACTED] per QALY gained. The company does not consider that pembrolizumab qualifies for any additional severity modifier in this indication. The EAG agrees that no severity weighting is needed as reported in Section 5.3.

Table 26: Company's deterministic base case cost-effectiveness results without severity weighting

-	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	[REDACTED]	[REDACTED]	[REDACTED]	1.28	[REDACTED]
SOC	[REDACTED]	[REDACTED]	-	-	-

The company considers a disease severity modifier of 1.0 is appropriate.

Table 27: Company's probabilistic base case cost-effectiveness results without severity weighting (1,000 iterations run by the EAG)

-	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative pembrolizumab + SOC	██████	████	██████	1.31	██████
SOC	██████	████	-	-	-

The company considers a disease severity modifier of 1.0 is appropriate.

The CS model presents disaggregated outcomes for the deterministic model in terms of costs accrued by different types of resource use and QALYs accrued in different health states. These results are presented in Table 28. The differences in costs are primarily driven by the higher acquisition costs of the perioperative pembrolizumab. The model suggests that compared with SOC, pembrolizumab + SOC results in patients accruing more QALYs in the EF health state.

Table 28: Base cases disaggregated outcomes for the post-clarification company's deterministic model

	Pembrolizumab + SOC	SOC
Disaggregated costs (discounted)		
Pembrolizumab and cisplatin acquisition and administration costs	██████	████
Surgery and radiotherapy costs (EF state)	██████	██████
Subsequent treatment costs (L/SR state)	████	██████
Subsequent treatment costs (IRP state)	██████	██████
AE costs	████	████
Disease management and PD-L1 testing costs	██████	██████
Terminal care costs	██████	██████
Total	██████	██████
Disaggregated QALYs (discounted)		

	Pembrolizumab + SOC	SOC
EF health state	████	████
L/SR health state	████	████
IRP health state	████	████
Adverse events	████	████
Total	████	████

Abbreviations: AE - adverse event; EF - event-free; IRP - incurable recurrence or progression; L/SR - local/salvageable recurrence; PF - progression-free; PD - progressed disease; QALYs - quality-adjusted life years; SOC - standard of care

5.1.2 Company's sensitivity and scenario analyses

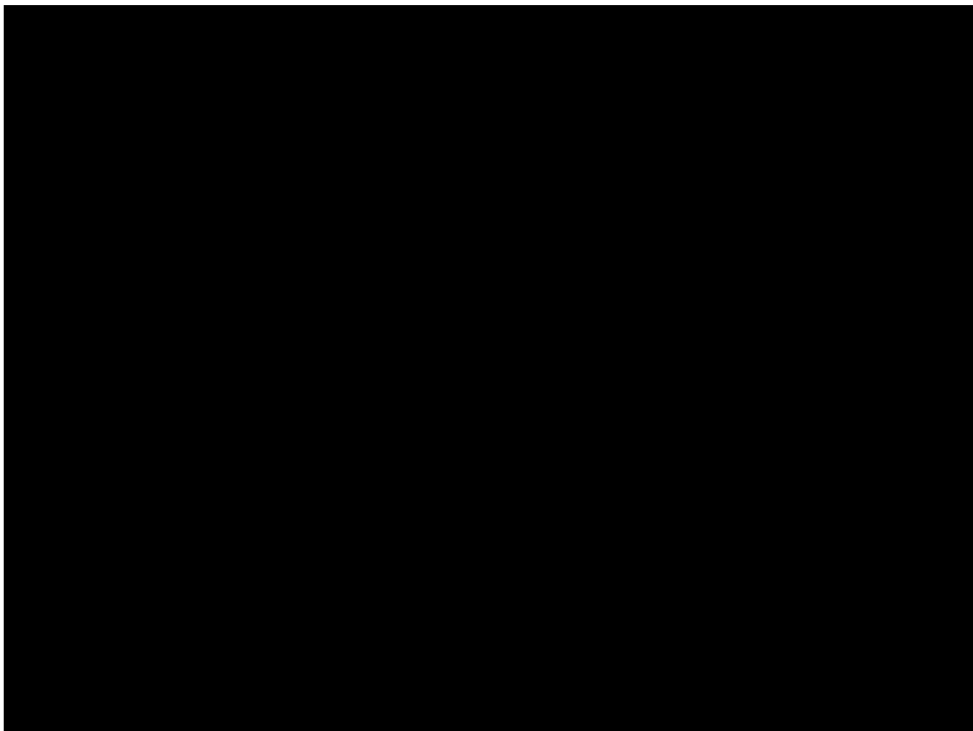
5.1.2.1 Probabilistic sensitivity analysis

The PSA scatterplot is presented in Figure 35 and cost-effectiveness acceptability curves (CEACs) are presented in Figure 36. Based on these analyses, the probability that pembrolizumab + SOC generates more net benefit than SOC is █████% at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained and █████% at a WTP threshold of £30,000 per QALY gained.

Figure 35: Cost-effectiveness plane - PSA scatterplot: pembrolizumab + SOC vs SOC



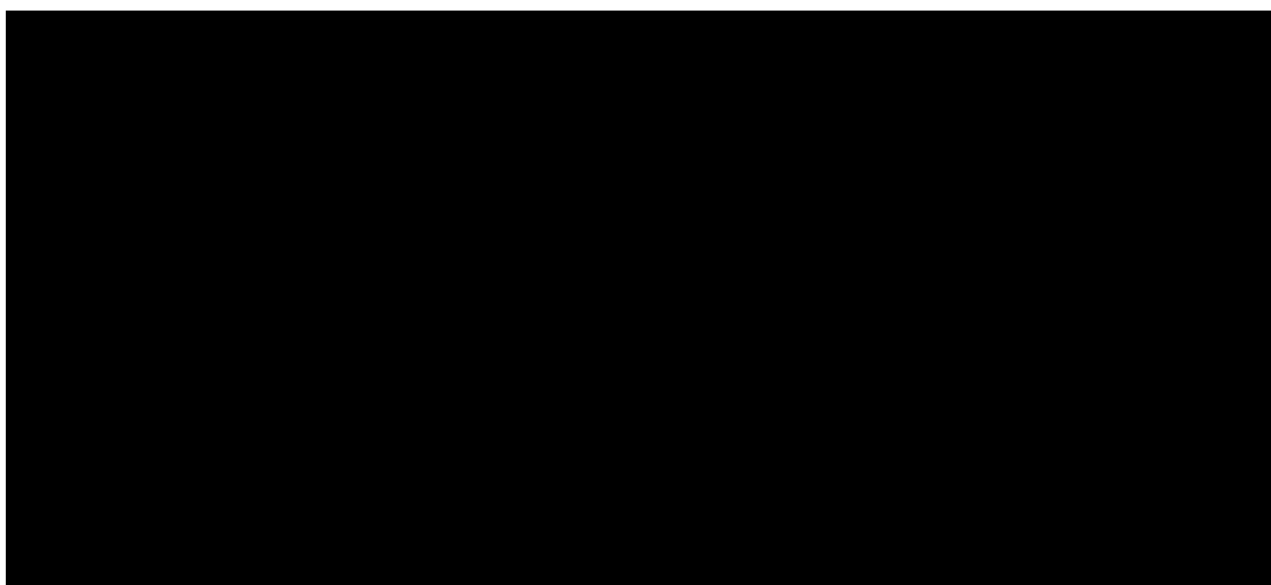
Figure 36: Cost-effectiveness acceptability curves: pembrolizumab + SOC vs SOC



5.1.2.2 Deterministic sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact, on the ICER, of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated using the tornado diagram in Figure 37. The ICER was most sensitive to the exponential hazard of transitions from L/SR to IRP, followed by the utility value for the post-progression IRP health state. In order of importance, unit costs of IV administration and initial surgery/adjuvant radiotherapy, and EF state management costs also had an impact. Across all the DSAs, the ICER ranges from £[REDACTED] to £[REDACTED] per QALY gained.

Figure 37: Tornado diagram presenting results of OWSA - 10 most sensitive parameters



5.1.2.3 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. These scenarios are presented in Table 29. The largest change in ICER occurred when alternative survival distributions were selected to model the transitions from the EF to L/SR and IRP health states. The ICER increased to £[REDACTED] per QALY when independently fit (Company's approach 1, detailed in Section 4.2.6.1) log-normal and Gompertz distributions were used for the EF to L/SR and IRP transitions, respectively. This was in contrast to when generalised gamma distributions were selected for both transitions where the ICER decreased to £[REDACTED] per QALY. Applying the cure assumption at five years moved both ICERs closer to the company's base case ICER.

Other scenarios of impact were: using the alternative censoring rule for EFS events where last known date alive is used instead of last disease assessment (ICER increased to £[REDACTED]), limiting the model time horizon to 20 years (ICER increased to £[REDACTED]), using the ITT instead of APaT population to

estimate costs of adjuvant treatments (ICER increased to £[REDACTED]), and using a discount rate of 1.5% (ICER decreased to £[REDACTED]). Applying the mix of subsequent treatments observed for recurrences classed as IRP to recurrences classed as L/SR decreased the ICER to £[REDACTED], but changing the assumptions regarding rechallenge with immunotherapy had minimal impact on the ICER. The scenarios exploring alternative utility values had a fairly small impact on the ICER suggesting the cost-effectiveness is not particularly sensitive to the utility value applied post progression for IRP, or the use of alternative utilities based on a mixed-effects model. Assuming 3 weekly dosing of pembrolizumab throughout the adjuvant treatment phase also had minimal impact on the ICERs.

Table 29 Company's scenario analyses on the primary base case (reproduced from Table 44 of the clarification response)

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
-	Base case				██████	1.28	██████	
1	Distributions used to model transitions from EF <i>(EF→L/SR/IRP/ death)</i>	Approach #1, Gompertz/ Gompertz/ Gen gamma	Approach #1: Gen gamma/ Gen gamma (pessimistic incremental EFS and OS benefit)	Explore range of impact based on most and least incremental EFS and OS benefit of the 10 finalist curve combinations.	██████	1.73	██████	██████
2			Approach #1: Log normal/ Gompertz/ Gen gamma (optimistic incremental EFS and OS benefit)		██████	1.00	██████	██████
3			Scenario 1 + Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years	Explore the impact of applying a cure assumption to alternative distributions using Approach #1 to model transitions for EF, to ensure a modelled pattern of recurrence in line with clinical expert opinion.	██████	1.49	██████	██████
4			Scenario 2 + Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years		██████	1.09	██████	██████
5			Approach #2: Gompertz/ Gompertz/ Gompertz (proportional hazards)	Test impact of assuming proportional hazards Best-fitting combination under Approach #2.	██████	1.38	██████	██████
6			Approach #3: Gompertz/ Gompertz/ Gompertz (time-varying proportional hazards)	Test impact of adopting a time-varying HR approach, given violation of proportional hazards for EFàL/SR. Best-fitting combination under Approach #3 (but not included	██████	1.54	██████	██████

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
				in the final 10 combination of distributions).				
7	Cure	No cure point applied	Instantaneous cure (95% risk reduction) applied to transitions from EF at 5 years	Reflect clinical expert opinion that patients are functionally cured at 5 years; similar to previous appraisals		1.26		
8	Censoring of transitions from EF state	Censoring rule as per protocol for KEYNOTE-689 trial (last disease assessment, as per EFS analysis)	Alternative censoring rule (last known date alive, as per OS analysis) – Approach #1: Gompertz/Gompertz/Gen Gamma	Explore impact of different censoring rules applied for per protocol analyses of EFS and OS in trial. Base case selection for alternative censoring rule (see Appendix J3)		1.12		
9			Alternative censoring rule (last known date alive, as per OS) – Approach #1: Gompertz/Gen Gamma/Gen Gamma	Explore impact of different censoring rules applied for per protocol analyses of EFS and OS in trial. Most optimistic for incremental EFS and OS benefit out of final combinations (see Appendix J3.4)		1.44		
10	Transitions from IRP→death	Based on PLD from KEYNOTE-689	Based on efficacy (from NMA) and market shares of 1L treatments for R/M HNSCC	Explore impact of approach to modelling IRP transitions, and aligned with method in previous appraisals		1.25		
11	IRP post-progression utility	EORTC-QLQ-C30 from EXTREME mapped to EQ-5D-	As per pre-progression IRP utility in KEYNOTE-689 (assumes no HRQoL decrement on progression)	Consistent utility source across all health states		1.26		

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
		3L, used in NICE TA172/TA473						
12	Pembrolizumab dosing (adjuvant)	200 mg Q3W for 1 dose, followed by 400 mg Q6W for up to 7 cycles	200 mg Q3W for up to 15 cycles	Reflect dosing in trial and possible variation in clinical practice		1.28		
13	Vial sharing (for weight-based treatments)	Permitted	Not permitted	Explore variation in practice in the UK NHS		1.28		
14	Mix of systemic treatment in L/SR state	Based on treatment patterns as observed for patients with L/SR in KEYNOTE-689	In L/SR setting, assume same treatment cost as per the 1L IRP setting	Explore impact of assuming more patients in L/SR are treated systemically, equal to patients in IRP		1.28		
15	1L treatment for IRP (SOC arm)	SOC arm: Nivolumab share as per trial SOC arm	SOC arm: Nivolumab share in trial SOC arm redistributed to pembrolizumab	Clinical advice indicates that most patients on anti-PD-1 get pembrolizumab rather than nivolumab		1.28		
16	1L treatment for IO-eligible patients in IRP (pembro arm)	<i>IO-eligible (recurrences post-18 months):</i> 1L treatment mix as per trial pembrolizumab arm	<i>IO-eligible (recurrences post-18 months):</i> 1L treatment mix as per trial SOC arm	Subsequent treatments in trial may disproportionately reflect early recurrences, and later recurrences may be more likely to receive further IO (as observed in SOC arm)		1.28		
17	PD-L1 tests required to identify 1	Based on prevalence of CPS $\geq$ 1 in	Based on prevalence of CPS $\geq$ 1 in KEYNOTE-048 (72%)	Prevalence of CPS $\geq$ 1 in the real-world population is unknown		1.28		

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
	CPS≥1 patient	KEYNOTE-689 (95.5%)						
18	Time horizon	Lifetime (40.1 years)	20 years	Understand impact of shorter time horizon (note: does not capture full lifetime costs and effects [██████% still alive at 30 years])	██████	1.05	██████	██████
19			30 years		██████	1.25	██████	██████
20	Discount rate	3.5% for costs & effects	1.5% for costs and effects	As per NICE guidance	██████	1.61	██████	██████
21	Apply relative dose intensity	Yes	No	Assuming 100% dose intensity	██████	1.28	██████	██████
New scenarios in response to clarification questions								
22	Utility values informed by KEYNOTE-689	Descriptive utility values pooled across treatment arms	Regression-based utilities using a mixed-effects model pooled across treatment arms	In response to CQ B22	██████	1.22	██████	██████
23	Transitions from EF state	Parametric distributions fitted to full time horizon	Use observed cumulative incidence to model transitions from EF state up to week 32	In response to CQ B2	██████	1.22	██████	██████
24	Distributions used to model transitions from EF (EF→L/SR/IRP/death)	Approach #1 Gompertz/Gompertz/Generalized gamma	Approach #1: Gompertz/Gompertz/Gompertz	In response to CQ B5	██████	1.13	██████	██████
25			Approach #1: Gompertz/Generalized Gamma/Gompertz		██████	1.42	██████	██████
26	Transitions for L/SR state	Transition probabilities	Transition probabilities pooled across treatment arms	In response to CQ B10	██████	1.23	██████	██████

#	Category	Base case setting	Scenario setting	Rationale	Perioperative pembrolizumab + SOC vs SOC			
					Δ Costs, (£)	Δ QALY	ICER (£/QALY)	% change
		specific to each treatment arm						
27	IO-rechallenge following perioperative pembrolizumab + SOC	IO-rechallenge possible after 18 months	No IO-rechallenge permitted	In response to CQ B32	██████	1.28	██████	██████
28	Treatment mix in IRP	As per the use of subsequent therapies in the KEYNOTE-689 trial	Methotrexate redistributed in 1L and cetuximab and cisplatin monotherapies redistributed in 2L	In response to CQ B33	██████	1.28	██████	██████
29	Source initial surgery, adjuvant RT and adjuvant cisplatin use	KEYNOTE-689 APaT	KEYNOTE-689 ITT	In response to CQ B41	██████	1.28	██████	██████

5.2 EAG's additional analyses

5.2.1 Model validation and face validity checks conducted by the EAG

The EAG performed cell checks and conducted face validity checks on the impact of cost effectiveness outcomes when inputs are varied. The EAG could not detect any logical inconsistencies or suspicious model behaviour, and it believes that the company's model is reliable for decision-making.

5.2.2 EAG's exploratory analyses using company's base case

The prices used in the company's model for 5-FU, carboplatin, cisplatin, docetaxel, gemcitabine, methotrexate, paclitaxel, pemetrexed (as stated in CS, Appendix I) were not up to date with the latest published prices provided to the EAG by NICE from the electronic Market Information Tool (eMIT) database (accessed in November 2025). The updated prices applied in EAG exploratory analysis 1 are provided in Table 30.

Table 30: Drug costs updated in the model per the latest eMIT update

Name	Form	Dose per unit, mg	Pack size	List price used in the company's model, £	List price update, £	NPC code
5-FU	vial	5,000	1	6.27	6.52	DHA137
Carboplatin	vial	450	1	23.18	22.41	DHE002
Cisplatin	vial	10	1	3.67	3.77	DHA013
Docetaxel	vial	80	1	9.73	9.03	DHC029
Gemcitabine	vial	2,000	1	19.74	25.52	DYC037
Methotrexate	vial	500	1	12.23	30.01	DHA035
Paclitaxel	vial	300	1	31.89	23.23	DHA210
Pemetrexed	vial	850	1	41.78	42.95	DZV051

As mentioned in Section 4.2.9.11, the EAG corrected two implementation errors. The first is related to the ratio of IV simple to complex administration costs for people receiving adjuvant pembrolizumab, whereas the second concerns how resource use frequency for the L/SR and IRP states were derived from TA490. The EAG corrected these errors in EAG exploratory analyses 2 and 3 and included these changes in its preferred base case.

The EAG preferred using the log-normal / generalised gamma / generalised gamma combination for extrapolating EFS and explored adding the cure assumption as a scenario analysis as discussed in Section 4.2.6.6. The EAG's preferred combination of models was applied in EAG exploratory analysis

4 and incorporated into the EAG's base case (see Section 5.2.3). The addition of the cure assumption to the EAG's base case was examined in EAG scenario analysis 1 (see Section 5.2.4).

Additionally, the EAG prefers the use of the ITT population to inform all model resource use inputs sourced from KEYNOTE-689 (Section 4.2.9.11). This was applied in EAG exploratory analysis 5 and included in its preferred base case.

In addition, the EAG preferred to use time-to-event data pooled from the two treatment arms to estimate transitions from the L/SR and IRP states as the treatment-specific data were too few and uncertain to be used for the L/SR state and there was uncertainty regarding whether pembrolizumab with SOC reduced or increased the risk of death from the IRP state. The model included the functionality to use pooled data for transitions from the L/SR state, however, this was not an available option for the transitions from the IRP state. The EAG added the option to use pooled data for transitions from the IRP state and death assuming an average of mortality rates from IRP from both arms in EAG exploratory analysis 6. This change was included in the EAG's preferred base case (see Section 5.2.3), but the EAG also presented a scenario analysis excluding this change (see Section 5.2.4).

Table 31 summarises the EAG's exploratory analysis using the company's base case model, whereas Table 32 reports the results for each individual analysis. The biggest impact on ICER was when the ITT population was used in place of the APaT population to inform proportions on adjuvant treatment where the ICER increased from £[REDACTED] to £[REDACTED] per QALY gained. The remaining analysis only varied the ICER between £[REDACTED] and £[REDACTED] per QALY gained.

Table 31: Summary of EAG’s exploratory analyses using company’s base case

Exploratory analysis number	Company’s base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	eMIT prices accessed in March 2025	eMIT prices accessed in November 2025	Updating drug acquisition prices	4.2.9.11
2	Inaccurate calculation of simple to complex IV administration costs of adjuvant chemotherapy	Calculation corrected	The █ receiving cisplatin is reported as part of the whole arm population and not only those who received pembrolizumab.	4.2.9.11
3	Frequency of resource use for the L/SR and IRP health states sourced from TA490 use rate/probability conversions to adjust for the difference in cycle length between the two appraisals	Simple conversion via division by the ratio of cycle lengths	Resources are not treated in the same way as one-off clinical events.	4.2.9.11
4	Gompertz/ Gompertz/ generalised gamma to model EFS	Log normal/ generalised gamma/ generalised gamma to model EFS	Avoiding the Gompertz models which exhibit effective plateaus.	4.2.6.5
5	APaT population is used to informing proportions undergoing initial surgery, radiotherapy, and adjuvant cisplatin	Preference of ITT population	Better reflection of the intended population and position of the technology	4.2.9.11
6	Assuming treatment-specific transitions from the L/SR and IRP states	Assuming the same transitions from the L/SR and IRP states for both arms	Scarce data informing the treatment-specific transitions, meaning it is better to pool data from both arms	4.2.6.7

Table 32: Results of EAG’s exploratory analyses using company’s base case

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Company base case – post-clarification (Deterministic)					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG exploratory analysis 1: Updating acquisition prices					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG exploratory analysis 2: Correcting IV admin costs for adjuvant pembrolizumab					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG exploratory analysis 3: Correcting frequency of resource use for later stages					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG exploratory analysis 4: Using Log normal / generalised gamma / generalised gamma to model EFS					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG exploratory analysis 5: Adopting the ITT population for informing resource use					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG exploratory analysis 6: Assuming the same transitions from the L/SR and IRP states for both arms					
Pembrolizumab with SOC	████	████	1.22	████	████
SOC	████	████	-	-	

Abbreviations: EFS, event-free survival; ICER, incremental net monetary benefit; IV, intravenous; ITT, intention-to-treat; QALYs, quality-adjusted life years; SOC, standard care

5.2.3 EAG’s preferred assumptions

The EAG base case combines all six exploratory analyses listed in Table 31. Table 33 presents the deterministic and probabilistic results for the EAG’s base case. It can be seen that the ICER in the EAG’s preferred base case is fairly similar to the ICER in the company’s base case.

Table 33 Results using EAG's preferred model assumptions

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Company base case – post-clarification (Deterministic)					
Pembrolizumab with SOC	████	████	1.28	████	████
SOC	████	████	-	-	
EAG base case applying analyses 1-6 (Deterministic)					
Pembrolizumab with SOC	████	████	1.21	████	████
SOC	████	████	-	-	
EAG base case applying analyses 1-6 (Probabilistic)					
Pembrolizumab with SOC	████	████	1.20	████	████
SOC	████	████	-	-	

Abbreviations: ICER, incremental net monetary benefit; QALYs, quality-adjusted life years; SOC, standard care

5.2.4 Scenario analyses using EAG's preferred assumptions

The EAG conducted several scenario analyses using its deterministic base case as the starting point. The analyses are described in Table 34, with results presented in Table 35. All scenarios generated ICERs in the range between £████ and £████ except when SMR values higher than 1 were used. Using SMRs between 1.6 and 2.7 provides ICERs between £████ and £████ per QALY gained.

Table 34: Summary of EAG's scenario analyses using EAG's preferred assumptions

-	EAG's base case assumption	EAG's scenario
1	No cure assumption applied after five years	Cure assumption applied after five years
2	Assuming equal transitions from the L/SR and IRP states for both treatment arms	Transitions from the L/SR and IRP states from KEYNOTE-689 as with the company's base case
3	Transitions from the IRP state are based on data from KEYNOTE-689 with event rates pooled across both arms.	Transitions from the IRP state are based on the efficacy and market shares of treatment mix used as with company scenario 10 from the clarification response
4	Immunotherapy-rechallenge permitted following perioperative pembrolizumab	No immunotherapy-rechallenge permitted following perioperative pembrolizumab
5	Treatment mix used in the IRP state reflective of that received in KEYNOTE-689	Treatment mix used in the IRP state reflective of the UK clinical practice
6	Using SMR of 1.0	Using SMR of 1.6
7	Using SMR of 1.0	Using SMR of 2.7

Table 35: Results of EAG's scenario analyses using EAG's preferred assumptions

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
EAG base case applying analyses 1-6 (Deterministic)					
Pembrolizumab with SOC	████	██████	1.21	██████	██████
SOC	████	██████	-	-	
EAG scenario 1 (Cure assumption applied after five years to 95% of the population)					
Pembrolizumab with SOC	████	██████	1.25	██████	██████
SOC	████	██████	-	-	
EAG scenario 2 (Transitions from the L/SR and IRP states derived from KEYNOTE-689 as with the company’s base case)					
Pembrolizumab with SOC	████	██████	1.28	██████	██████
SOC	████	██████	-	-	
EAG scenario 3 (Transitions from the IRP state are based on the efficacy and market shares of treatment mix used as with company scenario 10 from the clarification response)					
Pembrolizumab with SOC	████	██████	1.20	██████	██████
SOC	████	██████	-	-	
EAG scenario 4 (No immunotherapy-rechallenge permitted following perioperative pembrolizumab)					
Pembrolizumab with SOC	████	██████	1.21	██████	██████
SOC	████	██████	-	-	
EAG scenario 5 (Treatment mix used in the IRP state reflective of the UK clinical practice)					
Pembrolizumab with SOC	████	██████	1.21	██████	██████
SOC	████	██████	-	-	
EAG scenario 6 (Applying SMR of 1.6 to background mortality)					
Pembrolizumab with SOC	████	██████	1.15	██████	██████
SOC	████	██████	-	-	
EAG scenario 7 (Applying SMR of 2.7 to background mortality)					
Pembrolizumab with SOC	████	██████	1.06	██████	██████
SOC	████	██████	-	-	

Abbreviations: ICER, incremental net monetary benefit; IRP, incurable recurrence or progression; L/SR, local/salvageable recurrence; QALYs, quality-adjusted life years; SMR, standardised mortality rate; SOC, standard care

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company states in CS, Section 3.6 that it considers that pembrolizumab does not qualify for an additional severity modifier in this indication as the expected QALY loss for SOC versus the general population does not meet any severity modifier threshold. Although the company does not present its severity modifier calculation in the CS, the EAG has examined the company's QALY shortfall calculation within its submitted model and it agrees with the company's conclusion based on their calculation. The EAG has also corroborated their findings by using a published online QALY Shortfall Calculator,⁶⁴ and it is satisfied that the population does not meet the criteria, based on the information presented in Table 36.

The CS later goes on to state, in Section 3.13, that all other STAs for inoperable or metastatic HNSCC (i.e., TA661, TA736) were appraised under the previous End of Life guidance and approved under the end-of-life criteria. The EAG notes that firstly, this guidance no longer applies under current STA processes and secondly, the assessment of whether a severity modifier should apply should be based on QALY shortfall for patients at the point in the care pathway that the treatment is indicated for, which in this case is locally advanced resectable disease and not inoperable or metastatic disease.

Table 36 Summary of EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution, percentage female	21.1%	KEYNOTE-689 as reported in CS, Table 24.
Starting age	59.9	
Expected years of life under SoC	■	Company clarification response, Table 42 (deterministic base case)
Life-time QALYs under SoC	■	
Discount rate	3.5%	CS, Table 56
Life-time QALYs for general population	12.62	QALY Shortfall Calculator by Schneider <i>et al.</i> ^{64 a}
Absolute QALY shortfall	■	
Proportionate QALY shortfall	■	

^a Reference case utility source selected from the options provided by Schneider *et al.*⁶⁴ which employs life tables from England (2017-2019), the 1993 MVH study scoring algorithm, the HSE 2014 health state profiles and the ALDVM model by Hernandez Alava *et al.* (2022).

5.3.2 Uncaptured benefits

In CS, Section 3.13, the company describes several areas where it believes there are benefits which are not captured in the QALY calculations. These include the provision of a treatment that provides EFS and OS benefits in a disease that has seen few advancements over the last 20 years and where there are limited treatment options, especially for recurrent disease. However, the EAG considers that these aspects of the current care pathway and the potential benefits of pembrolizumab on EFS and OS are captured within the QALY calculation. The CS also describes the psychological distress associated with HNSCC and the broader impact on the patient and their family including social isolation from having a visible disability which impacts on basic functions such as speaking and swallowing. The company proposes that the opportunity to use an effective treatment prior to surgery has the potential to allow surgery to be de-escalated to be more organ-sparing due to tumour downstaging. It argues this potential benefit could not be captured in the trial as de-escalation of surgery was not permitted by the trial protocol. The EAG considers that further research would be required to provide evidence to support the claim that neoadjuvant pembrolizumab has the potential to provide better HRQoL through this mechanism, and also to confirm that the recurrence and mortality risk would not be adversely affected by de-escalation. The company also proposes that there are uncaptured benefits from the lower usage of cisplatin in the pembrolizumab with SOC arm, which is likely to have a positive impact on HRQoL

due to reduced toxicity. It claims this benefit is not captured in the model due to the application of pooled utilities across treatment arms. However, it notes that the study was not formally powered to ascertain differences in cisplatin usage across trial arms. The company argues that a reduction in recurrences would impact patients and carers in terms of work productivity, employment, finances and increases in out-of-pocket expenditure. The EAG considers that any impact of reduced recurrences on patient QALYs or NHS/PSS costs should be captured in the economic model and the other aspects mentioned by the company fall outside of the NICE reference case. The company notes that patients with HNSCC experience a higher rate of suicide and that the impact of bereavement from suicide is not factored into the economic analysis. The EAG agrees that QALY losses related to bereavement falling on both carers and other family members are not captured in the company's economic analysis. However, QALY losses related to bereavement are not usually included in NICE appraisals.

5.3.3 Health inequalities

No special considerations related to equity or equality are indicated with the company's description of the decision problem (CS, Table 1). However, the company describes a number of socioeconomic, sex-based, and racial/ethnic disparities in head and neck cancer in the UK in CS, Section 1.4. These are discussed further in Section 5.3.3. Firstly, there were disparities highlighted with regard to incidence. These related to a higher incidence in males than females, a higher incidence for females in the Asian ethnic group versus females in the White ethnic group, but lower incidences overall for people of Asian, Black or mixed/multiple ethnicity, compared with those of White ethnicity, and a higher incidence for people living in the most deprived areas. People living in the most deprived areas were also likely to be diagnosed with disease at a later stage and were noted to have a higher mortality rate than those living in the least deprived areas. However, the EAG considers that these disparities are unlikely to be impacted by whether this technology is reimbursed for this indication as they mostly relate to disease incidence or delayed diagnosis. The EAG also notes that the company states in the box at the start of CS, Section 1, that "*Use of this technology is not anticipated to raise any equity or equality considerations.*"

5.4 Confidential comparator and subsequent treatment prices

The PAS discount is applied to pembrolizumab within the model regardless of whether it is used first-line or as a subsequent treatment. For the EAG analyses presented in the confidential appendix to this report, confidential prices have been used that reflect the commercial agreements for pembrolizumab, nivolumab and cetuximab.

5.5 Conclusions of the cost-effectiveness section

The EAG was satisfied that the company's model was generally well programmed and suitable for decision making, although it noted two errors which it corrected in its EAG exploratory analyses. In addition, the EAG noted that the company's model structure did not allow for time-varying transition probabilities for patients leaving the intermediate health states. The EAG considered this to be a significant limitation, although the EAG accepted that incorporating time-varying transition probabilities for the two intermediate health states would add significant complexity to the company's model and any impact on the cost-effectiveness results was uncertain. The probabilistic version of the company's base case model provides an expected ICER of £[REDACTED] per QALY gained, which was similar to the deterministic ICER (£[REDACTED]). The company's deterministic scenario analyses provided ICERs ranging from £[REDACTED] to £[REDACTED] with the choice of distributions used to model transitions from the EF state being the factor associated with the most variation in the ICERs.

Most of the EAG's exploratory analyses had minimal impact on the ICER and the ICER for the EAG's preferred base case was similar to that provided by the company's base case (£[REDACTED] and £[REDACTED] for the probabilistic and deterministic ICERs respectively). However, the EAG's critique of the company's model identified several key uncertainties that could not be fully addressed within the EAG's exploratory analyses. The first key uncertainty relates to the choice of extrapolation models used to estimate transitions from the EFS and OS health states. Whilst the ICER when using the EAG's preferred choice of models is similar to that obtained in the company's base case, the company's most pessimistic and least pessimistic model selections, explored in the company scenario analyses, demonstrate the sensitivity of the ICER to this uncertainty. The EAG also notes that whilst there was some evidence to support the plausibility of a cure assumption, the decision regarding whether to apply a cure assumption remains uncertain and the company's preferred structural implementation of the cure assumption is somewhat simplistic.

The EAG notes that there is uncertainty in the long-term efficacy of pembrolizumab in combination with SOC because the CS is based on data from the first interim analysis (IA1) of KEYNOTE-689. The CS states that the overall survival data from KEYNOTE-689 beyond year 3 is subject to a high degree of censoring and should be treated with caution. However, the choice of models for the transitions from the EF state, which are subsequently used to generate EFS and OS predictions, relies on assessing the visual fit of the various model combinations to the data available from IA1. This means that there may be uncertainty in the model selection due to the high degree of censoring in OS. If longer-term data from KEYNOTE-689 were to become available, such as data from the second interim analysis (IA2), then this would reduce the censoring in the data set, reducing the uncertainty in the OS estimates beyond 3 years. Within the CS, the company states that the KEYNOTE-689 study is ongoing and thus may

provide additional evidence in the next 12 months. The later data cut-off may therefore result in a different combination of models being selected for the transitions from the EF state which could impact the predicted efficacy of pembrolizumab with SOC, the predicted efficacy of SOC and the decision regarding the application of the cure assumption.

The EAG notes that the impact of the company's decision to employ a state-transition model structure which restricted transitions from the intermediate states to be time-invariant (i.e. employing an exponential extrapolation model with fixed hazards over time) cannot be tested within scenario analyses. It also notes that the exponential models fitted to the observed transitions from the L/SR and IRP states provide limited fits to the data, due to the constraint of a constant hazard imposed by the exponential, and that there is considerable uncertainty in the transition from the L/SR state due to the low number of events reported in KEYNOTE-689 that are available to inform this transition. The EAG partially addressed the issue of low event numbers from the L/SR state in its scenario analysis by pooling the data across arms for transitions out of these later states. The EAG also notes the uncertainty in the IRP→Death transition, with contradicting transition rates for the individual arms dependent on the method used to estimate them. The EAG addressed this issue by pooling the data across arms for the IRP→Death transition. However, it still considers the use of the exponential models to extrapolate transitions out of these states to be a limitation of the company's chosen model structure.

The EAG also considers that there is some uncertainty regarding whether rechallenge with immunotherapy agents would be offered in clinical practice to patients who have experienced a recurrence/progression after receiving neoadjuvant/adjuvant pembrolizumab. Although it is noted that the impact on the ICER of assuming no rechallenge is fairly limited, this scenario analysis does not capture the full uncertainty, which includes whether rechallenge would be more or less successful than the mix of subsequent treatments offered in KEYNOTE-689, in which only small proportion of patients in the pembrolizumab with SOC arm received immunotherapy after IRP.

Finally, the company's model assumes that mortality for adults with untreated, newly diagnosed, resectable, LA HNSCC who have PD-L1 CPS $\geq$ 1 would be the same as general population mortality in patients who survive long enough for the general population mortality rates to apply within the model. However, the company provides no evidence to support this assumption, meaning the validity of this assumption is uncertain. The EAG exploratory analyses demonstrate that applying a SMR to the general population mortality rates, to reflect the potential for a higher risk of death in long-term survivors of LA HNSCC, has the potential to increase the ICER. However, the EAG considers that uncertainty remains regarding the most appropriate SMR and this could be reduced by a more comprehensive review of the literature.

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Single Technology Appraisal

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed resectable, locally advanced, squamous cell head and neck cancer [ID6477]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 17 November 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Referencing of Table 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
It is stated in the title caption of Table 9 of the EAG report that the KEYNOTE-689 analysis sets data are derived from Section B.2.4.1, Table 7 of the Company Submission. However, the content presented in the table is actually the text from section 2.4.2.1 – 2.4.2.3 of the Company Submission.	Change the part of the caption of Table 9 from “(modified from CS, Section B.2.4.1, Table 7)” to “(modified from CS, Sections 2.4.2.1 – 2.4.2.3)”.	Minor referencing correction.	Thank you, this reference has been amended.

Issue 2 Major pathological response acronym

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.3.2 and section 3.7, the outcome of major pathological response is sometime abbreviated to mPR and sometimes abbreviated to	Change the use of the abbreviation/acronym for major pathological response to consistently be mPR.	Minor abbreviation/acronym correction.	Thank you, this error has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
mPC, which can be confusing.			

Issue 3 References to section B of the Company Submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In various sections of the EAG report, "Section B..." of the Company Submission is referenced. However, the Company Submission for this appraisal was submitted using the new STA template where there is no longer a Document A/Document B, so these references can be confusing.	Change the references to the Company Submission section B to just the section number of the document.	Minor referencing correction.	Thank you, this referencing has been amended.

Issue 4 Pembrolizumab dosing schedule

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.3 (page 74) of the EAG report states “Pembrolizumab can be given as a 400 mg IV Q6W as an alternative to the Q3W dosing schedule”. This statement is factually correct; however, the company would like to clarify that whilst pembrolizumab can be given either Q3W or Q6W in both the neoadjuvant and adjuvant setting, clinical expert opinion to the company was that Q3W would continue to be used in the neoadjuvant setting. Meanwhile, Q6W is more likely to be used in the adjuvant setting to better manage capacity constraints as outlined in the Company Submission Section 3.2.3.1.	The company propose that this sentence is amended to “In the adjuvant setting, pembrolizumab can be given as a 400 mg IV Q6W as an alternative to the Q3W.”	Provide clarification that the context of this paragraph is in relating to the adjuvant setting and pembrolizumab Q3W continues to be applied for the neoadjuvant cycles in the company model.	Thank you, the proposed amendment has been added.

Issue 5 Clarification on patients entering the economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.4 (page 75) of the EAG report states that <i>“All patients enter the model in the EF health state following diagnosis and perioperative treatment and remain in this state until recurrence of disease or death”</i>. This statement incorrectly implies that patients enter the model after having received perioperative treatment; patients enter the model following diagnosis and receive perioperative treatment (according to the treatment arm) within the EFS health state.	The company propose a minor amendment to this statement to “All patients enter the model in the EF health state <u>following diagnosis</u> and remain in this state until recurrence or progression of disease or death”.	Statement could be misleading and lead to incorrect interpretation of the company economic model.	Thank you, the sentence has been amended as proposed.

Issue 6 Definition of intermediate health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.4 (page 75) of the EAG report states “Recurrence of disease in the model is defined as either locoregional recurrence (where subsequent treatment is given with curative intent) ...”. This incorrectly states the name of the intermediate health state and definition of what it encompasses. Patients in the health state may receive subsequent treatment with curative intent, however, a proportion of patients receive no subsequent treatment in this health states which should be reflected in the definition.	The company proposes that this statement is amended to “Recurrence of disease in the model is defined as either local or salvageable recurrence (where subsequent treatment, if any, is given with curative intent) ...”.	A clarification on the definition of health states in the model to prevent misinterpretation.	Thank you, the sentence has been amended as proposed.

Issue 7 Terminology of intermediate health state

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5 (Table 17, page 78) of the EAG report contains a minor spelling error. In the table, the L/SR state is incorrectly referred to as 'LR/S' on multiple occasions. In addition, the statement "As for EFS, but pooled across patients with locoregional / salvageable recurrence" incorrectly refers to the name of the health state which should instead be "local / salvageable recurrence".	Correction of spelling error; instances of "LR/S" to be amended to "L/SR". Correction of the name of the health state from "locoregional / salvageable recurrence" to "local / salvageable recurrence".	Minor amendment of spelling and incorrect health state terminology.	The spelling error is corrected in the two instances where there was misspellings. The name of the health state is also amended.

Issue 8 Drug administration costs tariff

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5 (Table 17, page 79) of the EAG report. The source of drug administration costs in the economic model is described as “NHS Cost Collection for administration of chemotherapy as an outpatient procedure”. Furthermore, in Section 4.2.9.2 (page 128) of the EAG report states “Administration costs for neoadjuvant pembrolizumab were based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS Cost Collection 2023-2024, which is £372 when administered as an outpatient procedure”. In response to the EAG clarification question B26 the company updated the	The company propose that the statement in Table 17 is update to “NHS Cost Collection for administration of chemotherapy, weighted average of outpatient procedures and day cases.” The company propose that the statement in Section 4.2.9.2 is amendment as follows “Administration costs for neoadjuvant pembrolizumab were based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS Cost Collection 2023-2024, which is £372 as the weighted average between an outpatient procedure and day case.”	Report not reflecting the current company economic model which may result in a misinterpretation of the evidence considered in the company model.	Thank you, the two sentences have been amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
drug administration tariffs in the economic model from outpatient procedure only to a weighted average between outpatient procedures and day cases. The EAG report Section 4.2 reads that “Unless otherwise stated, it reflects the version submitted following the clarification request”, however the updated drug administration costs in response to the clarification request have not been reflected in the EAG report.			

Issue 9 Source of utility value for the IRP health state

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.5 (page 126) of the EAG report states “Secondly, the company’s	The company propose that the EAG revises this statement to correctly reflect the source of	Incorrect interpretation of company response to clarification question B16.	Thank you for clarifying this further. We have amended the text in this paragraph so it now

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
response to clarification question B16 notes that the utility value in TA172 was evaluated using data from the oral cavity subgroup, and that in TA473 it was assumed that this was reflective for all tumour site locations.” and as a result concludes that there is uncertainty with regards to this value being applicable to the population in KEYNOTE-689. The company believe that the EAG have misinterpreted the company responses to clarification question B16 and would like to clarify. Table 8 in TA473 (which restricted the EXTREME regimen to the oral cavity subgroup) contains a footnote reading “<i>The utility scores for the oral cavity subgroup were</i>	the utility values from the EXTREME trial, and subsequently their conclusion of the applicability to the population in KEYNOTE-689.		only focuses on the lack of information available from TA172/TA473 regarding the methods used.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>assumed to be the same as those for all RM SCCHN tumour locations</i>". Therefore, MSD's interpretation is that the utilities reported in TA172 represent the full HNSCC population of the EXTREME trial, and these were subsequently assumed to be applicable to the oral cavity subgroup for the purposes of TA473.			

Issue 10 Summary of utility values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.4 (page 124) in EAG report, Table 21, states the source of utility values for EF (without AEs), L/SR and IRP (pre-progression) as "EQ-5D-3L values derived from patients	The company propose this statement is updated to "EQ-5D-5L values, mapped from EQ-5D-5L, from patients directly relevant to the decision problem (from KEYNOTE-689) using UK	Provide additional clarity on the source of the utility values derived from KEYNOTE-689.	This sentence is now updated to "EQ-5D-3L values, mapped from EQ-5D-5L derived from patients directly ..."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
directly relevant to the decision problem (from KEYNOTE-689) using UK value set, in line with the NICE reference case.” For clarity, the EQ-5D-3L values were mapped from EQ-5D-5L collected in KEYNOTE-689 using the algorithm from Hernandez Alava.	value set, in line with the NICE reference case”.		

Issue 11 Health state utilities in company economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.1 (page 122) of the EAG reports states “Utility estimates were estimated using a generalised estimating equations (GEE) regression model with an independence working correlation matrix.	The company proposes that the EAG revises this paragraph in the EAG report to accurately reflect the approach for deriving health state utility values in the company base case. Additional information is provided for clarity within this response.	Incorrect description of the company base case approach to health state utility values used in the economic model.	We thank the company for providing additional information to clarify the utility values used in their base case. We have made the necessary changes in Sections 4.2.8.1 and 4.2.8.5. We also thank the company for providing the GEE estimates as

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The empirical sandwich estimator was used to calculate the standard error. This approach accounts for the repeated measures collected within the KEYNOTE-689 trial and evaluates the marginal estimates of utility values for each of the states (EF without Grade 3+ AEs, EF with Grade 3+ AEs, L/SR and IRP pre-progression)." The company base case uses descriptive utility values that do not explicitly account for repeated measures. In clarification question B22, the EAG requested the company to provide a scenario analysis in which the potential relationship between repeated measures have been accounted for. Utility values using a linear mixed-			evidence to support the similarity between the descriptive means and the GEE estimates.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
effects regression model, pooled across treatment arms, were incorporated into the company economic model and provided as a scenario analysis. However, as per the company response to clarification question B22, the descriptive values used in the company base case can be viewed as equal to using a GEE approach to account for repeated measures, which results in equivalent point estimates but with some marginal increase in variance in the instance of GEE (see Table 1 provided at the end of this document). As such, using the GEE utilities will result in no difference to the deterministic base case results compared to using the descriptive health state			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
utility values, but will have a small impact on probabilistic results due to a higher standard error.			

Issue 12 Administration costs of cisplatin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.9.2 (page 128) of the EAG report states “For the third cycle of cisplatin of the pembrolizumab + SOC arm, this was costed as a simple parenteral chemotherapy (£372) as it does not coincide with pembrolizumab, therefore one third of this cost (£124) was allocated for each cisplatin cycle.” This description does not clearly explain how cisplatin costs are applied in model,	The company propose this description is amended to “The third cycle of cisplatin in the pembrolizumab + SOC arm does not coincide with pembrolizumab administration and therefore is costed as a simple parenteral chemotherapy (£372). This is applied in the economic model by allocating one third of this cost (£124) for each cisplatin cycle.”	Rephrasing for clarification on the method of applying cisplatin administration costs in the company economic model.	Thank you, this sentence is now rephrased.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
which may cause some confusion.			

Issue 13 Issue 2: Company's choice of extrapolation models to inform EFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3 (page 6) of the EAG report, and subsequent relevant sections (Section 4.2.6.7), states that “The company’s preferred set of models to extrapolate transitions out of the EF state (Gompertz/Gompertz/gamma for EF→LR/EF→IRP/EF→death) included Gompertz curves with negative rate parameters, which results in an improper survival distribution...” and as a result the EAG selected an alternative set of models from the EF health state. Firstly, the company’s preferred set of models is incorrectly stated. The company preferred set of models uses a <u>generalized gamma</u> distribution for EF→death, not gamma as stated above. Furthermore, despite being labelled as ‘rate’ in Column F of the ‘Raw_Param Estimates’ tab (row 12 for example), the Gompertz distribution in the	The company propose that the EAG revise ‘Issue 2’ as appropriate to reflect the correct use of the log(rate) parameter of the Gompertz distribution within the model.	Incorrect interpretation of negative parameter in the Gompertz distribution resulting in incorrect identification of issue in the company model.	The one sentence where it says gamma instead of generalised gamma is now updated (Issue 2 box page 6). Thank you for the clarification on the labelling of the parameters within the ‘Raw_Param Estimates’ tab. All references to a “negative rate parameter” have been removed from

Description of problem	Description of proposed amendment	Justification for amendment	EAG response																												
economic model is parameterised using <i>the log(rate)</i>, indicated as ‘Parameter B’, which is able to take on a negative value. The company apologises for any confusion caused by this labelling. The table below clarifies the definition of each distribution parameter in the economic model: <table><tr><th>Distribution</th><th>Parameter A</th><th>Parameter B</th><th>Parameter C</th></tr><tr><td>Exponential</td><td>Log(rate)</td><td></td><td></td></tr><tr><td>Weibull and Log-logistic</td><td>Log(scale)</td><td>Log(shape)</td><td></td></tr><tr><td>Gompertz</td><td>Shape</td><td>Log(rate)</td><td></td></tr><tr><td>Long-normal</td><td>Meanlog</td><td>Log(sdlog)</td><td></td></tr><tr><td>Gamma</td><td>Log(shape)</td><td>Log(rate)</td><td></td></tr><tr><td>Generalized gamma</td><td>Mu</td><td>Log(sigma)</td><td>Q</td></tr></table>	Distribution	Parameter A	Parameter B	Parameter C	Exponential	Log(rate)			Weibull and Log-logistic	Log(scale)	Log(shape)		Gompertz	Shape	Log(rate)		Long-normal	Meanlog	Log(sdlog)		Gamma	Log(shape)	Log(rate)		Generalized gamma	Mu	Log(sigma)	Q			Sections 1.1, Issue 2 box, Section 4.2.6, and Section 5.2.2. Our concerns regarding the effective plateauing behaviour of the Gompertz models for EF→L/SR and EF→IRP have been amended accordingly in the relevant sections.
Distribution	Parameter A	Parameter B	Parameter C																												
Exponential	Log(rate)																														
Weibull and Log-logistic	Log(scale)	Log(shape)																													
Gompertz	Shape	Log(rate)																													
Long-normal	Meanlog	Log(sdlog)																													
Gamma	Log(shape)	Log(rate)																													
Generalized gamma	Mu	Log(sigma)	Q																												

Issue 14 Resource use in L/SR and IRP

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.9.11 (page 136) of the EAG report identifies the following error in the company model: “The second error was related to the frequency of resource use for the L/SR and IRP health states sourced from TA490. The EAG does not believe such a rate/probability conversion is necessary as these resources are not one-off events”. The company agrees with the EAG that these resources are not one-off events. Nevertheless, in the original source (Nash Smyth et al. 2015), the frequencies of these resources were reported in terms of percentages of patients with each resource and not in terms of the mean number of each resource. The formula	The company propose that the identification of this error is removed from the EAG report, along with relevant scenario analyses and model adjustments.	Incorrect interpretation, and identification of error, in the company calculation to estimate the frequency of resource use in the L/SR and IRP health states.	The EAG does not think the company’s approach is accurate as the model already limits the resource use to 1 for those sourced from Nash Smyth et al. (column H57:H65 of ‘Raw – HCRU’ sheet, same for columns J and L) making it redundant and so the frequency needs to be reflected in proportions of patients. The company’s approach treats resource use as a probability of an event (i.e. limiting it between 0-1). On the other hand, the EAG’s approach allows for multiple use of resources within a cycle (i.e. allows for values >1), regardless of its length. As the EAG’s position on this has not changed, no

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
used in the company model reflects the proper conversion from monthly to weekly percentages of patients: • The original monthly percentages of patients from Nash Smyth et al. are converted into monthly rates • The monthly rates are divided by the number of weeks in a month to obtain weekly rates • The weekly rates are converted back into weekly percentages of patients Therefore, the company do not believe there to be an error in the calculation of resource use frequency for the L/SR and IRP health states.			amendment has been made to the report. However, the EAG notes that the correction it has made has minimal impact on the cost-effectiveness results (see EAG report Table 32).

(please cut and paste further tables as necessary)

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.2.9.1 page 128; <i>“....There is currently a Patient Access Scheme (PAS) discount in place for pembrolizumab....”</i> <u>MSD requests the complete removal of all commercially sensitive information from the EAG report to minimise risk of unintended accidental distribution.</u>	The discount and net price for pembrolizumab is stated in the EAG report. The company request that all information related to confidential pricing (i.e. discount and net price) for pembrolizumab is removed from the report in its entirety due to the high level of confidentiality and commercial sensitivity.	“There is currently a Patient Access Scheme (PAS) discount in place for pembrolizumab which is accounted for the economic model. The NICE AC should refer to Table 54 in Appendix I of the company submission for more information around this.”	The EAG has amended the text to say, “There is currently a Patient Access Scheme (PAS) discount in place for pembrolizumab which is accounted for the economic model. The NICE Committee should refer to Table 54 in Appendix I of the company submission for more information.”

(Please add further lines to the table as necessary)

Addendum: Health state utilities using Generalised Estimating Equations (GEE)

Health state utilities values using the Generalised Estimating Equations (GEE) approach to account for repeated measures is presented in **Table 1** below. The summary statistics presented are calculated using multiple records per participant, treating each record as independent while employing GEE with an independent working correlation structure. A robust sandwich variance estimator is utilised to compute standard errors.

Table 1. Health state utility values derived from KEYNOTE-689 using GEE

Health state	Patients, n	Records, m	EQ-5D-3L		Source
			Value	SE	
EF (without grade 3+ AEs)	■	■	■	■	KEYNOTE-689 IA1 (all comers)
EF (with grade 3+ AEs)	■	■	■	■	
L/SR	■	■	■	■	
IRP	■	■	■	■	

Abbreviations: AE: Adverse events; EF, event-free; IRP, incurable recurrence/progression; L/SR, local or salvageable recurrence; SE, standard error.

N = Number of participants with non-missing EQ-5D score

M = Number of records with non0missing EQ-5D score

With Grade 3+AE is referring to the duration of a single AE episode that started as or worsened into grade 3 or worse during that episode regardless of the starting and ending severity grade within the BICR-free health state

Database Cutoff Date: 25JUL2024