18 September 2025
EMADOC-1700519818-2242654
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMA/VR/0000245108

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
1L	first-line
2L	second-line
ADA	antidrug antibody
AE	adverse event
AEOSI	adverse event(s) of special interest
APaT	all participants as treated
BICR	blinded independent central review
BIPR	blinded independent pathological review
CI	confidence interval
CPS	combined positive score
CR	complete response
CRT	chemoradiotherapy
CSR	clinical study report
DFS	disease-free survival
DILI	drug-induced liver injury
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FU	fluorouracil
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HRQoL	health-related quality of life
IA1	first interim analysis
IHC	immunohistochemistry
IHC	immunohistochemistry
ITT	intention-to-Treat
IV	intravenous
KM	Kaplan-Meier
LA	locoregionally advanced
mAb	monoclonal antibody
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities

mPR	major pathological response
NCCN	National Comprehensive Cancer Network
NR	not reached
OS	overall survival
pCR	pathological complete response
PD-1	programmed death 1 receptor
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	pathological response
PRO	patient-reported outcome
PT	preferred term
pTR	pathologic tumor response
Q3W	every 3 weeks
Q6W	every 6 weeks
QLQ	quality of life questionnaire
QoL	quality of life
R/M	recurrent/metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	relapse free survival
RSD	reference safety dataset
RSI	reference safety information
RT	radiation therapy
SAE	serious adverse events
SCC	squamous cell carcinoma
SoC	standard of care
sSAP	supplemental statistical analysis plan
TE	pathologic treatment effect
TPS	tumor proportion score
US	United States
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 08 January 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include, KEYTRUDA as monotherapy, for the treatment of resectable locally advanced head and neck squamous cell carcinoma (HNSCC) as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without platinum-containing chemotherapy and then as monotherapy in adults, based on the results of study P689V01MK3475 (KEYNOTE-689); this is a Phase 3, randomised, open-label study evaluating pembrolizumab as neoadjuvant therapy and in combination with standard of care as adjuvant therapy for stage III or IVA, resectable, locoregionally advanced head and neck squamous cell carcinoma. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 48.1 has also been submitted. In addition, the MAH took the opportunity to introduce some minor editorial changes to the PI.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0043/2018 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH sought Scientific Advice at the CHMP (EMEA/H/SA/2437/20/2017/II, 20 July 2017) see 2.1.3. for more details.

International collaboration

The European Medicines Agency was an observer of the review conducted under the FDA project Orbis for this indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	08/01/2025
Start of procedure:	26/01/2025
CHMP Rapporteur Assessment Report	25/03/2025
PRAC Rapporteur Assessment Report	27/03/2025
PRAC Outcome	10/04/2025
CHMP members comments	14/04/2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17/04/2025
Request for supplementary information (RSI)	25/04/2025
CHMP Rapporteur Assessment Report	25/06/2025
PRAC Rapporteur Assessment Report	26/06/2025
PRAC Outcome	10/07/2025
CHMP members comments	14/07/2025
Updated CHMP Rapporteur Assessment Report	17/07/2025
Request for supplementary information (RSI)	24/07/2025
CHMP Rapporteur Assessment Report	28/08/2025
CHMP members comments	08/09/2025
Updated CHMP Rapporteur Assessment Report	12/09/2025
Opinion	18/09/2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

State the claimed the therapeutic indication

The initially proposed indication was:

KEYTRUDA as monotherapy is indicated for the treatment of resectable locally advanced HNSCC as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as monotherapy in adults.

The final agreed indication as adopted by CHMP is:

KEYTRUDA as monotherapy is indicated for the treatment of 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 whose tumours express PD-L1 with a CPS ≥ 1.

Epidemiology, risk factors, biologic features and pathogenesis

Head and neck cancer is the sixth most common cancer worldwide[1], the most frequent (over 90%) histological subtype being head and neck squamous cell carcinoma (HNSCC). These tumours consist of a group of carcinomas of the lip, oral cavity, pharynx, larynx, paranasal sinuses, or salivary glands[2]. Based on GLOBOCAN estimates, in 2022 in Europe there were 148,262 new cases and 65,685 deaths of head and neck cancers[3]. The age-standardized incidence (per 100,000) ranges by region, from 8.6 (Southern Europe) to 11.9 (Eastern Europe)[3]. The most common tumor sites are lip and oral cavity (42%), larynx (27%), oropharynx (20%), and hypopharynx (11%)[4].

Alcohol and tobacco are the main risk factors for cancers of the oral cavity, larynx, oropharynx, and hypopharynx and account for around 75% of HNSCC[5,6]. HPV infection is a main risk factor for oropharyngeal cancer. The incidence of HPV induced HNSCC varies from <10% to 70% of all oropharyngeal cancers depending on the geographic area, being more frequent in industrialized

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229-63.
[2] Gormley M, Creaney G, Schache A, Ingarfield K, Conway DI. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. Br Dent J. 2022 Nov 11;233(9):780-6.
[3] Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c1965-2024. Head and neck cancer, incidence, both sexes, in 2022; cited [2024 Oct 16]; [about 4 screens]. Available from: https://gco.iarc.fr/today/home.
[4] Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c1965-2024. Incidence, both sexes, in 2022 - Europe; [cited 2024 Oct 22].
[5] Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, risk factors, and prevention of head and neck squamous cell carcinoma. Med Sci. 2023 Jun 13;11:42.
[6] Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009 Feb;18(2):541-50.

countries[7]. Increased incidence of oropharyngeal cancer in North America and Western Europe is mostly related to increased HPV prevalence. HPV associated cancer are usually seen in younger and healthier individuals with little or no tobacco exposure, having better survival than traditional tobacco-associated cancers[8].

Clinical presentation and stage/prognosis

Around 50% of patients with HNSCC are diagnosed at a locally advanced (LA) stage[9]. According to ESMO Clinical Practice Guidelines for head and neck cancers (2020), locally advanced (LA) disease is defined as either stage III or IV oral cavity, larynx, hypopharynx and p16-negative oropharyngeal cancer as defined by the UICC TNM 8th edition. For p16-positive oropharyngeal cancer, LA disease corresponds to stages T3-4/N0-3 and T0-4/N1-3, also according to the UICC TNM 8th edition.

The 5-year OS rate of resectable locally advanced HNSCC is around 40-50%, despite multimodal treatment consisting of surgery followed by post-operative RT with or without platinum-containing chemotherapy[10,11,12]. Considering that HPV positive HNSCC is generally associated with a better prognosis than HPV negative disease, treatment de-escalation strategies for HPV positive HNSCC are being evaluated in ongoing clinical trials, but largely remain investigational, thus, to date, the treatment for participants with HPV positive LA HNSCC is generally consistent with the one of patients with HPV negative disease.

The most common primary tumor site locations in prior Phase 3 randomized controlled adjuvant studies RTOG9501[13,14] and EORTC 22931[15,] which both compared CRT versus RT as postoperative treatment for resected LA HNSCC, were the oral cavity or oropharynx followed by larynx and then hypopharynx[16].

Management

The objective of any treatment strategy for HNSCC is to achieve the highest possible cure rate with the lowest risk of morbidity. The optimal treatment strategy must be discussed in a multidisciplinary team and patients should be treated at high-volume facilities, as this has been reported as a strong and significant prognostic factor.

[7] Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022 May;19:306-27.
[8] Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015 Oct 10;33(29):3235-42.
[9] Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, risk factors, and prevention of head and neck squamous cell carcinoma. Med Sci. 2023 Jun 13;11:42.
[10] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005 Oct;27:843-50.
[11] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350(19):1937-44.
[12] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350(19):1945-52.
[13] Cooper JS, Pajak TF, Forastiere AA, et al; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004 May 6;350(19):1937-44.
[14] Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1198-205.
[15] Bernier J, Domenge C, Ozsahin M, et al; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004 May 6;350(19):1945-52.
[16] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005 Oct;27:843-50.

According to ESMO guidelines[17], the treatment choice for LA HNSCC depends on the location of the primary tumor, the stage of the disease, and the expected oncological and functional outcomes. Patients are generally classified in resectable and non-resectable. Standard options for LA HNSCC are either surgery plus adjuvant (chemo)radiotherapy [(C)RT] or primary CRT alone. The surgical option includes reconstruction plus risk-adapted postoperative RT or CRT. According to ESMO Guidelines, "primary surgical treatment is recommended for T3/T4 oral cavity and T4 laryngeal cancers. Advanced hypopharyngeal cancers may also be treated surgically, especially when there is laryngeal cartilage invasion (i.e. stage T4) or a non-functional larynx. Treatment of advanced oropharyngeal lesions is currently non-surgical for both HPV-positive and -negative disease, but surgery can be employed if RT is contraindicated". Primary combined concomitant CRT is the standard treatment in non-resectable patients and is also indicated in resectable patients when the anticipated functional outcome and/or the prognosis is so poor that mutilating surgery is not justified. When a surgical option is preferred as the primary treatment modality, postoperative RT may be required to decrease the risk of locoregional recurrence, for which several risk factors have been identified (e.g. pT3-4, close or positive resection margins, perineural infiltration, lymphovascular spread, >1 invaded lymphnodes, extracapsular nodal infiltration).

For patients with resectable LA HNSCC, neoadjuvant treatment or adjuvant treatment beyond radiation with or without cisplatin, remain investigational to date.

2.1.2. About the product

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

In the EU, KEYTRUDA was granted first approval by the European Commission on 17-JUL-2015 for patients with advanced melanoma, and it is currently approved for several indications in solid tumours.

For the indication of HNSCC, pembrolizumab is already approved for the following:

- 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 HNSCC in adults whose tumours express PD L1 with a CPS ≥1.
- KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PDL1 with a ≥50% TPS and progressing on or after platinum-containing chemotherapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Table 1: Overview of the Pembrolizumab Clinical Development Program in Resectable LA HNSCC

Study Number (Status)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary Endpoint(s)
KEYNOTE-412 (completed)	A randomized Phase 3 study of pembrolizumab given concomitantly with chemoradiation and as maintenance therapy versus	804 participants were randomized (402 in pembrolizumab + CRT followed by pembrolizumab group, 402 in	Gender: 660 M/144 F	EFS

[17] Machiels JP, Rene Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(11):1462-75.

Study Number (Status)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary Endpoint(s)
	chemoradiation alone in subjects with locally advanced head and neck squamous cell carcinoma (KEYNOTE-412)	placebo + CRT followed by placebo group)	Median age: 59.0 years	
KEYNOTE-689 (ongoing)	A Phase 3, randomized, active-controlled, multisite, open-label study of pembrolizumab as neoadjuvant therapy and pembrolizumab in combination with SoC RT ± cisplatin as post-surgical adjuvant therapy in treatment naïve participants with newly diagnosed Stage III-IVA, resectable LA HNSCC	714 participants with Stage III-IVA resectable LA HNSCC were randomized in a 1:1 ratio to receive either neoadjuvant therapy with pembrolizumab and adjuvant therapy with pembrolizumab in combination with SoC RT ± cisplatin followed by pembrolizumab monotherapy (N=363), or no neoadjuvant therapy prior to surgical resection and adjuvant therapy with SoC RT ± cisplatin (N=351)	Gender: 563 M/151 F Median age: 60.0 years	EFS in CPS ≥10, CPS ≥1, and all participants
CPS=combined positive score; CRT=chemo radiotherapy; EFS=event-free survival; F=female; HNSCC=head and neck squamous cell carcinoma; LA=locally advanced; M=male; RT=radiotherapy; SoC=standard of care.				

CHMP Scientific Advice was sought (EMEA/H/SA/2437/20/2017/II, 20 July 2017). The CHMP generally agreed with the proposed patient population, stratification factors, endpoints, statistical aspects, although highlighted that the study as designed would not allow to disentangle the contribution of the neoadjuvant to the adjuvant phases. An alternative design with second randomization after surgery was discussed and considered feasible by CHMP despite the increase of the sample size. Further, comment was raised on taking decision on subsequent, well established adjuvant chemo-radiotherapy based on pembrolizumab induced response. The duration of the adjuvant pembrolizumab was also considered not sufficiently justified.

A pre-submission meeting with EMA and (Co)Rapporteurs was held on 3 Dec 2024 to discuss the content of the planned Type II submission.

2.1.4. General comments on compliance with GCP

The assessment of the data has not raised concerns on the conduction according to GCP of the pivotal clinical trial.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular overview of clinical studies

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
[Ref. 5.3.5.1: P689V01MK3475]	3	Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Ireland, Israel, Japan, Poland, Portugal, Russia, South Korea, Spain, Switzerland, Taiwan, United Kingdom, United States of America and Ukraine	A Phase III, randomized, open-label study to evaluate pembrolizumab as neoadjuvant therapy and in combination with standard of care as adjuvant therapy for stage III-IVA resectable locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC)	randomized, double-open-label, active-controlled without placebo	Pembrolizumab Group: pembrolizumab: 200 mg IV q3w up to 17 cycles; cisplatin: 100 mg/m^2 q3w for 3 cycles; radiotherapy: low-risk participants: 2 Gy/day in 30 fractions for a total of 60 Gy; high-risk participants: 2 Gy/day in 33 fractions for a total of 66 Gy; participants with gross residual disease: 2 Gy/day in 35 fractions for a total of 70 Gy. SoC Group: radiotherapy: low-risk participants: 2 Gy/day in 30 fractions for a total of 60 Gy; high-risk participants: 2 Gy/day in 33 fractions for a total of 66 Gy; participants with gross residual disease: 2 Gy/day in 35 fractions for a total of 70 Gy; cisplatin: 100 mg/m2 IV; q3w for 3 cycles	Males/females Age: 22-87 years old; participants with Stage III-IVA resectable locoregionally advanced head and neck squamous cell carcinoma	Pembrolizumab Group: Pembrolizumab 200 mg: 361 participants cisplatin:100 mg/m^2 : 107 participants radiotherapy: 2 Gy/day: 274 participants SoC Group: pembrolizumab 200 mg: 1 participant cisplatin: 100 mg/m^2 : 139 participants radiotherapy: 2 Gy/day: 275 participants

2.3.2. Discussion on clinical pharmacology

A substantial characterization of the PK and immunogenicity of pembrolizumab have been provided in previous submissions, therefore no new clinical pharmacology analyses beyond those conducted previously have been generated. The description of the pharmacology of pembrolizumab in combination with chemotherapy in metastatic/locally advanced settings and the characterization of pembrolizumab immunogenicity in adjuvant settings were included in previous submissions. These analyses demonstrated that the PK and immunogenicity of pembrolizumab are not impacted by concomitant chemotherapy and the ADA incidence rates for pembrolizumab in the adjuvant setting are similar to the ADA incidence rates observed in metastatic/locally advanced settings.

An additional dosing regimen of 400 mg IV Q6W has been approved globally across various indications. These approvals were based on the expected similarity of PK exposures, target saturation, efficacy, and safety profile with those for the approved dosing regimen of 200 mg Q3W or 2 mg/kg Q3W. Based on the robust understanding of pembrolizumab clinical pharmacology and its well-established flat E-R profiles over a 5-fold dose range, the safety and efficacy of the 400 mg Q6W dosing regimen is expected to be similar to the approved 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in all treatment settings.

2.3.3. Conclusions on clinical pharmacology

No new clinical pharmacology analyses beyond those conducted previously have been generated. A substantial characterization of the PK and immunogenicity of pembrolizumab has been provided in previous submissions.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

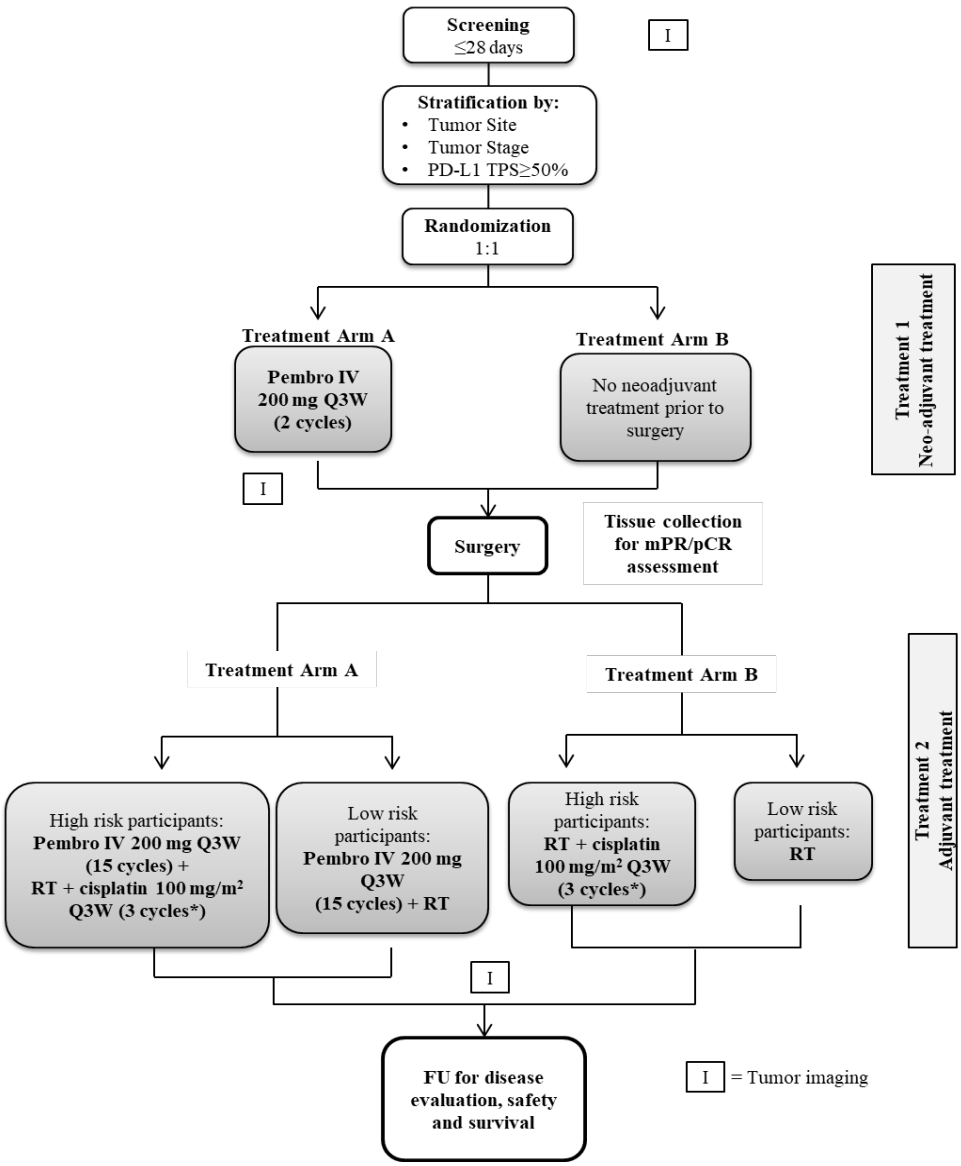
No dose-response studies were submitted as part of this application.

2.4.2. Main study(ies)

KEYNOTE-689*:* A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care

as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)

Figure 1: study design



*If there were delays in cisplatin treatment, cisplatin may have been continued for up to 1 week following completion of RT. Local pathology results were used to guide treatment decision.
Abbreviations: FU=follow-up; IV=intravenous; mPR=major pathological response; pCR=pathological complete response; PD-L1=programmed cell death ligand 1; Pembro=pembrolizumab; Q3W=every 3 weeks; RT=radiotherapy; TPS=tumor proportion score.

Methods

Study participants

Key Inclusion criteria

1. Had histologically confirmed new diagnosis of resectable, non-metastatic, squamous cell carcinoma as assessed by the Investigator based on baseline imaging and clinical assessment, with staging conducted using the AJCC Staging Manual, 8th edition, that is either:

a. Stage III oropharyngeal p16 positive that is T4 (N0-N2), M0, OR

b. Stage III or IVA oropharyngeal p16 negative, OR

c. Stage III or IVA larynx/hypopharynx/oral cavity (independent of p16).

Note: Prior surgical debulking, including tonsillectomy, for the head and neck cancer under study is not allowed.

2. Was eligible for primary surgery based on investigator decision and per local practice. This decision must be validated by members of a multidisciplinary team, including the surgical oncologist, medical oncologist and radiation oncologist.
3. Male/female participants who are at least 18 years of age
4. Had evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by CT scan or MRI, based on RECIST 1.1 as assessed by the local site investigator/radiology
5. Had provided newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for central PD-L1 biomarker analysis from a core or excisional biopsy (FNA was not adequate) for stratification prior to randomization
6. Have results from (local) testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using standard protocol (positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells). If local p16 testing results are not available, a tumor tissue sample must be submitted for p16 testing at the designated central laboratory
7. Had an ECOG performance status of 0 to 1 performed within 10 days of randomization
8. Had adequate organ function as defined in the protocol
9. Female participant not pregnant and not breastfeeding
10. Followed appropriate contraception as detailed in the protocol

<u>Key Exclusion criteria</u>

1. Had Stage T4B and/or N3 LA HNSCC and/or distant metastases.
2. Had cancer outside of the oropharynx, larynx, and hypopharynx or oral cavity, such as nasopharyngeal, sinus, other para-nasal, or other unknown primary HNC.
3. Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
4. Had received prior radiotherapy treatment or systemic anticancer therapy including investigational agents for the HNC under study prior to randomization/allocation.
5. Had received a live vaccine within 30 days prior to randomization.
6. Had a diagnosis of immunodeficiency or is receiving systemic steroid therapy (>10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.
7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., in situ cervical cancer or breast carcinoma) that have undergone potentially curative therapy are not excluded.

8. Had Grade 3-4 bleeding due to the underlying malignancy.
9. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy is allowed.
10. Had previous allogeneic tissue/solid organ transplant.
11. Had a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis, had an active infection requiring systemic therapy
12. Had a known history of HIV infection, known history of or is positive for Hepatitis B or known active Hepatitis C.
13. Had a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of investigator

Treatments

Group A (Pembrolizumab group): Pembrolizumab 200 mg IV Q3W (2 cycles) as neoadjuvant therapy followed by surgical resection and then continued as adjuvant treatment (3 cycles) in combination with SoC RT ± cisplatin 100 mg/m^2 IV Q3W (3 cycles) followed by pembrolizumab monotherapy (12 cycles) as maintenance.

Group B (SoC group): No neoadjuvant therapy prior to surgical resection and adjuvant therapy with SoC RT ± cisplatin (3 cycles).

Criteria for treatment discontinuation: Treatment continued until PD were verified by BICR, initiation of a new anticancer treatment, pregnancy, death, withdrawal of consent, study conclusion or early termination, whichever occurs first. A participant only discontinued from neoadjuvant treatment if PD precluded surgery.

Adjuvant part: After surgery, patients were classified locally in **Low Risk** or **High Risk**. High-risk of recurrence is based on the pathological features i.e., positive margins (< 1 mm) or extranodal extension in the surgical specimen, assessed by the local pathologist.

RT: IMRT was mandatory. It was recommended that RT started within 6 weeks after surgery. RT was given as follows:

- Low-risk participants: 2 Gy/day in 30 fractions for a total of 60 Gy
- High-risk participants: 2 Gy/day in 33 fractions for a total of 66 Gy
- Participants with gross residual disease: 2 Gy/day in 35 fractions for a total of 70 Gy

Three doses of **cisplatin** were administered to high-risk participants, in both treatment arms. Three doses of cisplatin were permitted in those participants who did not undergo planned surgery and proceeded directly to salvage CRT.

Tumor assessment: Tumor imaging was strongly preferred by CT with contrast. MRI was used when CT was contraindicated or when mandated by local practice, or for brain imaging. The same imaging technique should be used in a participant throughout the study.

Participant eligibility was determined by investigator assessment based on RECIST 1.1. All images were submitted to the central imaging vendor for BICR. When the investigator identified radiographic progression per RECIST 1.1, images were submitted for verification of progression by BICR.

Initial tumor imaging at screening was performed within 28 days prior to the date of randomization. For participants in the pembrolizumab arm (Arm A), the first on-study imaging assessment was performed after completion of 2 cycles of pembrolizumab, before surgery. In the SoC arm (Arm B), the screening imaging served as the pre-surgery imaging. The first post-surgery imaging was performed 12 weeks after the end of RT ± cisplatin. Subsequent tumor imaging was performed every 3 months, or more frequently if clinically indicated, until end of Year 3 after randomization, then every 6 months until end of Year 5.

Objectives and endpoints

Objective/Hypothesis	Endpoint
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 tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. • Hypothesis #1: EFS in participants whose tumors express PD-L1 CPS≥10 • Hypothesis #2: EFS in participants whose tumors express PD-L1 CPS≥1 • Hypothesis #3: EFS in all participants	**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. *Exception: Participants who undergo a definitive biopsy of the progressed lesion and are found to have no histologic evidence of invasive cancer will not meet criteria for an event.
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 tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. • Hypothesis #4: mPR at the time of surgery in participants whose tumors express PD-L1 CPS≥10 • Hypothesis #5: mPR at the time of surgery in participants whose tumors express PD-L1 CPS≥1 • Hypothesis #6: 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 tumor specimen and all sampled regional lymph nodes

Objective 3: To compare pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to OS in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. • Hypothesis #7: OS in participants whose tumors express PD-L1 CPS≥10 • Hypothesis #8: OS in participants whose tumors express PD-L1 CPS≥1 • Hypothesis #9: OS in all participants	**OS** – time from the date of randomization to the date of death due to any cause
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 tumors express PDL1 CPS≥10, CPS≥1, and in all participants regardless of CPS status.	**pCR** – having no residual invasive squamous cell carcinoma within the resected primary tumor 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 tumors 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
Exploratory	
Objective 7: To compare pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy to only RT ± chemotherapy as adjuvant therapy, with respect to: - Local Regional Control - Distant Metastases-Free Survival (DMFS) - Incidence of second Head and Neck and Other Cancers	• Local regional control-time from date of randomization to the date of first record of radiographic disease progression (exceptions specified in protocol), local recurrence as assessed with imaging or biopsy as indicated • DMFS – time from date of randomization to the date of first record of appearance of distant metastasis or death due to any cause • Number of second Head and Neck and Other Cancers
Objective 8: To compare EFS and OS between participant who receive pembrolizumab neoadjuvant	• EFS – time from the date of randomization to the date of first record of any of the

therapy and pembrolizumab with RT ± cisplatin as adjuvant therapy and participants who receive only RT ± cisplatin as adjuvant therapy in: - High risk participants - Low risk participants	following events: radiographic disease progression (exceptions specified in protocol), radiographic disease progression during the neoadjuvant phase that precludes surgery, local or distant 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 • OS – time from date of randomization to date of death due to any cause
Objective 9: To characterize health utilities in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status	EuroQol-5 dimensions (EQ-5D-5L)
Objective 12: To compare pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to mPR, EFS, and OS in participants whose tumors express CPS ≥50.	• mPR– having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes • EFS– time from the date of randomization to the date of first record of any of the following events: radiographic disease progression (exceptions specified in protocol), local or distant progression or recurrence, as assessed with imaging or biopsy as indicated, death due to any cause • OS– time from date of randomization to date of death due to any cause
Objective 13: to compare pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy on the rate of in situ carcinoma /dysplasia observed in surgically resected specimens.	The presence of in situ carcinoma or dysplasia present in any of the surgically resected specimens from the primary tumor site and/or neck lymph nodes.

Sample size

Sample size calculation was based on the following assumptions:

- EFS is the primary endpoint;
- the overall type I error is strongly controlled at alpha = 2.5% (one-sided)
- alpha = 2.5% is initially allocated to the hypothesis for EFS in participants whose tumors express PD-L1 CPS≥10;
- the alpha is shifted by using the graphical approach of Mauer and Bretz [Maurer, W. 2013] across the primary endpoints (EFS) and key secondary endpoint (mPR and OS) and across multiple populations (PD-L1 CPS≥10, PD-L1 CPS≥1, all participants);
- the enrolment duration is assumed to be 58 months, and the yearly drop-out rate is assumed to be 5% for both arms;

- two IAs for efficacy are planned (IA1: inferential analysis for EFS, mPR and OS; IA2: inferential analysis for EFS and OS; FA: inferential analysis for OS) (IA2 is the final analysis for EFS);
- Group sequential methods are used to allocate alpha among the interim and final analyses;
- bounds and boundary properties for each analysis of EFS (as well as for OS) are derived by using the Lan-DeMets O'Brien-Fleming α-spending function based on information fraction.

The duration of EFS in the SoC arm is assumed to follow a Poisson mixture model with ~34% of participants achieving excellent long-term results (i.e., cure rate of 34%), a cumulative EFS rate of 90% at 4 months and 42% at 34 months based on historical data [Cooper, J. S., et al 2004].

The EFS hypothesis testing strategy was designed for α=0.025 (one-sided) and power of 94.9% to detect a HR of 0.62 with 232 EFS events for participants whose tumors express PD-L1 CPS≥10 at IA2 (the final EFS analysis). In addition, at α=0.025 (one-sided), the EFS hypothesis for participants whose tumors express PD-L1 CPS≥1 yields 91.2% power to detect a HR of 0.70 with 354 events at IA2; EFS hypothesis for all participants yields 92.5% power to detect a HR of 0.70 with 371 events at IA2.

The duration of OS in the SoC arm is assumed to follow a Poisson mixture model (Appendix 9) with ~34% of participants achieving excellent long-term results (ie, cure rate of 34%), a cumulative OS rate of 95% at 4 months and 49% at 49 months based on historical data [Cooper, J. S., et al 2004].

At α =0.0245 (one-sided), the final OS hypothesis for participants whose tumors express PD-L1 CPS≥10 test yields 84.9% power to detect a HR of 0.65 with 201 deaths observed; the final OS hypothesis for participants whose tumors express PD-L1 CPS≥1 yields 69.7% power to detect a HR of 0.75 with 309 events; and the final OS hypothesis for all participants yields 71.9% power to detect a HR of 0.75 with 324 deaths observed.

If the underlying mPR rate in the SoC arm is 2%, based on 462 participants whose tumors express PD-L1 CPS≥10, the study has approximately >99.9% power to detect a true mPR rate difference of 25 percentage points, at alpha = 0.0005 (one-sided). Based on 680 participants whose tumors express PD-L1 CPS≥1, the study has approximately >99.9% power to detect a true mPR rate difference of 20 percentage points, at alpha = 0.0005 (one-sided). Under the same assumptions, 714 all participants will result in higher power to detect a true mPR rate difference of 20 percentage points.

Power and IA calculations for EFS and OS were performed using the gsDesign R package.

Randomisation

Participants were randomized in a 1:1 ratio between the two treatment arms, stratified by:

- primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx)
- tumor stage (III vs. IVA)
- PD-L1 status (TPS ≥50% vs. TPS <50%).

The stratification factor PD-L1 status was introduced with protocol Amendment 04 (17 June 2019); specifically, it substituted the third stratification factor of the original protocol (HPV p16 status: Oropharynx – p16 positive vs. Oropharynx – p16 negative or larynx/hypopharynx/oral cavity HNSCC).

The sponsor generated the randomization allocation schedule(s) for study treatment assignment, and the randomization was implemented centrally using an interactive voice response system/integrated web response system (IVRS/IWRS).

Blinding (masking)

This is an open-label trial. Therefore, the Sponsor, investigators and participant were aware of the study treatment administered.

The participant-level PD-L1 biomarker results was masked in the database to the investigator.

Imaging and pathology data for the planned study analyses were centrally reviewed by independent radiologist(s) and pathologist(s), respectively, without knowledge of participant treatment assignment.

Rules for managing results of planned interim analyses were pre-defined, and the extent to which individuals are unblinded with respect to results of interim analyses are planned to be documented by the unblinded team.

Additional documents provided detailed the process and the responsibility concerning data collection and data analysis established to guarantee not disclosing the results of unblinded analyses to the study team or other individuals at the study sponsor who are not part of the executive oversight committee.

Statistical methods

Strata: Stratified statistical methods (stratified log-rank test, stratified Cox model, and stratified Miettinen & Nurminen method) were used for the analysis of efficacy endpoints. Starting from strata used at randomization, if small strata were observed, these strata were planned to be combined for the purpose of analyses to ensure a sufficient number of participants, responses or events in each stratum. For participants randomized prior to Amendment 04 for whom the stratification factor for PD-L1 status was not collected at randomization, the TPS raw score was used retrospectively to derive the stratification factor for PD-L1 status in the analyses. As reported in the sSAP, based on a blinded review conducted prior to IA1, four strata were obtained for the stratified analysis:

- Hypopharynx/oropharynx/oral cavity and Stage III
- Hypopharynx/oropharynx/oral cavity and Stage IVA
- Larynx and Stage III
- Larynx and Stage IVA

The same strata were used for the stratified analyses for EFS, OS, and mPR in CPS≥10, CPS≥1, and ITT populations.

EFS: The EFS curve in each treatment group was estimated by the non-parametric Kaplan-Meier method. The treatment difference in EFS was assessed by the stratified log-rank test and the p-value was provided. A stratified Cox proportional hazard (PH) model with Efron's method of tie handling with a single treatment covariate was used to assess the magnitude of the treatment difference (i.e., HR) between the treatment arms. The HR and its 95% CI were reported.

The strata defined for statistical analyses were applied to both the stratified log-rank test and the stratified Cox model.

Since PD (disease progression)/recurrence is assessed periodically, PD/recurrence can occur at any time in the time interval between the last assessment where the event was not documented and the assessment when the event is first documented. The true date of PD/recurrence was approximated by the date of the first assessment at which the event is objectively documented.

The primary analysis follows the intention-to-treat principle.

The censoring rules for primary and sensitivity analyses are summarized in table below:

Table 3: censoring rules for primary and sensitivity analyses of EFS

Situation	Primary Analysis	Sensitivity Analysis
PD, recurrence, or death documented after ≤ 1 missed disease assessment and before new anticancer therapy, if any	EFS event at date of documented PD, recurrence, or death	EFS event at date of documented PD, recurrence, or death
PD, recurrent or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anticancer therapy, if any	EFS event at date of documented PD, recurrence, or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed visits and new anticancer therapy, if any
No PD, no recurrence and no death; and new anticancer therapy is not initiated	Censored at last disease assessment	Censored at last disease assessment
No PD, no recurrence and no death; new anticancer therapy is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer therapy
Abbreviations: EFS = event-free survival; PD = progressive disease.		

OS: The non-parametric Kaplan-Meier method was used to estimate the survival curves. The treatment difference in survival was assessed by the stratified log-rank test. A stratified Cox PH model with Efron's method of tie handling and a single treatment covariate was used to assess the magnitude of the treatment difference (i.e., HR). The HR and its 95% CI were reported. Participants without documented death at the time of analysis were censored at the date the participant was last known to be alive.

mPR: The stratified M&N method (Miettinen & Nurminen, 1985) with strata weighting by sample size was used for the comparison of mPR rates (proportions of participants with an mPR) between the pembrolizumab arm and the SoC arm. The strata obtained for statistical analyses were applied to the stratified Miettinen & Nurminen's. Participants who were discontinued from the study treatment and continue with other neoadjuvant treatment not specified by the study prior to definitive surgery, were classified as not having an mPR (non-responders) in the efficacy analyses, regardless of the results obtained from the surgery. Participants who were discontinued from study treatment due to reasons that precluded surgery were also considered non-responders.

Interim analyses: Two IAs and the FA were planned for efficacy in the last version of the protocol/sSAP:

• IA1:

- Timing: ~207 EFS events in participants whose tumors express PD-L1 CPS≥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

• IA2:

- Timing: ~232 EFS events in participants whose tumors express PD-L1 CPS≥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

• FA:

- Timing: ~201 deaths in participants whose tumors express PD-L1 CPS≥10 and ~34 months after last participant randomized (estimated to be 92 months after the first participant is randomized).

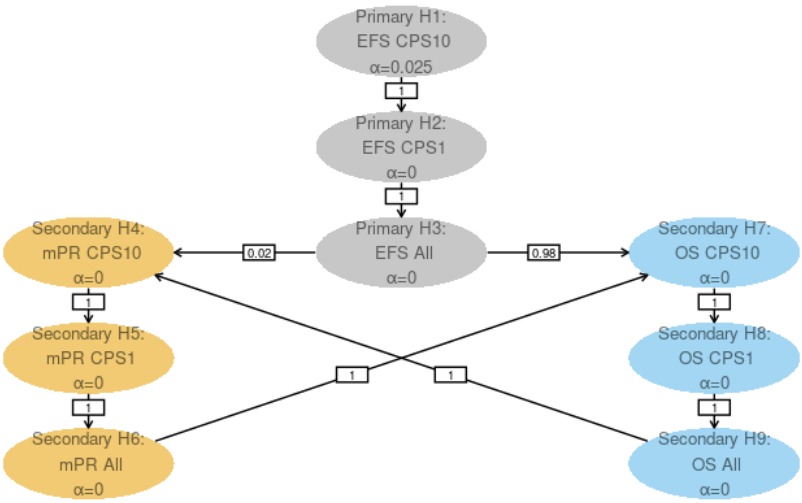
- Testing: Inferential analysis for OS.

Note that for IA1, IA2 and FA, if the EFS events or the OS events in participants whose tumors express PD-L1 CPS≥10 accrued slower than expected, the analysis would be delayed up to 3 months after the projected timing. For IA2 and FA, if the EFS events or OS events in participants whose tumors express PD-L1 CPS≥10 accrued faster than expected (i.e., ~ targeted number of events have been observed prior to the projected timing of analysis), the analysis would be conducted at least ~10 months after the timing of prior IA.

If the study was stopped early for efficacy, the study would continue to follow participants for survival update.

Multiplicity control for efficacy interim analyses: The overall Type I error across the primary endpoint (EFS) and the key secondary endpoints (mPR and OS) and across multiple populations was strongly controlled at alpha = 2.5% (one-sided), with alpha = 2.5% initially allocated to the hypothesis for EFS in participants whose tumors express PD-L1 CPS≥10 (H1). Alpha could be reallocated using the graphical approach of Mauer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control across the primary efficacy hypothesis regarding EFS, and the 2 key secondary efficacy hypotheses regarding mPR rate and OS, as well as across 3 populations regarding participants whose tumors express PD-L1 CPS≥10 and PD-L1 CPS≥1, and all participants.

Figure 2: Multiplicity Graph for Type I Error Control of Study Hypotheses



Bounds and boundary properties: Bounds and boundary properties for each interim analysis were derived using a Lan-DeMets O'Brien-Fleming α-spending function based on information fraction.

Table 4: Efficacy Boundaries and Properties for EFS Analyses, participants whose tumours express PD-L1≥10

Analysis†	Value	α = 0.025
IA1: 89%	Z	2.1082
N: 462	p (1-sided)	0.0175
Events: 207	~HR at bound	0.7456
Month: 64	P(Cross) if HR=1	0.0175
	P(Cross) if HR=0.62	0.9061
IA2	Z	2.0502
N: 462	p (1-sided)	0.0202
Events: 232	~HR at bound	0.7639
Month: 80	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.62	0.9488

† This column displays the number (Events) and percentage (%) of needed EFS events, the expected sample size (N) and the estimated months (Month) after first participant is randomized for each analysis.
p (1-sided): the nominal α for testing.
~HR at bound: the approximate hazard ratio required to reach an efficacy bound.
P(Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis
P(Cross if HR=0.62): the probability of crossing a bound at or before each analysis under the alternative hypothesis.
Abbreviations: CPS = combined positive score; EFS = event-free survival; HR = hazard ratio; IA = interim analysis; PD-L1 = programmed cell death ligand 1.

Table 5 Efficacy Boundaries and Properties for EFS Analyses, participants whose tumours express PD-L1≥1

Analysis†	Value	α = 0.025
IA1: 89%	Z	2.1082
N: 680	p (1-sided)	0.0175
Events: 315	~HR at bound	0.7884
Month: 64	P(Cross) if HR=1	0.0175
	P(Cross) if HR=0.7	0.8537
IA2	Z	2.0502
N: 680	p (1-sided)	0.0202
Events: 354	~HR at bound	0.8040
Month: 80	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.7	0.9122

† This column displays the number (Events) and percentage (%) of needed EFS events, the expected sample size (N) and the estimated months (Month) after first participant is randomized for each analysis.
p (1-sided): the nominal α for testing.
~HR at bound: the approximate hazard ratio required to reach an efficacy bound.
P(Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis
P(Cross if HR=0.7): the probability of crossing a bound at or before each analysis under the alternative hypothesis.
Abbreviations: CPS = combined positive score; EFS = event-free survival; HR = hazard ratio; IA = interim analysis; PD-L1 = programmed cell death ligand 1.

Table 6 Efficacy Boundaries and Properties for EFS Analyses, all participants

Analysis†	Value	α = 0.025
IA1: 89%	Z	2.1082
N: 714	p (1-sided)	0.0175
Events: 331	~HR at bound	0.7929
Month: 64	P(Cross) if HR=1	0.0175
	P(Cross) if HR=0.70	0.8707
IA2	Z	2.0502
N: 714	p (1-sided)	0.0202
Events: 371	~HR at bound	0.8082
Month: 80	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.70	0.9245

† This column displays the number (Events) and percentage (%) of needed EFS events, the expected sample size (N) and the estimated months (Month) after first participant is randomized for each analysis.
p (1-sided): the nominal α for testing.
~HR at bound: the approximate hazard ratio required to reach an efficacy bound.
P(Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis
P(Cross if HR=0.70): the probability of crossing a bound at or before each analysis under the alternative hypothesis.
Abbreviations: CPS = combined positive score; EFS = event-free survival; HR = hazard ratio; IA = interim analysis; PD-L1 = programmed cell death ligand 1.

Efficacy boundaries were defined by pre-specifying the number of expected events at the IAs. The actual boundaries were determined using the same alpha-spending function based on the actual number of events at the time of the IA in case event accumulation was faster or slower than expected.

The EFS final analysis at IA2 used the remaining Type I error not spent at IA1, regardless of the actual number of events observed at the final analysis.

If the EFS hypotheses (H1, H2, and H3) are rejected at any analysis, the α = 0.025 (one-sided) was to be split, and α = 0.0005 (one-sided) rolled over to the mPR test for participants whose tumors express PD-L1 CPS≥10 (H4), and α = 0.0245 (one-sided) will be rolled over to the OS test for participants whose tumors express PD-L1 CPS≥10 (H7).

Analysis populations:

Efficacy analysis population - Intention-to-Treat (ITT) population consisted of all randomized participants. Participants were included in the treatment group to which they were randomized for the analysis of efficacy data.

Safety analysis population - All Participants as Treated (APaT) consisted of all randomized participants who received study treatment (note that surgery is part of study treatment). Participants were included in the treatment group corresponding to the study treatment they actually received.

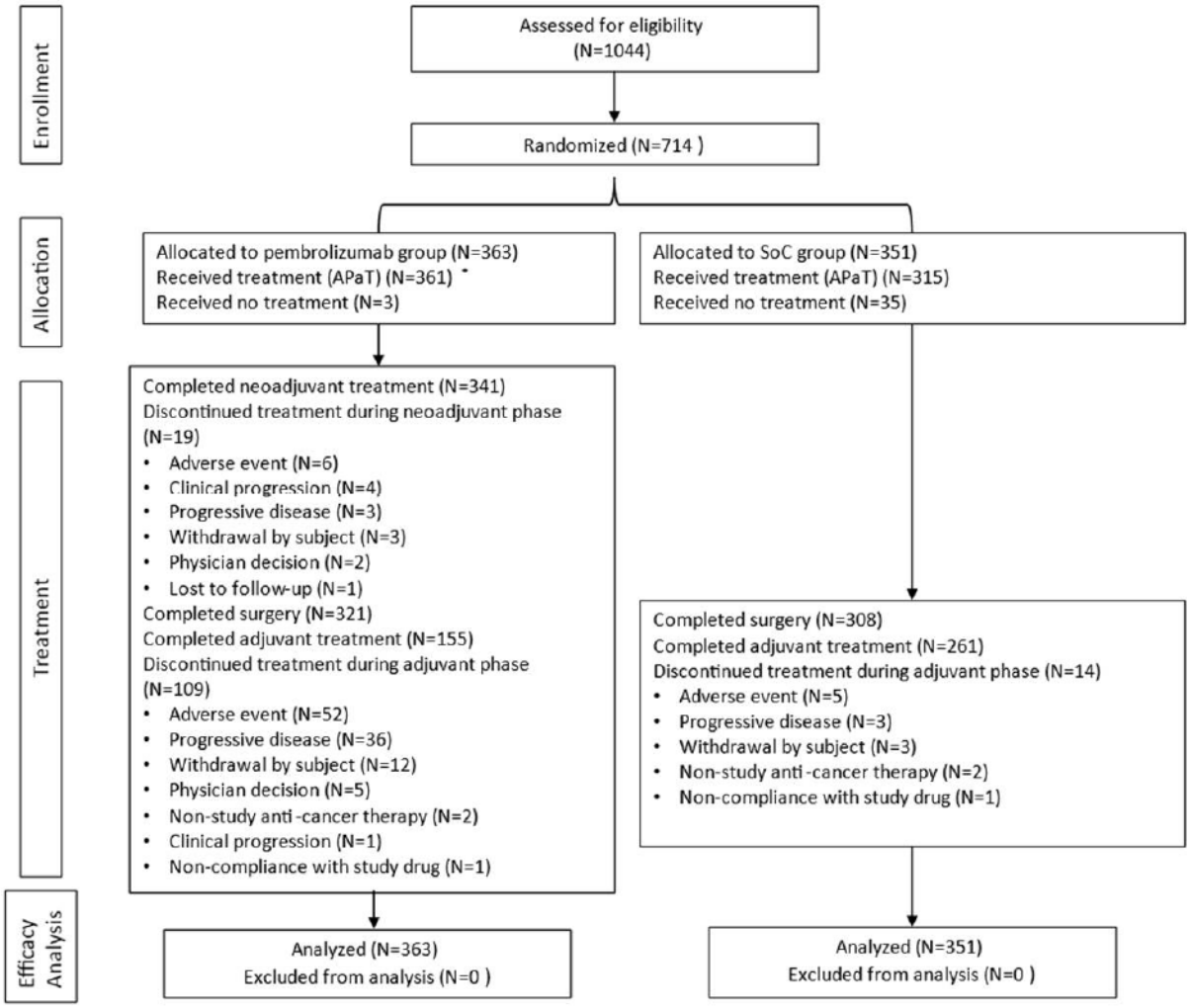
Population for analysis of Patient Reported Outcome - PRO Full Analyses Set (FAS) population, defined as participants who received treatment and had at least one PRO assessment available.

Subgroup analyses: To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints was estimated and plotted within each category of the following classification variables: Primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx); Tumor Stage (III vs. IVA); PD-L1 status (TPS≥50% vs. 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). The consistency of the treatment effect was assessed descriptively. Unstratified methods was used for estimation, and a forest plot was produced. If the number of participants in a category of a subgroup variable is less than 10% of the analysis population whose tumors express PDL1-CPS≥10, the subgroup analysis was not performed for this category of the subgroup variable, and the forest plot did not display this category of the subgroup variable.

Results

Participant flow

Figure 3: Consort Diagram Disposition of Participants



*The total number of participants allocated to receive treatment (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.

A total of 330 participants were screened but not randomized. Main reasons for screen failure were lack of providing informed consent (11%), had no histological confirmed new diagnosis of HNSCC stage III-IVA (10.7%), had history or evidence of conditions that might confound study results (8.9%), had Stage T4B and/or N3 LA HNSCC and/or distant metastases (7.6%).

Table 7: Disposition of Participants (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Status for Neoadjuvant Study Treatment						
Started	360		2		362	
Completed	341	(94.7)	0	(0.0)	341	(94.2)
Discontinued	19	(5.3)	0	(0.0)	19	(5.2)

Adverse Event	6	(1.7)	0	(0.0)	6	(1.7)
Clinical Progression	4	(1.1)	0	(0.0)	4	(1.1)
Lost To Follow-Up	1	(0.3)	0	(0.0)	1	(0.3)
Physician Decision	2	(0.6)	0	(0.0)	2	(0.6)
Associated with COVID-19	1	(0.3)	0	(0.0)	1	(0.3)
Progressive Disease	3	(0.8)	0	(0.0)	3	(0.8)
Withdrawal By Subject	3	(0.8)	0	(0.0)	3	(0.8)
Status Not Recorded	0	(0.0)	2	(100.0)	2	(0.6)
Status for In-study Surgery						
Started	322		308		630	
Completed	321	(99.7)	308	(100.0)	629	(99.8)
Discontinued	1	(0.3)	0	(0.0)	1	(0.2)
Tumor Found To Be Surgically Unresectable	1	(0.3)	0	(0.0)	1	(0.2)
Status for Adjuvant Study Treatment						
Started	275		275		550	
Completed	155	(56.4)	261	(94.9)	416	(75.6)
Discontinued	109	(39.6)	14	(5.1)	123	(22.4)
Adverse Event	52	(18.9)	5	(1.8)	57	(10.4)
Associated with COVID-19	1	(0.4)	0	(0.0)	1	(0.2)
Clinical Progression	1	(0.4)	0	(0.0)	1	(0.2)
Non-Compliance With Study Drug	1	(0.4)	1	(0.4)	2	(0.4)
Non-Study Anti-Cancer Therapy	2	(0.7)	2	(0.7)	4	(0.7)
Physician Decision	5	(1.8)	0	(0.0)	5	(0.9)
Associated with COVID-19	1	(0.4)	0	(0.0)	1	(0.2)
Progressive Disease	36	(13.1)	3	(1.1)	39	(7.1)
Withdrawal By Subject	12	(4.4)	3	(1.1)	15	(2.7)
Participants Ongoing	11	(4.0)	0	(0.0)	11	(2.0)
Status for Study Treatment (Overall)						
Started	360		316		676	
Completed	155	(43.1)	261	(82.6)	416	(61.5)
Discontinued	194	(53.9)	55	(17.4)	249	(36.8)
Adverse Event	65	(18.1)	16	(5.1)	81	(12.0)
Associated with COVID-19	2	(0.6)	0	(0.0)	2	(0.3)
Clinical Progression	3	(0.8)	1	(0.3)	4	(0.6)
Lost To Follow-Up	1	(0.3)	0	(0.0)	1	(0.1)
Non-Compliance With Study Drug	2	(0.6)	3	(0.9)	5	(0.7)
Non-Study Anti-Cancer Therapy	4	(1.1)	3	(0.9)	7	(1.0)
Physician Decision	13	(3.6)	9	(2.8)	22	(3.3)
Associated with COVID-19	2	(0.6)	0	(0.0)	2	(0.3)
Progressive Disease	79	(21.9)	10	(3.2)	89	(13.2)
Withdrawal By Subject	27	(7.5)	13	(4.1)	40	(5.9)
Participants Ongoing	11	(3.1)	0	(0.0)	11	(1.6)
Status for Trial						
Discontinued	123	(33.9)	146	(41.6)	269	(37.7)
Death	109	(30.0)	127	(36.2)	236	(33.1)
Associated with COVID-19	2	(0.6)	4	(1.1)	6	(0.8)
Lost To Follow-Up	2	(0.6)	3	(0.9)	5	(0.7)
Withdrawal By Subject	12	(3.3)	16	(4.6)	28	(3.9)
COVID-19 association unspecified, Subsequently died	4	(1.1)	4	(1.1)	8	(1.1)
Participants Ongoing	240	(66.1)	205	(58.4)	445	(62.3)

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

Database Cutoff Date: 25JUL2024

Data on patients who did not and who did proceed to surgery by treatment arms are shown in the table below:

Table 8: Surgery Status (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
With in-study Surgery	322		308		630	
Without in-study Surgery	41		43		84	
Reason for in-study surgery not performed						
Adjuvant Treatment without Surgery[a]	8	(2.2)	8	(2.3)	16	(2.2)
Adverse Event	1	(0.3)	1	(0.3)	2	(0.3)
Physician Decision	2	(0.6)	2	(0.6)	4	(0.6)
Tumor Found To Be Surgically Unresectable	2	(0.6)	0	(0.0)	2	(0.3)
Withdrawal By Subject	3	(0.8)	5	(1.4)	8	(1.1)
Discontinued Treatment Prior to Surgery[b]	30	(8.3)	0	(0.0)	30	(4.2)
Adverse Event	4	(1.1)	0	(0.0)	4	(0.6)
Lost To Follow-Up	1	(0.3)	0	(0.0)	1	(0.1)
Non-Study Anti-Cancer Therapy	1	(0.3)	0	(0.0)	1	(0.1)
Physician Decision	2	(0.6)	0	(0.0)	2	(0.3)
Progressive Disease	15	(4.1)	0	(0.0)	15	(2.1)
Withdrawal By Subject	7	(1.9)	0	(0.0)	7	(1.0)
Randomized but Not Treated[c]	3	(0.8)	35	(10.0)	38	(5.3)

[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.

For the patients classified as "randomized but not treated" in the table above, reason for not receiving surgical treatment is shown below:

Table 9: Disposition of Participants (Randomized Not Treated)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	3		35	
Randomized but Not Treated				
Adverse Event	0	(0.0)	4	(11.4)
Clinical Progression	0	(0.0)	6	(17.1)
Physician Decision	1	(33.3)	4	(11.4)
Protocol Violation	0	(0.0)	1	(2.9)
Randomized By Mistake Without Study Treatment	0	(0.0)	1	(2.9)
Withdrawal By Subject	2	(66.7)	19	(54.3)

Participants in population is used as the denominator for the percentage calculation.
Participants in this group did not continue to any phase of treatment (including surgery) following randomization.
Database Cutoff Date: 25JUL2024

For patients who proceeded to surgery, information on site of surgery, timings and surgery outcome is shown below:

Table 10: Summary of Surgery (Participants Who Underwent Surgery)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	323		307		630	
Surgery Procedure						
Lip and oral cavity surgery	194	(60.1)	191	(62.2)	385	(61.1)
Larynx surgery	71	(22.0)	66	(21.5)	137	(21.7)
Pharynx surgery	59	(18.3)	50	(16.3)	109	(17.3)
Surgery Outcome						
Complete Resection	287	(88.9)	261	(85.0)	548	(87.0)
Incomplete Resection-R1	30	(9.3)	32	(10.4)	62	(9.8)
Incomplete Resection-R2	5	(1.5)	13	(4.2)	18	(2.9)
Attempted Resection	1	(0.3)	0	(0.0)	1	(0.2)
Unknown	0	(0.0)	1	(0.3)	1	(0.2)
Time Since Start of Neoadjuvant[a] to Surgery (weeks)						
< 4 weeks	12	(3.7)	265	(86.3)	277	(44.0)
4 to <5 weeks	47	(14.6)	27	(8.8)	74	(11.7)
5 to <6 weeks	92	(28.5)	11	(3.6)	103	(16.3)
>=6 weeks	172	(53.3)	4	(1.3)	176	(27.9)
Participants with data	323		307		630	
Mean	6.1		2.2		4.2	
SD	1.7		1.4		2.5	
Median	6.0		1.9		4.4	
Range	0.3 to 16.1		0.3 to 10.4		0.3 to 16.1	
Time Since End of Neoadjuvant[a] to Surgery (weeks)						
< 4 weeks	249	(77.1)	265	(86.3)	514	(81.6)
4 to <5 weeks	45	(13.9)	27	(8.8)	72	(11.4)
5 to <6 weeks	17	(5.3)	11	(3.6)	28	(4.4)
>=6 weeks	12	(3.7)	4	(1.3)	16	(2.5)
Participants with data	323		307		630	
Mean	3.2		2.2		2.7	
SD	1.6		1.4		1.6	
Median	3.0		1.9		2.4	
Range	0.3 to 12.9		0.3 to 10.4		0.3 to 12.9	

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Time since Surgery to First Adjuvant Treatment (weeks)						
Participants with data	267		267		534	
Mean	6.5		7.2		6.9	
SD	2.0		2.5		2.3	
Median	6.1		6.3		6.1	
Range	1.7 to 17.0		3.1 to 24.7		1.7 to 24.7	
Days of Hospitalization from Surgery to Discharge						
Participants with data	322		307		629	
Mean	20		20		20	
SD	16		14		15	
Median	17		17		17	
Range	2 to 140		1 to 114		1 to 140	
Surgery Delay Status						
Yes	38	(11.8)	10	(3.3)	48	(7.6)
Adverse Experience	11	(3.4)	1	(0.3)	12	(1.9)
Scheduling Change	9	(2.8)	2	(0.7)	11	(1.7)
Patient Non-Compliance	1	(0.3)	0	(0.0)	1	(0.2)
Other Due to COVID-19	4	(1.2)	1	(0.3)	5	(0.8)
Other Not Due to COVID-19	13	(4.0)	6	(2.0)	19	(3.0)
No	285	(88.2)	297	(96.7)	582	(92.4)
Post Surgery Adjuvant CRT/RT						
With in-study surgery and adjuvant CRT	100	(31.0)	132	(43.0)	232	(36.8)
With in-study surgery and adjuvant RT	266	(82.4)	267	(87.0)	533	(84.6)

[a] Time since randomization to surgery is summarized for participants who did not receive neoadjuvant treatment.
Database Cutoff Date: 25JUL2024.

For patients who did have surgery but did not proceed to adjuvant treatment, reasons were as follows:

Table 11: Disposition of participants (Participants who Completed Surgery but did Not receive adjuvant therapy, ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	54		41		95	
Status for Study Treatment (Overall)						
Discontinued	54	(100.0)	41	(100.0)	95	(100.0)
Adverse Event	9	(16.7)	11	(26.8)	20	(21.1)
Clinical Progression	2	(3.7)	1	(2.4)	3	(3.2)
Non-Compliance With Study Drug	1	(1.9)	2	(4.9)	3	(3.2)
Non-Study Anti-Cancer Therapy	1	(1.9)	1	(2.4)	2	(2.1)
Physician Decision	6	(11.1)	9	(22.0)	15	(15.8)
Progressive Disease	27	(50.0)	7	(17.1)	34	(35.8)
Withdrawal By Subject	8	(14.8)	10	(24.4)	18	(18.9)
Participants in population is used as the denominator for the percentage calculation. Database Cutoff Date: 25JUL2024						

In the adjuvant phase following surgery, a total of 275 patients in each arm received adjuvant SoC treatment (RT+/- cisplatin). For patients who received adjuvant treatment, the following chemo-RT was administered:

Table 12: adjuvant chemo/RT treatment

	Pembrolizumab	**SoC**
Total nb of patients who received adjuvant treatment	*275*	*275*
Patients who received RT+/- cisplatin	274	275
Patients who received RT+cisplatin	107 (38.9%)	139 (50.5%)
Patients who received RT alone	167 (60.7%)	136 (49.5%)

(table made by Assessor based on tables in CSR 10-1, 14.1-2, 14.1-32, 14.1-33)

In both treatment arms, 267 patients did proceed to adjuvant treatment after surgery, while 8 patients received adjuvant treatment although surgery was not performed.

Regarding adjuvant pembrolizumab in the experimental arm, a total of 255 of the 275 participants received adjuvant pembrolizumab, while 20 of the 275 participants received RT ± cisplatin only. 36 completed 3 or less cycles of pembrolizumab and 219 completed more than 3 cycles of pembrolizumab. 151 patients completed 15 cycles.

Table 13: Participants With Subsequent Treatment by Type for HNSCC (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Post-Study Radiotherapy						
Yes	47	(12.9)	39	(11.1)	86	(12.0)
No	316	(87.1)	312	(88.9)	628	(88.0)
Post-Study Surgery						
Yes	15	(4.1)	10	(2.8)	25	(3.5)
No	348	(95.9)	341	(97.2)	689	(96.5)
Post-Study Systemic Therapy						
Yes	70	(19.3)	78	(22.2)	148	(20.7)
No	293	(80.7)	273	(77.8)	566	(79.3)
Post-Study 1L R/M Systemic Therapy						
Yes	70	(19.3)	78	(22.2)	148	(20.7)

No	293	(80.7)	273	(77.8)	566	(79.3)
Post-Study 2L R/M Systemic Therapy						
Yes	20	(5.5)	24	(6.8)	44	(6.2)
No	343	(94.5)	327	(93.2)	670	(93.8)
Post-Study 3L R/M Systemic Therapy						
Yes	8	(2.2)	12	(3.4)	20	(2.8)
No	355	(97.8)	339	(96.6)	694	(97.2)
Post-Study 4L R/M Systemic Therapy						
Yes	2	(0.6)	2	(0.6)	4	(0.6)
No	361	(99.4)	349	(99.4)	710	(99.4)
Post-Study 5L or Greater R/M Systemic Therapy						
Yes	1	(0.3)	0	(0.0)	1	(0.1)
No	362	(99.7)	351	(100.0)	713	(99.9)
Database Cutoff Date: 25JUL2024.						

Table 14: Participants With Subsequent Anti-cancer Treatment by Type for HNSCC (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	87		91		178	
Treatment Modality						
Post-Study Surgery Alone	4	(4.6)	5	(5.5)	9	(5.1)
Post-Study Radiotherapy Alone	13	(14.9)	8	(8.8)	21	(11.8)
Post-Study Systemic Therapy Alone	29	(33.3)	45	(49.5)	74	(41.6)
Post-Study Systemic Therapy with Surgery	7	(8.0)	2	(2.2)	9	(5.1)
Post-Study Systemic Therapy with Radiotherapy	30	(34.5)	28	(30.8)	58	(32.6)
Post-Study Systemic Therapy with Surgery and Radiotherapy	4	(4.6)	3	(3.3)	7	(3.9)
Database Cutoff Date: 25JUL2024.						

Recruitment

This study was conducted at 192 centers in 24 countries.

First participant randomized: 17-DEC-2018; last participant randomized: 25-OCT-2023.

The study is ongoing.

Interim Analysis 1 (IA1, first interim for EFS and OS and final for mPR) had data cut-off date of 25-JUL-2024, database lock date 28-AUG-2024. Median follow-up at IA1 was of 27.1 months (range 0.5, 66.5). The last patient was randomized about 9 months before IA1.

Table 15: Summary of Follow-up Duration (ITT Population)

Follow-up duration (months)[a]	Pembrolizumab (N=363)	SoC (N=351)	Total (N=714)
Median (Range)	30.0 (0.8, 64.9)	23.4 (0.5, 66.5)	27.1 (0.5, 66.5)
Mean (SD)	31.1 (17.9)	27.5 (18.4)	29.3 (18.2)
[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive. Database Cutoff Date: 25JUL2024.			

Conduct of the study

Protocol amendments

Table 16: Protocol amendments

Document	Date of Issue	Overall Rationale
3475-689-09	29-MAR-2024	To update the assumptions of the survival distribution of the control group based on historical data and update with more conservative HR assumption for EFS in CPS≥10 population based on study data from KEYNOTE-412.
3475-689-08	07-SEP-2023	To amend the statistical analysis plan, update the EFS definition, update the endpoint of mPR from a primary endpoint to a secondary endpoint and remove original efficacy IA1 (inferential analysis of mPR only), and to modify CPS cutoff to add evaluation of pCR for CPS≥10.
3475-689-07	07-JUN-2022	To update contraception language to include required duration of contraception for males and women of childbearing potential (WOCBP) after radiotherapy (RT). Additional minor updates, corrections, and clarifications were also made.
3475-689-06	03-MAR-2022	1) To add pregnancy testing for women of childbearing potential (WOCBP) at monthly intervals during study treatment until 120 days after the last dose of pembrolizumab and 180 days after the last dose of cisplatin, including at the end of treatment visit. 2) To allow imaging and/or biopsy assessments to continue for participants who have not experienced an event. 3) To update the contraception requirements and make additional minor corrections and clarifications throughout the protocol.
3475-689-05	13-MAY-2021	To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
3475-689-04	17-JUN-2019	To add both biomarker-driven hypotheses and the stratification factor of tumor proportion score (TPS) ≥50%. The rationale for these modifications is that higher PD-L1 expression was associated with improved response to pembrolizumab for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) enrolled on the KN040 and KN048 randomized phase III studies. It is reasonable to expect that biomarker enrichment effects are also likely to be seen in locally advanced HNC.
3475-689-03	02-AUG-2018	To clarify the definitions of residual disease used in the pathological assessment used for this study and to clarify the roles of the local and central pathologists, to align the pembrolizumab dose modification table with the most current safety information, and to remove iRECIST assessment which is not relevant for this study. Additional clarifications and corrections were also made.
3475-689-02	10-MAY-2018	To align with regulatory requirements at German and French sites as well as to align with the cisplatin SmPC as required for German and French sites.
3475-689-01	13-JAN-2018	To provide for more frequent pregnancy testing and to extend the prohibition of live vaccines to 3 months after the end of study treatment
3475-689-00	24-AUG-2017	Initial protocol

Change in the EFS definition: In the original protocol 689-00, EFS was defined as the time from randomization to the first of the following events: 1) Radiographic disease progression per RECIST 1.1 as assessed by BICR, 2) Local or distant recurrence (for participants who are disease free after surgery), 3) Death due to any cause. In Protocol/Amendment NO: 689-08, EFS definition was updated. It was specified that "Radiographic disease progression during neoadjuvant phase that precludes surgery will be considered an event", to clarify that, radiographic disease progression during neoadjuvant phase that does not preclude surgery will not be considered an EFS event.

Change in primary and secondary endpoints: Initially, mPR and EFS were both primary endpoints. In protocol MK-3475-689-08, the endpoint of mPR was changed from a primary to a secondary endpoint and EFS was updated as the singular primary endpoint of the trial. Consequently, original efficacy IA1 (inferential analysis of mPR only) was removed. Plan of interim and final analyses was updated accordingly.

Protocol deviations

A total of 78 (21.5%) patients in the pembrolizumab arm vs 51 (14.5%) patients in the experimental arm had one or more important protocol deviations. Of those, protocol deviations considered clinically important (i.e. deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) are listed below:

Table 17: Summary of Important Protocol Deviations Considered to be Clinically Important (ITT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	363		351	
with one or more clinically important protocol deviations	17	(4.7)	12	(3.4)
with no clinically important protocol deviations	346	(95.3)	339	(96.6)
Discontinuation Criteria	**1**	**(0.3)**	**0**	**(0.0)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	1	(0.3)	0	(0.0)
Inclusion/ Exclusion Criteria	**0**	**(0.0)**	**1**	**(0.3)**
Primary tumor location is not oropharynx, oral cavity, hypopharynx, or larynx.	0	(0.0)	1	(0.3)
Safety Reporting	**1**	**(0.3)**	**1**	**(0.3)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	1	(0.3)	1	(0.3)
Study Intervention	**5**	**(1.4)**	**1**	**(0.3)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	5	(1.4)	0	(0.0)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	0	(0.0)	1	(0.3)
Trial Procedures	**11**	**(3.0)**	**9**	**(2.6)**
Post surgery specimens sufficient for central review of mPR/pCR/HRPF were not submitted.	11	(3.0)	9	(2.6)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 25JUL2024.

Baseline data

Table 18: Participant Characteristics (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Sex						
Male	286	(78.8)	277	(78.9)	563	(78.9)
Female	77	(21.2)	74	(21.1)	151	(21.1)
Age (Years)						
< 65	249	(68.6)	227	(64.7)	476	(66.7)
>= 65	114	(31.4)	124	(35.3)	238	(33.3)
Mean	59.4		60.6		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	51	(14.0)	44	(12.5)	95	(13.3)
Black Or African American	9	(2.5)	9	(2.6)	18	(2.5)
Multiple	9	(2.5)	20	(5.7)	29	(4.1)
American Indian Or Alaska Native, Black Or African American, White	2	(0.6)	4	(1.1)	6	(0.8)
American Indian Or Alaska Native, White	1	(0.3)	8	(2.3)	9	(1.3)
Black Or African American, White	4	(1.1)	7	(2.0)	11	(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	284	(78.2)	270	(76.9)	554	(77.6)
Missing	9	(2.5)	6	(1.7)	15	(2.1)
Ethnicity						
Hispanic Or Latino	55	(15.2)	46	(13.1)	101	(14.1)
Not Hispanic Or Latino	300	(82.6)	298	(84.9)	598	(83.8)
Not Reported	4	(1.1)	4	(1.1)	8	(1.1)
Unknown	0	(0.0)	2	(0.6)	2	(0.3)
Missing	4	(1.1)	1	(0.3)	5	(0.7)
Region						
North America	64	(17.6)	49	(14.0)	113	(15.8)
European Union	138	(38.0)	145	(41.3)	283	(39.6)
Rest of World	161	(44.4)	157	(44.7)	318	(44.5)
PD-L1 Status by TPS Score						
TPS <50%	257	(70.8)	242	(68.9)	499	(69.9)
TPS >=50%	103	(28.4)	107	(30.5)	210	(29.4)
Missing	3	(0.8)	2	(0.6)	5	(0.7)
PD-L1 Status by CPS Score (CPS50)						
CPS <50	244	(67.2)	224	(63.8)	468	(65.5)
CPS >=50	116	(32.0)	125	(35.6)	241	(33.8)
Missing	3	(0.8)	2	(0.6)	5	(0.7)
PD-L1 Status by CPS Score (CPS10)						
CPS <10	126	(34.7)	118	(33.6)	244	(34.2)
CPS >=10	234	(64.5)	231	(65.8)	465	(65.1)
Missing	3	(0.8)	2	(0.6)	5	(0.7)
PD-L1 Status by CPS Score (CPS1)						
CPS <1	13	(3.6)	14	(4.0)	27	(3.8)
CPS >=1	347	(95.6)	335	(95.4)	682	(95.5)
Missing	3	(0.8)	2	(0.6)	5	(0.7)
Primary Tumor Site						
Oropharynx	35	(9.6)	38	(10.8)	73	(10.2)
Oral Cavity	219	(60.3)	213	(60.7)	432	(60.5)
Larynx	81	(22.3)	73	(20.8)	154	(21.6)
Hypopharynx	28	(7.7)	26	(7.4)	54	(7.6)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
ECOG PS						
0	199	(54.8)	209	(59.5)	408	(57.1)
1	164	(45.2)	142	(40.5)	306	(42.9)
HPV Status						
Positive	12	(3.3)	15	(4.3)	27	(3.8)
Negative	351	(96.7)	335	(95.4)	686	(96.1)
Unknown	0	(0.0)	1	(0.3)	1	(0.1)
Overall Cancer Staging at Baseline						
III	90	(24.8)	93	(26.5)	183	(25.6)
IVA	271	(74.7)	257	(73.2)	528	(73.9)
IVB	2	(0.6)	0	(0.0)	2	(0.3)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer T Staging at Baseline						
T1	9	(2.5)	4	(1.1)	13	(1.8)
T2	49	(13.5)	47	(13.4)	96	(13.4)
T3	110	(30.3)	113	(32.2)	223	(31.2)

T4	11	(3.0)	15	(4.3)	26	(3.6)
T4A	184	(50.7)	170	(48.4)	354	(49.6)
T4B	0	(0.0)	1	(0.3)	1	(0.1)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer N Staging at Baseline						
N0	94	(25.9)	88	(25.1)	182	(25.5)
N1	81	(22.3)	72	(20.5)	153	(21.4)
N2	32	(8.8)	31	(8.8)	63	(8.8)
N2A	12	(3.3)	7	(2.0)	19	(2.7)
N2B	83	(22.9)	88	(25.1)	171	(23.9)
N2C	58	(16.0)	64	(18.2)	122	(17.1)
N3	1	(0.3)	0	(0.0)	1	(0.1)
N3B	2	(0.6)	0	(0.0)	2	(0.3)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer M Staging at Baseline						
M0	363	(100.0)	350	(99.7)	713	(99.9)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Smoking Status						
Never Smoker	64	(17.6)	81	(23.1)	145	(20.3)
Former Smoker	176	(48.5)	144	(41.0)	320	(44.8)
Current Smoker	117	(32.2)	123	(35.0)	240	(33.6)
Unknown	6	(1.7)	3	(0.9)	9	(1.3)
Cigarette use (packs per year)						
0 (No Cigarette use)	64	(17.6)	81	(23.1)	145	(20.3)
<=10	67	(18.5)	73	(20.8)	140	(19.6)
>10	216	(59.5)	186	(53.0)	402	(56.3)
Unknown	16	(4.4)	11	(3.1)	27	(3.8)
Alcohol use						
Yes	250	(68.9)	238	(67.8)	488	(68.3)
No	107	(29.5)	110	(31.3)	217	(30.4)
Unknown	6	(1.7)	3	(0.9)	9	(1.3)

SD=Standard deviation.

European Union category in this table includes European Economic Area, United Kingdom and Switzerland.

Database Cutoff Date: 25JUL2024.

Table 19: PD-L1 CPS Status by Primary Tumor Site Summary (ITT Population, SoC Arm)

	Oropharynx		Oral Cavity		Larynx		Hypopharynx		Missing	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	38		213		73		26		1	
PD-L1 Status by CPS Score (CPS10)										
CPS <10	16	(42.1)	55	(25.8)	38	(52.1)	8	(30.8)	1	(100.0)
CPS >=10	22	(57.9)	156	(73.2)	35	(47.9)	18	(69.2)	0	(0.0)
Missing	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
PD-L1 Status by CPS Score (CPS1)										
CPS <1	1	(2.6)	6	(2.8)	6	(8.2)	1	(3.8)	0	(0.0)
CPS >=1	37	(97.4)	205	(96.2)	67	(91.8)	25	(96.2)	1	(100.0)
Missing	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)

Database Cutoff Date: 25JUL2024.

Table 20: Participant Characteristics (participants with CPS≥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)
>= 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)
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 Tumor 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						
III	86	(24.8)	88	(26.3)	174	(25.5)
IVA	259	(74.6)	246	(73.4)	505	(74.0)
IVB	2	(0.6)	0	(0.0)	2	(0.3)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer T Staging at Baseline						
T1	8	(2.3)	4	(1.2)	12	(1.8)
T2	48	(13.8)	47	(14.0)	95	(13.9)
T3	107	(30.8)	109	(32.5)	216	(31.7)
T4	10	(2.9)	14	(4.2)	24	(3.5)
T4A	174	(50.1)	159	(47.5)	333	(48.8)
T4B	0	(0.0)	1	(0.3)	1	(0.1)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer N Staging at Baseline						
N0	90	(25.9)	80	(23.9)	170	(24.9)
N1	74	(21.3)	71	(21.2)	145	(21.3)
N2	31	(8.9)	29	(8.7)	60	(8.8)
N2A	12	(3.5)	7	(2.1)	19	(2.8)
N2B	80	(23.1)	87	(26.0)	167	(24.5)
N2C	57	(16.4)	60	(17.9)	117	(17.2)
N3	1	(0.3)	0	(0.0)	1	(0.1)
N3B	2	(0.6)	0	(0.0)	2	(0.3)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer M Staging at Baseline						
M0	347	(100.0)	334	(99.7)	681	(99.9)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Smoking Status						
Never Smoker	61	(17.6)	76	(22.7)	137	(20.1)
Former Smoker	170	(49.0)	135	(40.3)	305	(44.7)
Current Smoker	110	(31.7)	121	(36.1)	231	(33.9)
Unknown	6	(1.7)	3	(0.9)	9	(1.3)
Cigarette use (packs per year)						
0 (No Cigarette use)	61	(17.6)	76	(22.7)	137	(20.1)
<=10	64	(18.4)	68	(20.3)	132	(19.4)
>10	206	(59.4)	180	(53.7)	386	(56.6)
Unknown	16	(4.6)	11	(3.3)	27	(4.0)
Alcohol use						
Yes	238	(68.6)	228	(68.1)	466	(68.3)
No	103	(29.7)	104	(31.0)	207	(30.4)
Unknown	6	(1.7)	3	(0.9)	9	(1.3)

SD=Standard deviation.
European Union category in this table includes European Economic Area, United Kingdom and Switzerland.
Database Cutoff Date: 25JUL2024.

Numbers analysed

Table 21: Study 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	361	1	362
Number of Participants Who Underwent In-Study Surgery	323	307	630
Number of Participants Who Received the Adjuvant Treatment	275	275	550
Number of Participants Who Received In-Study Radiation Therapy	274	275	549
Number of Participants Who Received Cisplatin	107	139	246
Number of Participants Who Received Cisplatin + In-Study Radiation Therapy	107	139	246
Database Cutoff Date: 25JUL2024.			

Table 22: Study populations by PD-L1 expression

	Pembrolizumab	**SoC**	**Total**
ITT	363	351	714
CPS≥1	347	335	682 (95.5%)
CPS≥10	243	231	465 (65.1%)

Outcomes and estimation

The efficacy data are based on results of the first interim analysis (IA1) of KEYNOTE-689 study, with data cutoff date of 25-JUL-2024.

The prespecified primary analysis for EFS was conducted in participants with CPS ≥10, CPS ≥1, and all participants, sequentially according to the multiplicity strategy. At IA1, EFS was statistically significant in all the three populations analysed.

Statistical significance was also reached in mPR in all the populations analysed (CPS ≥10, CPS ≥1, and all participants).

For OS, in the CPS ≥10 population the observed p-value did not cross the p-value boundary (0.0104). Per the multiplicity strategy prespecified in the SAP, OS was not formally tested at CPS ≥1 or in all participants.

Table 23: Summary of efficacy results of KEYNOTE-689 at IA1

	All participants		**PD-L1 CPS≥1**		**PD-L1 CPS≥10**	
	Pembro+SoC (N=363)	SoC (N=351)	Pembro+SoC (N=347)	SoC (N=335)	Pembro+SoC (N=234)	SoC (N=231)
EFS – by BICR per RECIST 1.1 - primary efficacy outcome						
Number of events (%)	136 (37.5)	159 (45.3)	128 (36.9)	156 (46.6)	85 (36.3)	107 (46.3)
Median (months)[a] (95%CI)	51.8 (37.5, NR)	30.4 (21.8, 50.1)	59.7 (37.9, NR)	29.6 (19.5, 41.9)	59.7 (41.1, NR)	26.9 (18.3, 51.5)
HR (95%CI)[b]	0.73 (0.58, 0.92)		0.70 (0.55, 0.89)		0.66 (0.49, 0.88)	
p-value[c]	0.00411 (stat sign)		0.00140 (stat sign)		0.00217 (stat sign)	
EFS Rate at 6 months, % (95% CI)	86.3 (82.1, 89.5)	80.3 (75.5, 84.2)	86.2 (82.0, 89.5)	80.0 (75.1, 84.0)	85.7 (80.4, 89.7)	79.4 (73.3, 84.2)

EFS Rate at 12 months, % (95% CI)	75.1 (70.0, 79.4)	62.5 (56.9, 67.5)	74.8 (69.6, 79.2)	61.3 (55.5, 66.5)	74.0 (67.6, 79.3)	60.0 (53.0, 66.3)
EFS Rate at 24 months, % (95% CI)	65.0 (59.4, 70.1)	54.6 (48.7, 60.1)	64.6 (58.8, 69.8)	53.4 (47.4, 59.1)	65.1 (58.2, 71.2)	53.2 (45.9, 59.9)
mPR – secondary efficacy outcome						
Number of mPR	34	0	34	0	32	0
mPR Rate (%) (95% CI)	9.4 (6.6, 12.8)	0.0 (0.0, 1.0)	9.8 (6.9, 13.4)	0.0 (0.0, 1.1)	13.7 (9.5, 18.8)	0.0 (0.0, 1.6)
p-Value[d]	<0.00001 (stat sign)		<0.00001 (stat sign)		<0.00001 (stat sign)	
OS – secondary efficacy outcome						
Number of events (%)	113 (31.1)	131 (37.3)	106 (30.5)	128 (38.2)	73 (31.2)	89 (38.5)
Median (months)[a] (95%CI)	NR (61.9, NR)	61.8 (50.1, NR)	NR (NR, NR)	61.8 (49.2, NR)	NR (NR, NR)	61.8 (49.2, NR)
HR (95%CI)[b]	0.76 (0.59, 0.98)		0.72 (0.56, 0.94)		0.72 (0.52, 0.98)	
p-value[c]	0.01529 (not tested)		0.00666 (not tested)		0.01793 (not stat sign)	
OS Rate at 6 months, % (95% CI)	94.2 (91.2, 96.2)	88.6 (84.8, 91.5)	94.2 (91.2, 96.2)	88.4 (84.4, 91.4)	93.6 (89.5, 96.1)	88.7 (83.9, 92.2)
OS Rate at 12 months, % (95% CI)	86.7 (82.7, 89.8)	77.9 (73.2, 81.9)	86.3 (82.2, 89.5)	77.5 (72.6, 81.6)	85.8 (80.6, 89.7)	77.8 (71.9, 82.7)
OS Rate at 24 months, % (95% CI)	75.9 (70.9, 80.1)	67.9 (62.5, 72.7)	75.3 (70.2, 79.7)	67.3 (61.7, 72.2)	74.8 (68.5, 80.0)	67.1 (60.4, 73.0)

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 tumor site and tumor stage
c) One-sided p-vale based on log-rank test stratified by primary tumor site and tumor stage
d) One-sided p-value

p-value crossing boundary for statistical significance: EFS in CPS≥10 = 0.0138, EFS in CPS≥1 = 0.0124, EFS in all participants = 0.0120; improvement in mPR in CPS≥10 = 0.0005, mPR in CPS≥1 = 0.0005, mPR in all participants = 0.0005; OS in CPS≥10 = 0.0104 (not crossed), OS was not formally tested at CPS≥1 or in all participants.

Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CPS=Combined positive score; mPR=major pathological response; HR=Hazard ratio; ITT=Intention to treat; OS=Overall survival; EFS=Event-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1; NR= not reached

Database Cutoff Date: 25JUL2024
(table made by assessor based on CSR)

Primary endpoint – EFS by BICR per RECIST 1.1

CPS≥10

Table 24: Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS≥10, ITT Population)

	Pembrolizumab (N=234)	SoC (N=231)
Number of Events (%)	85 (36.3)	107 (46.3)
Death	43 (18.4)	37 (16.0)
Distant PD	15 (6.4)	39 (16.9)
Local And Distant PD	2 (0.9)	2 (0.9)
Local PD/Recurrence	25 (10.7)	29 (12.6)
Number of Censored (%)	149 (63.7)	124 (53.7)
Last assessment showing no progression	148 (63.2)	116 (50.2)
Randomization	1 (0.4)	8 (3.5)
Kaplan-Meier Estimates (months)[a]		

Median (95% CI) [Q1, Q3]	59.7 (41.1, NR) [10.9, NR]	26.9 (18.3, 51.5) [6.5, NR]
Person-months	5605.3	4244.6
Event Rate / 100 Person-months	1.5	2.5
vs SoC		
Hazard Ratio (95% CI)[b]	0.66 (0.49, 0.88)	
p-value[c]	0.00217	
EFS Rate at month 6 (%) (95% CI)	85.7 (80.4, 89.7)	79.4 (73.3, 84.2)
EFS Rate at month 12 (%) (95% CI)	74.0 (67.6, 79.3)	60.0 (53.0, 66.3)
EFS Rate at month 24 (%) (95% CI)	65.1 (58.2, 71.2)	53.2 (45.9, 59.9)
EFS Rate at month 36 (%) (95% CI)	59.8 (52.3, 66.5)	45.9 (38.0, 53.4)
EFS Rate at month 48 (%) (95% CI)	55.9 (47.7, 63.4)	44.4 (36.3, 52.2)

[a] From product-limit (Kaplan-Meier) method for censored data.

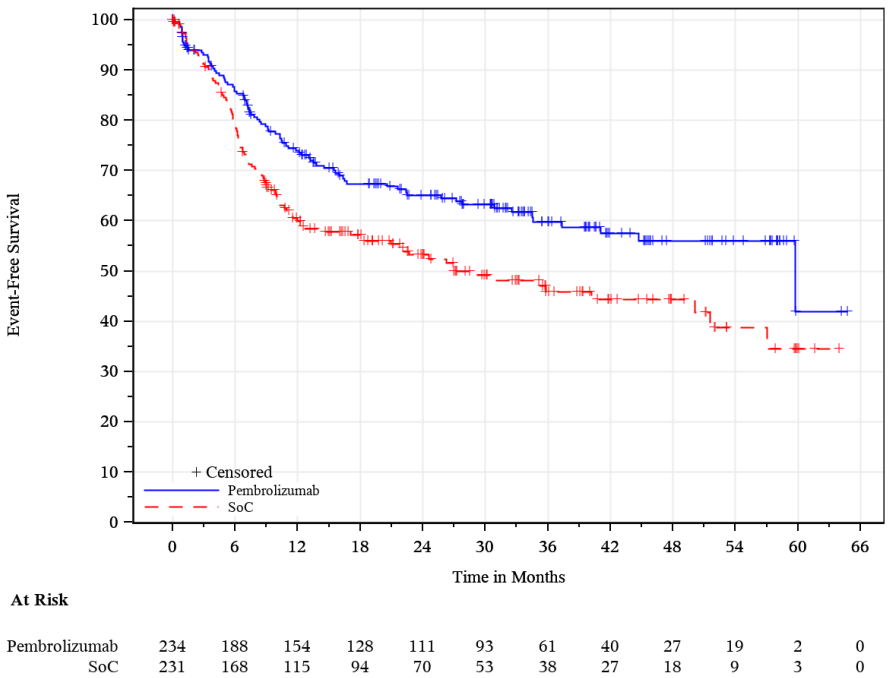
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

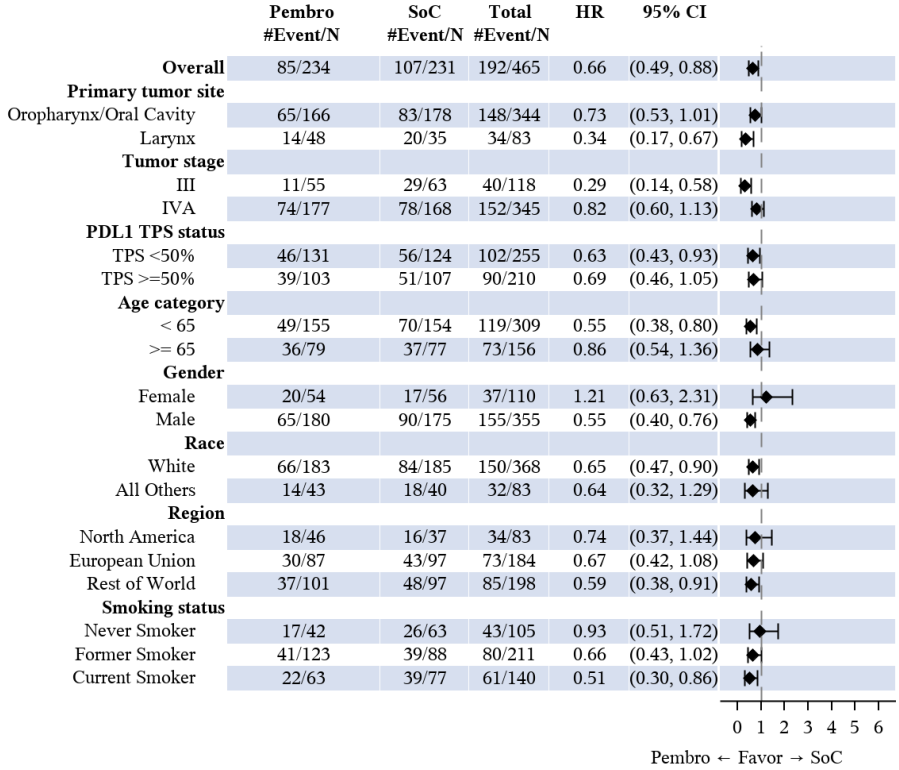
Database Cutoff Date: 25JUL2024

Figure 4: Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS≥10, ITT Population)



Database Cutoff Date: 25JUL2024.

Figure 5: Forest Plot of EFS Hazard Ratio by Subgroup Factors Based on BICR per RECIST 1.1 (Primary Censoring Rule) (Participants with CPS≥10, ITT Population)



CPS≥1

Table 25: Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS≥1, ITT Population)

	Pembrolizumab (N=347)	SoC (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	7751.6	6245.2
Event Rate / 100 Person-months	1.7	2.5
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)	86.2 (82.0, 89.5)	80.0 (75.1, 84.0)
EFS Rate at month 12 (%) (95% CI)	74.8 (69.6, 79.2)	61.3 (55.5, 66.5)
EFS Rate at month 24 (%) (95% CI)	64.6 (58.8, 69.8)	53.4 (47.4, 59.1)

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)	52.1 (45.0, 58.8)	42.8 (35.9, 49.4)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor 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 tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

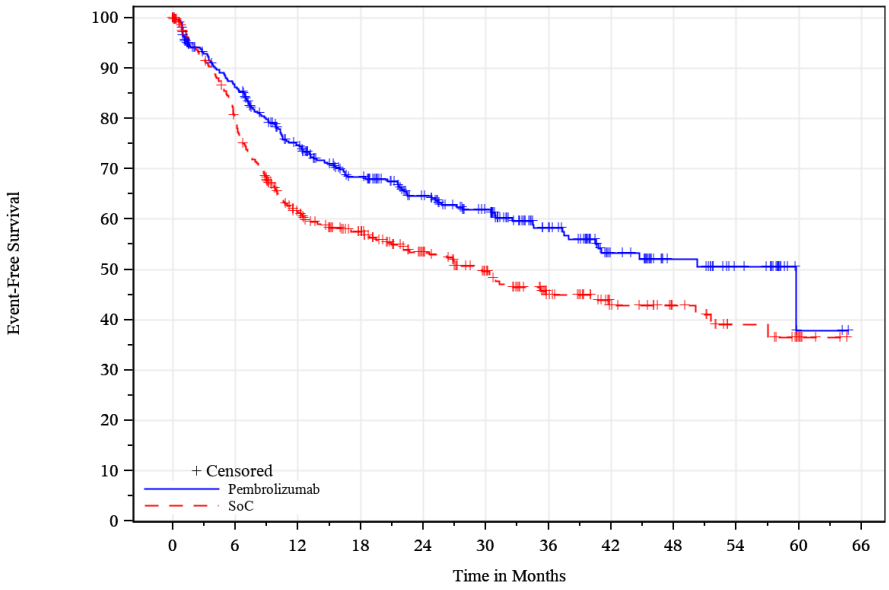
Database Cutoff Date: 25JUL2024

Table 26: details on EFS censoring by situation (Participants with CPS≥1)

Number of Censored (%)	219 (63.1)	179 (53.4)
No PD, no recurrence and no death; and new anticancer therapy is initiated	22 (6.3)	19 (5.7)
No PD, no recurrence and no death; and new anticancer therapy is not initiated	197 (56.8)	160 (47.8)

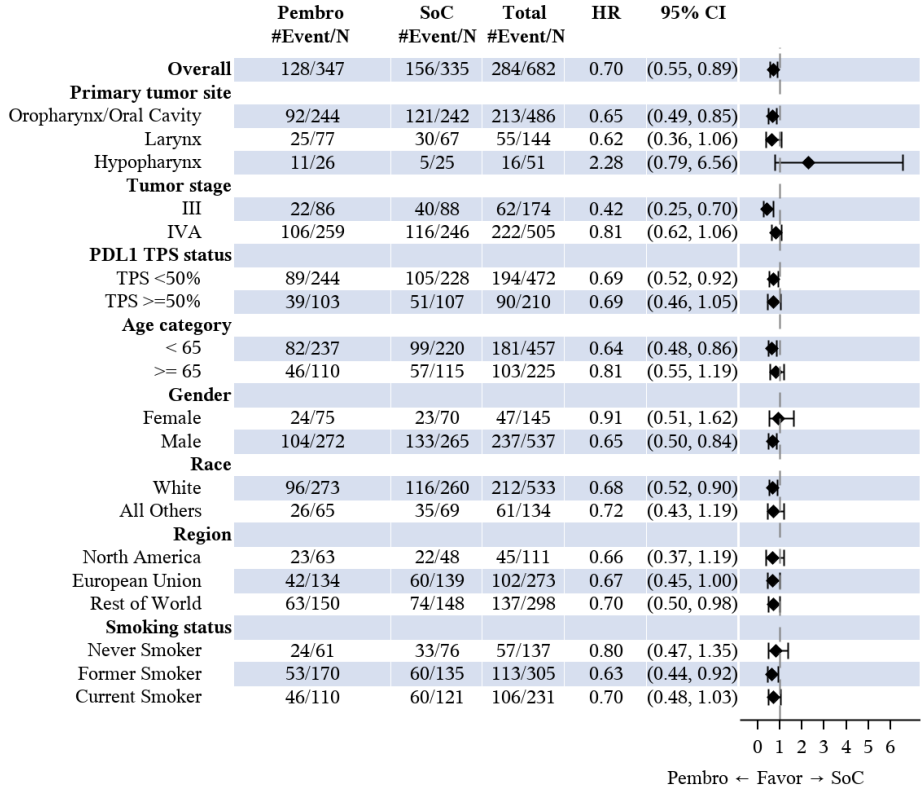
Database Cutoff Date: 25JUL2024

Figure 6: Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024.

Figure 7: Forest Plot of EFS Hazard Ratio by Subgroup Factors Based on BICR per RECIST 1.1 (Primary Censoring Rule) (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024

All participants

Table 27: Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)

	Pembrolizumab (N=363)	SoC (N=351)
Number of Events (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local And Distant PD	4 (1.1)	7 (2.0)
Local PD/Recurrence	39 (10.7)	37 (10.5)
Number of Censored (%)	227 (62.5)	192 (54.7)
Last assessment showing no progression	224 (61.7)	181 (51.6)
Randomization	3 (0.8)	11 (3.1)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	51.8 (37.5, NR)	30.4 (21.8, 50.1)
[Q1, Q3]	[12.1, NR]	[6.9, NR]
Person-months	8166.9	6588.2
Event Rate / 100 Person-months	1.7	2.4
vs SoC		
Hazard Ratio (95% CI)[b]	0.73 (0.58, 0.92)	
p-value[c]	0.00411	

EFS Rate at month 6 (%) (95% CI)	86.3 (82.1, 89.5)	80.3 (75.5, 84.2)
EFS Rate at month 12 (%) (95% CI)	75.1 (70.0, 79.4)	62.5 (56.9, 67.5)
EFS Rate at month 24 (%) (95% CI)	65.0 (59.4, 70.1)	54.6 (48.7, 60.1)
EFS Rate at month 36 (%) (95% CI)	57.6 (51.5, 63.3)	46.4 (40.0, 52.5)
EFS Rate at month 48 (%) (95% CI)	52.0 (45.1, 58.4)	44.2 (37.5, 50.8)

[a] From product-limit (Kaplan-Meier) method for censored data.

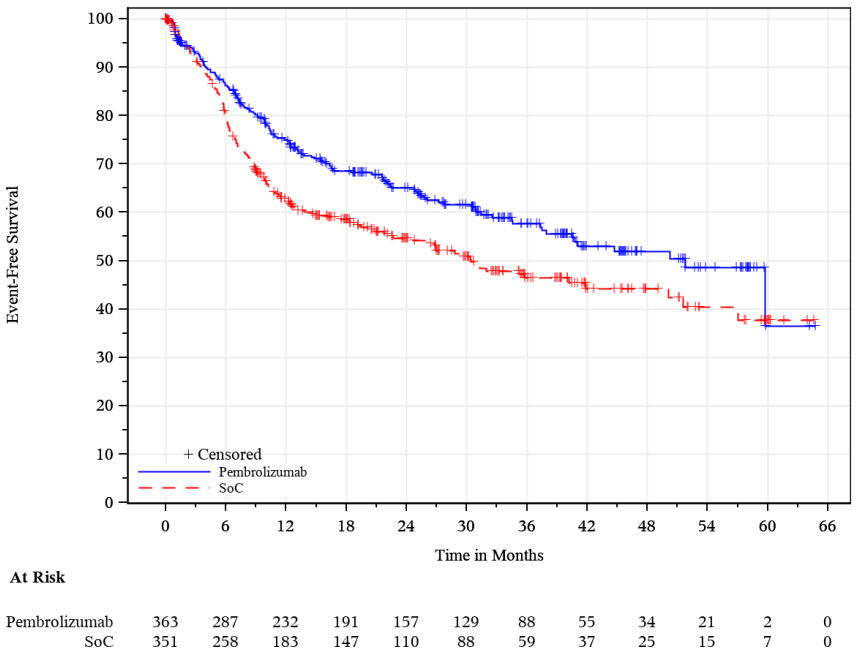
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

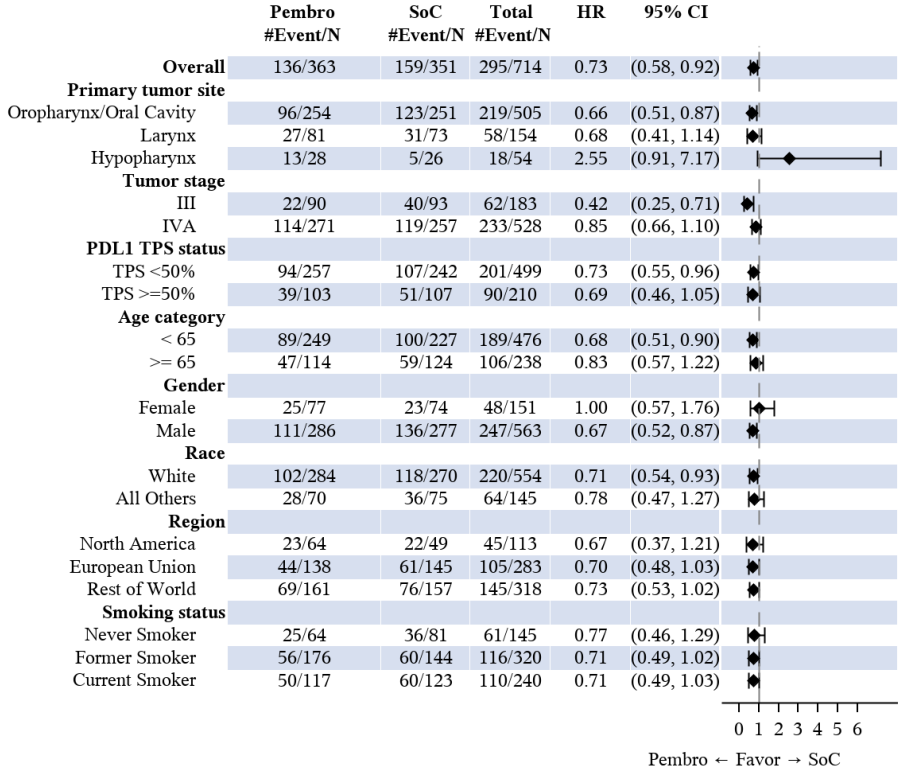
Database Cutoff Date: 25JUL2024

Figure 8: Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)



Database Cutoff Date: 25JUL2024.

Figure 9: Forest Plot of EFS Hazard Ratio by Subgroup Factors Based on BICR per RECIST 1.1 (Primary Censoring Rule) (ITT Population)



Database Cutoff Date: 25JUL2024.

Secondary endpoint – Major Pathological Response (mPR)

CPS≥1

Table 28: 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)		

[a] Based on Miettinen & Nurminen method stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

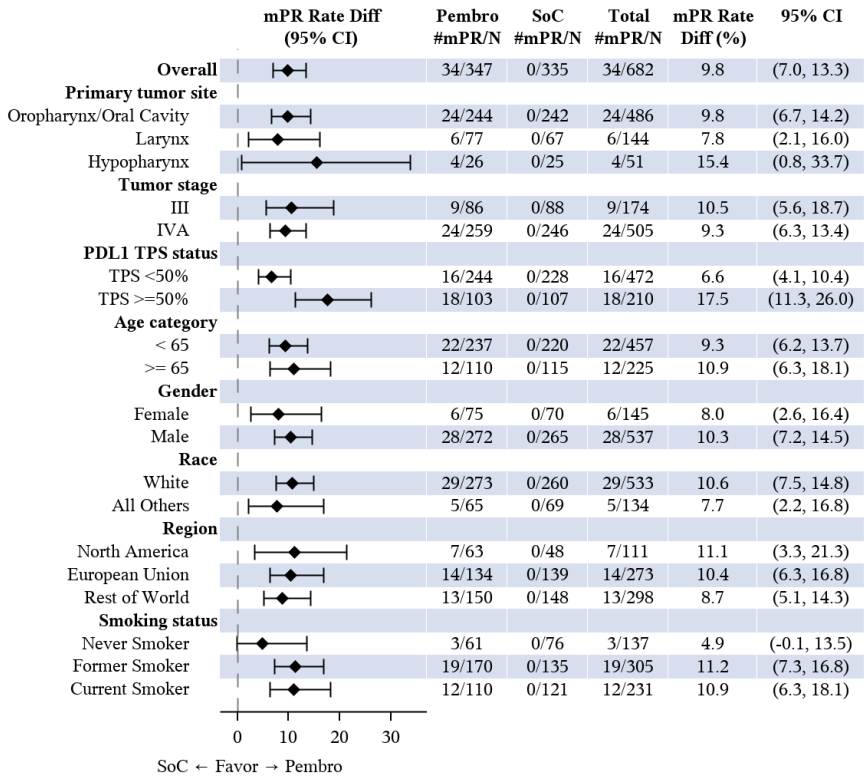
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

mPR = Major Pathological Response.

BIPR = Blinded independent pathologist review.

Database Cutoff Date: 25JUL2024.

Figure 10: Forest Plot of Difference in mPR Rate by Subgroup Factors Based on BIPR Assessment (Participants with CPS≥1, ITT Population)



For overall population, analysis is based on Miettinen and Nurminen method stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor 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

Secondary endpoint – Overall Survival

CPS≥10

Table 29: Analysis of Overall Survival (Participants with CPS≥10, ITT Population)

	Pembrolizumab (N=234)	SoC (N=231)
Number of Events (%)	73 (31.2)	89 (38.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
[Q1, Q3]	[22.4, NR]	[14.6, NR]
Person-months	7314.8	6337.5
Event Rate / 100 Person-months	1.0	1.4
vs SoC		
Hazard Ratio (95% CI)[b]	0.72 (0.52, 0.98)	
p-value[c]	0.01793	
OS Rate at month 6 (%) (95% CI)	93.6 (89.5, 96.1)	88.7 (83.9, 92.2)
OS Rate at month 12 (%) (95% CI)	85.8 (80.6, 89.7)	77.8 (71.9, 82.7)
OS Rate at month 24 (%) (95% CI)	74.8 (68.5, 80.0)	67.1 (60.4, 73.0)

OS Rate at month 36 (%) (95% CI)	68.2 (61.3, 74.2)	59.2 (51.7, 65.9)
OS Rate at month 48 (%) (95% CI)	63.5 (55.7, 70.2)	58.1 (50.4, 65.0)
OS Rate at month 60 (%) (95% CI)	61.0 (52.0, 68.8)	52.5 (42.9, 61.1)

[a] From product-limit (Kaplan-Meier) method for censored data.

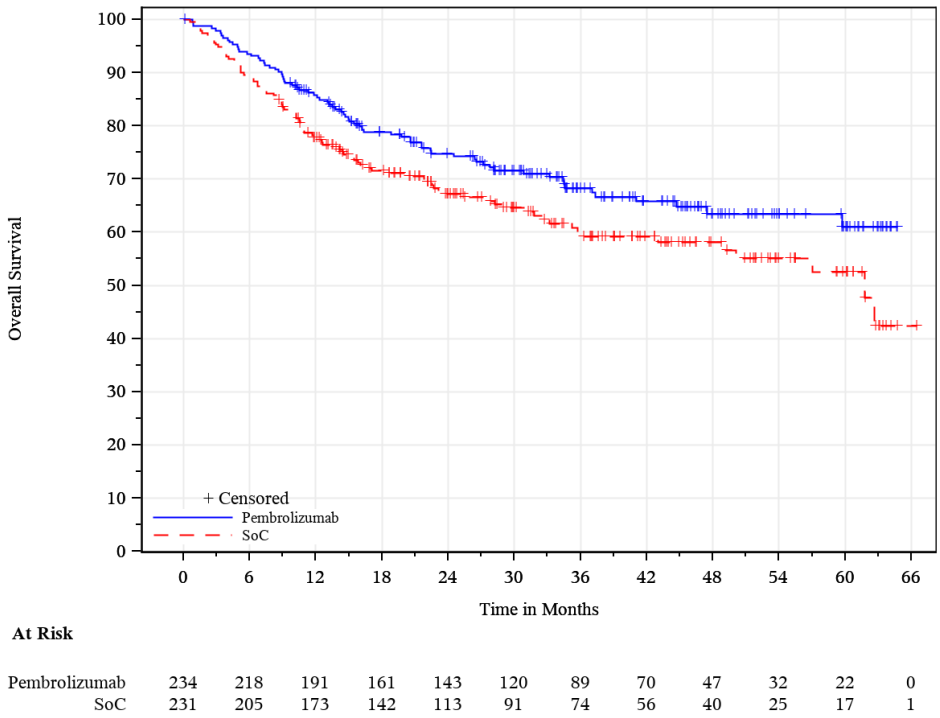
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 25JUL2024

Figure 11: Kaplan-Meier Plot of Overall Survival (Participants with CPS≥10, ITT Population)

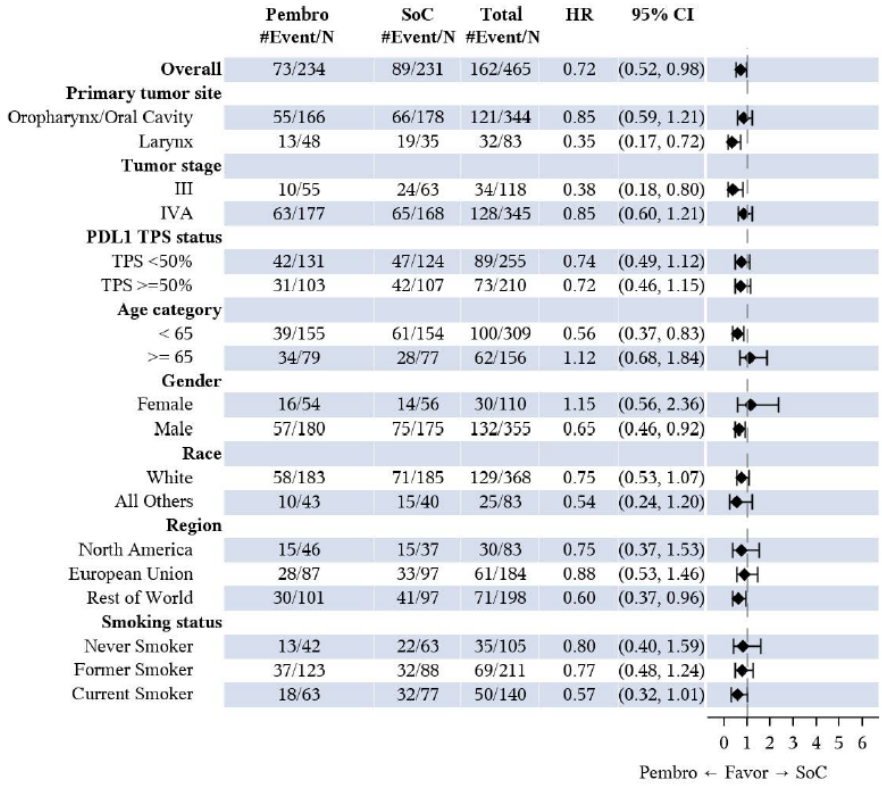


At Risk

Pembrolizumab	234	218	191	161	143	120	89	70	47	32	22	0
SoC	231	205	173	142	113	91	74	56	40	25	17	1

Database Cutoff Date: 25JUL2024.

Figure 12: Forest Plot of OS Hazard Ratio by Subgroup Factors (Participants with CPS≥10, ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor 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>=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

CPS≥1

Table 30: Analysis of Overall Survival (Participants with CPS≥1, ITT Population)

	Pembrolizumab (N=347)	SoC (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	10621.2	9081.0
Event Rate / 100 Person-months	1.0	1.4
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)	94.2 (91.2, 96.2)	88.4 (84.4, 91.4)
OS Rate at month 12 (%) (95% CI)	86.3 (82.2, 89.5)	77.5 (72.6, 81.6)
OS Rate at month 24 (%) (95% CI)	75.3 (70.2, 79.7)	67.3 (61.7, 72.2)
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)	64.0 (57.6, 69.6)	57.0 (50.4, 63.0)
OS Rate at month 60 (%) (95% CI)	60.1 (52.4, 66.8)	51.7 (43.8, 59.1)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor 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 tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 25JUL2024

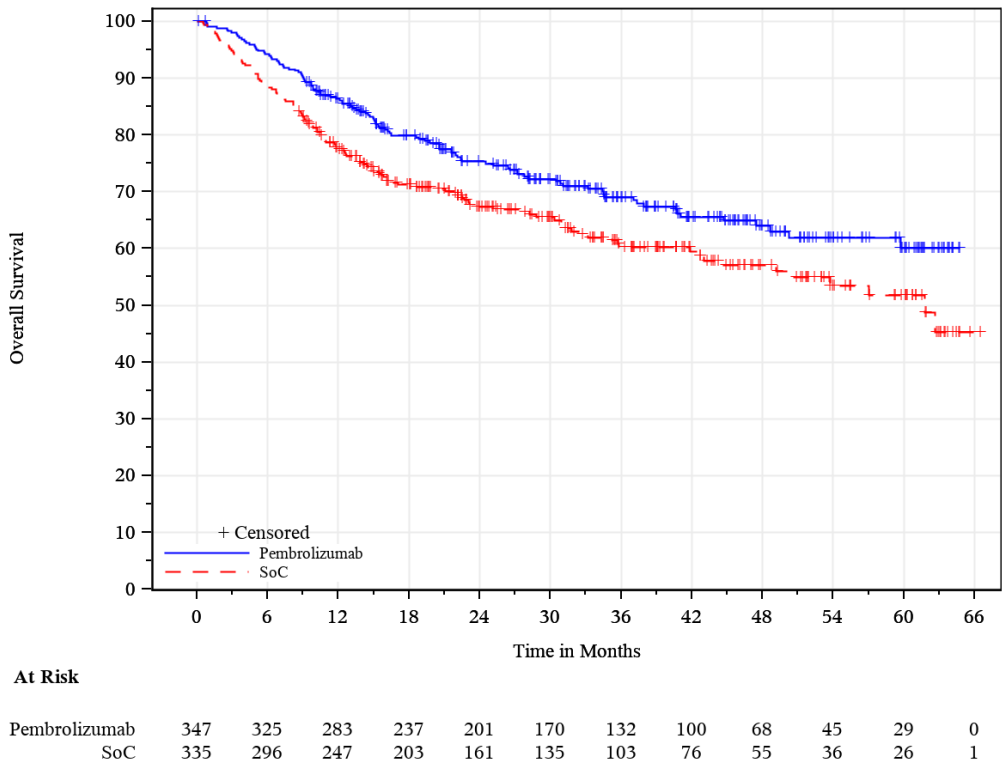
Table 31: Overall Survival Events and Censoring Descriptions (Participants with CPS>=1, ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	347		335		682	
Events and Censored						
Death	106	(30.5)	128	(38.2)	234	(34.3)
Censored	241	(69.5)	207	(61.8)	448	(65.7)
In Survival Follow Up	232	(66.9)	193	(57.6)	425	(62.3)
Withdrawal by Subject	7	(2.0)	11	(3.3)	18	(2.6)
Lost to Follow-Up	2	(0.6)	3	(0.9)	5	(0.7)

Participants in population is used as the denominator for the percentage calculation.

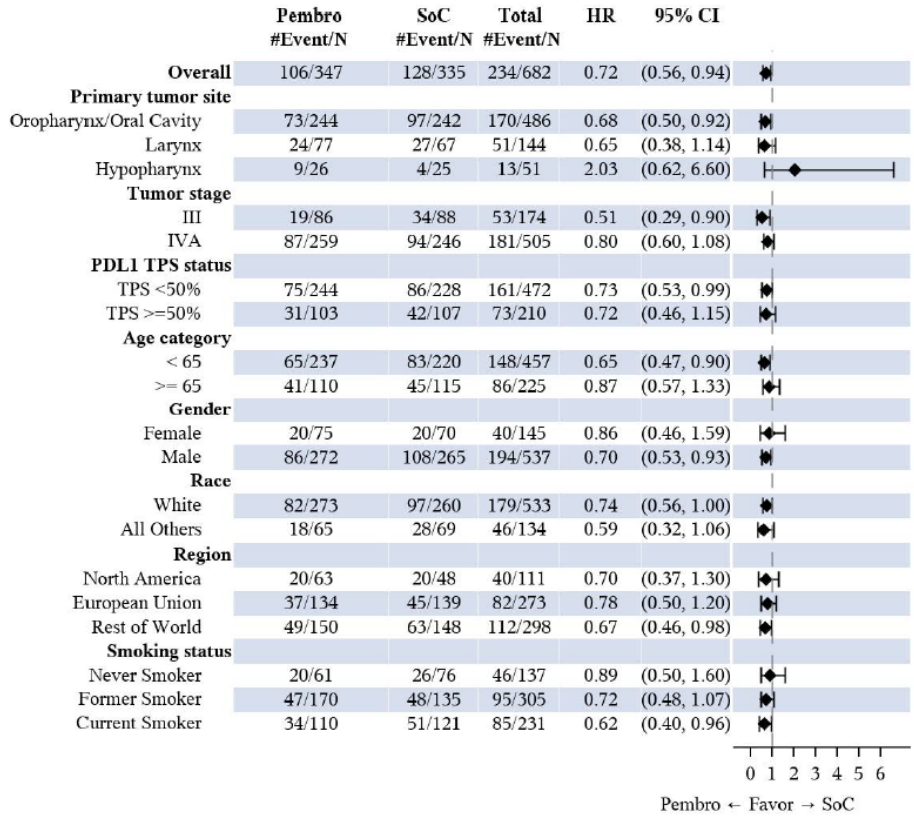
Database Cutoff Date: 25JUL2024

Figure 13: Kaplan-Meier Plot of Overall Survival (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024.

Figure 14: Forest Plot of OS Hazard Ratio by Subgroup Factors (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024.

All participants

Table 32: Analysis of Overall Survival (ITT Population)

	Pembrolizumab (N=363)	SoC (N=351)
Number of Events (%)	113 (31.1)	131 (37.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (61.9, NR)	61.8 (50.1, NR)
[Q1, Q3]	[25.2, NR]	[14.4, NR]
Person-months	11133.5	9550.7
Event Rate / 100 Person-months	1.0	1.4
vs SoC		
Hazard Ratio (95% CI)[b]	0.76 (0.59, 0.98)	
p-value[c]	0.01529	
OS Rate at month 6 (%) (95% CI)	94.2 (91.2, 96.2)	88.6 (84.8, 91.5)
OS Rate at month 12 (%) (95% CI)	86.7 (82.7, 89.8)	77.9 (73.2, 81.9)
OS Rate at month 24 (%) (95% CI)	75.9 (70.9, 80.1)	67.9 (62.5, 72.7)
OS Rate at month 36 (%) (95% CI)	68.4 (62.9, 73.3)	61.1 (55.1, 66.5)
OS Rate at month 48 (%) (95% CI)	63.6 (57.4, 69.1)	58.0 (51.6, 63.9)
OS Rate at month 60 (%) (95% CI)	59.8 (52.4, 66.4)	52.9 (45.2, 60.0)

[a] From product-limit (Kaplan-Meier) method for censored data.

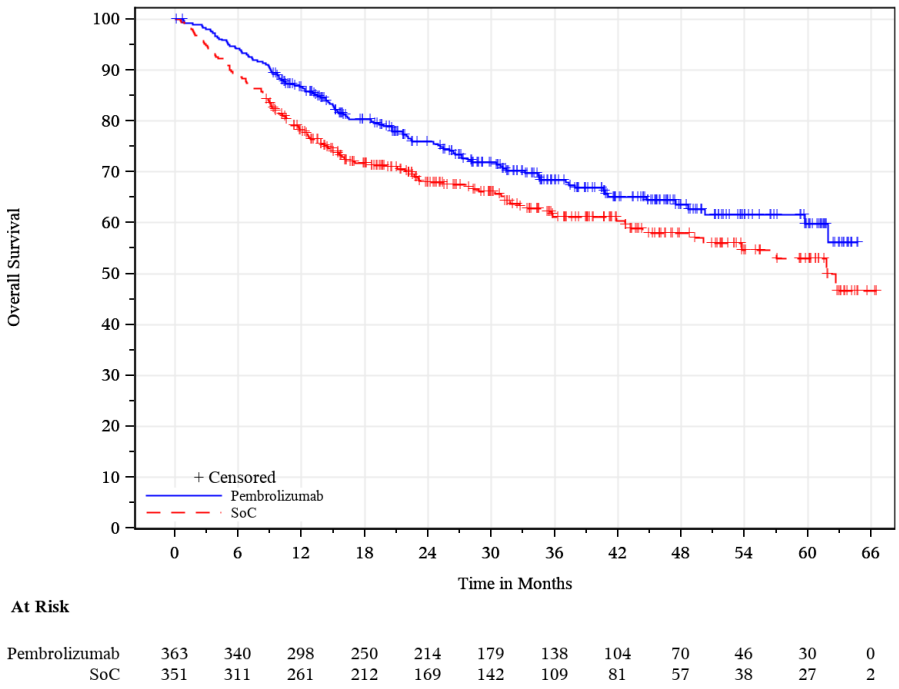
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

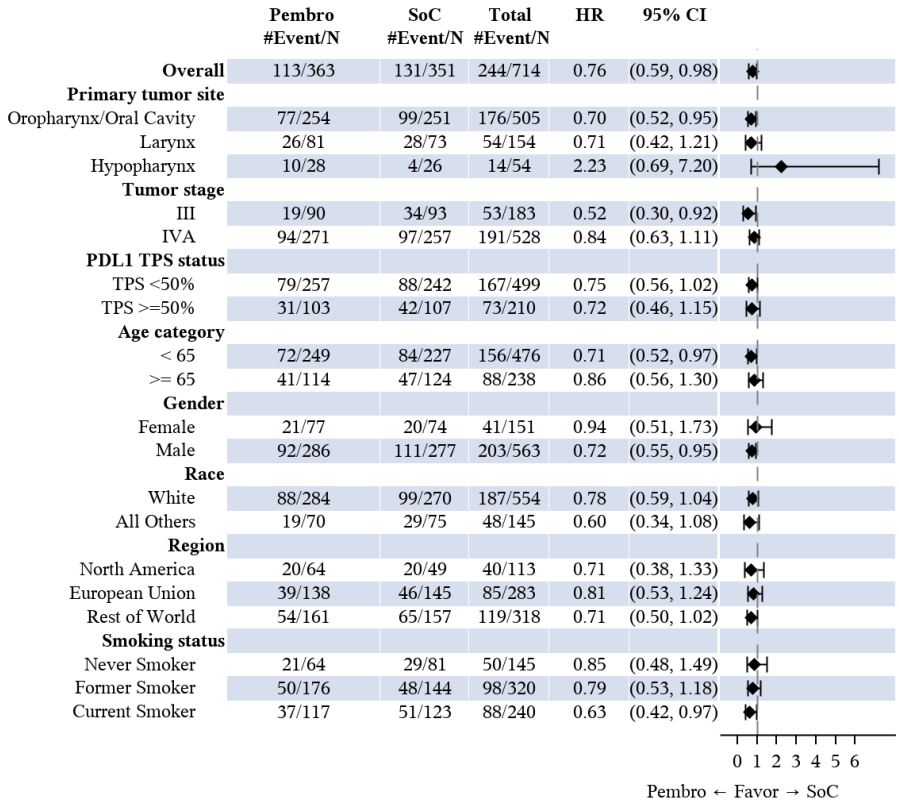
Database Cutoff Date: 25JUL2024

Figure 15: Kaplan-Meier Plot of Overall Survival (ITT Population)



Database Cutoff Date: 25JUL2024.

Figure 16: Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population)



Database Cutoff Date: 25JUL2024.

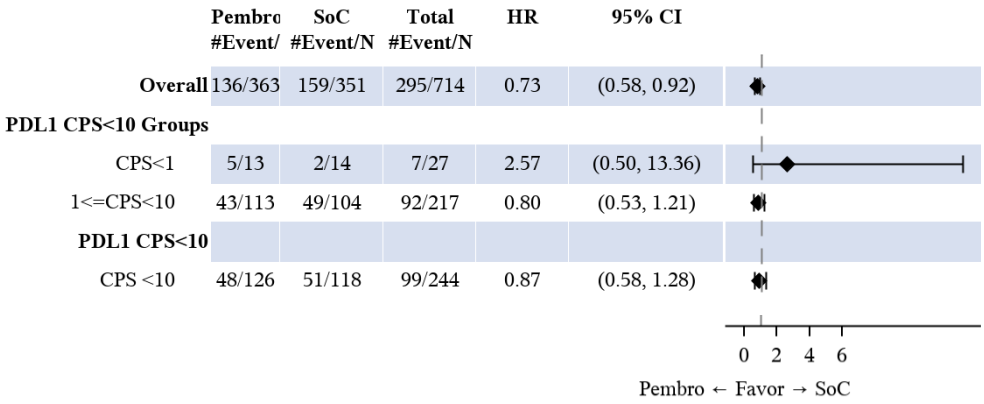
Ancillary analyses

Post-hoc Analysis in the CPS <1, CPS 1-9, and CPS <10 Populations

Table 33: patients by PD-L1 expression

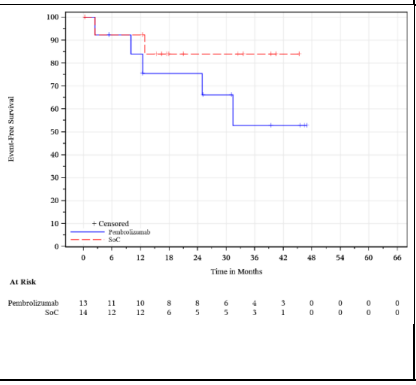
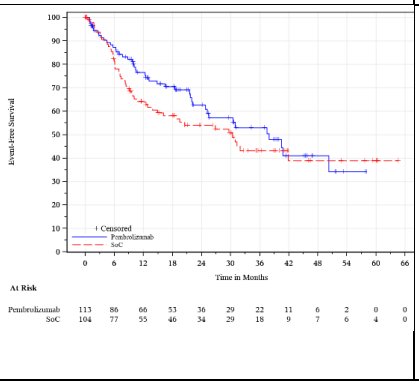
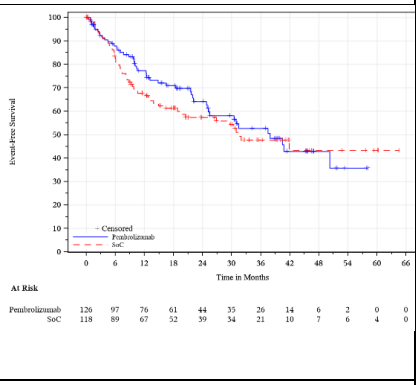
	Pembrolizumab	SoC	Total
CPS <1	13	14	27
CPS 1-9	113	104	217
CPS <10	126	118	244

Figure 17: Forest Plot of EFS Hazard Ratio by Subgroup Factors (Post-hoc) Based on BICR per RECIST 1.1 (Primary Censoring Rule) (ITT Population)



For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. Database Cutoff Date: 25JUL2024

Figure 18: Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 by PD-L1 expression (ITT population)

CPS<1	CPS>=1 and CPS<10	CPS<10
		

Database Cutoff Date: 25JUL2024.

Figure 19: Forest Plot of Difference in mPR Rate by Subgroup Factors (Post-hoc) Based on BIPR Assessment (ITT Population)

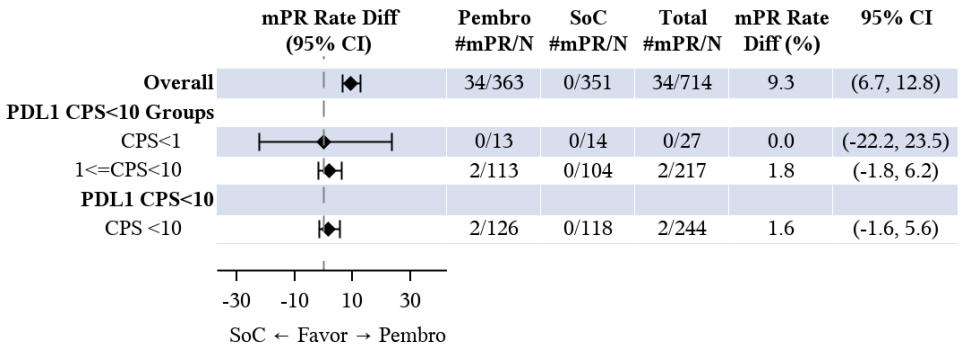


Figure 20: Forest Plot of OS Hazard Ratio by Subgroup Factors (Post-hoc) (ITT Population)

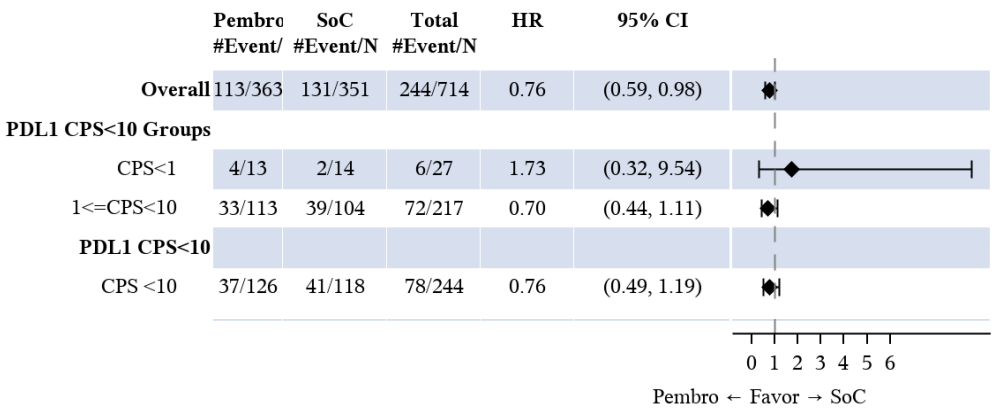
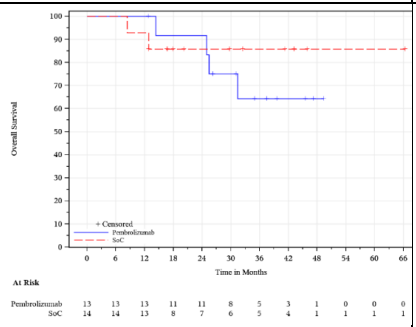
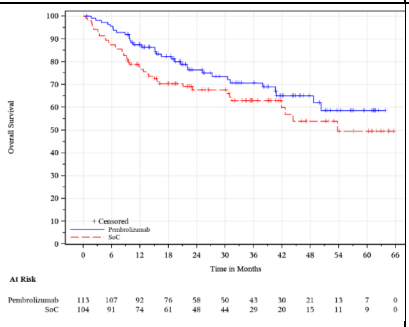
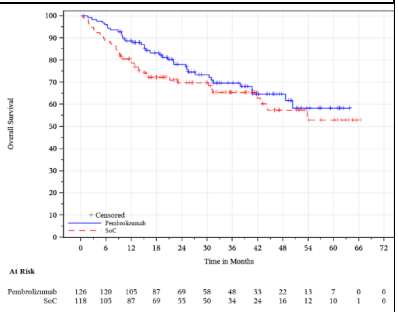


Figure 21: Kaplan-Meier Plot of Overall Survival Based on BICR per RECIST 1.1 by PD-L1 expression (ITT Population)

CPS<1	CPS>=1 and CPS<10	CPS<10
		
Database Cutoff Date: 25JUL2024.		

Incidence of Second Head and Neck and Other Cancers

A total of 9 (2.5%) of patients in the pembrolizumab arm and 18 (5.1%) in the SoC arm had one or more second head and neck and other cancer. Sensitivity EFS analysis including secondary incidence of head and neck and other cancers as an event in CPS≥1 showed HR 0.67 (0.53, 0.84).

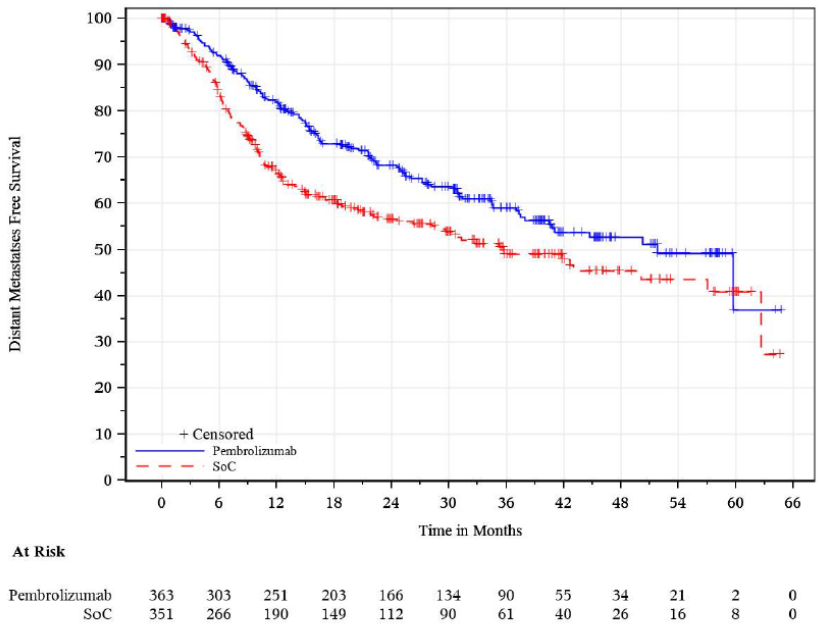
Distant Metastases Free Survival (DMFS)

Table 34: Analysis of Distant Metastases Free Survival Based on BICR per RECIST 1.1 (ITT Population)

	Pembrolizumab (N=363)	SoC (N=351)
Number of Events (%)	127 (35.0)	148 (42.2)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	51.8 (37.9, NR)	35.7 (26.3, 57.0)
[Q1, Q3]	[16.2, NR]	[8.8, NR]
Person-months	8557.8	6785.5
Event Rate / 100 Person-months	1.5	2.2
vs SoC		
Hazard Ratio (95% CI)[b]	0.71 (0.56, 0.90)	
p-value[c]	0.00252	
DMFS Rate at month 6 (%) (95% CI)	92.0 (88.5, 94.4)	84.2 (79.7, 87.7)
DMFS Rate at month 12 (%) (95% CI)	81.9 (77.3, 85.7)	66.5 (61.0, 71.5)
DMFS Rate at month 24 (%) (95% CI)	68.3 (62.6, 73.2)	56.6 (50.7, 62.1)
DMFS Rate at month 36 (%) (95% CI)	59.1 (52.8, 64.8)	49.0 (42.5, 55.3)
DMFS Rate at month 48 (%) (95% CI)	52.6 (45.6, 59.2)	45.4 (38.1, 52.4)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor 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 tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
NR = Not reached.
Database Cutoff Date: 25JUL2024

Figure 22: Kaplan-Meier Plot of Distant Metastases Free Survival Based on BICR per RECIST 1.1 (ITT Population)



Database Cutoff Date: 25JUL2024.

Local Regional Control Based on BICR

Table 35: Analysis of Local Regional Control Based on BICR per RECIST 1.1 (ITT Population)

	Pembrolizumab (N=363)	SoC (N=351)
Number of Events (%)	136 (37.5)	159 (45.3)
Number of Competing Events (%)	93 (25.6)	115 (32.8)
vs SoC		
Hazard Ratio (95% CI)[a]	0.92 (0.61, 1.41)	
p-value[b]	0.3539	
Event cumulative incidence at 6 months (%) (95% CI)	6.9 (4.6, 9.9)	7.4 (4.9, 10.6)
Event cumulative incidence at 12 months (%) (95% CI)	10.7 (7.6, 14.2)	11.5 (8.3, 15.3)
Event cumulative incidence at 18 months (%) (95% CI)	12.0 (8.8, 15.8)	11.5 (8.3, 15.3)
Event cumulative incidence at 24 months (%) (95% CI)	12.4 (9.1, 16.2)	11.5 (8.3, 15.3)
Event cumulative incidence at 36 months (%) (95% CI)	13.4 (9.9, 17.5)	14.3 (10.4, 18.7)
Event cumulative incidence at 48 months (%) (95% CI)	13.4 (9.9, 17.5)	15.3 (11.1, 20.1)

[a] Based on Cox regression model for competing-risks data with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

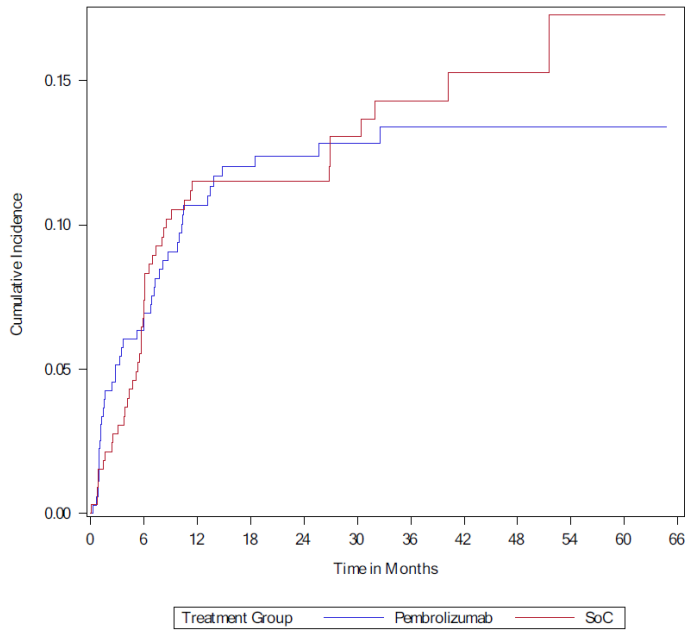
[b] One-sided p-value based on Gray's test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

Distant metastases diagnosed before any locoregional failure and death in the absence of locoregional failures are not considered events of interest, but as competing risk events.

Cumulative incidence at specified time points is based on nonparametric estimation of cumulative incidence of the event of interest accounting for competing risk events.

Database Cutoff Date: 25JUL2024.

Figure 23: Kaplan-Meier Plot of Local Regional Control Based on BICR per RECIST 1.1 (ITT Population)



Database Cutoff Date: 25JUL2024.

Exploratory EFS and OS by post-surgical risk categorization

Patients who did have surgery were thereafter classified in **low risk** and **high risk** according to local pathology report. Post-surgical risk categorization after central revision (18.2% discordance) was as follows:

Table 36: Summary of Post-Surgical Risk Categorization (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Risk Category by Central Assessment						
HIGH RISK	118	(32.5)	156	(44.4)	274	(38.4)
LOW RISK	196	(54.0)	148	(42.2)	344	(48.2)
Missing	49	(13.5)	47	(13.4)	96	(13.4)

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 tumor site and neck lymph nodes.
Database Cutoff Date: 25JUL2024.

Figure 24: Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (High/Low Risk Participants, ITT Population)

High risk population	**Low risk population**

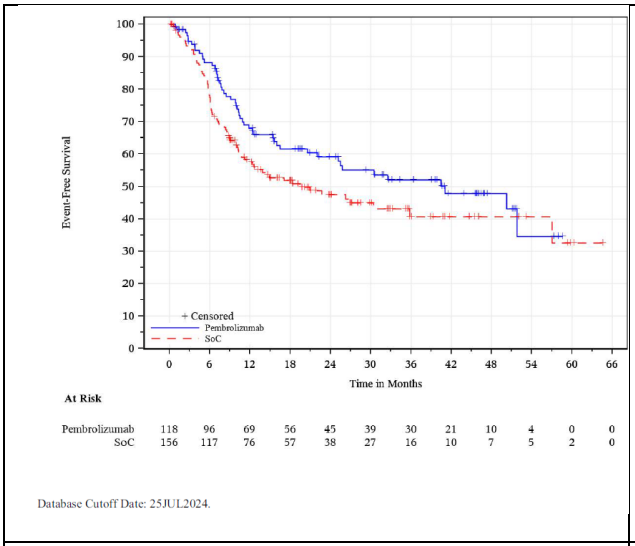
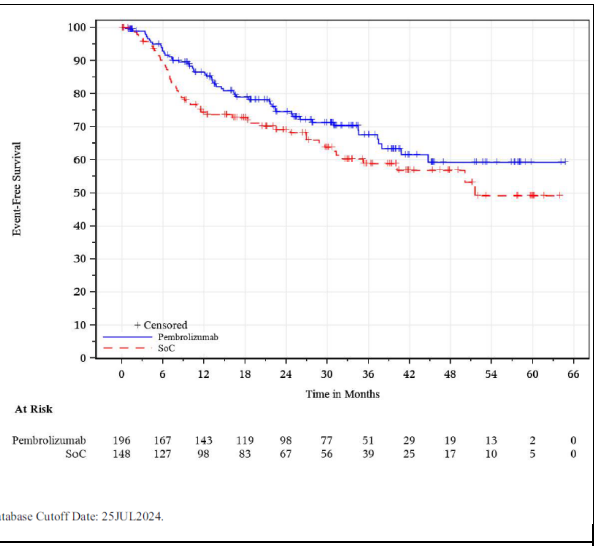
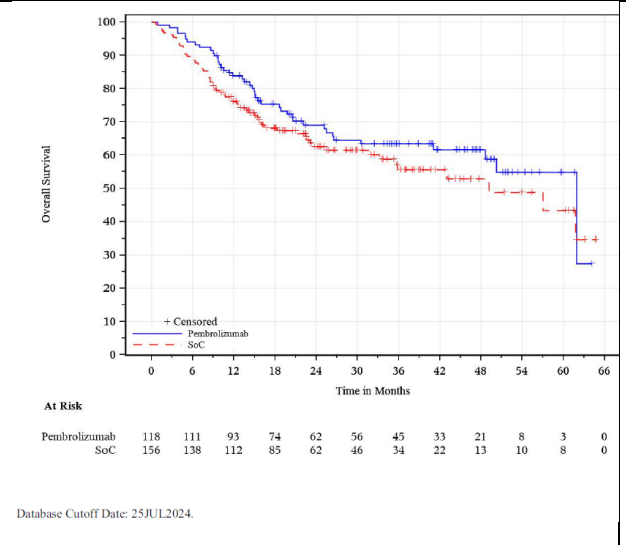
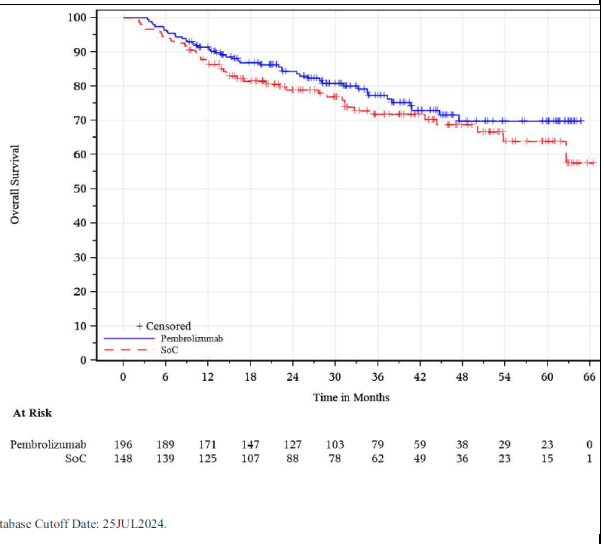
	
HR 0.73 (0.52, 1.05)	HR 0.74 (0.51, 1.08)

Figure 25: Kaplan-Meier Plot of Overall Survival (High/Low Risk Participants, ITT Population)

High risk population	Low risk population
	
HR 0.79 (0.53, 1.16)	HR 0.79 (0.52, 1.20)

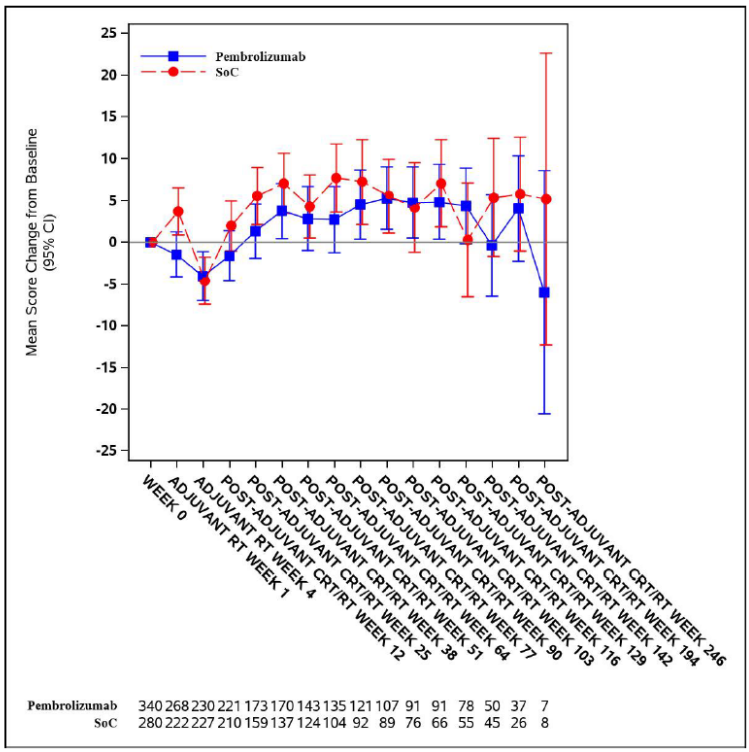
Patient-reported Outcomes

PROs were evaluated using EORTC QLQ-C30, EORTC QLQ-H&N35 (secondary endpoints), and EQ-5D-5L (exploratory endpoint). Analysis of mean change from baseline in the EORTC QLQ-C30 global health status/QoL and physical functioning scores and swallowing, speech and pain symptoms using the EORTC QLQ-H&N35 was calculated in all participants for IA1. For the EORTC QLQ-C30 global health status/QoL and functional domains, a higher score denotes better HRQoL or function. For EORTC QLQ-H&N35, a higher score indicates a decline or more severe symptoms and a decreased score indicates improvement.

Mean change from baseline in the EORTC QLQ-C30 global health status/QoL scores were similar in all participants and the CPS≥1 and CPS≥10 populations in the pembrolizumab group at Week 4 and Week

6 (neoadjuvant). Mean change from baseline global health status/QoL scores were similar between the pembrolizumab and SoC groups in all 3 populations at post adjuvant RT ± cisplatin Week 25 and 51.

Figure 26: 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 (PRO FAS Population)



Database Cutoff Date: 25JUL2024

Mean change from baseline in the EORTC QLQ-C30 physical functioning domain, QLQH& N 35 swallowing, speech, pain scores and EQ-5D-VAS remained stable over time in all participants in the pembrolizumab group at Week 4 and 6 (neoadjuvant phase). No differences were observed in the change in baseline for physical functioning at post adjuvant RT ± cisplatin Week 25 and 51 between the pembrolizumab and the SoC groups in all participants. In all participants, mean change from baseline EORTC QLQ-H&N35 swallowing, speech, and pain symptom scores were generally similar between the pembrolizumab and SoC groups at post adjuvant RT ± cisplatin Week 25 [Figure 14.2-38]. Mean change from baseline pain scores were observed to improve in both groups.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37 Summary of Efficacy for trial KEYNOTE-689

Title: A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)	
Study identifier	MK-3475-689-09 (EudraCT: 2017-001139-38; EU CT: 2022-500254-41-00; NCT: NCT03765918)

Design	Phase III, randomized, open-label, multi-centre		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Up to 7 years not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Group A (pembrolizumab)		Pembrolizumab 200 mg q3w (2 cycles) as neoadjuvant → surgical resection → adjuvant pembrolizumab 200 mg q3w (3 cycles) in combination with SoC RT ± cisplatin 100 mg/m2 q3w (3 cycles) followed by pembrolizumab maintenance 200 mg q3w (12 cycles). N=363
	Group B (SoC)		surgical resection → adjuvant SoC RT ± cisplatin 100 mg/m2 q3w (3 cycles) N=351
Endpoints and definitions	Primary endpoint	EFS by BICR per RECIST 1.1	Time from the date of randomization to the date of first record of any of the following events: radiographic PD, radiographic PD during the neoadjuvant phase that precludes surgery, local or distant PD or recurrence as assessed with imaging or biopsy as indicated, death due to any cause (a secondary primary malignancy is not an EFS event)
	Secondary endpoint	mPR by BIPR	Less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes
	Secondary endpoint	OS	Time from the date of randomization to the date of death due to any cause
Database lock	28-AUG-2024		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (n=714) Interim Analysis 1 (data cut-off 25 July 2024)			
Descriptive statistics and estimate variability	Treatment group		**Pembrolizumab**	**SoC**
	Number of subjects	CPS≥10 CPS≥1 All participants	234 347 363	231 335 351
	EFS median months (95%CI)	CPS≥10 CPS≥1 All participants	59.7 (41.1, NR) 59.7 (37.9, NR) 51.8 (37.5, NR)	26.9 (18.3, 51.5) 29.6 (19.5, 41.9) 30.4 (21.8, 50.1)
	mPR rate % (95%CI)	CPS≥10 CPS≥1 All participants	13.7 (9.5, 18.8) 9.8 (6.9, 13.4) 9.4 (6.6, 12.8)	0.0 (0.0, 1.6) 0.0 (0.0, 1.1) 0.0 (0.0, 1.0)
	OS median months (95%CI)	CPS≥10 CPS≥1 All participants	NR (NR, NR) NR (NR, NR) NR (61.9, NR)	61.8 (49.2, NR) 61.8 (49.2, NR) 61.8 (50.1, NR)

Effect estimate per comparison	Primary endpoint	Comparison groups		**Pembrolizumab vs SoC**
	EFS	HR	CPS≥10 CPS≥1 All participants	0.66 0.70 0.73

		95%CI	CPS≥10 CPS≥1 All participants	(0.49, 0.88) (0.55, 0.89) (0.58, 0.92)
		P-value (1sided)	CPS≥10 CPS≥1 All participants	0.00217 0.00140 0.00411
	Secondary endpoint mPR	Comparison groups		**Pembrolizumab vs SoC**
		Difference in rate %	CPS≥10 CPS≥1 All participants	13.7 9.8 9.3
		95%CI	CPS≥10 CPS≥1 All participants	(9.7, 18.7) (7.0, 13.3) (6.7, 12.8)
		P-value (1sided)	CPS≥10 CPS≥1 All participants	<0.00001 <0.00001 <0.00001
	Secondary endpoint OS	Comparison groups		**Pembrolizumab vs SoC**
		HR	CPS≥10 CPS≥1 All participants	0.72 0.72 0.76
		95%CI	CPS≥10 CPS≥1 All participants	(0.52, 0.98) (0.56, 0.94) (0.59, 0.98)
		P-value (1sided)	CPS≥10 CPS≥1 All participants	0.01793 0.00666 (nominal) 0.01529 (nominal)
Notes	At IA1, EFS and mPR in all 3 populations (CPS≥10, CPS≥1, and All participants) were statistically significant. OS in the CPS≥10 did not cross the p-value boundary thus did not reach statistical significance, therefore OS in CPS≥1 and All participants was not statistically tested per multiplicity strategy (nominal p-values were provided). OS will continue to be tested at the next IA.			

Analysis performed across trials (pooled analyses and meta-analysis)

None.

Clinical studies in special populations

Table 38. Clinical studies in special populations

	Pembrolizumab	**SoC**
Renal impairment* patients (Subjects number /total number)	11 / 363	12 / 351
Hepatic impairment** patients (Subjects number /total number)	0 / 363	1 / 351
Paediatric patients <18 years (Subjects number /total number)	0 / 363	0 / 351
Age 65-74 (Subjects number /total number)	92/ 363	100 / 351
Age 75-84 (Subjects number /total number)	22 / 363	22 / 351

Age 85+ (Subjects number /total number)	0 / 363	2 / 351
Other (Subjects number /total number)	249 / 363	227 / 351

* Renal impairment is defined as having measured or calculated creatinine clearance < 60 mL/min
** Hepatic impairment is defined as having total bilirubin > 1.5 x ULN and direct bilirubin > ULN, or AST > 2.5 x ULN, or ALT > 2.5 x ULN.
Total number of subjects includes all randomized participants.

Supportive study(ies)

None.

2.4.3. Discussion on clinical efficacy

The MAH applied for an extension of indication of Keytruda as monotherapy for the treatment of resectable locally advanced HNSCC as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without platinum-containing chemotherapy and then as monotherapy supported by the pivotal study KEYNOTE-689.

Design and conduct of clinical studies

KEYNOTE-689 (KN-689) is a phase 3, randomized, multicenter, open-label study, in adult patients with resectable non metastatic squamous cell carcinoma of the head and neck. The study included stage III or IVA larynx/hypopharynx/oral cavity, stage III or IVA oropharyngeal p16 negative or stage III oropharyngeal p16 positive that is T4 (N0-N2) M0, according to AJCC 8th edition, who were considered resectable and for whom primary surgery was the treatment of choice per investigator; eligibility for primary surgery was also to be validated by a multidisciplinary team. No prior RT or systemic therapy, including anti-PD(L)1 agents, was allowed.

A total of 714 participants were enrolled (363 in the pembrolizumab arm and 351 in the control arm) stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx), tumour stage (III vs IVA), and PD-L1 status (TPS ≥50% vs <50%), the latter assessed centrally from a tissue biopsy. PD-L1 expression replaced HPV as stratification factor based on accumulating evidence of the predictive role of PD-L1 expression in HNSCC (KEYNOTE-012[18], KEYNOTE-40[19], KEYNOTE-048[20]). Although there are doubts for using different PD-L1 score biomarkers for randomization (TPS) and for biomarker driven hypotheses (CPS), post-hoc analyses were reassuring in this regard.

Baseline characteristics were well balanced between treatment arms, with the only exception being a slightly higher number of non-smokers (17.6% vs 23.1%) and subjects with ECOG 0 (54.8% vs 58.5%) in the control arm. Baseline characteristics in the CPS≥1 and ≥10 population, as well as in the APAT, were consistent with the ITT population. As expected, based on the epidemiology of the disease, most patients were male, with a median age of 60 years (≥65 33%), mostly former (45%) or current (34%) smokers and with a history of alcohol use (68%). Only 4% of patients had HPV positive tumours, one of the main risk factors for oropharyngeal tumours, as compared to studies in advanced/metastatic [KEYNOTE-048 (22%) and KEYNOTE-040 (24%)] and locally advanced HNSCC

[18] Chow LQM, Haddad R, Gupta S, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol. 2016 Nov 10;34(32):3838-3845.
19 EMA/543713/2018/corr. EPAR Keytruda EMEA/H/C/003820/II/0042
[20] EMA/CHMP/591139/2019/corr. EPAR Keytruda EMEA/H/C/003820/II/0065

[KEYNOTE-412 (26%)[21]]. The higher rate of patients with HPV negative tumours in KEYNOTE-689 was justified as reflective of the high proportion of patients with non-oropharyngeal cancer (about 90%), also in comparison to the other pembrolizumab clinical studies, as well as the restricted eligibility criterion based upon HPV status.

KEYNOTE-689 included 95.5% of patients with CPS≥1 and 65.1% of patients with CPS≥10, well balanced between the two treatment arms. Patients with PD-L1 negative tumours (CPS<1) were only 3.8% of the overall population, less than prior HNSCC studies (10% in KN-412, 15% in KN-48 and 20% in KN-040). There is limited data regarding the real-world prevalence of PD-L1 expression in the locally advanced setting. As investigators were blinded to PD-L1 status, and patients with negative/low PD-L1 tumour expression were enrolled during each period of randomization between amendments, those alleviate concerns regarding possible bias. PD-L1 CPS<1 tumours were excluded from the indication during the procedure (see below).

Patients in the experimental arm received neoadjuvant therapy consisting of 2 cycles of pembrolizumab, surgical resection, and adjuvant therapy with pembrolizumab in combination with SoC radiotherapy (RT) with or without concomitant cisplatin every 3 weeks (3 cycles) followed by pembrolizumab monotherapy (12 cycles, approximately 1 year overall). In the control arm, no neoadjuvant therapy was administered, as patients had immediate surgery, followed by adjuvant therapy with SoC RT +/- cisplatin. Although the control arm reflected the SoC treatment in the eligible population, due to the study design which included a neoadjuvant phase only in the experimental arm, efficacy assessments were carried out at later time since randomization in the pembrolizumab group with respect to SoC (median difference 3.7 weeks at first efficacy assessment, maintained in times to subsequent efficacy assessments). This issue of EFS assessment, together with the updated EFS definition, may have led to an overestimation of the beneficial effect of pembrolizumab (see below).

The MAH's rationale of using neoadjuvant pembrolizumab was based on pathological responses induced in prior small exploratory studies in HNSCC [22,23,24,] and the concurrent administration of pembrolizumab with RT ± cisplatin was justified based on preclinical studies demonstrating increased PD-L1 expression and superior survival in HNSCC murine models [25]. According to the MAH, all components of the perioperative regimen evaluated in KEYNOTE-689 may contribute to providing clinical benefit in EFS observed in KEYNOTE-689 because trials evaluating pembrolizumab either concurrently with RT (PembroRad) or concurrently with CRT followed by maintenance treatment (KEYNOTE-412) were unable to provide an EFS benefit. However, KEYNOTE-689 as designed is not able to disentangle the effect of the neoadjuvant and adjuvant parts, and the MAH did not implement alternative study design considered feasible by the CHMP at the time of the Scientific Advice.

Also, the optimized treatment duration of adjuvant pembrolizumab remains unknown based on KN-689.

[21] Machiels JP, Tao Y, Licitra L, Burtness B, Tahara M, Rischin D, Alves G, Lima IPF, Hughes BGM, Pointreau Y, Aksoy S, Laban S, Greil R, Burian M, Hetnał M, Delord JP, Mesía R, Taberna M, Waldron JN, Simon C, Grégoire V, Harrington KJ, Swaby RF, Zhang Y, Gumuscu B, Bidadi B, Siu LL; KEYNOTE-412 Investigators. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2024 May;25(5):572-587.
[22] Wise-Draper TM, Gulati S, Palackdharry S, Hinrichs BH, Worden FP, Old MO, et al. Phase II clinical trial of neoadjuvant and adjuvant pembrolizumab in resectable local-regionally advanced head and neck squamous cell carcinoma. Clin Cancer Res. 2022 Apr 1;28(7):1345-52.
[23] Oliveira G, Egloff AM, Afeyan AB, Wolff JO, Zeng Z, Chernock RD, et al Preexisting tumor-resident T cells with cytotoxic potential associate with response to neoadjuvant anti-PD-1 in head and neck cancer. Sci Immunol. 2023 Sep 8;8:eadf4968.
[24] Uppaluri R, Campbell KM, Egloff AM, Zolkind P, Skidmore ZL, Nussenbaum B, et al. Neoadjuvant and adjuvant pembrolizumab in resectable locally advanced, human papillomavirus-unrelated head and neck cancer: a multicenter, phase II trial. Clin Cancer Res. 2020 Oct 1;26(19):5140-52.
[25] Oweida A, Lennon S, Calame D, Korpela S, Bhatia S, Sharma J, et al. Ionizing radiation sensitizes tumors to PD-L1 immune checkpoint blockade in orthotopic murine head and neck squamous cell carcinoma. Oncoimmunology. 2017;6(10):e1356153.

Unbalanced number of patients randomized but not treated was observed (3 vs 35). Acknowledging the limits of the interpretation due to the small sample size, this might suggest worse disease status that likely led to increased patient dropout in this SoC arm, given the open-label nature of this study. Additional sensitivity analyses requested (data not shown) however suggested that by controlling for possible confounding in undergoing surgery or starting adjuvant therapy did not affect study findings.

Few more patients were able to undergo complete R0 resection after neoadjuvant pembrolizumab as compared to the control arm (88.9% vs 85%). Also,less patients were classified as "high-risk" (i.e. extranodal extension and/or positive resection margins, factors chosen based on literature data[26]) in the pembrolizumab arm after surgery; accordingly, less intense post-surgical treatment was used in this group (combined chemo-RT 29% vs 40%). Although exploratory analysis by risk classification suggests EFS benefit of pembrolizumab over SoC regardless of risk classification, post-hoc analyses based on post-randomized outcomes should be interpreted with caution.

Reassuringly, discontinuation rate of RT and cisplatin due to side effect was similar in both arms. The percentage of patients completing the whole treatment (43%) was similar to what was seen in other adjuvant pembrolizumab studies (48%-53%)[27] [28] [29], and discontinuation of pembrolizumab due to AE was similar to other Keytruda studies (e.g. KN-671 or KN-412). Therefore, the impact of adjuvant pembrolizumab toxicity in treatment discontinuation is generally as expected for this drug (see also clinical safety). The percentages of participants who received post-study treatments (RT, surgery, systemic therapy) was similar across treatment groups.

Primary endpoint of the study was event free survival (EFS) as assessed by independent review (BICR) per RECIST 1.1. Assessment by BICR is supported in the context of an open-label study. Of note, the definition of EFS was changed late during the course of the study with Amendment 08, as it was specified that "Radiographic disease progression during neoadjuvant phase that precludes surgery will be considered an event". Indeed, in the original EFS definition, all PD occurring before surgery (regardless of whether the surgery was performed) were considered events. Most of the participants with pre-surgery radiographic PD that did not preclude surgery were observed in the pembrolizumab arm (77 vs 13), which is partly also due to the different planned radiographic assessment by arm, mostly already at the time of Amendment 08. It is reassuring that most of those patients who had PD that did not preclude surgery in the pembrolizumab arm were able to undergo a complete R0 resection, although at a slight lower rate than the overall population (83% vs 88.9%). However, it is not possible to appropriately interpret the post-surgical/adjuvant treatment pathway of those patients due to the changes in discontinuation criteria throughout the study secondary to the changes in the EFS definition.

Differently from results of primary analysis, in a post-hoc EFS analyses carried out by considering radiographic disease progressions during neoadjuvant phase that did not preclude surgery as EFS events – an extreme scenario – there was no evidence of efficacy of pembrolizumab [in population with CPS≥1, HR (95%CI): 1.00 (0.80,1.24); p=0.47990] (data not shown).

[26] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefèbvre JL. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005 Oct;27(10):843-50.
[27] Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024 Sep 28;404:1240-52.
[28] O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022 Oct;23:1274-86.
[29] Machiels JP, Tao Y, Licitra L, Burtness B, Tahara M, Rischin D, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2024 May;25:572-87.

The MAH stated that the amendment of the EFS definition was done without any knowledge of treatment group level results, and that the study team did not generate any results or summaries by randomized treatment assignment or actual treatment received until IA1. Also, the process and the responsibility concerning data collection and data analysis to guarantee not disclosing the results of unblinded analyses described by the MAH is considered acceptable. However, the lateness of amendment 08 in KEYNOTE-689 updating EFS definition to exclude progressive disease that did not preclude surgery remains not fully justified from a clinical perspective. It is acknowledged that one of the MAH's justifications for updating EFS definition was that the same was used in other neoadjuvant studies, including the ones leading to prior EU regulatory approval (KEYNOTE-522[30], KEYNOTE-671[31], Checkmate-816[32]). However, KEYNOTE-689 included a neoadjuvant phase only in the experimental arm, and, as noted in the FDA guidance[33] balanced timing of assessments among treatment arms is critical for the EFS endpoint.

Although the results of several post-hoc conservative analyses represent hypothetical scenarios, obtained results show that the EFS HR estimates in KEYNOTE-689 may be affected by differences in EFS assessments among arms and by management of disease progression that do not preclude surgery who were early lost after randomization (data not shown). Overall, such results suggest likely overestimation of the pembrolizumab effect on EFS in HNSCC. Therefore, in KEYNOTE-689, weakness of study design and analyses need to be recognized, and caution is needed in interpreting obtained EFS estimates.

Overall survival (OS) and major pathological response (mPR) were secondary endpoints. mPR was downgraded from primary to secondary endpoint, which is considered acceptable from a clinical perspective given the unclear clinical relevance of mPR in HNSCC.

The overall Type I error was strongly controlled at alpha = 2.5% (one-sided) across the primary endpoint EFS and the secondary endpoints mPR and OS and across multiple populations CPS≥10, CPS≥1 and All participants. Biomarker-driven hypotheses were included with protocol Amendment based on external data from KN-040 and KN-048 studies showing the predictive value of PD-L1 expression in R/M HNSCC.

Overall, the statistical methods are considered acceptable. Not adherence of the randomization procedure to the study protocol has emerged, although the MAH stated that there was no impact on the validity of randomization or study integrity.

Efficacy data and additional analyses

The MAH submitted the results of the **IA1** (data cut-off 25 July 2024), corresponding to an interim analysis for EFS and OS, and the final analysis for mPR. At IA1, median follow-up time of 27.1 months, and only 4% of subjects in the pembrolizumab arm were still receiving active treatment.

The addition of perioperative pembrolizumab to SoC resulted in a statistically significant and clinically meaningful improvement in **EFS,** as assessed by BICR, compared with SoC across all populations analysed. A trend towards improved EFS benefit in populations with higher PD-L1 expression is seen: **all participants** (HR: **0.73**; 95% CI: 0.58, 0.92; p=0.00411), **CPS ≥1** (HR: **0.70**; 95% CI: 0.55, 0.89; p=0.00140), **CPS ≥10** (HR: **0.66**; 95% CI: 0.49, 0.88; p=0.00217). EFS events occurred in approximately 41% of the population (37.5% vs 45.3% in the pembro vs control arm of all participants). The difference in EFS events is mainly due to a decrease in distant PD rate between

[30] EMA/257879/2022 – EPAR Keytruda EMEA/H/C/003820/II/0110
[31] EMA/118494/2024 – EPAR Keytruda EMEA/H/C/003820/II/0134
[32] EMA/287093/2023 – EPAR Opdivo EMEA/H/C/003985/II/0117
[33] FDA - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics – Guidance for industry – December 2018

experimental and control arm. The KM EFS curves diverge clearly from month 3 onwards in favour of the pembrolizumab arm across all three populations analysed (EFS rates difference of approximately 10%), although a high level of censoring is seen overall. Median EFS were 51.8 vs 30.4, 59.7 vs 29.6, 59.7 vs 26.9 months in all participants, CPS ≥1, and CPS ≥10, respectively. The results of the EFS sensitivity analyses were overall consistent with the primary analysis. The exploratory endpoint DMFS further confirmed the benefit of pembrolizumab. However, as discussed above, the obtained estimates of treatment effect in terms of EFS could potentially be overestimated.

mPR rate difference was also statistically significant, but the rate of response to pembrolizumab was limited and of dubious clinical relevance, with low rates of pCR (about 3%). As for EFS, a trend toward higher mPR following two cycles of neoadjuvant pembrolizumab in the patient population with higher PD-L1 expression was observed, with no major pathological responses in patients with CPS<1 expression.

Regarding **OS**, the observed p-value in the CPS ≥10 population did not cross the multiplicity-adjusted one-sided boundary, therefore OS was not formally tested in the CPS ≥1 population or in all participants, in line with the prespecified multiplicity strategy. However, the results suggest a trend towards improved survival with the addition of neoadjuvant/adjuvant pembrolizumab to SoC. Consistently with the EFS and mPR results, the benefit of adding pembrolizumab seems related to PD-L1 expression: **all participants** (HR: **0.76**; 95% CI: 0.59, 0.98; nominal p=0.01529), **CPS ≥1** (HR: **0.72;** 95% CI: 0.56, 0.94; nominal p=0.00666), **CPS ≥10** (HR: **0.72**; 95% CI: 0.52, 0.98; p=0.01793). OS events occurred overall in approximately 35% of the population (31.1% vs 37.3% in all participants). The KM OS curves diverge reassuringly from the beginning in favour of the pembrolizumab arms across all populations, although all curves are highly censored from month 9 onwards.

As discussed above, the OS data in the approvable CPS ≥1 population does suggest a beneficial effect of pembrolizumab, although not formally statistically tested due to the prespecified multiplicity rules. Moreover, the low rate of censoring due to withdrawal/lost to follow-up observed in the control arm - similar to that observed in the pembrolizumab arm - support accuracy of the obtained estimate of OS effect. Considering that OS is a robust and clinically meaningful endpoint, this partially alleviates the weakness and methodological concerns on EFS endpoint. Based on available data, it is not expected that the OS trend will meaningfully change with longer follow-up. However, as OS has not been formally tested in the CPS≥1 population, and considering the early disease setting, the MAH has committed to provide final OS results post-approval **(REC)**.

The MAH has provided post-hoc exploratory subgroup analyses for patients with negative or low PD-L1 expression, i.e. **CPS<1, CPS 1-9 and CPS<10**. Both EFS and OS results in the CPS 1-9 subgroup suggest a positive trend for the pembrolizumab-containing arm compared with control: EFS HR 0.80 (0.53, 1.21), OS HR 0.70 (0.44, 1.11), although the activity of pembrolizumab appears limited (mPR rate 1.8%). The subgroup of patients with CPS<1 was small, as it included only 27 patients overall (3.8% of the ITT). In this subgroup, EFS HR was 2.57 (0.50, 13.36) and OS HR was 1.73 (0.32, 9.54), with no mPR recorded. Therefore, acknowledging the limitations related to the limited sample size, small exploratory subgroup analyses suggest a potential trend towards an EFS and OS detriment for CPS<1 patients. This observation is supported by biological plausibility, indeed external data from all prior clinical trials with pembrolizumab in HNSCC showed a predictive value of PD-L1 and lack of pembrolizumab benefit in PD-L1 negative tumors, in the R/M setting (KN-048, KN-040 and KN-012 studies, EU approved Keytruda indications in HNSCC excluded PD-L1 low expressors), as well as in the unresectable HNSCC (KN-412). Therefore, the final wording of the indication was restricted to the PD-L1 CPS ≥1 population. In addition, as all patients in the pivotal study received cisplatin monotherapy

concomitantly with RT, and cisplatin concomitantly to RT is recommended as SoC in this setting in ESMO guidelines, the wording of the final indication was revised to clarify this.

Subgroup analyses in the small subset of patients with **hypopharynx** as the primary tumour site (7.6% of the ITT population, 28 vs 26 patients) suggested a potential detrimental effect with the addition of pembrolizumab [EFS HR 2.55 (0.91,7.17), OS HR 2.13 (0.62, 6.60)]. This was a small subgroup, and imbalances were observed in tumor staging (more T2 in pembrolizumab and more T4 in the SoC arm) and treatment pathway (more incomplete surgeries and fewer patients receiving CRT in the pembrolizumab arm). These factors may have contributed to the observed differences in outcomes, considering the lack of biological rationale[34] to expect differential efficacy in the hypopharynx tumours compared with other head and neck locations.

2.4.4. Conclusions on the clinical efficacy

KEYNOTE-689 study showed at the interim analysis a statistically significant and clinically relevant improvement in EFS in patients with resectable HNSCC who received pembrolizumab as neoadjuvant and adjuvant treatment, in addition to and continued after, post-operative RT+/-cisplatin, compared with adjuvant RT+/-cisplatin alone. A favourable trend in OS was also observed, although formal statistical testing at CPS ≥1 or in all participants was not performed at this stage.

A potential detriment cannot be excluded in the small subgroup of patients with PD-L1 negative tumors (CPS<1), which is biologically plausible and consistent with the predictive role of PD-L1 expression observed across prior clinical trials of pembrolizumab in HNSCC. The MAH has thus restricted the indication to the PD-L1 CPS ≥1 population, which is one of the pre-defined populations analysed in KN-689.

In addition, as all patients in the pivotal study received cisplatin monotherapy concomitantly with RT, and cisplatin concomitantly to RT is recommended as SoC in this setting in ESMO guidelines, the wording of the final indication was revised to clarify this.

However, in KEYNOTE-689, weakness of study design and analyses need to be recognized, and caution is needed in interpreting obtained estimates of treatment effect in terms of EFS. Indeed, this open-label study included a neoadjuvant phase only in the experimental arm, thus timing of the radiographic assessments was different between the two treatment groups. Further to this, the definition of EFS was amended late during the study excluding patients who had disease progression who did not preclude surgery from EFS events. The results of several post-hoc analyses that considered both issues together suggested likely overestimation of the beneficial effect in EFS. It is reassuring that the MAH stated that the amendment of the EFS definition was done without any knowledge of treatment group level results.

A beneficial effect of pembrolizumab in terms of OS is however suggested in CPS≥1, and data support accuracy of the obtained estimate of OS effect. Considering that OS is a robust and clinically meaningful endpoint, this partially alleviates the weakness and methodological concerns on EFS endpoint.

Final OS results are to be provided post-approval **(REC)**.

[34] Leemans CR, Braakhuis BJM, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer. 2011 Jan;11:9-22

2.5. Clinical safety

Introduction

The safety profile of pembrolizumab as neoadjuvant treatment and continued as adjuvant treatment in combination with radiation therapy with or without cisplatin (SoC) and then as monotherapy in adults for the treatment of resectable, locally advanced HNSCC is based on an interim analysis of the Phase 3 study KEYNOTE-689 with a data cutoff date of 25 JUL-2024.

As reported, in the experimental arm of the study protocol, the exposure to pembrolizumab contemplates different phases:

- 2 cycles of neoadjuvant therapy as perioperative treatment regimen of pembrolizumab monotherapy, followed by surgical resection

- 3 cycles of adjuvant treatment in combination with SoC RT ± cisplatin

- 12 cycles of pembrolizumab monotherapy for up to one year

In the control arm, subjects were candidate to receive:

- Surgical resection

- 3 cycles of SoC RT ± cisplatin

As results, patients enrolled in the two arms presented a different duration of exposure to study treatments.

Safety database includes data from subjects treated with pembrolizumab group vs. SoC group in the KEYNOTE-689 study. In addition to that, a comparison with the known safety profile of pembrolizumab monotherapy in participants with HNSCC using pooled safety data from previous pembrolizumab monotherapy in R/M HNSCC participants (KEYNOTE-012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055) and with the established safety profile of pembrolizumab monotherapy using pooled safety data from pembrolizumab monotherapy studies (RSD).

Table 39 Summary of Clinical Safety Datasets and Nomenclature

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-689 pembrolizumab	(N=361): Safety data from participants with Stage III-IVA resectable LA HNSCC who received pembrolizumab in the neoadjuvant phase and continued as adjuvant therapy in combination with RT ± cisplatin followed by pembrolizumab monotherapy in KEYNOTE-689	KN689: Pembrolizumab	pembrolizumab group
KEYNOTE-689 SoC	(N=315): Safety data from participants with Stage III-IVA resectable LA HNSCC who received no study treatment prior to surgery and who received RT ± cisplatin in the adjuvant phase in KEYNOTE-689	KN689: SoC	SoC group
Pembrolizumab monotherapy HNSCC	(N=909): Pooled safety data from participants with R/M HNSCC treated with pembrolizumab monotherapy from KEYNOTE-012, KEYNOTE-040, KEYNOTE-048 and KEYNOTE-055. RT was not part of protocol specified study treatment for any of these studies.	Pembrolizumab Monotherapy HNSCC Pool	Pooled Pembrolizumab Monotherapy HNSCC Dataset
Pembrolizumab monotherapy	(N=7631): Pooled safety data from participants treated with pembrolizumab monotherapy, including 2559 participants with advanced melanoma from	Pembrolizumab monotherapy RSD	pembrolizumab RSD

reference safety	KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-054, and KEYNOTE-716; 2022 participants with NSCLC from KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042; 909 participants with HNSCC from KEYNOTE-012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055; 636 participants with bladder cancer from KEYNOTE-045 and KEYNOTE-052; 488 participants with RCC from KEYNOTE-564; 475 participants with MSI-H tumors from KEYNOTE-158 and KEYNOTE-164; 389 participants with HL from KEYNOTE-013, KEYNOTE-087, and KEYNOTE-204; and 153 participants with MSI-H CRC from KEYNOTE-177		
Abbreviations: CRC=colorectal cancer; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; LA=locally advanced; KN=KEYNOTE; MSI-H=microsatellite instability-high; N=number; NSCLC=non-small cell lung cancer; R/M=recurrent and/or metastatic; RCC=renal cell carcinoma; RSD=reference safety dataset; RT=radiotherapy; SoC=standard of care.			

Participants were categorized as "high risk" if extranodal extension and/or positive margins of resection were assessed to be present. Postsurgical treatment decisions involving cisplatin were guided based on local pathology results.

Patient exposure

Disposition of patients

As of the IA1 data cutoff (25-JUL-2024), 361 participants in the pembrolizumab group and 315 participants in the SoC group received at least 1 dose of study treatment (pembrolizumab monotherapy, pembrolizumab in combination with RT ± cisplatin, RT ± cisplatin) or in-study surgery in KEYNOTE-689.

Table 40 Summary of drug exposure (overall) (APaT Population)

	Pembrolizumab (N=361)	SoC (N=315)
Study Days on Therapy (months)		
n	361	315
Mean (SD)	8.0 (5.1)	2.7 (1.2)
Median	9.1	2.9
Range	0.03 to 22.3	0.03 to 7.2
Treatment includes study drugs, in-study surgery and in-study radiotherapy. Database Cutoff Date: 25JUL2024		

Table 41 Duration of exposure in the pembrolizumab arm and SoC arm

	Pembrolizumab (N=361)			SoC (N=315)		
	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure						
> 0 m	361	(100.0)	240.5	315	(100.0)	70.9
≥ 1 m	326	(90.3)	238.7	274	(87.0)	70.7
≥ 3 m	272	(75.3)	231.9	125	(39.7)	37.1
≥ 6 m	216	(59.8)	211.4	2	(0.6)	1.2
≥ 9 m	182	(50.4)	191.2	0	(0.0)	0.0
≥ 12 m	142	(39.3)	155.0	0	(0.0)	0.0
≥ 15 m	5	(1.4)	7.1	0	(0.0)	0.0
≥ 18 m	1	(0.3)	1.9	0	(0.0)	0.0
Each participant is counted once on each applicable duration category row. Duration of exposure is the time from the first treatment date to the last treatment date. Treatment includes study drugs, in-study surgery and in-study radiotherapy. Database Cutoff Date: 25JUL2024						

As of the data cutoff, a total of 155 participants (43.1%) in the pembrolizumab group and 261 (82.6%) in the SoC group completed study treatment and 11 participants (3.1%) were still receiving overall study treatment in the pembrolizumab group, while no participants in the SoC group were continuing treatment (see table disposition of participants in the clinical efficacy section).

Table 42 Drug Exposure by Duration (APaT Population)

	KN-689 Pembrolizumab (N=361)	KN-689 SoC (N=315)	Pembrolizumab Monotherapy HNSCC Pool (N=909)	Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)
Duration on Therapy (months)				
Mean	7.99	2.70	5.43	7.85
Median	9.10	2.89	3.02	5.78
SD	5.07	1.20	6.09	6.91
Range	0.03 to 22.34	0.03 to 7.20	0.03 to 29.70	0.03 to 38.01
Number of Administrations				
Mean	10.16	1.25	8.74	12.33
Median	12.00	1.00	5.00	9.00
SD	6.76	1.33	9.08	10.12
Range	1.00 to 19.00	0.00 to 4.00	1.00 to 58.00	1.00 to 59.00
Duration of exposure (months) is calculated as ((last treatment date - first treatment date + 1) / 30.4367) Database cutoff date for KN-689: 25JUL2024				

Table 43. Drug Exposure by Duration (APaT Population)

	KN-689 Pembrolizumab (N=361)			KN-689 SoC (N=315)			Pembrolizumab Monotherapy HNSCC Pool (N=909)			Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
> 0 month	361	(100.0)	240.5	315	(100.0)	70.9	909	(100.0)	411.6	7,631	(100.0)	4,995.0
>=1 month	326	(90.3)	238.7	274	(87.0)	70.7	734	(80.7)	405.9	6,637	(87.0)	4,962.4
>=3 months	272	(75.3)	231.9	125	(39.7)	37.1	459	(50.5)	360.6	5,023	(65.8)	4,693.1
>=6 months	216	(59.8)	211.4	2	(0.6)	1.2	281	(30.9)	296.9	3,781	(49.5)	4,240.0
>=9 months	182	(50.4)	191.2	0	(0.0)	0.0	165	(18.2)	227.3	2,984	(39.1)	3,755.6
>=12 months	142	(39.3)	155.0	0	(0.0)	0.0	118	(13.0)	187.1	1,673	(21.9)	2,558.8
>=15 months	5	(1.4)	7.1	0	(0.0)	0.0	90	(9.9)	156.0	1,092	(14.3)	1,920.3
>=18 months	1	(0.3)	1.9	0	(0.0)	0.0	66	(7.3)	122.6	783	(10.3)	1,497.5

Each participant is counted once on each applicable duration category row.
Duration of exposure (months) is calculated as ((last treatment date - first treatment date + 1) / 30.4367)
Database cutoff date for KN-689: 25JUL2024
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Summary of Drug Exposure to Adjuvant Pembrolizumab and Cisplatin

Table 44. Summary of Drug Exposure to Adjuvant Pembrolizumab

	Pembrolizumab (N=275)	SoC (N=275)
Total Dose Cycle 1 (mg)		
n	255	0
Mean (SD)	199.4 (6.0)	0
Median	199.8	0
Range	108.0 to 203.2	0
Total Dose Cycle 2 (mg)		
n	236	0
Mean (SD)	197.7 (15.2)	0
Median	199.8	0
Range	58.0 to 200.5	0
Total Dose Cycle 3 (mg)		
n	225	0
Mean (SD)	197.0 (18.1)	0
Median	199.8	0
Range	58.0 to 201.9	0
Total Dose Cycle 4 (mg)		
n	219	0
Mean (SD)	198.0 (14.6)	0
Median	199.8	0
Range	58.0 to 203.2	0
Total Dose Cycle 5 (mg)		
n	214	0
Mean (SD)	198.3 (13.4)	0
Median	199.8	0
Range	58.0 to 200.5	0
Total Dose Cycle 6 (mg)		

n	206	0
Mean (SD)	197.4 (16.5)	0
Median	199.8	0
Range	58.0 to 200.6	0
Total Dose Cycle 7 (mg)		
n	196	0
Mean (SD)	198.7 (12.0)	0
Median	199.8	0
Range	58.0 to 200.5	0
Total Dose Cycle 8 (mg)		
n	192	0
Mean (SD)	197.9 (13.7)	0
Median	199.8	0
Range	100.0 to 203.2	0
Total Dose Cycle 9 (mg)		
n	182	0
Mean (SD)	198.3 (12.4)	0
Median	199.8	0
Range	100.0 to 200.4	0
Total Dose Cycle 10 (mg)		
n	179	0
Mean (SD)	197.8 (13.9)	0
Median	199.8	0
Range	100.0 to 203.1	0
Total Dose Cycle 11 (mg)		
n	174	0
Mean (SD)	198.9 (9.8)	0
Median	199.9	0
Range	108.0 to 204.4	0
Total Dose Cycle 12 (mg)		
n	166	0
Mean (SD)	197.3 (16.7)	0
Median	199.8	0
Range	58.0 to 200.5	0
Total Dose Cycle 13 (mg)		
n	160	0
Mean (SD)	198.1 (13.2)	0
Median	199.9	0
Range	100.4 to 203.1	0
Total Dose Cycle 14 (mg)		
n	157	0
Mean (SD)	198.7 (10.8)	0
Median	199.8	0

Range	100.0 to 201.9	0
Total Dose Cycle 15 (mg)		
n	151	0
Mean (SD)	197.7 (15.9)	0
Median	199.8	0
Range	58.0 to 200.3	0
Total Dose Cycle 16 (mg)		
n	2	0
Mean (SD)	200.1 (0.4)	0
Median	200.1	0
Range	199.8 to 200.3	0
Database Cutoff Date: 25JUL2024		

Table 45. Summary of Drug Exposure to Cisplatin (Participants Who Received Adjuvant Treatment)

	Pembrolizumab (N=275)	SoC (N=275)
Dose Intensity (mg/week)		
n	107	139
Mean (SD)	46.5 (22.0)	45.0 (14.8)
Median	45.2	45.3
Range	7.4 to 210.8	12.5 to 66.7
Dose intensity of cisplatin (mg/week) is defined as the total dose of cisplatin (mg) received divided by the planned 9 week duration of cisplatin treatment. Database Cutoff Date: 25JUL2024		

Demographic and baseline characteristics

Table 46. Participant Characteristics (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
Sex								
Male	284	(78.7)	248	(78.7)	752	(82.7)	4,889	(64.1)
Female	77	(21.3)	67	(21.3)	157	(17.3)	2,742	(35.9)
Age (Years)								
<65	247	(68.4)	202	(64.1)	586	(64.5)	4,524	(59.3)
>=65	114	(31.6)	113	(35.9)	323	(35.5)	3,107	(40.7)
Mean	59.4		60.6		60.6		59.9	
SD	10.0		10.0		9.8		13.4	
Median	60.0		61.0		61.0		62.0	
Range	29 to 82		22 to 87		19 to 94		15 to 94	
Race								
American Indian Or Alaska Native	0	(0.0)	1	(0.3)	9	(1.0)	59	(0.8)
Asian	50	(13.9)	40	(12.7)	109	(12.0)	826	(10.8)
Black Or African American	8	(2.2)	7	(2.2)	28	(3.1)	146	(1.9)
Multiracial	9	(2.5)	15	(4.8)	18	(2.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	1	(0.3)	0	(0.0)	5	(0.1)
White	284	(78.7)	245	(77.8)	723	(79.5)	5,838	(76.5)
Missing	9	(2.5)	6	(1.9)	22	(2.4)	671	(8.8)
Ethnicity								
Hispanic Or Latino	54	(15.0)	37	(11.7)	83	(9.1)	604	(7.9)
Not Hispanic Or Latino	299	(82.8)	271	(86.0)	733	(80.6)	6,064	(79.5)
Not Reported	4	(1.1)	4	(1.3)	52	(5.7)	808	(10.6)
Unknown	0	(0.0)	2	(0.6)	41	(4.5)	145	(1.9)
Missing	4	(1.1)	1	(0.3)	0	(0.0)	10	(0.1)
Age category (year)								
<65	247	(68.4)	202	(64.1)	586	(64.5)	4,524	(59.3)
65-74	92	(25.5)	91	(28.9)	264	(29.0)	2,173	(28.5)
>=75	22	(6.1)	22	(7.0)	59	(6.5)	934	(12.2)
ECOG performance scale								
[0] Normal Activity	199	(55.1)	191	(60.6)	294	(32.3)	4,016	(52.6)
[1] Symptoms, but ambulatory	162	(44.9)	124	(39.4)	612	(67.3)	3,440	(45.1)
Other/Missing	0	(0.0)	0	(0.0)	3	(0.3)	175	(2.3)

Adverse events

Table 47. Adverse Event Summary (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	348	(96.4)	305	(96.8)	882	(97.0)	7,375	(96.6)
with no adverse event	13	(3.6)	10	(3.2)	27	(3.0)	256	(3.4)
with drug-related[a] adverse events	294	(81.4)	258	(81.9)	562	(61.8)	5,462	(71.6)
with toxicity grade 3-5 adverse events	275	(76.2)	233	(74.0)	512	(56.3)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	161	(44.6)	135	(42.9)	134	(14.7)	1,208	(15.8)
with serious adverse events	179	(49.6)	116	(36.8)	404	(44.4)	2,742	(35.9)

with serious drug-related adverse events	69	(19.1)	33	(10.5)	88	(9.7)	840	(11.0)
who died	25	(6.9)	24	(7.6)	79	(8.7)	346	(4.5)
who died due to a drug-related adverse event	4	(1.1)	1	(0.3)	8	(0.9)	42	(0.6)
discontinued drug due to an adverse event	88	(24.4)	45	(14.3)	120	(13.2)	1,066	(14.0)
discontinued drug due to a drug-related adverse event	64	(17.7)	39	(12.4)	50	(5.5)	639	(8.4)
discontinued drug due to a serious adverse event	47	(13.0)	11	(3.5)	96	(10.6)	714	(9.4)
discontinued drug due to a serious drug-related adverse event	27	(7.5)	8	(2.5)	32	(3.5)	347	(4.5)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.03

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

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

Database cutoff date for KN-689: 25JUL2024

Table 48. Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN-689 Pembrolizumab	KN-689 SoC	Pembrolizumab Monotherapy HNSCC Pool	Pembrolizumab Monotherapy Reference Safety Dataset
Number of subjects exposed	361	315	909	7,631
Total exposure[b] in person-months	3223.81	1154.36	5723.39	66570.95
Total events (rate)				
adverse events	5,349 (165.92)	3,513 (304.32)	8,467 (147.94)	76,878 (115.48)
drug-related[c] adverse events	2,044 (63.40)	1,590 (137.74)	1,976 (34.53)	24,542 (36.87)
toxicity grade 3-5 adverse events	923 (28.63)	728 (63.07)	1,230 (21.49)	7,463 (11.21)
toxicity grade 3-5 drug-related adverse events	307 (9.52)	289 (25.04)	201 (3.51)	1,770 (2.66)
serious adverse events	350 (10.86)	202 (17.50)	760 (13.28)	4,801 (7.21)
serious drug-related adverse events	92 (2.85)	47 (4.07)	114 (1.99)	1,093 (1.64)
adverse events leading to death	26 (0.81)	29 (2.51)	81 (1.42)	353 (0.53)
drug-related adverse events leading to death	4 (0.12)	1 (0.09)	8 (0.14)	42 (0.06)
adverse events resulting in drug discontinuation	106 (3.29)	47 (4.07)	130 (2.27)	1,165 (1.75)
drug-related adverse events resulting in drug discontinuation	78 (2.42)	41 (3.55)	58 (1.01)	703 (1.06)
serious adverse events resulting in drug discontinuation	50 (1.55)	11 (0.95)	99 (1.73)	753 (1.13)
serious drug-related adverse events resulting in drug discontinuation	28 (0.87)	8 (0.69)	33 (0.58)	363 (0.55)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.

[b] Drug exposure is defined as the interval between the first treatment date and the earliest of the last treatment date + 30, death date or the database cutoff date, then + 1 day since the first treatment date is Day 1.

[c] Determined by the investigator to be related to the drug.

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

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

Grades are based on NCI CTCAE version 4.03

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

For KN001 and KN054, a new AE episode was recorded when there was any AE change in grade, relationship, or seriousness. If the episode date ranges were continuous, then these records were counted as one AE episode.

Database cutoff date for KN-689: 25JUL2024

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adae]

Most frequently reported Adverse Events

Table 49 Participants With Adverse Events By Decreasing Frequency of Preferred Term (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	KN-689 Pembrolizumab	KN-689 SoC	Pembrolizumab Monotherapy HNSCC Pool	Pembrolizumab Monotherapy

							Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	348	(96.4)	305	(96.8)	882	(97.0)	7,375	(96.6)
with no adverse events	13	(3.6)	10	(3.2)	27	(3.0)	256	(3.4)
Stomatitis	150	(41.6)	172	(54.6)	29	(3.2)	201	(2.6)
Radiation skin injury	144	(39.9)	151	(47.9)	4	(0.4)	13	(0.2)
Weight decreased	129	(35.7)	86	(27.3)	128	(14.1)	628	(8.2)
Anaemia	123	(34.1)	105	(33.3)	204	(22.4)	982	(12.9)
Dysphagia	105	(29.1)	100	(31.7)	91	(10.0)	190	(2.5)
Constipation	97	(26.9)	70	(22.2)	177	(19.5)	1,179	(15.5)
Hypothyroidism	89	(24.7)	17	(5.4)	147	(16.2)	937	(12.3)
Nausea	88	(24.4)	87	(27.6)	151	(16.6)	1,534	(20.1)
Fatigue	85	(23.5)	52	(16.5)	281	(30.9)	2,368	(31.0)
Dry mouth	81	(22.4)	81	(25.7)	50	(5.5)	388	(5.1)
Diarrhoea	78	(21.6)	33	(10.5)	133	(14.6)	1,678	(22.0)
Lymphocyte count decreased	65	(18.0)	48	(15.2)	38	(4.2)	130	(1.7)
Insomnia	64	(17.7)	25	(7.9)	72	(7.9)	528	(6.9)
Vomiting	59	(16.3)	32	(10.2)	96	(10.6)	945	(12.4)
Dysgeusia	55	(15.2)	60	(19.0)	22	(2.4)	150	(2.0)
Alanine aminotransferase increased	53	(14.7)	29	(9.2)	42	(4.6)	572	(7.5)
Hypokalaemia	52	(14.4)	40	(12.7)	78	(8.6)	324	(4.2)
Hyponatraemia	49	(13.6)	25	(7.9)	93	(10.2)	387	(5.1)
Oral pain	48	(13.3)	28	(8.9)	22	(2.4)	53	(0.7)
Decreased appetite	47	(13.0)	42	(13.3)	150	(16.5)	1,312	(17.2)
Pyrexia	45	(12.5)	17	(5.4)	108	(11.9)	934	(12.2)
Neutrophil count decreased	44	(12.2)	61	(19.4)	6	(0.7)	53	(0.7)
Aspartate aminotransferase increased	43	(11.9)	23	(7.3)	56	(6.2)	538	(7.1)
White blood cell count decreased	43	(11.9)	55	(17.5)	14	(1.5)	70	(0.9)
Rash	41	(11.4)	5	(1.6)	101	(11.1)	1,175	(15.4)
Asthenia	39	(10.8)	39	(12.4)	64	(7.0)	880	(11.5)
Pruritus	38	(10.5)	6	(1.9)	87	(9.6)	1,435	(18.8)
Oral candidiasis	37	(10.2)	19	(6.0)	24	(2.6)	101	(1.3)
Cough	33	(9.1)	13	(4.1)	145	(16.0)	1,392	(18.2)
Arthralgia	31	(8.6)	17	(5.4)	105	(11.6)	1,449	(19.0)
Headache	30	(8.3)	13	(4.1)	95	(10.5)	946	(12.4)
Procedural pain	30	(8.3)	32	(10.2)	6	(0.7)	60	(0.8)
Pneumonia	26	(7.2)	26	(8.3)	99	(10.9)	487	(6.4)
Dyspnoea	20	(5.5)	16	(5.1)	138	(15.2)	1,130	(14.8)
Back pain	13	(3.6)	5	(1.6)	73	(8.0)	847	(11.1)

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

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

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

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

Database cutoff date for KN-689: 25JUL2024

Drug-related Adverse Events

Table 50. Participants with Drug-Related Adverse Events By Decreasing Frequency of Preferred Term (Incidence ≥ 5% in One or More Treatment Groups)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	294	(81.4)	258	(81.9)	562	(61.8)	5,462	(71.6)
with no adverse events	67	(18.6)	57	(18.1)	347	(38.2)	2,169	(28.4)
Radiation skin injury	142	(39.3)	148	(47.0)	0	(0.0)	1	(0.0)
Stomatitis	140	(38.8)	164	(52.1)	12	(1.3)	103	(1.3)
Hypothyroidism	70	(19.4)	6	(1.9)	107	(11.8)	810	(10.6)
Fatigue	65	(18.0)	41	(13.0)	146	(16.1)	1,476	(19.3)
Nausea	64	(17.7)	67	(21.3)	46	(5.1)	675	(8.8)
Dry mouth	63	(17.5)	68	(21.6)	13	(1.4)	209	(2.7)
Dysgeusia	46	(12.7)	56	(17.8)	8	(0.9)	79	(1.0)
Neutrophil count decreased	42	(11.6)	59	(18.7)	5	(0.6)	34	(0.4)
Lymphocyte count decreased	41	(11.4)	28	(8.9)	14	(1.5)	64	(0.8)
Vomiting	39	(10.8)	25	(7.9)	18	(2.0)	248	(3.2)
White blood cell count decreased	39	(10.8)	50	(15.9)	6	(0.7)	34	(0.4)
Dysphagia	37	(10.2)	49	(15.6)	5	(0.6)	22	(0.3)
Weight decreased	35	(9.7)	34	(10.8)	25	(2.8)	148	(1.9)
Anaemia	32	(8.9)	34	(10.8)	43	(4.7)	234	(3.1)
Decreased appetite	30	(8.3)	29	(9.2)	55	(6.1)	525	(6.9)
Pruritus	29	(8.0)	1	(0.3)	59	(6.5)	1,143	(15.0)
Rash	29	(8.0)	0	(0.0)	74	(8.1)	884	(11.6)
Hyperthyroidism	27	(7.5)	5	(1.6)	15	(1.7)	352	(4.6)
Alanine aminotransferase increased	23	(6.4)	16	(5.1)	24	(2.6)	336	(4.4)
Diarrhoea	23	(6.4)	7	(2.2)	52	(5.7)	904	(11.8)
Oral candidiasis	23	(6.4)	15	(4.8)	7	(0.8)	17	(0.2)
Dermatitis	21	(5.8)	15	(4.8)	7	(0.8)	46	(0.6)
Odynophagia	21	(5.8)	25	(7.9)	1	(0.1)	7	(0.1)
Aspartate aminotransferase increased	20	(5.5)	8	(2.5)	29	(3.2)	312	(4.1)
Asthenia	19	(5.3)	19	(6.0)	26	(2.9)	491	(6.4)
Oral pain	19	(5.3)	17	(5.4)	2	(0.2)	13	(0.2)
Pneumonitis	19	(5.3)	0	(0.0)	34	(3.7)	268	(3.5)
Blood creatinine increased	16	(4.4)	16	(5.1)	3	(0.3)	105	(1.4)
Pharyngeal inflammation	15	(4.2)	19	(6.0)	0	(0.0)	0	(0.0)

Platelet count decreased	14	(3.9)	24	(7.6)	5	(0.6)	43	(0.6)
Arthralgia	10	(2.8)	2	(0.6)	32	(3.5)	672	(8.8)

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

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

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

Database cutoff date for KN-689: 25JUL2024

Grade 3 to 5 Adverse Events

Table 51. Participants With Grade 3-5 Adverse Events By Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	275	(76.2)	233	(74.0)	512	(56.3)	3,514	(46.0)
with no adverse events	86	(23.8)	82	(26.0)	397	(43.7)	4,117	(54.0)
Weight decreased	50	(13.9)	30	(9.5)	12	(1.3)	35	(0.5)
Stomatitis	45	(12.5)	42	(13.3)	2	(0.2)	9	(0.1)
Dysphagia	44	(12.2)	34	(10.8)	23	(2.5)	31	(0.4)
Anaemia	38	(10.5)	35	(11.1)	58	(6.4)	275	(3.6)
Lymphocyte count decreased	33	(9.1)	36	(11.4)	13	(1.4)	33	(0.4)
Hyponatraemia	28	(7.8)	16	(5.1)	44	(4.8)	169	(2.2)
Neutrophil count decreased	20	(5.5)	37	(11.7)	1	(0.1)	10	(0.1)
Hypokalaemia	19	(5.3)	17	(5.4)	22	(2.4)	70	(0.9)
White blood cell count decreased	17	(4.7)	29	(9.2)	0	(0.0)	5	(0.1)
Radiation skin injury	15	(4.2)	18	(5.7)	0	(0.0)	0	(0.0)
Wound infection	15	(4.2)	8	(2.5)	2	(0.2)	7	(0.1)
Pneumonia	14	(3.9)	22	(7.0)	64	(7.0)	270	(3.5)
Alanine aminotransferase increased	12	(3.3)	4	(1.3)	4	(0.4)	97	(1.3)
Gamma-glutamyltransferase increased	11	(3.0)	1	(0.3)	4	(0.4)	56	(0.7)
Pneumonia aspiration	10	(2.8)	3	(1.0)	26	(2.9)	31	(0.4)
Wound dehiscence	10	(2.8)	7	(2.2)	0	(0.0)	1	(0.0)
Diarrhoea	9	(2.5)	2	(0.6)	12	(1.3)	114	(1.5)
Aspartate aminotransferase increased	8	(2.2)	5	(1.6)	13	(1.4)	95	(1.2)
Colitis	8	(2.2)	0	(0.0)	1	(0.1)	74	(1.0)
Hyperkalaemia	8	(2.2)	4	(1.3)	3	(0.3)	30	(0.4)
Pulmonary embolism	8	(2.2)	4	(1.3)	12	(1.3)	101	(1.3)
Acute kidney injury	7	(1.9)	10	(3.2)	5	(0.6)	65	(0.9)
Hypocalcaemia	7	(1.9)	6	(1.9)	3	(0.3)	11	(0.1)
Nausea	7	(1.9)	9	(2.9)	5	(0.6)	58	(0.8)
Postoperative wound infection	7	(1.9)	14	(4.4)	0	(0.0)	2	(0.0)

Respiratory failure	7	(1.9)	2	(0.6)	10	(1.1)	33	(0.4)
Decreased appetite	6	(1.7)	5	(1.6)	15	(1.7)	77	(1.0)
Hyperglycaemia	6	(1.7)	3	(1.0)	11	(1.2)	83	(1.1)
Hypertension	6	(1.7)	7	(2.2)	9	(1.0)	148	(1.9)
Hypophosphataemia	6	(1.7)	11	(3.5)	16	(1.8)	52	(0.7)
Pleural effusion	1	(0.3)	0	(0.0)	6	(0.7)	73	(1.0)
Post procedural hypoparathyroidism	1	(0.3)	3	(1.0)	0	(0.0)	0	(0.0)
Post procedural hypothyroidism	1	(0.3)	3	(1.0)	0	(0.0)	0	(0.0)
Sepsis	1	(0.3)	1	(0.3)	16	(1.8)	60	(0.8)
Tumour pain	1	(0.3)	1	(0.3)	9	(1.0)	33	(0.4)
Back pain	0	(0.0)	0	(0.0)	9	(1.0)	72	(0.9)
Tracheostomy infection	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)

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

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

Grades are based on NCI CTCAE version 4.03

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

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

Database cutoff date for KN-689: 25JUL2024

Figure 27. Between-Treatment Comparisons in Grade 3-5 Adverse Events Selected Adverse Events(≥ 5% Incidence) and Sorted by Risk Difference (APaT Population)

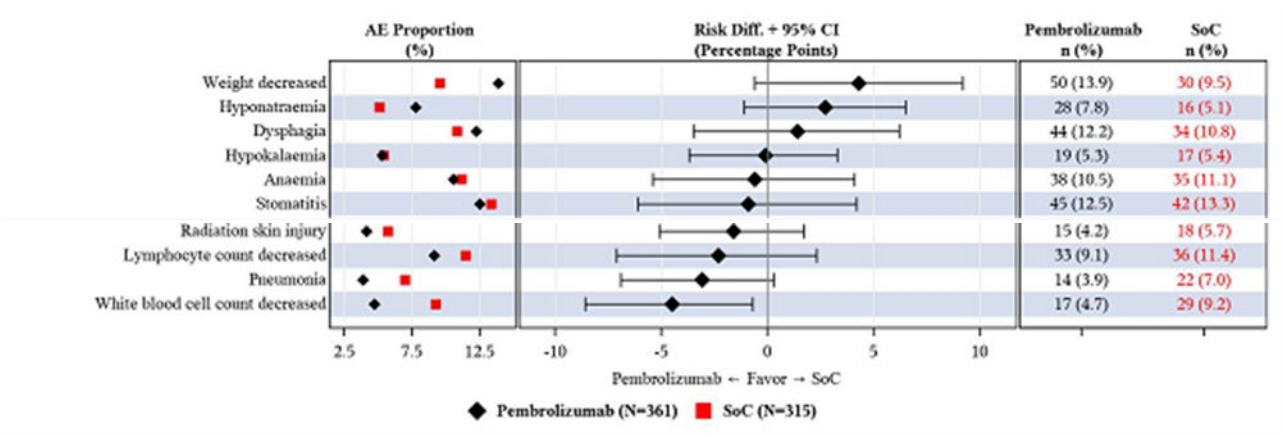


Table 52. Time to Onset of Grade 3-5 Adverse Events (APaT Population)

	Pembrolizumab	SoC
Participants in population	**361**	**315**
Participants with Grade 3-5 Adverse Events (%)	275 (76.2)	233 (74.0)
Time to Onset of First Grade 3-5 Adverse Events (days)[a]		
Mean (SD)	80.0 (72.2)	41.5 (40.9)
Median	55.0	29.0
Range	1 to 611	1 to 193

(%) = Number of participants with Grade 3-5 Adverse Events / Number of participants in population.
[a] Time to onset statistics are based on number of participants with Grade 3-5 Adverse Events.
SD = Standard Deviation.
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

Source: [P689V01MK3475: adam-adsl; adae]

Grade 3-5 Drug Related Adverse Events

Table 53. Participants With Drug-Related Grade 3-5 Adverse Events By Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	161	(44.6)	135	(42.9)	134	(14.7)	1,208	(15.8)
with no adverse events	200	(55.4)	180	(57.1)	775	(85.3)	6,423	(84.2)
Stomatitis	42	(11.6)	42	(13.3)	2	(0.2)	5	(0.1)
Lymphocyte count decreased	20	(5.5)	21	(6.7)	2	(0.2)	9	(0.1)
Neutrophil count decreased	19	(5.3)	37	(11.7)	1	(0.1)	6	(0.1)
Radiation skin injury	15	(4.2)	18	(5.7)	0	(0.0)	0	(0.0)
White blood cell count decreased	13	(3.6)	28	(8.9)	0	(0.0)	2	(0.0)
Weight decreased	11	(3.0)	12	(3.8)	1	(0.1)	8	(0.1)
Dysphagia	10	(2.8)	10	(3.2)	2	(0.2)	4	(0.1)
Hyponatraemia	9	(2.5)	4	(1.3)	9	(1.0)	32	(0.4)
Anaemia	8	(2.2)	3	(1.0)	7	(0.8)	33	(0.4)
Colitis	7	(1.9)	0	(0.0)	1	(0.1)	67	(0.9)
Alanine aminotransferase increased	5	(1.4)	4	(1.3)	3	(0.3)	56	(0.7)
Immune-mediated hepatitis	5	(1.4)	0	(0.0)	0	(0.0)	3	(0.0)
Nausea	5	(1.4)	8	(2.5)	1	(0.1)	13	(0.2)
Pneumonitis	5	(1.4)	0	(0.0)	10	(1.1)	91	(1.2)
Adrenal insufficiency	4	(1.1)	0	(0.0)	2	(0.2)	24	(0.3)
Decreased appetite	4	(1.1)	4	(1.3)	4	(0.4)	23	(0.3)
Hyperkalaemia	4	(1.1)	1	(0.3)	0	(0.0)	3	(0.0)
Hypokalaemia	4	(1.1)	3	(1.0)	2	(0.2)	12	(0.2)
Diarrhoea	3	(0.8)	0	(0.0)	6	(0.7)	75	(1.0)
Dry mouth	3	(0.8)	3	(1.0)	0	(0.0)	1	(0.0)
Fatigue	3	(0.8)	2	(0.6)	10	(1.1)	75	(1.0)
Acute kidney injury	2	(0.6)	7	(2.2)	2	(0.2)	16	(0.2)
Febrile neutropenia	2	(0.6)	5	(1.6)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(0.3)	1	(0.3)	9	(1.0)	47	(0.6)
Dermatitis	1	(0.3)	5	(1.6)	0	(0.0)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Database cutoff date for KN-689: 25JUL2024
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adae]

Serious adverse event/deaths/other significant events

Serious adverse events

Table 54. Participants With Serious Adverse Events Up to 90 Days of Last Dose By Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	179	(49.6)	116	(36.8)	404	(44.4)	2,742	(35.9)
with no adverse events	182	(50.4)	199	(63.2)	505	(55.6)	4,889	(64.1)
Pneumonia	13	(3.6)	18	(5.7)	61	(6.7)	272	(3.6)
Pneumonia aspiration	8	(2.2)	2	(0.6)	20	(2.2)	25	(0.3)
Wound dehiscence	8	(2.2)	2	(0.6)	0	(0.0)	2	(0.0)
Dysphagia	7	(1.9)	2	(0.6)	11	(1.2)	18	(0.2)
Pyrexia	7	(1.9)	1	(0.3)	7	(0.8)	79	(1.0)
Acute kidney injury	6	(1.7)	9	(2.9)	5	(0.6)	65	(0.9)
Colitis	6	(1.7)	0	(0.0)	4	(0.4)	71	(0.9)
Pulmonary embolism	6	(1.7)	2	(0.6)	8	(0.9)	78	(1.0)
Stomatitis	6	(1.7)	2	(0.6)	2	(0.2)	5	(0.1)
Immune-mediated hepatitis	5	(1.4)	0	(0.0)	0	(0.0)	3	(0.0)
Pneumonitis	5	(1.4)	0	(0.0)	14	(1.5)	136	(1.8)
Postoperative wound infection	5	(1.4)	9	(2.9)	0	(0.0)	0	(0.0)
Respiratory failure	5	(1.4)	1	(0.3)	9	(1.0)	30	(0.4)
Skin infection	5	(1.4)	1	(0.3)	0	(0.0)	4	(0.1)
Adrenal insufficiency	4	(1.1)	0	(0.0)	2	(0.2)	30	(0.4)
Diarrhoea	4	(1.1)	2	(0.6)	11	(1.2)	70	(0.9)
Dyspnoea	4	(1.1)	0	(0.0)	20	(2.2)	91	(1.2)
Mouth haemorrhage	4	(1.1)	0	(0.0)	6	(0.7)	6	(0.1)
Post procedural complication	4	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary sepsis	4	(1.1)	1	(0.3)	2	(0.2)	4	(0.1)
Septic shock	4	(1.1)	4	(1.3)	2	(0.2)	14	(0.2)
Wound infection	4	(1.1)	3	(1.0)	2	(0.2)	6	(0.1)
Anaemia	3	(0.8)	3	(1.0)	9	(1.0)	65	(0.9)
Cellulitis	3	(0.8)	1	(0.3)	10	(1.1)	36	(0.5)
Death	3	(0.8)	2	(0.6)	13	(1.4)	49	(0.6)
Tumour haemorrhage	3	(0.8)	0	(0.0)	23	(2.5)	27	(0.4)
COVID-19	2	(0.6)	3	(1.0)	0	(0.0)	0	(0.0)
Hypercalcaemia	2	(0.6)	2	(0.6)	18	(2.0)	39	(0.5)
Oropharyngeal fistula	2	(0.6)	4	(1.3)	0	(0.0)	0	(0.0)
Syncope	2	(0.6)	3	(1.0)	8	(0.9)	22	(0.3)
Dehydration	1	(0.3)	2	(0.6)	9	(1.0)	44	(0.6)

Febrile neutropenia	1	(0.3)	5	(1.6)	0	(0.0)	8	(0.1)
Nausea	1	(0.3)	3	(1.0)	4	(0.4)	30	(0.4)
Pleural effusion	1	(0.3)	0	(0.0)	12	(1.3)	88	(1.2)
Sepsis	1	(0.3)	1	(0.3)	14	(1.5)	56	(0.7)

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

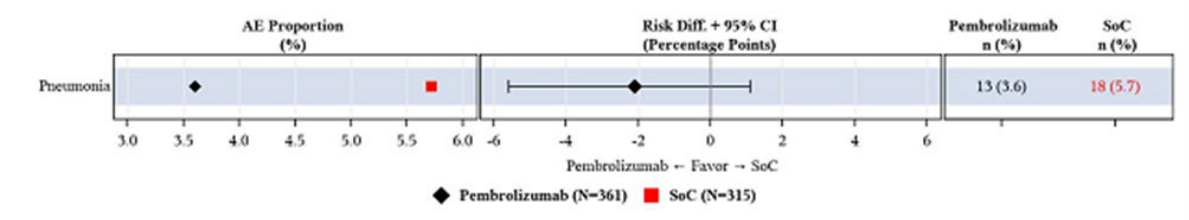
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Serious adverse events up to 90 days of last treatment are included.

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

Database cutoff date for KN-689: 25JUL2024

Figure 28. Between-Treatment Comparisons in Serious Adverse Events Pneumonia Events (>= 5% Incidence) and Sorted by Risk Difference (APaT Population)



Drug related Serious Adverse Events

Table 55. Participants With Drug-Related Serious Adverse Events Up to 90 Days of Last Dose By Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	69	(19.1)	33	(10.5)	88	(9.7)	840	(11.0)
with no adverse events	292	(80.9)	282	(89.5)	821	(90.3)	6,791	(89.0)
Colitis	6	(1.7)	0	(0.0)	4	(0.4)	63	(0.8)
Stomatitis	6	(1.7)	2	(0.6)	2	(0.2)	3	(0.0)
Immune-mediated hepatitis	5	(1.4)	0	(0.0)	0	(0.0)	3	(0.0)
Pneumonitis	5	(1.4)	0	(0.0)	12	(1.3)	129	(1.7)
Adrenal insufficiency	4	(1.1)	0	(0.0)	2	(0.2)	25	(0.3)
Acute kidney injury	2	(0.6)	6	(1.9)	2	(0.2)	19	(0.2)
Febrile neutropenia	1	(0.3)	4	(1.3)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	3	(1.0)	1	(0.1)	7	(0.1)

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

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

Serious adverse events up to 90 days of last treatment are included.

Database cutoff date for KN-689: 25JUL2024

Deaths

Of the 25 deaths recorded in the pembrolizumab arm, 4 of them were considered drug related by the investigator.

Table 56. Participants With Drug-Related Adverse Events Resulting in Death Up to 90 Days of Last Dose By Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	4	(1.1)	1	(0.3)	8	(0.9)	42	(0.6)
with no adverse events	357	(98.9)	314	(99.7)	901	(99.1)	7,589	(99.4)
COVID-19 pneumonia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Death	1	(0.3)	0	(0.0)	1	(0.1)	3	(0.0)
Pneumonitis	1	(0.3)	0	(0.0)	2	(0.2)	8	(0.1)
Renal failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Acute kidney injury	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Encephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
General physical health deterioration	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ileus paralytic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Interstitial lung disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Large intestine perforation	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	1	(0.1)	4	(0.1)
Myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Pneumonia klebsiella	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary embolism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Superior vena cava syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urinary tract obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

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

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

Database cutoff date for KN-689: 25JUL2024

Safety analysis by risk categories

As reported, patients were stratified in high risk and low risk group basing on the presence or not of positive margins of resection after surgery.

Table 57. Summary of High-Risk vs Low-Risk participants

	HIGH RISK				LOW RISK			
	Pembrolizumab		SoC		Pembrolizumab		SoC	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	119		154		196		148	
with one or more adverse events	118	(99.2)	150	(97.4)	193	(98.5)	143	(96.6)
with no adverse event	1	(0.8)	4	(2.6)	3	(1.5)	5	(3.4)
with drug-related[a] adverse events	100	(84.0)	127	(82.5)	168	(85.7)	121	(81.8)
with toxicity grade 3-5 adverse events	101	(84.9)	125	(81.2)	148	(75.5)	99	(66.9)
with toxicity grade 3-5 drug-related adverse events	62	(52.1)	83	(53.9)	84	(42.9)	45	(30.4)
with serious adverse events	66	(55.5)	67	(43.5)	96	(49.0)	42	(28.4)
with serious drug-related adverse events	23	(19.3)	22	(14.3)	39	(19.9)	7	(4.7)
who died	10	(8.4)	11	(7.1)	11	(5.6)	9	(6.1)
who died due to a drug-related adverse event	2	(1.7)	0	(0.0)	2	(1.0)	0	(0.0)
discontinued drug due to an adverse event	30	(25.2)	28	(18.2)	52	(26.5)	13	(8.8)
discontinued drug due to a drug-related adverse event	22	(18.5)	27	(17.5)	39	(19.9)	9	(6.1)
discontinued drug due to a serious adverse event	16	(13.4)	6	(3.9)	28	(14.3)	4	(2.7)
discontinued drug due to a serious drug-related adverse event	10	(8.4)	6	(3.9)	17	(8.7)	1	(0.7)

[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.
Database Cutoff Date: 25JUL2024.

Source: [P689V01MK3475: adam-adsl; adae]

Grade 3-5 Adverse Event: The incidence of Grade 3 to 5 AEs by high- and low-risk category across treatment groups was generally similar.

Deaths due to Serious Adverse Events: The incidence of deaths by high- and low- risk category was generally similar across the 2 treatment groups.

SAE: The incidence of SAEs by high- and low- risk category was generally similar between treatment groups

AE leading to discontinuation: The incidence of AEs leading to any study treatment discontinuations by high- and low-risk category was generally similar in the pembrolizumab group compared with the SoC group

Adverse Events of Special Interest (AEOSI)

Table 58. Adverse Event Summary For AEOSI (APaT Population)

	KN-689 Pembrolizumab		KN-689 SoC		Pembrolizumab Monotherapy HNSCC Pool		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	361		315		909		7,631	
with one or more adverse events	158	(43.8)	34	(10.8)	244	(26.8)	2,095	(27.5)
with no adverse event	203	(56.2)	281	(89.2)	665	(73.2)	5,536	(72.5)
with drug-related[a] adverse events	128	(35.5)	13	(4.1)	186	(20.5)	1,815	(23.8)
with toxicity grade 3-5 adverse events	36	(10.0)	2	(0.6)	49	(5.4)	543	(7.1)
with toxicity grade 3-5 drug-related adverse events	34	(9.4)	0	(0.0)	40	(4.4)	475	(6.2)
with serious adverse events	29	(8.0)	1	(0.3)	47	(5.2)	527	(6.9)
with serious drug-related adverse events	27	(7.5)	0	(0.0)	38	(4.2)	462	(6.1)
who died	1	(0.3)	0	(0.0)	3	(0.3)	13	(0.2)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)	3	(0.3)	13	(0.2)
discontinued drug due to an adverse event	28	(7.8)	0	(0.0)	23	(2.5)	363	(4.8)
discontinued drug due to a drug-related adverse event	28	(7.8)	0	(0.0)	23	(2.5)	356	(4.7)
discontinued drug due to a serious adverse event	17	(4.7)	0	(0.0)	17	(1.9)	231	(3.0)
discontinued drug due to a serious drug-related adverse event	17	(4.7)	0	(0.0)	17	(1.9)	229	(3.0)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.03
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Database cutoff date for KN-689: 25JUL2024
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adae]

Table 59. Participants With Adverse Events of Special Interest (AEOSI) (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	158	(43.8)	34	(10.8)
with no adverse events	203	(56.2)	281	(89.2)
Adrenal Insufficiency	**7**	**(1.9)**	**0**	**(0.0)**
Adrenal insufficiency	6	(1.7)	0	(0.0)
Primary adrenal insufficiency	1	(0.3)	0	(0.0)
Colitis	**9**	**(2.5)**	**1**	**(0.3)**
Colitis	9	(2.5)	1	(0.3)
Gastritis	**5**	**(1.4)**	**1**	**(0.3)**
Gastritis	5	(1.4)	1	(0.3)
Hepatitis	**8**	**(2.2)**	**1**	**(0.3)**
Autoimmune hepatitis	1	(0.3)	0	(0.0)
Hepatitis	1	(0.3)	1	(0.3)
Hepatitis acute	1	(0.3)	0	(0.0)
Immune-mediated hepatitis	5	(1.4)	0	(0.0)
Hyperthyroidism	**32**	**(8.9)**	**10**	**(3.2)**
Hyperthyroidism	32	(8.9)	10	(3.2)
Hypoparathyroidism	**1**	**(0.3)**	**1**	**(0.3)**
Hypoparathyroidism	1	(0.3)	1	(0.3)
Hypophysitis	**2**	**(0.6)**	**1**	**(0.3)**
Hypophysitis	1	(0.3)	0	(0.0)
Hypopituitarism	1	(0.3)	1	(0.3)
Hypothyroidism	**89**	**(24.7)**	**17**	**(5.4)**
Hypothyroidism	89	(24.7)	17	(5.4)
Infusion Reactions	**4**	**(1.1)**	**2**	**(0.6)**
Drug hypersensitivity	1	(0.3)	1	(0.3)
Hypersensitivity	2	(0.6)	1	(0.3)
Infusion related reaction	1	(0.3)	0	(0.0)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Myocarditis	**1**	**(0.3)**	**0**	**(0.0)**
Myocarditis	1	(0.3)	0	(0.0)
Myositis	**1**	**(0.3)**	**0**	**(0.0)**
Myositis	1	(0.3)	0	(0.0)
Nephritis	**3**	**(0.8)**	**0**	**(0.0)**
Glomerulonephritis acute	1	(0.3)	0	(0.0)
Immune-mediated nephritis	1	(0.3)	0	(0.0)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)
Pancreatitis	**5**	**(1.4)**	**0**	**(0.0)**
Autoimmune pancreatitis	1	(0.3)	0	(0.0)
Pancreatitis	3	(0.8)	0	(0.0)
Pancreatitis acute	1	(0.3)	0	(0.0)
Pneumonitis	**20**	**(5.5)**	**0**	**(0.0)**
Interstitial lung disease	2	(0.6)	0	(0.0)
Pneumonitis	19	(5.3)	0	(0.0)
Severe Skin Reactions	**10**	**(2.8)**	**2**	**(0.6)**
Dermatitis exfoliative	1	(0.3)	0	(0.0)
Erythema multiforme	3	(0.8)	0	(0.0)
Exfoliative rash	1	(0.3)	0	(0.0)
Pruritus	2	(0.6)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Rash maculo-papular	2	(0.6)	0	(0.0)
Skin necrosis	1	(0.3)	2	(0.6)
Thyroiditis	**2**	**(0.6)**	**1**	**(0.3)**
Thyroiditis	2	(0.6)	1	(0.3)
Uveitis	**1**	**(0.3)**	**0**	**(0.0)**
Iridocyclitis	1	(0.3)	0	(0.0)

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.

Source: [P689V01MK3475: adam-adsl; adae]

Table 60. Exposure-Adjusted AEOSI Adverse Events (Including Multiple Occurrences of Events) (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]	
	Pembrolizumab	SoC
Number of participants exposed	361	315
Total exposure[b] in person-months	3223.81	1154.36
Adrenal Insufficiency	**7 (0.22)**	**0 (0.00)**
Adrenal insufficiency	6 (0.19)	0 (0.00)
Primary adrenal insufficiency	1 (0.03)	0 (0.00)
Colitis	**11 (0.34)**	**1 (0.09)**
Colitis	11 (0.34)	1 (0.09)
Gastritis	**5 (0.16)**	**1 (0.09)**
Gastritis	5 (0.16)	1 (0.09)
Hepatitis	**8 (0.25)**	**1 (0.09)**
Autoimmune hepatitis	1 (0.03)	0 (0.00)
Hepatitis	1 (0.03)	1 (0.09)
Hepatitis acute	1 (0.03)	0 (0.00)
Immune-mediated hepatitis	5 (0.16)	0 (0.00)
Hyperthyroidism	**33 (1.02)**	**10 (0.87)**
Hyperthyroidism	33 (1.02)	10 (0.87)
Hypoparathyroidism	**1 (0.03)**	**1 (0.09)**
Hypoparathyroidism	1 (0.03)	1 (0.09)
Hypophysitis	**2 (0.06)**	**1 (0.09)**
Hypophysitis	1 (0.03)	0 (0.00)
Hypopituitarism	1 (0.03)	1 (0.09)
Hypothyroidism	**94 (2.92)**	**19 (1.65)**
Hypothyroidism	94 (2.92)	19 (1.65)
Infusion Reactions	**5 (0.16)**	**2 (0.17)**
Drug hypersensitivity	1 (0.03)	1 (0.09)
Hypersensitivity	3 (0.09)	1 (0.09)
Infusion related reaction	1 (0.03)	0 (0.00)
Myocarditis	**1 (0.03)**	**0 (0.00)**
Myocarditis	1 (0.03)	0 (0.00)
Myositis	**1 (0.03)**	**0 (0.00)**
Myositis	1 (0.03)	0 (0.00)
Nephritis	**3 (0.09)**	**0 (0.00)**
Glomerulonephritis acute	1 (0.03)	0 (0.00)
Immune-mediated nephritis	1 (0.03)	0 (0.00)
Tubulointerstitial nephritis	1 (0.03)	0 (0.00)

	Event Count and Rate (Events/100 person-months)[a]	
	Pembrolizumab	SoC
Pancreatitis	**5 (0.16)**	**0 (0.00)**
Autoimmune pancreatitis	1 (0.03)	0 (0.00)
Pancreatitis	3 (0.09)	0 (0.00)
Pancreatitis acute	1 (0.03)	0 (0.00)
Pneumonitis	**22 (0.68)**	**0 (0.00)**
Interstitial lung disease	2 (0.06)	0 (0.00)
Pneumonitis	20 (0.62)	0 (0.00)
Severe Skin Reactions	**11 (0.34)**	**2 (0.17)**
Dermatitis exfoliative	1 (0.03)	0 (0.00)
Erythema multiforme	3 (0.09)	0 (0.00)
Exfoliative rash	1 (0.03)	0 (0.00)
Pruritus	2 (0.06)	0 (0.00)
Rash	1 (0.03)	0 (0.00)
Rash maculo-papular	2 (0.06)	0 (0.00)
Skin necrosis	1 (0.03)	2 (0.17)
Thyroiditis	**2 (0.06)**	**1 (0.09)**
Thyroiditis	2 (0.06)	1 (0.09)
Uveitis	**1 (0.03)**	**0 (0.00)**
Iridocyclitis	1 (0.03)	0 (0.00)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[b] Drug exposure is defined as the interval between the first treatment date and the earliest of the last treatment date + 30, death date or the database cutoff date, then + 1 day since the first treatment date is Day 1.
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.

The overall number of reported outcomes of AEOSIs in the pembrolizumab group and in the SoC group were 158 (43.8%) and 34 (10.8%), respectively. Outcomes of AEOSIs by group were:

• Pembrolizumab group: 61 (38.6%) not resolved, 23 (14.6%) resolving, 63 (39.9%) resolved, 1 (0.6%) fatal, 9 (5.7%) sequelae, 1 (0.6%) unknown.

• SoC group: 12 (35.3%) not resolved, 5 (14.7%) resolving, 16 (47.1%) resolved, 0 (0.0%) fatal, 1 (2.9%) sequela, 0 (0.0%) unknown.

The overall incidence of participants who discontinued any drug due to an AEOSI was 7.8% in the pembrolizumab group and 0.0% in the SoC group.

Of the 158 participants with ≥ 1 AEOSI in the pembrolizumab group, 41 (25.9%) participants were treated with systemic corticosteroid. A total of 30 (19.0%) participants in the pembrolizumab group were treated with a high starting dose, while 11 (7.0%) participants were treated with a low starting dose.

The median high and low starting doses of concomitant corticosteroid use in the pembrolizumab group were 62.5 mg/day and 20.0 mg/day, respectively. The median duration of high and low starting doses were 6.0 days and 5.0 days, respectively.

Discontinuation due to adverse events

All adverse events leading to discontinuation

The incidence of AEs leading to discontinuation of any study treatment in the pembrolizumab group (24.4%) was higher than the SoC group (14.3%), as expected for an add-on therapy.

Table 61 Participants With Adverse Events Resulting in Any Treatment Discontinuation (Sorted by Decreasing Incidence) (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	88	(24.4)	45	(14.3)
with no adverse events	273	(75.6)	270	(85.7)
Neutrophil count decreased	7	(1.9)	10	(3.2)
Pneumonitis	7	(1.9)	0	(0.0)
Colitis	6	(1.7)	0	(0.0)
Acute kidney injury	4	(1.1)	7	(2.2)
Immune-mediated hepatitis	4	(1.1)	0	(0.0)
Stomatitis	4	(1.1)	4	(1.3)
White blood cell count decreased	4	(1.1)	1	(0.3)
Alanine aminotransferase increased	3	(0.8)	1	(0.3)
Arthralgia	3	(0.8)	0	(0.0)
Death	3	(0.8)	0	(0.0)
Fatigue	3	(0.8)	0	(0.0)
Pneumonia	3	(0.8)	0	(0.0)
Blood creatinine increased	2	(0.6)	4	(1.3)
COVID-19 pneumonia	2	(0.6)	1	(0.3)
Deafness	2	(0.6)	1	(0.3)
Diarrhoea	2	(0.6)	0	(0.0)
Dysphagia	2	(0.6)	0	(0.0)
Interstitial lung disease	2	(0.6)	0	(0.0)
Pancreatitis	2	(0.6)	0	(0.0)
Post procedural complication	2	(0.6)	0	(0.0)
Adenocarcinoma of colon	1	(0.3)	0	(0.0)
Anaemia	1	(0.3)	1	(0.3)
Atypical pneumonia	1	(0.3)	0	(0.0)
Clostridial infection	1	(0.3)	0	(0.0)
Dermatitis	1	(0.3)	0	(0.0)
Dermatitis exfoliative	1	(0.3)	0	(0.0)
Enteritis	1	(0.3)	0	(0.0)
Gastrointestinal haemorrhage	1	(0.3)	0	(0.0)
Hepatitis acute	1	(0.3)	0	(0.0)
Hypercalcaemia	1	(0.3)	0	(0.0)
Hypoacusis	1	(0.3)	1	(0.3)
Immune-mediated nephritis	1	(0.3)	0	(0.0)
Metabolic disorder	1	(0.3)	0	(0.0)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Myocardial infarction	1	(0.3)	1	(0.3)
Nausea	1	(0.3)	1	(0.3)
Neutropenia	1	(0.3)	0	(0.0)
Obstructive airways disorder	1	(0.3)	0	(0.0)
Orocutaneous fistula	1	(0.3)	0	(0.0)
Pancreatitis acute	1	(0.3)	0	(0.0)
Platelet count decreased	1	(0.3)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Primary adrenal insufficiency	1	(0.3)	0	(0.0)
Psoriasis	1	(0.3)	0	(0.0)
Pulmonary haemorrhage	1	(0.3)	0	(0.0)
Pulmonary sepsis	1	(0.3)	0	(0.0)
Radiation skin injury	1	(0.3)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Renal failure	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	0	(0.0)
Septic shock	1	(0.3)	0	(0.0)
Skin infection	1	(0.3)	0	(0.0)
Staphylococcal infection	1	(0.3)	0	(0.0)
Thrombosis mesenteric vessel	1	(0.3)	0	(0.0)
Tinnitus	1	(0.3)	1	(0.3)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)
Type 2 diabetes mellitus	1	(0.3)	0	(0.0)
Vomiting	1	(0.3)	2	(0.6)
Weight decreased	1	(0.3)	1	(0.3)
Wound dehiscence	1	(0.3)	0	(0.0)
Asthenia	0	(0.0)	2	(0.6)
Chronic kidney disease	0	(0.0)	1	(0.3)
Feeding intolerance	0	(0.0)	1	(0.3)
General physical health deterioration	0	(0.0)	1	(0.3)
Oral candidiasis	0	(0.0)	1	(0.3)
Pharyngeal inflammation	0	(0.0)	1	(0.3)
Pulmonary embolism	0	(0.0)	1	(0.3)
Renal injury	0	(0.0)	1	(0.3)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Upper respiratory tract infection	0	(0.0)	1	(0.3)

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 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.
Database Cutoff Date: 25JUL2024.

The incidence of drug-related AEs resulting in pembrolizumab discontinuation were:

- Pembrolizumab: 13.0%. The most frequently reported (incidence ≥1%) AEs resulting in pembrolizumab discontinuation were pneumonitis, colitis, and immune-mediated hepatitis

- Cisplatin: 22.4% in the pembrolizumab group and 27.3% the SoC group. The most frequently reported (incidence ≥3%) drug-related AEs resulting in cisplatin discontinuation were neutrophil count decreased and white blood cell count decreased in the pembrolizumab group and neutrophil count decreased and acute kidney injury

-RT: 1.5% in the pembrolizumab group and 0.4% the SoC group (0.4%). The most frequently reported AEs leading to RT discontinuation were stomatitis in the pembrolizumab group and alanine aminotransferase increased in the SoC group.

After adjusting for exposure, event rates for AEs leading to discontinuation of any study treatment were higher in the SoC group (3.29 events/100 person-months vs 4.07) (see Table 48).

The incidence of AEs leading to discontinuation of any study treatment in the pembrolizumab group was higher than reported in both the Pooled Pembrolizumab Monotherapy HNSCC and RSD Dataset (24.4% vs 13.2% vs 14.0%). Pneumonia was the most frequently reported AEs (incidence ≥1%) leading to discontinuation in both the comparison groups and is recognized as a pembrolizumab-related known risk.

The same trend can be noted when the rates for AEs leading to discontinuation were adjusted for exposure (3.29 events/100 person-months vs 2.27 vs 1.75), reflecting the higher risk due to the combination therapy (see Table 48).

Drug-related Adverse Events Leading to Treatment Discontinuation

Table 62. Participants With Drug-Related Adverse Events Resulting in Any Treatment Discontinuation (Sorted by Decreasing Incidence) (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	64	(17.7)	39	(12.4)
with no adverse events	297	(82.3)	276	(87.6)
Pneumonitis	7	(1.9)	0	(0.0)
Colitis	6	(1.7)	0	(0.0)
Neutrophil count decreased	6	(1.7)	10	(3.2)
Immune-mediated hepatitis	4	(1.1)	0	(0.0)
Stomatitis	4	(1.1)	4	(1.3)
White blood cell count decreased	4	(1.1)	1	(0.3)
Acute kidney injury	3	(0.8)	7	(2.2)
Arthralgia	3	(0.8)	0	(0.0)
Alanine aminotransferase increased	2	(0.6)	1	(0.3)
Blood creatinine increased	2	(0.6)	4	(1.3)
Deafness	2	(0.6)	1	(0.3)
Diarrhoea	2	(0.6)	0	(0.0)
Fatigue	2	(0.6)	0	(0.0)
Interstitial lung disease	2	(0.6)	0	(0.0)
Pancreatitis	2	(0.6)	0	(0.0)
Anaemia	1	(0.3)	0	(0.0)
COVID-19 pneumonia	1	(0.3)	0	(0.0)
Death	1	(0.3)	0	(0.0)
Dermatitis	1	(0.3)	0	(0.0)
Dermatitis exfoliative	1	(0.3)	0	(0.0)
Dysphagia	1	(0.3)	0	(0.0)
Enteritis	1	(0.3)	0	(0.0)
Hepatitis acute	1	(0.3)	0	(0.0)
Hypoacusis	1	(0.3)	1	(0.3)
Immune-mediated nephritis	1	(0.3)	0	(0.0)
Metabolic disorder	1	(0.3)	0	(0.0)
Nausea	1	(0.3)	1	(0.3)
Neutropenia	1	(0.3)	0	(0.0)
Orocutaneous fistula	1	(0.3)	0	(0.0)
Pancreatitis acute	1	(0.3)	0	(0.0)
Platelet count decreased	1	(0.3)	0	(0.0)
Pneumonia	1	(0.3)	0	(0.0)
Primary adrenal insufficiency	1	(0.3)	0	(0.0)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Psoriasis	1	(0.3)	0	(0.0)
Radiation skin injury	1	(0.3)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Renal failure	1	(0.3)	0	(0.0)
Tinnitus	1	(0.3)	1	(0.3)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)
Type 2 diabetes mellitus	1	(0.3)	0	(0.0)
Vomiting	1	(0.3)	2	(0.6)
Wound dehiscence	1	(0.3)	0	(0.0)
Asthenia	0	(0.0)	1	(0.3)
Chronic kidney disease	0	(0.0)	1	(0.3)
General physical health deterioration	0	(0.0)	1	(0.3)
Oral candidiasis	0	(0.0)	1	(0.3)
Pharyngeal inflammation	0	(0.0)	1	(0.3)
Pulmonary embolism	0	(0.0)	1	(0.3)
Renal injury	0	(0.0)	1	(0.3)
Weight decreased	0	(0.0)	1	(0.3)

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.

All Adverse Events Leading to Treatment Interruption

The incidence of AEs leading to interruption of any study treatment was higher in the pembrolizumab group (31.3%) compared with the SoC group (16.8%).

The most frequently reported AEs (incidence ≥1%) leading to interruption in the pembrolizumab group were nausea, stomatitis, vomiting, COVID-19, cellulitis, radiation skin injury, AST increased, and rash. In the SoC group, the most frequently reported AEs (incidence ≥1%) were neutrophil count decreased, WBC count decreased, stomatitis, radiation skin injury, and blood creatinine increased.

The incidence was also similar among the experimental arm and both reference groups (31.3% vs 27.7% vs 26.1%); the most frequently reported AEs (incidence ≥1%) in the pembrolizumab group were generally consistent with the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD.

Drug-Related Adverse Events Resulting in Any Treatment Interruption

Table 63. Participants With Drug-Related Adverse Events Resulting in Any Treatment Interruption (Sorted by Decreasing Incidence) (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	66	(18.3)	45	(14.3)
with no adverse events	295	(81.7)	270	(85.7)
Neutrophil count decreased	10	(2.8)	24	(7.6)
Stomatitis	10	(2.8)	5	(1.6)
White blood cell count decreased	6	(1.7)	12	(3.8)
Radiation skin injury	5	(1.4)	3	(1.0)
Vomiting	4	(1.1)	0	(0.0)
Colitis	3	(0.8)	0	(0.0)
Nausea	3	(0.8)	1	(0.3)
Platelet count decreased	3	(0.8)	2	(0.6)
Rash	3	(0.8)	0	(0.0)
Adrenal insufficiency	2	(0.6)	0	(0.0)
Blood alkaline phosphatase increased	2	(0.6)	0	(0.0)
Fatigue	2	(0.6)	1	(0.3)
Hyponatraemia	2	(0.6)	0	(0.0)
Pneumonitis	2	(0.6)	0	(0.0)
Rash maculo-papular	2	(0.6)	0	(0.0)
Acute kidney injury	1	(0.3)	0	(0.0)
Alanine aminotransferase increased	1	(0.3)	0	(0.0)
Anaemia	1	(0.3)	2	(0.6)
Arthralgia	1	(0.3)	0	(0.0)
Aspartate aminotransferase increased	1	(0.3)	0	(0.0)
Asthenia	1	(0.3)	0	(0.0)
Cellulitis	1	(0.3)	0	(0.0)
Chronic kidney disease	1	(0.3)	0	(0.0)
Dermatitis	1	(0.3)	1	(0.3)
Dermatitis allergic	1	(0.3)	0	(0.0)
Diarrhoea	1	(0.3)	0	(0.0)
Dysphagia	1	(0.3)	0	(0.0)
Febrile neutropenia	1	(0.3)	2	(0.6)
Haemoptysis	1	(0.3)	0	(0.0)
Hyperglycaemia	1	(0.3)	0	(0.0)
Hypokalaemia	1	(0.3)	0	(0.0)
Hypopituitarism	1	(0.3)	0	(0.0)
Hypothyroidism	1	(0.3)	0	(0.0)
Hypoxia	1	(0.3)	0	(0.0)
Implant tissue necrosis	1	(0.3)	0	(0.0)
Leukopenia	1	(0.3)	0	(0.0)
Lip ulceration	1	(0.3)	0	(0.0)
Liver disorder	1	(0.3)	0	(0.0)
Malaise	1	(0.3)	0	(0.0)
Mouth ulceration	1	(0.3)	0	(0.0)
Myalgia	1	(0.3)	0	(0.0)
Noninfective sialoadenitis	1	(0.3)	0	(0.0)
Oesophageal stenosis	1	(0.3)	0	(0.0)
Osteonecrosis of jaw	1	(0.3)	0	(0.0)
Osteoradionecrosis	1	(0.3)	0	(0.0)
Pharyngitis	1	(0.3)	0	(0.0)
Pneumonia	1	(0.3)	1	(0.3)
Prerenal failure	1	(0.3)	0	(0.0)
Pruritus	1	(0.3)	0	(0.0)
Pulmonary fibrosis	1	(0.3)	0	(0.0)
Pyrexia	1	(0.3)	0	(0.0)
Radiation associated pain	1	(0.3)	0	(0.0)
Swelling	1	(0.3)	0	(0.0)
Swelling face	1	(0.3)	0	(0.0)
Upper respiratory tract inflammation	1	(0.3)	0	(0.0)
Urticaria	1	(0.3)	0	(0.0)
Wound dehiscence	1	(0.3)	0	(0.0)
Agitation	0	(0.0)	1	(0.3)
Blood creatinine increased	0	(0.0)	1	(0.3)
Deafness	0	(0.0)	1	(0.3)
Decreased appetite	0	(0.0)	1	(0.3)
Hypernatraemia	0	(0.0)	1	(0.3)
Hyperuricaemia	0	(0.0)	1	(0.3)
Lymphocyte count decreased	0	(0.0)	1	(0.3)
Neutropenia	0	(0.0)	1	(0.3)
Oesophagitis	0	(0.0)	2	(0.6)
Sialoadenitis	0	(0.0)	1	(0.3)

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.

Safety Analysis for Neoadjuvant, surgery and Adjuvant phase separately

Neoadjuvant phase

Adverse Events

Table 64. Summary of Adverse Events during Neoadjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		1	
with one or more adverse events	242	(67.0)	0	(0.0)
with no adverse event	119	(33.0)	1	(100.0)
with drug-related[a] adverse events	110	(30.5)	0	(0.0)
with toxicity grade 3-5 adverse events	75	(20.8)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	18	(5.0)	0	(0.0)
with serious adverse events	39	(10.8)	0	(0.0)
with serious drug-related adverse events	11	(3.0)	0	(0.0)
who died	4	(1.1)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(3.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	7	(1.9)	0	(0.0)
discontinued drug due to a serious adverse event	4	(1.1)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	1	(0.3)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

AEs beginning on or after the first dose of neoadjuvant treatment up to the day prior to surgery, or, in participants without surgery, prior to the start date of any adjuvant treatment are included. For participants without surgery or adjuvant treatment, non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the neoadjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.t Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 25JUL2024.

Grade 3-5 Adverse Events and Drug-Related Grade 3-5 Adverse Events

During the neoadjuvant phase, the overall incidence of one or more G 3-5 AE was 20.8%; no AEs with a frequency > 1% were reported. The frequency of drug-related G 3-5 AE was 5%; event in this case, no AEs with a frequency > 1% were reported.

Serious Adverse Events and Drug-Related Serious Adverse Events

The overall incidence of SAE was 10.8%; no AEs with a frequency > 1% were reported. SAE considered drug-related were 3%; also in this case, no AEs with a frequency > 1% were reported.

Deaths

Four deaths (1.1%) were recorded during the neoadjuvant phase; no AEs with a frequency > 1% were reported.

Discontinuation and Interruption due to Adverse Events

Discontinuation: The overall frequency of discontinuation was 2.8%; no AEs with a frequency > 1% were reported.

Interruption: the overall frequency of interruption was 2.8; no AEs with a frequency > 1% were reported.

Adverse Events of Special Interest (AEOSIs)

Table 65. Participants With AEOSI during Neoadjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		1	
with one or more adverse events	35	(9.7)	0	(0.0)
with no adverse events	326	(90.3)	1	(100.0)
Colitis	**1**	**(0.3)**	**0**	**(0.0)**
Colitis	1	(0.3)	0	(0.0)
Hepatitis	**2**	**(0.6)**	**0**	**(0.0)**
Immune-mediated hepatitis	2	(0.6)	0	(0.0)
Hyperthyroidism	**12**	**(3.3)**	**0**	**(0.0)**
Hyperthyroidism	12	(3.3)	0	(0.0)
Hypothyroidism	**7**	**(1.9)**	**0**	**(0.0)**
Hypothyroidism	7	(1.9)	0	(0.0)
Infusion Reactions	**2**	**(0.6)**	**0**	**(0.0)**
Hypersensitivity	1	(0.3)	0	(0.0)
Infusion related reaction	1	(0.3)	0	(0.0)
Myocarditis	**1**	**(0.3)**	**0**	**(0.0)**
Myocarditis	1	(0.3)	0	(0.0)
Myositis	**1**	**(0.3)**	**0**	**(0.0)**
Myositis	1	(0.3)	0	(0.0)
Pneumonitis	**4**	**(1.1)**	**0**	**(0.0)**
Pneumonitis	4	(1.1)	0	(0.0)
Severe Skin Reactions	**5**	**(1.4)**	**0**	**(0.0)**
Erythema multiforme	2	(0.6)	0	(0.0)
Exfoliative rash	1	(0.3)	0	(0.0)
Pruritus	1	(0.3)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Thyroiditis	**1**	**(0.3)**	**0**	**(0.0)**

Surgery

Adverse Events

Table 66. Summary of AEs Summary during Surgery Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	323		307	
with one or more adverse events	263	(81.4)	258	(84.0)
with no adverse event	60	(18.6)	49	(16.0)
with drug-related[a] adverse events	49	(15.2)	9	(2.9)
with toxicity grade 3-5 adverse events	144	(44.6)	133	(43.3)

with toxicity grade 3-5 drug-related adverse events	15	(4.6)	4	(1.3)
with serious adverse events	76	(23.5)	67	(21.8)
with serious drug-related adverse events	9	(2.8)	0	(0.0)
who died	7	(2.2)	11	(3.6)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)
discontinued drug due to an adverse event	9	(2.8)	1	(0.3)
discontinued drug due to a drug-related adverse event	5	(1.5)	1	(0.3)
discontinued drug due to a serious adverse event	7	(2.2)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	4	(1.2)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

AEs beginning on or after surgery and prior to the first dose of adjuvant treatment are included. For participants without adjuvant treatment, non-serious AEs up to 30 days and serious AEs up to 90 days after 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.

Table 67. Participants With Adverse Events during Surgery Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	323		307	
with one or more adverse events	263	(81.4)	258	(84.0)
with no adverse events	60	(18.6)	49	(16.0)
Anaemia	51	(15.8)	64	(20.8)
Dysphagia	44	(13.6)	48	(15.6)
Weight decreased	40	(12.4)	36	(11.7)

Every participant is counted a single time for each applicable row and column.i A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

AEs beginning on or after surgery and prior to the first dose of adjuvant treatment are included. For participants without adjuvant treatment, non-serious AEs up to 30 days and serious AEs up to 90 days after 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.

Database Cutoff Date: 25JUL2024.

Grade 3 to 5 Adverse Events and Drug-related G 3-5 Adverse Events

The overall incidence of G 3-5 AEs was 44.6% in the pembrolizumab arm and 43.3% in the SoC; most frequently reported AEs were dysphagia (8.4% vs 8.1%, respectively) and anaemia (5.6% vs 9.1%, respectively.)

Drug related G 3-5 AEs were reported in the 4.6% of the pembrolizumab arm and in the 1.3% of the SoC.

Serious Adverse Events and drug related Serious Adverse Events

Serious Adverse Events were described with a frequency of 23.5% in the pembrolizumab arm and in the 21.8%, in absence of a clear trend of association with a specific type of AEs.

Same conclusions can be made about the drug-related serious adverse events: the overall frequency was 2.8% in the pembrolizumab group and 0 in the SoC.

Deaths Due to Adverse Events

The overall frequency of deaths reported during the surgery phase was 2.2 in the pembrolizumab arm and 3.6 in the SoC; no AEs with a frequency > 1% were reported.

Discontinuations and Interruptions Due to Adverse Events

Discontinuations: the frequency of discontinuation registered during the surgery phase was 2.8% and 0% in the pembrolizumab and SoC arm, respectively; no AEs with a frequency > 1% were reported.

Interruptions: Identical percentages were reported also for the interruptions.

Adverse Events of Special Interest (AEOSI)

Table 68. Participants With Adverse Events of Special Interest (AEOSI) during Surgery Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	323		307	
with one or more adverse events	33	(10.2)	13	(4.2)
with no adverse events	290	(89.8)	294	(95.8)
Adrenal Insufficiency	**3**	**(0.9)**	**0**	**(0.0)**
Adrenal insufficiency	3	(0.9)	0	(0.0)
Colitis	**2**	**(0.6)**	**0**	**(0.0)**
Colitis	2	(0.6)	0	(0.0)
Gastritis	**1**	**(0.3)**	**0**	**(0.0)**
Gastritis	1	(0.3)	0	(0.0)
Hepatitis	**0**	**(0.0)**	**1**	**(0.3)**
Hepatitis	0	(0.0)	1	(0.3)
Hyperthyroidism	**6**	**(1.9)**	**1**	**(0.3)**
Hyperthyroidism	6	(1.9)	1	(0.3)
Hypoparathyroidism	**1**	**(0.3)**	**0**	**(0.0)**
Hypoparathyroidism	1	(0.3)	0	(0.0)
Hypophysitis	**2**	**(0.6)**	**0**	**(0.0)**
Hypophysitis	1	(0.3)	0	(0.0)
Hypopituitarism	1	(0.3)	0	(0.0)
Hypothyroidism	**14**	**(4.3)**	**10**	**(3.3)**
Hypothyroidism	14	(4.3)	10	(3.3)
Nephritis	**1**	**(0.3)**	**0**	**(0.0)**
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)
Pneumonitis	**2**	**(0.6)**	**0**	**(0.0)**
Interstitial lung disease	1	(0.3)	0	(0.0)
Pneumonitis	2	(0.6)	0	(0.0)
Severe Skin Reactions	**3**	**(0.9)**	**2**	**(0.7)**
Dermatitis exfoliative	1	(0.3)	0	(0.0)
Erythema multiforme	1	(0.3)	0	(0.0)
Skin necrosis	1	(0.3)	2	(0.7)

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

AEs beginning on or after surgery and prior to the first dose of adjuvant treatment are included. For participants without adjuvant treatment, non-serious AEs up to 30 days and serious AEs up to 90 days after 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.

Database Cutoff Date: 25JUL2024.

Adjuvant Phase

Adverse Events

Table 69. Summary of Adverse Event Summary during Adjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	268	(97.5)	268	(97.5)
with no adverse event	7	(2.5)	7	(2.5)
with drug-related[a] adverse events	257	(93.5)	258	(93.8)
with toxicity grade 3-5 adverse events	189	(68.7)	165	(60.0)
with toxicity grade 3-5 drug-related adverse events	141	(51.3)	134	(48.7)
with serious adverse events	101	(36.7)	63	(22.9)
with serious drug-related adverse events	50	(18.2)	33	(12.0)
who died	14	(5.1)	13	(4.7)
who died due to a drug-related adverse event	3	(1.1)	1	(0.4)
discontinued drug due to an adverse event	68	(24.7)	44	(16.0)
discontinued drug due to a drug-related adverse event	52	(18.9)	38	(13.8)
discontinued drug due to a serious adverse event	36	(13.1)	11	(4.0)
discontinued drug due to a serious drug-related adverse event	22	(8.0)	8	(2.9)

[a] Determined by the investigator to be related to the drug.

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment 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.

Table 70. Participants With Adverse Events during the Adjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	268	(97.5)	268	(97.5)
with no adverse events	7	(2.5)	7	(2.5)
Radiation skin injury	144	(52.4)	150	(54.5)
Stomatitis	144	(52.4)	172	(62.5)
Dry mouth	73	(26.5)	74	(26.9)
Nausea	72	(26.2)	79	(28.7)
Hypothyroidism	70	(25.5)	8	(2.9)
Weight decreased	70	(25.5)	54	(19.6)
Anaemia	62	(22.5)	48	(17.5)
Lymphocyte count decreased	60	(21.8)	44	(16.0)
Constipation	56	(20.4)	44	(16.0)

Vomiting	52	(18.9)	28	(10.2)
Dysgeusia	49	(17.8)	59	(21.5)
Fatigue	49	(17.8)	45	(16.4)
Diarrhoea	48	(17.5)	12	(4.4)
Dysphagia	48	(17.5)	54	(19.6)
Neutrophil count decreased	44	(16.0)	60	(21.8)
White blood cell count decreased	43	(15.6)	54	(19.6)
Decreased appetite	35	(12.7)	38	(13.8)
Oral candidiasis	34	(12.4)	19	(6.9)
Hyponatraemia	32	(11.6)	14	(5.1)
Hypokalaemia	31	(11.3)	22	(8.0)
Platelet count decreased	17	(6.2)	28	(10.2)

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

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Grade 3 to 5 Adverse Events

Table 71. Participants With Grade 3-5 Adverse Events during the Adjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	189	(68.7)	165	(60.0)
with no adverse events	86	(31.3)	110	(40.0)
Stomatitis	44	(16.0)	42	(15.3)
Lymphocyte count decreased	32	(11.6)	33	(12.0)
Weight decreased	26	(9.5)	15	(5.5)
Neutrophil count decreased	20	(7.3)	37	(13.5)
Hyponatraemia	17	(6.2)	8	(2.9)
White blood cell count decreased	17	(6.2)	29	(10.5)
Anaemia	15	(5.5)	7	(2.5)
Radiation skin injury	15	(5.5)	18	(6.5)

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

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Drug-related Grade 3 to 5 AEs

Table 72. Participants With Drug-Related Grade 3-5 Adverse Events during the Adjuvant Phase (Frequency > 5%)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	141	(51.3)	134	(48.7)
with no adverse events	134	(48.7)	141	(51.3)

Stomatitis	41	(14.9)	42	(15.3)
Lymphocyte count decreased	20	(7.3)	21	(7.6)
Neutrophil count decreased	19	(6.9)	37	(13.5)
Radiation skin injury	15	(5.5)	18	(6.5)
White blood cell count decreased	13	(4.7)	28	(10.2)

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

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Serious Adverse Events

Table 73. Participants With Serious Adverse Events during Adjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	101	(36.7)	63	(22.9)
with no adverse events	174	(63.3)	212	(77.1)

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

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Drug-related Serious Adverse Events

Table 74. Participants With Serious Drug-Related Adverse Events during adjuvant Phase

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	50	(18.2)	33	(12.0)
with no adverse events	225	(81.8)	242	(88.0)
Stomatitis	6	(2.2)	2	(0.7)
Colitis	5	(1.8)	0	(0.0)
Pneumonitis	4	(1.5)	0	(0.0)
Immune-mediated hepatitis	3	(1.1)	0	(0.0)
Acute kidney injury	2	(0.7)	6	(2.2)
Febrile neutropenia	1	(0.4)	4	(1.5)
Nausea	0	(0.0)	3	(1.1)

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

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Deaths Due to Adverse Events

Table 75. Participants With Adverse Events Resulting in Death during Adjuvant Phase (Frequency > 1%)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	14	(5.1)	13	(4.7)
with no adverse events	261	(94.9)	262	(95.3)
Death	3	(1.1)	1	(0.4)

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Discontinuations and Interruptions due to Adverse Events

Discontinuations: discontinuations were registered in 17.1% of patients in the pembrolizumab arm and 0% in the SoC; pneumonitis (2.2%), colitis (1.8%), deaths (1.1%) and immune-mediated hepatitis (1.1%) were the most frequently recorded.

Interruptions: interruptions were reported with a frequency of 28% in the pembrolizumab arm and 0% in the SoC. Stomatitis (2.5%), COVID-19, cellulitis, rash (1.5% for each) were the most frequent.

Adverse Events of Special (AEOSI)

Table 76. Adverse Event Summary AEOSI Overall Adjuvant Phase (Participants Who Received Adjuvant Treatment)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	275		275	
with one or more adverse events	115	(41.8)	22	(8.0)
with no adverse events	160	(58.2)	253	(92.0)
Adrenal Insufficiency	**4**	**(1.5)**	**0**	**(0.0)**
Adrenal insufficiency	3	(1.1)	0	(0.0)
Primary adrenal insufficiency	1	(0.4)	0	(0.0)
Colitis	**6**	**(2.2)**	**1**	**(0.4)**
Colitis	6	(2.2)	1	(0.4)
Gastritis	**4**	**(1.5)**	**1**	**(0.4)**
Gastritis	4	(1.5)	1	(0.4)
Hepatitis	**6**	**(2.2)**	**0**	**(0.0)**
Autoimmune hepatitis	1	(0.4)	0	(0.0)
Hepatitis	1	(0.4)	0	(0.0)
Hepatitis acute	1	(0.4)	0	(0.0)
Immune-mediated hepatitis	3	(1.1)	0	(0.0)
Hyperthyroidism	**15**	**(5.5)**	**9**	**(3.3)**
Hyperthyroidism	15	(5.5)	9	(3.3)
Hypoparathyroidism	**0**	**(0.0)**	**1**	**(0.4)**
Hypoparathyroidism	0	(0.0)	1	(0.4)
Hypophysitis	**0**	**(0.0)**	**1**	**(0.4)**
Hypopituitarism	0	(0.0)	1	(0.4)

Hypothyroidism	**70**	**(25.5)**	**8**	**(2.9)**
Hypothyroidism	70	(25.5)	8	(2.9)
Infusion Reactions	**3**	**(1.1)**	**2**	**(0.7)**
Drug hypersensitivity	1	(0.4)	1	(0.4)
Hypersensitivity	2	(0.7)	1	(0.4)
Nephritis	**2**	**(0.7)**	**0**	**(0.0)**
Glomerulonephritis acute	1	(0.4)	0	(0.0)
Immune-mediated nephritis	1	(0.4)	0	(0.0)
Pancreatitis	**5**	**(1.8)**	**0**	**(0.0)**
Autoimmune pancreatitis	1	(0.4)	0	(0.0)
Pancreatitis	3	(1.1)	0	(0.0)
Pancreatitis acute	1	(0.4)	0	(0.0)
Pneumonitis	**14**	**(5.1)**	**0**	**(0.0)**
Interstitial lung disease	1	(0.4)	0	(0.0)
Pneumonitis	13	(4.7)	0	(0.0)
Severe Skin Reactions	**2**	**(0.7)**	**0**	**(0.0)**
Pruritus	1	(0.4)	0	(0.0)
Rash maculo-papular	2	(0.7)	0	(0.0)
Thyroiditis	**1**	**(0.4)**	**1**	**(0.4)**
Thyroiditis	1	(0.4)	1	(0.4)
Uveitis	**1**	**(0.4)**	**0**	**(0.0)**
Iridocyclitis	1	(0.4)	0	(0.0)

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

AEs beginning on or after the first dose of any adjuvant treatment up to 30 days for non-serious AEs or 90 days for serious AEs following the last administration of any adjuvant treatment are included.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Safety data in participants who received pembrolizumab + CRT vs. pembrolizumab + RT in adjuvant phase

Adverse Events (AE)

Table 77. Adverse Event Summary in Adjuvant Phase (Individuals Who Received Adjuvant Pembrolizumab + RT/CRT)

	Pembrolizumab+CRT		Pembrolizumab+RT	
	n	(%)	n	(%)
Participants in population	100		154	
with one or more adverse events	96	(96.0)	142	(92.2)
with no adverse event	4	(4.0)	12	(7.8)
with drug-related[a] adverse events	93	(93.0)	135	(87.7)
with toxicity grade 3-5 adverse events	72	(72.0)	70	(45.5)
with toxicity grade 3-5 drug-related adverse events	62	(62.0)	56	(36.4)
with serious adverse events	19	(19.0)	23	(14.9)
with serious drug-related adverse events	11	(11.0)	16	(10.4)
who died	1	(1.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	24	(24.0)	11	(7.1)
discontinued drug due to a drug-related adverse event	22	(22.0)	10	(6.5)
discontinued drug due to a serious adverse	3	(3.0)	8	(5.2)

event discontinued drug due to a serious drug-related adverse event	2	(2.0)	7	(4.5)

[a] Determined by the investigator to be related to the drug.

AEs beginning on or after the first dose of any adjuvant treatment and prior to the day after the last exposure of RT/CRT are included.

Participants in the pembrolizumab arm who did not receive adjuvant pembrolizumab are not included even if they received adjuvant radiation +/- cisplatin.

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.

Subjects treated with Pembrolizumab + CRT

The overall incidence of AEs was 96%: stomatitis (50%), radiation skin injury (48%), nausea (41%), constipation (30%) and haematological toxicity (neutrophil count decreased [33%], anaemia [26%]) were the most frequently reported AEs in this group.

Subjects treated with Pembrolizumab + RT

The overall incidence of AEs was 92.2%: stomatitis (55.8%), radiation skin injury (53.9%), dry mouth (23.4%), constipation (30%) weight decreased (18.2%) and lymphocyte decreased (17.5%) were the most frequently reported AEs in this group.

Grade 3 to 5 Adverse Events and Drug-Related Grade 3-5 Adverse Events

Grade 3-5 Adverse Events

Grade 3-5 AEs were reported in the 72% of subjects treated with pembrolizumab +CRT and in the 45.5% of patients treated with pembrolizumab + RT.

Neutrophil count decreased (18%), stomatitis (15%), white blood cell count decreased (13%) and lymphocyte count decreased (11%) were the most frequent grade 3-5 AEs in the first group, while stomatitis (17.5%) and lymphocyte count decreased (11%) were more frequently described in the second one.

Drug-related grade 3-5 Adverse Events

Drug-related grade 3-5 adverse events were reported in 62% and 36.4% of subjects treated with pembrolizumab + CRT and pembrolizumab + RT arms, respectively. Neutrophil count decreased (18%), stomatitis (15%), and white blood count cell decreased (13%) were the most frequently reported in the first group, while stomatitis (15.6%) and lymphocyte count decreased (5.8%) in the second one.

Serious Adverse Events and Drug-related Serious Adverse Events

Serious Adverse Events (SAE)

SAE were reported in 19% of subjects treated with pembrolizumab + CRT and 14.9% of patients treated with pembrolizumab +RT.

Drug-Related Serious Adverse Events

Drug-related SAE were reported in 11% of subjects treated with pembrolizumab + CRT and in 10.4% of subjects treated with pembrolizumab + RT.

Deaths Due to Adverse Events

Deaths were recorded with a frequency of 1% in the pembrolizumab + CRT group, while no deaths were registered in the pembrolizumab + RT cohort.

Discontinuations and Interruptions Due to Adverse Events

Discontinuations: discontinuations were recorded in the 24% of patients of the pembrolizumab + CRT and in the 7.1% of the pembrolizumab + CRT arm. In the first group, the most common AEs leading to discontinuation was neutrophil count decreased (7%).

Interruptions: AEs leading to interruption were registered in the 33% of patients in the pembrolizumab + CRT group and in the 11.7% of patients in the pembrolizumab + RT, respectively. Neutrophil count decreased (9%), stomatitis (6%), white blood cell count decreased (6%) and radiation skin injury (5%) were the most frequent AEs reported in the first group; no AEs with frequency >5% were reported in the second one.

Adverse Events of Special Interest

Table 78. Participants With Adverse Events of Special Interest (AEOSI) during Adjuvant Phase (Individuals Who Received Adjuvant Pembrolizumab + RT/CRT)

	Pembrolizumab+CRT		Pembrolizumab+RT	
	n	(%)	n	(%)
Participants in population	100		154	
with one or more adverse events	12	(12.0)	29	(18.8)
with no adverse events	88	(88.0)	125	(81.2)
Adrenal Insufficiency	**0**	**(0.0)**	**1**	**(0.6)**
Adrenal insufficiency	0	(0.0)	1	(0.6)
Colitis	**0**	**(0.0)**	**2**	**(1.3)**
Colitis	0	(0.0)	2	(1.3)
Gastritis	**0**	**(0.0)**	**2**	**(1.3)**
Gastritis	0	(0.0)	2	(1.3)
Hepatitis	**0**	**(0.0)**	**4**	**(2.6)**
Hepatitis	0	(0.0)	1	(0.6)
Hepatitis acute	0	(0.0)	1	(0.6)
Immune-mediated hepatitis	0	(0.0)	2	(1.3)
Hyperthyroidism	**7**	**(7.0)**	**5**	**(3.2)**
Hyperthyroidism	7	(7.0)	5	(3.2)
Hypothyroidism	**5**	**(5.0)**	**12**	**(7.8)**
Hypothyroidism	5	(5.0)	12	(7.8)
Infusion Reactions	**0**	**(0.0)**	**1**	**(0.6)**
Hypersensitivity	0	(0.0)	1	(0.6)
Nephritis	**0**	**(0.0)**	**1**	**(0.6)**
Immune-mediated nephritis	0	(0.0)	1	(0.6)
Pneumonitis	**0**	**(0.0)**	**2**	**(1.3)**
Pneumonitis	0	(0.0)	2	(1.3)

Severe Skin Reactions	**0**	**(0.0)**	**1**	**(0.6)**
Pruritus	0	(0.0)	1	(0.6)
Rash maculo-papular	0	(0.0)	1	(0.6)

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

AEs beginning on or after the first dose of any adjuvant treatment and prior to the day after the last exposure of RT/CRT are included.

Participants in the pembrolizumab arm who did not receive adjuvant pembrolizumab are not included even if they received adjuvant radiation +/- cisplatin.

MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.

Database Cutoff Date: 25JUL2024.

Laboratory findings

Clinical laboratory evaluations

The most frequently reported laboratory abnormalities in the pembrolizumab plus chemotherapy group reflected events associated with the combination of pembrolizumab with chemotherapy. Most laboratory abnormalities were Grade 1 or 2 and were generally consistent with the pooled pembrolizumab plus chemotherapy SD. Most frequently abnormalities were recorded for liver, bone marrow and kidney tests; the most frequently observed (incidence ≥10%) Grade 3 or 4 laboratory abnormalities in the pembrolizumab plus chemotherapy group were haemoglobin decreased (12.4%), leukocytes decreased (10.9%) lymphocytes decreased (49.9.4%), neutrophils decreased (12.7%), sodium decreased (15.5%), and gamma GT transferase increase (50%).

Overall, the incidence of Grade 3 to 4 lab abnormalities was higher with combination therapy in respect to the monotherapy reference datasets; a difference ≥20% was noted for haemoglobin decreased, leukocytes decreased, and lymphocytes decreased.

Safety in special populations

Intrinsic Factors
Age

Table 79. Adverse Event Summary by Age Category (<65, 65-74, ≥75 Years) (APaT Population)

	KN-689 Pembrolizumab						KN-689 SoC					
	<65		65-74		>=75		<65		65-74		>=75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	247		92		22		202		91		22	
with one or more adverse events	240	(97.2)	88	(95.7)	20	(90.9)	194	(96.0)	90	(98.9)	21	(95.5)
with no adverse event	7	(2.8)	4	(4.3)	2	(9.1)	8	(4.0)	1	(1.1)	1	(4.5)
with drug-related[a] adverse events	203	(82.2)	75	(81.5)	16	(72.7)	162	(80.2)	81	(89.0)	15	(68.2)
with toxicity grade 3-5 adverse events	192	(77.7)	68	(73.9)	15	(68.2)	152	(75.2)	66	(72.5)	15	(68.2)
with toxicity grade 3-5 drug-related adverse events	118	(47.8)	35	(38.0)	8	(36.4)	83	(41.1)	47	(51.6)	5	(22.7)
with serious adverse events	118	(47.8)	52	(56.5)	9	(40.9)	74	(36.6)	33	(36.3)	9	(40.9)
with serious drug-related adverse events	45	(18.2)	22	(23.9)	2	(9.1)	23	(11.4)	9	(9.9)	1	(4.5)
who died	13	(5.3)	8	(8.7)	4	(18.2)	12	(5.9)	6	(6.6)	6	(27.3)
who died due to a drug-related adverse event	3	(1.2)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)
discontinued drug due to an adverse event	54	(21.9)	27	(29.3)	7	(31.8)	21	(10.4)	19	(20.9)	5	(22.7)
discontinued drug due to a drug-related adverse event	40	(16.2)	21	(22.8)	3	(13.6)	17	(8.4)	18	(19.8)	4	(18.2)
discontinued drug due to a serious adverse event	26	(10.5)	16	(17.4)	5	(22.7)	5	(2.5)	4	(4.4)	2	(9.1)
discontinued drug due to a serious drug-related adverse event	15	(6.1)	11	(12.0)	1	(4.5)	3	(1.5)	4	(4.4)	1	(4.5)

Table 80. Adverse Event Summary for Elderly Participants by Age (APaT Population)

	Age (Years)													
	Pembrolizumab							SoC						
	< 65		65 - 74		75 - 84		>= 85	< 65		65 - 74		75 - 84		>= 85
	n	(%)	n	(%)	n	(%)	n (%)	n	(%)	n	(%)	n	(%)	n (%)
Participants in Population	247		92		22		0	202		91		20		2
with one or more adverse events	240	(97.2)	88	(95.7)	20	(90.9)	0 (0.0)	194	(96.0)	90	(98.9)	19	(95.0)	2 (100.0)
who died	13	(5.3)	8	(8.7)	4	(18.2)	0 (0.0)	12	(5.9)	6	(6.6)	6	(30.0)	0 (0.0)
with serious adverse events	118	(47.8)	52	(56.5)	9	(40.9)	0 (0.0)	74	(36.6)	33	(36.3)	9	(45.0)	0 (0.0)
discontinued due to an adverse event	54	(21.9)	27	(29.3)	7	(31.8)	0 (0.0)	21	(10.4)	19	(20.9)	4	(20.0)	1 (50.0)
CNS (confusion/extrapyramidal)	51	(20.6)	16	(17.4)	4	(18.2)	0 (0.0)	31	(15.3)	12	(13.2)	2	(10.0)	0 (0.0)
AE related to falling	25	(10.1)	8	(8.7)	2	(9.1)	0 (0.0)	10	(5.0)	5	(5.5)	0	(0.0)	0 (0.0)
CV events	71	(28.7)	30	(32.6)	5	(22.7)	0 (0.0)	43	(21.3)	18	(19.8)	3	(15.0)	0 (0.0)
Cerebrovascular events	16	(6.5)	4	(4.3)	2	(9.1)	0 (0.0)	12	(5.9)	5	(5.5)	2	(10.0)	0 (0.0)
Infections	141	(57.1)	48	(52.2)	15	(68.2)	0 (0.0)	97	(48.0)	42	(46.2)	9	(45.0)	1 (50.0)

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.
Database Cutoff Date: 25JUL2024.

Source: [P689V01MK3475: adam-adsl; adae]

Table 81. Adverse Event Summary by Age Category in respect to the reference datasets (<65, ≥65 Years) (APaT Population)

	KN-689 Pembrolizumab				KN-689 SoC				Pembrolizumab Monotherapy HNSCC Pool				Pembrolizumab Monotherapy Reference Safety Dataset			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	247		114		202		113		586		323		4,524		3,107	
with one or more adverse events	240	(97.2)	108	(94.7)	194	(96.0)	111	(98.2)	566	(96.6)	316	(97.8)	4,364	(96.5)	3,011	(96.9)
with no adverse event	7	(2.8)	6	(5.3)	8	(4.0)	2	(1.8)	20	(3.4)	7	(2.2)	160	(3.5)	96	(3.1)
with drug-related[a] adverse events	203	(82.2)	91	(79.8)	162	(80.2)	96	(85.0)	349	(59.6)	213	(65.9)	3,231	(71.4)	2,231	(71.8)
with toxicity grade 3-5 adverse events	192	(77.7)	83	(72.8)	152	(75.2)	81	(71.7)	330	(56.3)	182	(56.3)	1,917	(42.4)	1,597	(51.4)
with toxicity grade 3-5 drug-related adverse events	118	(47.8)	43	(37.7)	83	(41.1)	52	(46.0)	77	(13.1)	57	(17.6)	629	(13.9)	579	(18.6)
with serious adverse events	118	(47.8)	61	(53.5)	74	(36.6)	42	(37.2)	256	(43.7)	148	(45.8)	1,457	(32.2)	1,285	(41.4)
with serious drug-related adverse events	45	(18.2)	24	(21.1)	23	(11.4)	10	(8.8)	55	(9.4)	33	(10.2)	451	(10.0)	389	(12.5)
who died	13	(5.3)	12	(10.5)	12	(5.9)	12	(10.6)	47	(8.0)	32	(9.9)	158	(3.5)	188	(6.1)
who died due to a drug-related adverse event	3	(1.2)	1	(0.9)	0	(0.0)	1	(0.9)	6	(1.0)	2	(0.6)	21	(0.5)	21	(0.7)
discontinued drug due to an adverse event	54	(21.9)	34	(29.8)	21	(10.4)	24	(21.2)	70	(11.9)	50	(15.5)	554	(12.2)	512	(16.5)
discontinued drug due to a drug-related adverse event	40	(16.2)	24	(21.1)	17	(8.4)	22	(19.5)	31	(5.3)	19	(5.9)	333	(7.4)	306	(9.8)
discontinued drug due to a serious adverse event	26	(10.5)	21	(18.4)	5	(2.5)	6	(5.3)	58	(9.9)	38	(11.8)	366	(8.1)	348	(11.2)

discontinued drug due to a serious drug-related adverse event	15	(6.1)	12	(10.5)	3	(1.5)	5	(4.4)	20	(3.4)	12	(3.7)	177	(3.9)	170	(5.5)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.03
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN-689: 25JUL2024
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adae]

Table 82. Adverse Event Summary by Gender Category in respect to the reference datasets (APaT Population)

	KN-689 Pembrolizumab				KN-689 SoC				Pembrolizumab Monotherapy HNSCC Pool				Pembrolizumab Monotherapy Reference Safety Dataset			
	Male		Female		Male		Female		Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	284		77		248		67		752		157		4,889		2,742	
with one or more adverse events	272	(95.8)	76	(98.7)	240	(96.8)	65	(97.0)	731	(97.2)	151	(96.2)	4,711	(96.4)	2,664	(97.2)
with no adverse event	12	(4.2)	1	(1.3)	8	(3.2)	2	(3.0)	21	(2.8)	6	(3.8)	178	(3.6)	78	(2.8)
with drug-related[a] adverse events	232	(81.7)	62	(80.5)	206	(83.1)	52	(77.6)	460	(61.2)	102	(65.0)	3,457	(70.7)	2,005	(73.1)
with toxicity grade 3-5 adverse events	206	(72.5)	69	(89.6)	187	(75.4)	46	(68.7)	423	(56.3)	89	(56.7)	2,265	(46.3)	1,249	(45.6)
with toxicity grade 3-5 drug-related adverse events	121	(42.6)	40	(51.9)	114	(46.0)	21	(31.3)	112	(14.9)	22	(14.0)	814	(16.6)	394	(14.4)
with serious adverse events	134	(47.2)	45	(58.4)	94	(37.9)	22	(32.8)	334	(44.4)	70	(44.6)	1,797	(36.8)	945	(34.5)
with serious drug-related adverse events	48	(16.9)	21	(27.3)	26	(10.5)	7	(10.4)	70	(9.3)	18	(11.5)	566	(11.6)	274	(10.0)
who died	19	(6.7)	6	(7.8)	19	(7.7)	5	(7.5)	59	(7.8)	20	(12.7)	240	(4.9)	106	(3.9)
who died due to a drug-related adverse event	3	(1.1)	1	(1.3)	1	(0.4)	0	(0.0)	3	(0.4)	5	(3.2)	27	(0.6)	15	(0.5)
discontinued drug due to an adverse event	63	(22.2)	25	(32.5)	35	(14.1)	10	(14.9)	96	(12.8)	24	(15.3)	695	(14.2)	371	(13.5)
discontinued drug due to a drug-related adverse event	45	(15.8)	19	(24.7)	30	(12.1)	9	(13.4)	36	(4.8)	14	(8.9)	418	(8.5)	221	(8.1)
discontinued drug due to a serious adverse event	31	(10.9)	16	(20.8)	9	(3.6)	2	(3.0)	76	(10.1)	20	(12.7)	473	(9.7)	241	(8.8)
discontinued drug due to a serious drug-related adverse event	16	(5.6)	11	(14.3)	6	(2.4)	2	(3.0)	22	(2.9)	10	(6.4)	233	(4.8)	114	(4.2)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.03
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN-689: 25JUL2024
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Eastern Cooperative Oncology Group Performance Status

The AE profile based on ECOG in the pembrolizumab group was generally similar between participants with an ECOG status of 0 and 1.

Extrinsic Factors

Geographic Region

AEs were assessed in subgroups of participants for the extrinsic factor of geographic region (North America vs Western Europe vs ROW) for the APaT population. In the pembrolizumab group, Grade 3 to 5 AEs were higher in North America and Western Europe compared with others. Since these are nonrandomized comparisons, and similar regional differences were not seen in the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD, they do not appear to reflect a difference in the safety profile of pembrolizumab based on region.

Safety related to drug-drug interactions and other interactions

General considerations made about DDI for pembrolizumab are valid also for this extension of indication. No dedicated DDI studies have been performed.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. As systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential

side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was previously assessed as part of the population pharmacokinetic analysis in previous procedures.

Adverse drug reactions (ADRs) in section 4.8 of the SmPC

Section 4.8 of the SmPC is updated to include the KEYNOTE-689 population into the current 'pembrolizumab in combination with chemotherapy, radiation therapy (RT) or chemoradiotherapy (CRT)' pooled dataset.

The below encompasses the adverse reactions included in Table 2 of the SmPC with related frequency categories and incidence percentages from the latest pooled dataset from combination therapy (pembrolizumab plus chemotherapy or radiation therapy or chemoradiotherapy) studies as follows:

- Non-small cell lung cancer: KEYNOTE-021 (Cohorts A, C, and G), KEYNOTE-189, KEYNOTE-407, and KEYNOTE-671
- Head and neck squamous cell carcinoma: KEYNOTE-048 and KEYNOTE-689
- Gastric, oesophageal or gastroesophageal cancer: KEYNOTE-590, KEYNOTE-811, and KEYNOTE-859
- Triple negative breast cancer: KEYNOTE-355 and KEYNOTE-522
- Cervical cancer: KEYNOTE-826 and KEYNOTE-A18
- Biliary tract carcinoma: KEYNOTE-966
- Endometrial cancer: KEYNOTE-868
- Malignant pleural mesothelioma: KEYNOTE-483

Table 83 Adverse Reactions in Patients Treated With Pembrolizumab in Combination With Chemotherapy (Approved in the Current EUPI Plus New Population Under Review) (APaT Population)

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.7% (450)	247
Blood and lymphatic system disorders			
Very common	Anaemia	50.5% (3378)	1174
Very common	Neutropenia	21.9% (1464)	885
Very common	Thrombocytopenia	12.0% (805)	242
Common	Febrile Neutropenia	4.9% (326)	315
Common	Leukopenia	8.8% (588)	235
Common	Lymphopenia	3.0% (200)	91
Uncommon	Haemolytic Anaemia[a]	0.1% (8)	7
Uncommon	Eosinophilia	0.7% (47)	4
Rare	Immune Thrombocytopenia	0.04% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	6.8% (453)	77
Rare	Sarcoidosis	0.03% (2)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	14.1% (945)	18
Common	Adrenal Insufficiency[d]	1.1% (75)	31
Common	Hyperthyroidism[e]	5.8% (391)	8
Common	Thyroiditis[f]	1.1% (74)	7
Uncommon	Hypophysitis[g]	0.7% (45)	24
Rare	Hypoparathyroidism	0.04% (3)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.9% (799)	241
Very common	Decreased Appetite	25.8% (1728)	125
Common	Hyponatraemia	8.5% (570)	216
Common	Hypocalcaemia	4.7% (313)	51
Uncommon	Type 1 Diabetes Mellitus[h]	0.3% (20)	19
Psychiatric disorders			
Very common	Insomnia	11.1% (746)	10

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Nervous system disorders			
Very common	Neuropathy Peripheral	12.9% (867)	57
Very common	Headache	13.5% (904)	20
Common	Dizziness	9.7% (651)	17
Common	Dysgeusia	8.9% (599)	3
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Epilepsy	0.1% (7)	3
Uncommon	Lethargy	0.97% (65)	2
Rare	Myasthenic Syndrome[j]	0.07% (5)	5
Rare	Guillain-Barre Syndrome[k]	0.06% (4)	4
Rare	Myelitis	0.01% (1)	1
Rare	Optic Neuritis	0.01% (1)	1
Rare	Meningitis (Aseptic)	0.01% (1)	1
Eye disorders			
Common	Dry Eye	2.9% (191)	1
Uncommon	Uveitis[l]	0.2% (13)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	3.9% (264)	61
Uncommon	Myocarditis[n]	0.2% (12)	10
Uncommon	Pericardial Effusion	0.4% (27)	10
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.8% (458)	182
Uncommon	Vasculitis[o]	0.5% (35)	6
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.9% (799)	86
Very common	Cough	14.8% (991)	5
Common	Pneumonitis[p]	3.9% (264)	95
Gastrointestinal disorders			
Very common	Diarrhoea	34.7% (2320)	253

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Very common	Nausea	50.9% (3406)	201
Very common	Vomiting	27.2% (1821)	189
Very common	Abdominal Pain[q]	18.2% (1219)	82
Very common	Constipation	31.9% (2138)	24
Common	Colitis[r]	2.6% (177)	87
Common	Gastritis[s]	2.0% (133)	9
Common	Dry Mouth	5.4% (360)	6
Uncommon	Pancreatitis[t]	0.5% (32)	23
Uncommon	Gastrointestinal Ulceration[u]	0.4% (26)	4
Rare	Pancreatic Exocrine Insufficiency	(0)	0
Rare	Small Intestinal Perforation	0.03% (2)	2
Rare	Coeliac Disease	(0)	0
Hepatobiliary disorders			
Common	Hepatitis[v]	1.1% (73)	54
Rare	Cholangitis Sclerosing[w]	0.03% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Rash[x]	20.0% (1336)	7
Very common	Alopecia	21.9% (1463)	6
Very common	Pruritus[y]	14.0% (935)	6
Common	Severe Skin Reactions[z]	2.5% (167)	136
Common	Erythema	3.3% (219)	5
Common	Dermatitis	1.7% (115)	5
Common	Dry Skin	5.1% (341)	2
Common	Dermatitis Acneiform	2.0% (137)	2
Common	Eczema	1.2% (78)	2
Uncommon	Psoriasis	0.6% (41)	5
Uncommon	Lichenoid Keratosis[aa]	0.1% (8)	1
Uncommon	Vitiligo[bb]	0.5% (35)	0
Uncommon	Papule	0.2% (11)	0
Rare	Stevens-Johnson Syndrome	0.04% (3)	3

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Rare	Erythema Nodosum	0.07% (5)	0
Rare	Hair Colour Changes	0.01% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[cc]	12.9% (865)	43
Very common	Arthralgia	15.4% (1031)	42
Common	Myositis[dd]	8.6% (576)	25
Common	Pain In Extremity	7.0% (469)	13
Common	Arthritis[ee]	1.6% (104)	9
Uncommon	Tenosynovitis[ff]	0.3% (21)	1
Rare	Sjogren's Syndrome	0.03% (2)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (216)	109
Uncommon	Nephritis[gg]	0.7% (45)	26
Uncommon	Cystitis Noninfective	0.3% (18)	0
General disorders and administration site conditions			
Very common	Fatigue	35.5% (2374)	279
Very common	Asthenia	16.7% (1116)	167
Very common	Pyrexia	17.5% (1173)	49
Very common	Oedema[hh]	13.3% (889)	27
Common	Influenza Like Illness	2.6% (177)	2
Common	Chills	2.9% (197)	0
Investigations			
Very common	Alanine Aminotransferase Increased	16.7% (1120)	192
Very common	Aspartate Aminotransferase Increased	16.2% (1085)	159
Common	Blood Bilirubin Increased	4.6% (305)	52
Common	Blood Alkaline Phosphatase Increased	6.5% (437)	49
Common	Blood Creatinine Increased	9.6% (645)	35
Common	Hypercalcaemia	1.7% (117)	25

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Uncommon	Amylase Increased	0.6% (42)	10

Every participant is counted a single time for each applicable row.

a. Haemolytic Anaemia (Autoimmune Haemolytic Anaemia, Coombs Negative Haemolytic Anaemia, Haemolytic Anaemia)

b. Infusion Reactions (Anaphylactic Reaction, Cytokine Release Syndrome, Drug Hypersensitivity, Hypersensitivity, Infusion Related Hypersensitivity Reaction, Infusion Related Reaction, Serum Sickness)

c. Hypothyroidism (Autoimmune Hypothyroidism, Hypothyroidism, Immune-Mediated Hypothyroidism)

d. Adrenal Insufficiency (Addison's Disease, Adrenal Insufficiency, Primary Adrenal Insufficiency)

e. Hyperthyroidism (Graves' Disease, Hyperthyroidism)

f. Thyroiditis (Autoimmune Thyroiditis, Immune-Mediated Thyroiditis, Silent Thyroiditis, Thyroid Disorder, Thyroiditis, Thyroiditis Acute)

g. Hypophysitis (Hypophysitis, Hypopituitarism)

h. Type 1 Diabetes Mellitus (Diabetic Ketoacidosis, Type 1 Diabetes Mellitus)

i. Encephalitis (Encephalitis, Encephalitis Autoimmune)

j. Myasthenic Syndrome (Myasthenia Gravis, Myasthenic Syndrome)

k. Guillain-Barre Syndrome (Demyelinating Polyneuropathy, Guillain-Barre Syndrome)

l. Uveitis (Iridocyclitis, Iritis, Uveitis)

m. Cardiac Arrhythmia (Including Atrial Fibrillation) (Arrhythmia, Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, Atrioventricular Block, Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block, Cardiac Flutter, Electrocardiogram Qt Prolonged, Electrocardiogram Repolarisation Abnormality, Extrasystoles, Heart Rate Irregular, Sinus Arrhythmia, Sinus Bradycardia, Sinus Node Dysfunction, Sinus Tachycardia, Supraventricular Extrasystoles, Supraventricular Tachycardia, Ventricular Arrhythmia, Ventricular Extrasystoles, Ventricular Tachycardia)

n. Myocarditis (Autoimmune Myocarditis, Myocarditis)

o. Vasculitis (Central Nervous System Vasculitis, Vasculitis)

p. Pneumonitis (Autoimmune Lung Disease, Immune-Mediated Lung Disease, Interstitial Lung Disease, Organising Pneumonia, Pneumonitis)

q. Abdominal Pain (Abdominal Discomfort, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper)

r. Colitis (Autoimmune Colitis, Colitis, Colitis Microscopic, Enterocolitis, Immune-Mediated Enterocolitis)

s. Gastritis (Gastritis, Gastritis Erosive, Immune-Mediated Gastritis)

t. Pancreatitis (Autoimmune Pancreatitis, Pancreatitis, Pancreatitis Acute)

u. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)

v. Hepatitis (Autoimmune Hepatitis, Drug-Induced Liver Injury, Hepatitis, Hepatitis Acute, Immune-Mediated Hepatitis)

w. Cholangitis Sclerosing (Cholangitis Sclerosing, Immune-Mediated Cholangitis)

x. Rash (Genital Rash, Rash, Rash Erythematous, Rash Follicular, Rash Macular, Rash Maculo-Papular, Rash Papular, Rash Pruritic, Rash Vesicular)

y. Pruritus (Pruritus, Pruritus Genital, Urticaria)

z. Severe Skin Reactions (Cutaneous Vasculitis, Dermatitis Bullous, Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Erythema Multiforme, Exfoliative Rash, Pemphigoid, Pruritus, Rash, Rash Erythematous, Rash Maculo-Papular, Rash Pruritic, Rash Pustular, Skin Necrosis, Stevens-Johnson Syndrome, Toxic Skin Eruption)

aa. Lichenoid Keratosis (Lichen Planus, Lichenoid Keratosis)

bb. Vitiligo (Skin Depigmentation, Skin Hypopigmentation, Vitiligo)

cc. Musculoskeletal Pain (Back Pain, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness, Torticollis)

dd. Myositis (Myalgia, Myopathy, Myositis, Polymyalgia Rheumatica, Rhabdomyolysis)

ee. Arthritis (Arthritis, Immune-Mediated Arthritis, Joint Effusion, Joint Swelling, Polyarthritis)

ff. Tenosynovitis (Synovitis, Tendon Pain, Tendonitis, Tenosynovitis)

gg. Nephritis (Autoimmune Nephritis, Glomerulonephritis Acute, Immune-Mediated Nephritis, Nephritis, Nephrotic Syndrome, Tubulointerstitial Nephritis)

hh. Oedema (Eyelid Oedema, Face Oedema, Fluid Retention, Generalised Oedema, Lip Oedema, Localised Oedema, Oedema, Oedema Peripheral, Periorbital Oedema)

Database cutoff date for HNSCC (KN689: 25JUL2024)

The list of studies and database cutoff dates for the aggregate safety dataset within this table are provided in the appendix of the memorandum in support of SmPC section 4.8.

2.5.1. Discussion on clinical safety

The safety profile of pembrolizumab as neoadjuvant treatment and continued as adjuvant in combination with radiation therapy with or without cisplatin (SoC) and then as monotherapy in adults for the treatment of resectable locally advanced HNSCC is based on an interim analysis of the Phase 3 study KEYNOTE-689with a data cutoff date of 25 JUL-2024.

The safety database includes data from subjects treated with pembrolizumab group compared with SoC group in the KEYNOTE-689 study. In addition, a comparison with the known safety profile of pembrolizumab monotherapy in participants with HNSCC using the pooled safety data from previous pembrolizumab monotherapy in R/M HNSCC participants (KEYNOTE-012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055) and with the established safety profile of pembrolizumab monotherapy using the pooled safety data from pembrolizumab monotherapy studies (RSD) was added.

Patient exposure

As of the IA1 data cutoff (25-JUL-2024), 361 participants in the pembrolizumab group and 315 participants in the SoC group had received at least 1 dose of study treatment, either pembrolizumab monotherapy, pembrolizumab in combination with RT ± cisplatin or RT ± cisplatin or underwent in-study surgery in KEYNOTE-689.

As reported, the planned treatment per protocol for the pembrolizumab group included up to 17 cycles (approximately 12 months) of pembrolizumab treatment with 2 doses administered before and 15 doses administered after surgery. The SoC group received no neoadjuvant treatment and proceeded straight to surgery with the overall maximum duration of adjuvant RT treatment ± cisplatin planned to be 6 to 7 weeks. This study design led to a longer duration of treatment exposure in the experimental arm (9.1 months vs 2.9 months), with a consequent high risk of occurrence of events during the treatment exposure. The adjuvant therapy with pembrolizumab was allowed to be administered for 15 cycles at a planned dose of 200 mg per cycle. The median dose of adjuvant pembrolizumab administered per cycle ranged from 199.8-200.1 mg during the adjuvant phase, which resulted aligned to the dose of 200 per cycle mg that was originally planned. The median dose of cisplatin was similar in the pembrolizumab (45.2 mg/week) and the SOC group (45.3 mg/week), excluding a substantial difference in terms of exposure that could have had a role in the occurrence of AEs.

Consequently, the two treatment arms presented different durations of treatment exposure, and this was reflected in the safety profile of the study.

This difference was reflected also in the rate of study completion in both arms: at data cut-off, a total of 155 participants (43.1%) in the pembrolizumab group and 261 (82.6%) in the SoC group completed study treatment. Only a total of 11 participants (3.1%) were still receiving overall study treatment in the pembrolizumab group.

Participant characteristics

Demographic and other baseline characteristics were generally well balanced between the treatment groups and were representative of participants with resectable LA HNSCC. Overall, most participants in the pembrolizumab group were male (78.7%), white (78.7%), <65 years of age (68.4%), and had ECOG PS 0 (55.1%). When the pembrolizumab group was compared with the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD, differences ≥10% were noted in favour of the pembrolizumab arm in terms of ECOG status (ECOG PS 0: [55.1% vs 32.3%, respectively]), and origin from Western Europe (38.2% vs 26.3%). The proportion of males was higher in the pembrolizumab group compared with the pembrolizumab RSD (78.7% vs 64.1%, respectively).

Most frequently reported Adverse Events and Drug-Related Adverse Events

The overall frequency of 1 or more AEs was similar in both pembrolizumab and SoC groups (96.4% vs 96.8%) and most of them considered drug-related (81.4% vs SoC: 81.9%). The most frequently reported (incidence ≥20%) AEs in the pembrolizumab group were stomatitis, radiation skin injury, weight decreased, anaemia, dysphagia, constipation, hypothyroidism, nausea, fatigue, dry mouth, and diarrhoea; the most frequently drug-related AEs were radiation skin injury and stomatitis.

A difference in terms of frequencies (>10%) affecting the pembrolizumab arm was recorded for hypothyroidism (24.7% vs 7.9%) and insomnia (17,7% vs 7.9%), while the analysis for drug correlation confirmed the discrepancy for hypothyroidism (19.4% vs 1.9%), but also for stomatitis (52.2% vs 38.8%).

When rates were adjusted for time of exposure, a difference can be noted in favour of the pembrolizumab arm in respect to the SoC for both AEs (165.9 events/100 person-months vs 304.3) and drug-related AEs (63.4 events/100 person-months vs 137.7), reflecting the impact of the different treatment exposure durations on the crude incidence rates.

The comparison with both the Pembrolizumab Monotherapy in HNSCC group and the Reference Dataset showed a similar risk of AEs (96.4% vs 97.0% vs 96.6%), while a higher frequency in respect to the monotherapy settings can be noted in terms of drug-related AEs (81.4% vs 61.8% vs 71.6%). The AEs and drug-related AEs most frequently recorded are commonly associated with cytotoxic chemo/radiotherapy, like stomatitis, radiation skin injuries, weight decreased, haematological toxicities, dysphagia, constipation, dry mouth. In general, pembrolizumab combination therapy, when compared to the monotherapy ones, was associated with a higher risk of AEs also after adjustment for treatment exposure (AE: pembrolizumab KN689: 165.9 events/100 person-months vs 147.9 vs 115.5, Drug-Related AE: 63.4 vs 34 vs 36).

Overall, most of the more frequently reported AEs and drug-related AEs are known risks of either pembrolizumab monotherapy, RT, or cisplatin.

Grade 3-5 Adverse Events and Drug-Related 3-5 Adverse Events

Regarding Grade 3-5 AEs, the rate of patients experiencing 1 or more Grade 3 to 5 AEs in the pembrolizumab group was similar compared with the SoC group (76.2% vs 74.0%); when grade 3-5 events were analysed for drug correlation in the same setting, an overall rate of 44.6% and 44.9% was recorded, confirming a similar trend in incidence rates.

The most frequently reported Grade 3 to 5 AEs (incidence >10%) in the pembrolizumab group were weight decreased, stomatitis, dysphagia, and anaemia. The global incidence of drug-related 3-5 AEs was minor (≥5%) and the most recorded in the pembrolizumab arm were stomatitis, lymphocyte count decreased, and neutrophil count decreased. The median time-to-onset of Grade 3 to 5 AEs was greater in the pembrolizumab group (55.0 days) compared with the SoC group (29.0 days) and this difference can be attributed to the longer treatment duration in the pembrolizumab arm.

The adjustment for exposure confirmed the higher probability of Grade 3-5 events in the SoC group (28.6 events/100 person-months vs 63.1), and this is consistent with what was observed also in the Grade 3-5 drug-related AEs (9.5 vs 25.4).

With regards to the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the RSD, the incidence of Grade 3- 5 AEs in the pembrolizumab group was higher compared with the others (76.2% vs 56.3% vs 46%); a similar trend can be noted also for drug related Grade 3-5 AEs (44.6% vs 14.7% vs 15.8%). A difference >10% affecting the pembrolizumab arm of study KN-689 was noted for stomatitis (12.5% vs 0.2% vs 0.1%) and weight decrease (13.9% vs 1.3% vs 0.5%).

The results after adjustment for exposure were consistent with previous results (Grade 3-5 AE: 28.6 events/100 person-month in pembrolizumab vs 21.5 in HNSCC vs 11.2 pooled RSD; Grade 3-5 drug-related AEs: 9.5 events/100-person months vs 3.5 vs 2.7) and confirmed an overall higher risk associated with the combination therapy compared to the monotherapy (see Table 48).

Serious Adverse Events (SAE) and drug-related SAE

SAEs were more frequent in the pembrolizumab group (49.6% vs 36.8%); the 19.1% in the pembrolizumab group and 10.5% in the SoC group were considered as drug-related. The most frequently reported (incidence ≥1%) pembrolizumab-related SAEs were colitis, stomatitis, immune-mediated hepatitis, pneumonitis, and adrenal insufficiency.

After adjusting for exposure, event rates for SAEs were slightly lower in pembrolizumab group compared with the SoC group (10.9 events/100 person-months vs 17.5). In respect to that, the value of an exposure-adjusted toxicity assessment in a (neo)adjuvant setting like this is considered limited, considering that a one-year-treatment of pembrolizumab is added to SOC (chemoradiotherapy or radiotherapy). Therefore, the higher incidence of SAEs and drug-related SAEs in the pembrolizumab cohort is considered relevant, although the B/R benefit-risk balance of the product in the sought indication is not considered to be affected.

Pneumonia was recorded with an incidence > 5% also in the SoC group (pembrolizumab 3.6%, SoC 5.7%), but it is believed that there is not a greater risk difference for pembrolizumab group compared with the SoC one, given that the lower bound of the 95% CI for the treatment difference is >0. The same trend is confirmed for the drug-related SAEs (2.8 events/100 person-months vs 4.07).

When the incidence in the Pembrolizumab group is compared with both the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pooled Pembrolizumab RSD, a similar incidence can be noted in respect to the HNSCC, while it resulted slightly higher in respect to the RSD group (49.6% vs 44.4% vs 35.9%). The same pattern can be noted also for drug-related SAE (19.1% vs 9.7% vs 11%), with pneumonitis as the most frequently reported (incidence ≥1%) across all the analysed groups, reflecting the acknowledged risk of pneumonitis in pembrolizumab treated patients. These differences appeared to be reduced when an adjustment for exposure was made (10.9 events/100 person-months vs 13.3 vs 7.2 for SAEs and 2.8 events/100 person-months vs 2.0 vs 1.6 for drug-related SAEs).

Deaths due to Adverse Events

The comparative evaluation of deaths is largely influenced by several factors different from pembrolizumab therapy, such as the use of combination therapy with cytotoxic agents and surgery procedures. Moreover, when the indirect comparison with monotherapy datasets was done, other intrinsic confounding factors like different stage of disease (pooled monotherapy reference group) and disease setting (pooled reference safety dataset) should be considered.

The overall incidence of fatal AEs in the pembrolizumab group, SoC, Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD were generally similar: 6.9% (n=25), 7.6% (n=24), 8.7% (n=79) and 4.5% (n=346), respectively. Of the 25 deaths registered in the pembrolizumab arm of study KN-689, 4 of them were considered drug related.

The overall drug-related AEs leading to death (as assessed by the investigator) in the pembrolizumab group, SoC, Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD were reported for 1.1% (n=4), 0.3% (n=1), 0.9% (n=8), and 0.6% (n=42) participants, respectively.

The most frequently reported drug-related AEs resulting in death in the pembrolizumab group were COVID-19 pneumonia, death, pneumonitis and renal failure (0.3% each); notably, in 3 cases reported in this group, the cause of death was recorded as "death". In all 3 cases, the investigator assessed the deaths as unrelated to the treatment with pembrolizumab or radiotherapy and, in 1 case, death was related to cisplatin.

The global rate of drug related deaths in the SoC arm was low (1 case of acute kidney injury): overall the small numbers recorded in both trials do not allow to have any conclusions about a possible excess of toxicity when pembrolizumab is added to common therapy. On the contrary, the larger number of patients enrolled in both datasets showed a higher number of drug-related deaths, as expected.

Pneumonitis was the only cause of death which can be noted in all groups of patients treated with pembrolizumab, although with very low rate of occurrence (0.3% vs 02% vs 0.1%).

All AEs and drug-related AEs Leading to Treatment Discontinuation and Interruption

The risk of discontinuation or interruption for drug-related AEs resulted higher in the experimental arm (Discontinuation: 17.7% vs 12.4%; Interruption: 18.3% vs 14.3%), as expected considering the addition of pembrolizumab to the RT± chemo protocol. Pneumonia was the most frequently drug-related AE that led to discontinuation (1.9%), which is recognized as a pembrolizumab-related known risk.

After adjusting for exposure, event rates for drug-related AEs leading to discontinuation were slightly lower in the experimental arm in respect to the SoC, (2.4 events/100 person months vs 3.6), reflecting a role of the duration of therapy in the probability of discontinuation. The comparison analysis in respect to the reference monotherapy datasets (HNSCC and RSD) confirmed a higher incidence of discontinuation when pembrolizumab is used in combination (17.7% vs 5.5% vs 8.4% for drug related AE leading to discontinuation and 2.4 events/100 person months vs 1.0 vs 1.1, respectively).

Adverse Events of Special Interest (AEOSI)

The incidence of AEOSI was higher in the pembrolizumab group (43.8%) compared with the SoC group (10.8%); most of the events were considered drug-related (35.5% vs 4.1%).

The most frequently reported (incidence ≥10%) AEOSI for participants in the pembrolizumab group was hypothyroidism (24.7% vs 5.4%); all events were either Grade 1 or Grade 2. AEOSI with an incidence between 10 and 5% were hyperthyroidism (8.9% vs 3.2%) and pneumonitis (5.5% vs 0%). No cases of G >3 of hyperthyroidism were recorded, while 2 cases of G4 (0.6%) and 1 case of G5 (0.3%) pneumonitis were registered in the pembrolizumab arm. A low incidence was recorded also for the other immune-mediated AEs: colitis (2.3% vs 0.3%), hepatitis (2.2% vs 0.3%), nephritis (0.8% vs 0) with a similar trend confirmed also after adjustment for exposure. When incidence was adjusted for the different exposure to treatments, the difference between the two arms in respect to the most common registered AEOSI became less apparent (Hypothyroidism 2.92 vs 1.65 events/100-person months, hyperthyroidism: 1.02 vs 0.87, pneumonitis 0.68 vs 0).

The comparison with monotherapy dataset showed a higher incidence of AEOSI in the pembrolizumab group in respect to the Pooled Pembrolizumab Monotherapy HNSCC Dataset and RSD (43.8% vs 26.8% vs 27.5%), with drug-related AEOSI also having higher incidence in the combination therapy (35.5% vs 20.5% vs 23.8%). Adjustment for exposure showed a similar trend, although the difference among groups resulted less important (6.58 events/100-person months vs 3.28 vs 4.47). With regards to the thyroid disfunctions, they resulted higher in the experimental arm if compared with both the reference groups (Hypothyroidism 24.7% vs 16.2% vs 12.3%, Hyperthyroidism 8.9% vs 2.0% vs 5.2%); similarly, the difference resulted less important when incidence was adjusted for exposure to drugs (Hypothyroidism 2.92 events/100-person months vs 2.72 vs 1.51, Hyperthyroidism 1.02 vs 0.31 vs 0.63).

Most of the AEOSI were non-serious, while the 10.0% of participants had Grade 3 to 5 AEOSI, including 1 (0.3%) participant with fatal AEOSI (pneumonitis) as reported above. The majority of the AEOSI were manageable with standard clinical practice: administration of corticosteroids was needed in 25.9% of cases in the experimental arm, in respect to the 5.9% in the SoC group; high doses were required in 19% of patients treated with pembrolizumab who experienced AEOSI.

The overall reported outcomes of AEOSIs in the pembrolizumab group and in the SoC group was available for the 43.8% in the pembrolizumab group and for 10.8% in the SoC. Overall, no major differences were noted between the two groups in terms of resolution.

The incidence of Grade 3 to 5 AEOSI, serious AEOSI, and AEOSI that led to treatment discontinuation in the pembrolizumab group were generally similar to those observed in both the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD; most of them were Grade 1 (10.2%) or Grade 2 (23.5%) in severity, similar with the Pooled Pembrolizumab Monotherapy HNSCC and RSD datasets. A similar incidence can be observed also for Grade 3-5 AEOSI.

In general, in the experimental arm no new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified with the addition of RT ± cisplatin. The higher incidence of AEOSI in the experimental arm with regards to both the SoC and monotherapy settings can be explained with the addition of pembrolizumab to a cytotoxic backbone (radiotherapy +/- cisplatin). Notably, thyroid disfunctions (Hypo and Hyperthyroidism) were recorded also in the SoC arm: this was expected since that thyroid toxicity is a well-known adverse event when radiotherapy is applied to the head/neck district. Given the overall incidence, a synergic effect of pembrolizumab and radiotherapy seems unlikely but cannot be excluded, considering the comparison of the exposure-adjusted rate of incidence obtained in the experimental arm in respect to both the monotherapy groups.

Safety Analysis by risk categories

As reported, patients were stratified in high risk and low risk group basing on the presence or not of positive margins of resection after surgery.

The incidences of AEs by toxicity grade between the pembrolizumab and SoC treatment groups were generally similar among high-risk and low-risk participants, except for Grade 2 hypothyroidism, which was higher in the pembrolizumab group compared with the SoC in both groups. In the high-risk category, the incidence of SAEs and discontinuations due to SAEs were higher in the pembrolizumab 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 group compared with the SoC group. In the high-risk category, the incidence of AEOSI was generally similar between treatment groups except for drug-related AEOSI. In the low-risk category, the incidence of AEOSI was generally similar except for drug-related AEOSI, Grade 3 to 5 AEOSI, and drug-related Grade 3 to 5 AEOSI. After adjusting for exposure, the event rates for AEOSI were generally similar between treatment groups. In both the high-risk and low-risk categories, the incidence of hypothyroidism was higher in the pembrolizumab group than in the SoC group.

Overall, no differences were observed between the two groups in terms of safety.

Clinical laboratory evaluation

At IA1 the most frequently reported laboratory abnormalities in the pembrolizumab group reflected events associated with the established safety profiles of pembrolizumab monotherapy and the chemotherapy and RT regimens. Most of the recorded events were low in grade (Grade 1-3), while no Grade 5 laboratory abnormalities.

The incidences of Grade 3 to 4 laboratory abnormalities in the pembrolizumab group were generally similar to the Pooled Pembrolizumab Monotherapy HNSCC Dataset and the pembrolizumab RSD except for clinical laboratory signs of bone marrow cytotoxicity of radio/chemotherapy (anaemia, leukopenia, thrombocytopenia), but this finding was largely expected.

There were no participants in the pembrolizumab group that met predetermined criteria for potential DILI, predefined as ALT or AST ≥3 × ULN, bilirubin ≥2 × ULN, and ALP <2 × ULN, while 1 participant in the SoC group who met the prespecified criteria for potential DILI.

Safety analysis for the neoadjuvant, surgery, and adjuvant phases

- Neoadjuvant phase

The total number of subjects included in this analysis counted 361 patients in the experimental arm and 1 patient in the SOC. Given the virtual absence of a control arm, the results of this analysis are considered descriptive.

In general, the global incidence of AEs (all types) was inferior to what reported in the overall analysis for the experimental arm; AEs were reported in 67% of patients, Grade 3-5 AEs in the 20.8%, SAEs in the 10.8% and deaths in the 1.1%. The most frequently reported AE (incidence ≥10%) was fatigue. A correlation between pembrolizumab and occurrence of AEs was found in the 30% of AEs, 5% of Grade 3-5 AEs, 3% of SAE, respectively.

As expected, the incidence of AEOSI reported during this phase was low (9.7%) and most of them were considered drug related (7.8%): thyroid dysfunctions were the most frequently reported AEOSI (hyperthyroidism 3.3%, hypothyroidism 1.3%). The analysis of discontinuation or interruption of study treatment is considered relevant, considering the effects on the prosecution of the whole treatment program: in both cases, the overall rate of discontinuation and interruption were low (3.3% and 2.8%, respectively). An indirect comparison with the general safety analysis showed a reduced incidence also for these two items.

In general, the safety profile of the neoadjuvant phase is considered acceptable, with an incidence of all type of AEs that seemed to be inferior to what reported in the general analysis. An indirect comparison with the Pembrolizumab Monotherapy HNSCC groups (considered partially similar to the monotherapy schedule in the neoadjuvant setting) showed a better safety profile for all the type of AEs analysed. Finally, the effects of neoadjuvant treatment seemed to be not able to affect the prosecution on the subsequent phases of treatments in the majority of patients.

- Surgery

Although the use of pembrolizumab was not contemplated during the surgery phase, the analysis of the safety profile in the surgery phase is considered of clinical importance, given the potential impact of the neoadjuvant phase on the outcome of the surgical procedure.

In general, the reported incidence of AEs (all types) during surgery phase was lower if compared to the general incidence. The incidence of 1 or more AEs was similar in the pembrolizumab group (81.4%) and the SoC group (84.0%). Similar incidences between the experimental and SOC arms were found also for Grade 3-5 AEs (44.6% vs 43.3%), SAEs (23.5% vs 21.8%) and Deaths (2.2% vs 3.6%). The correlation with pembrolizumab was overall low, (Drug-Related AEs 15.2%, D-R Grade 3-5 AEs 4.6%, D-R SAEs 2.8%) and this is expected, since the absence of a direct administration of pembrolizumab; nevertheless, it is plausible to infer a possible correlation with the previous administration of pembrolizumab.

The most frequently reported (incidence ≥10%) AEs in the pembrolizumab and the SoC groups were anaemia, dysphagia, and weight decreased, all of which were reported at a similar incidence in both groups; the most frequently reported (incidence ≥5%) Grade 3 to 5 AEs in the pembrolizumab and the SoC groups were dysphagia and anaemia. The incidences of other classes of AEs were lower than 5% in both arms.

As expected, the incidence of AEOSI (10.2% vs 4.2%) was significantly lower if compared to that reported in the general analysis. A possible role of surgery in the occurrence of thyroid dysfunctions (mostly hypothyroidism) cannot be excluded, considering the anatomical site of surgical intervention in the neck district and this confirmed by the presence of cases of hypothyroidism also in the SOC arm (3.3%).

The specific rate of discontinuations and interruptions during surgery was low (pembrolizumab: 2.8% vs SOC 0% for both items); to note, in some cases, the interruption was reported as caused by AEs usually defined as pembrolizumab-specific AEOSIs: in general, these adverse events did not impact the administration of the perioperative approach or prejudicated the start of the adjuvant phase.

- Adjuvant phase

The planned treatment per KEYNOTE-689 protocol in the experimental arm included 15 additional cycles (45 weeks) of pembrolizumab treatment after surgery as adjuvant therapy, in association with RT treatment ± cisplatin planned to be 6 to 7 weeks. In general, the evaluation of a causal relationship with administered therapy included also cisplatin and RT.

During the adjuvant phase, the incidence of 1 or more AEs was similar between the pembrolizumab and the SoC groups (97.5% each) and, in general, the majority of AE categories were reported at a similar incidence (<10% difference in incidence) between the two groups (DR- AEs 93.5% vs 93.8%, G 3-5 AEs: 68.7% vs 60%, Deaths: 5.1% vs 4.7%). The most frequently reported AEs (incidence ≥25%) in the pembrolizumab group were stomatitis and radiation skin injury, while the most frequently reported (incidence ≥10%) Grade 3 to 5 AEs were stomatitis and lymphocyte count decreased; most of them were considered as drug related.

SAEs were reported with a difference in incidence ≥10% (pembrolizumab 36.7% vs 22.9%); when the difference between the two groups were analysed in terms of correlation of study drug, the difference became less important (18.2% vs 12%). There were no SAEs reported at an incidence ≥5% during the adjuvant phase, while for drug-related SAEs (incidence ≥1%) in the pembrolizumab group were stomatitis, colitis, pneumonitis, and immune-mediated hepatitis.

As a consequence of the presence of an active long-term treatment in the experimental arm, AEs leading to discontinuation and interruption of pembrolizumab were reported more frequently in the experimental arms (discontinuation: 17.1% vs 0%, interruptions 28% vs 0%). The most frequently reported AEs (incidence ≥1.0%) leading to discontinuation of pembrolizumab were pneumonitis (2.2%), colitis (1.8%), death (not otherwise specified) and immune-mediated hepatitis (1.1% each). The most frequent causes (incidence ≥1.0%) leading to interruption of pembrolizumab were stomatitis, COVID-19, cellulitis, rash, AST increased.

Overall, the incidence of all types of Adverse Events during the adjuvant phase was more similar to what reported in the general analysis, but this is expected considering that most of systemic treatments in both arms were administered during this phase.

Finally, among participants who received adjuvant pembrolizumab + RT versus pembrolizumab +CRT, the incidence of 1 or more AEs was similar in both groups (pembrolizumab + CRT: 96.0%; pembrolizumab + RT: 92.2%). The incidence and types of AEs, drug-related AEs, SAEs, drug-related SAEs, and AEs leading to death were similar between the pembrolizumab + CRT and the pembrolizumab + RT groups (<10% difference in incidence). The incidences of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, AEs leading to treatment discontinuation, and drug-related AEs leading to treatment discontinuation were higher in the pembrolizumab + CRT group compared with the pembrolizumab + RT group (≥10% difference in incidence). The most frequently reported (incidence ≥ 10%) Grade 3 to 5 AEs were neutrophil count decreased, stomatitis, WBC count decreased, and lymphocyte count decreased in the pembrolizumab + CRT group and stomatitis and lymphocyte count decreased in the pembrolizumab + RT group; most of them were reported as being drug-related.

Age, Gender, ECOG and geographic region

The AE profile in the pembrolizumab group was generally similar between participants who were <65 years and ≥65 years.

Very limited data are available on patients ≥85 years of age: a higher proportion of participants in the ≥75 years age category experienced death, discontinuation due to AEs and discontinuation due to SAEs compared with participants <65 years. The AE profile for categories of interest in the pembrolizumab group was generally similar across age groups of <65, 65-74, and 75- 84 years except for AEs related to infections, which resulted higher in the 75 - 84 years age group. In general, the same pattern was observed between the age groups in the Pooled Pembrolizumab Monotherapy HNSCC Dataset and in the pembrolizumab RSD.

Overall, the smaller number of participants aged 75 to 85 years, together with the absence of non-randomized comparisons and the presence of other comorbidities limits the interpretation of observed differences based on age and does not support a variation in the safety profile of pembrolizumab among the different age groups. A possible role of the combination therapy in infections in elderly patients cannot be excluded.

The presence of a non-randomized comparisons, together with the absence of differences in respect to both reference datasets RSD, precludes a meaningful comparison of the AE summary profile by geographic region, ECOG status. Although a higher rate of AEs (all types) was reported in females compared to males, definitive conclusions are limited due to the small sample size of female participants. Given that no pre-specified capping in enrolment associated with gender, the reported difference in gender can be mainly attributed to the higher incidence of HSCNN in male patients.

Section 4.8 of the SmPC has been updated with pooled safety data including 6695 patients across different trials of pembrolizumab in combination with chemotherapy, RT and chemoradiotherapy. Based on the updated safety data pool, the frequency of the ADR dizziness has been updated from very common to common.

Finally, the safety profile seems to be in line with that already known for pembrolizumab when it is associated to chemotherapy regimens in other authorised indications; a descriptive, indirect comparison with other approved combinations of pembrolizumab with platinum-based chemotherapies (treatment of resectable non-small cell lung carcinoma and newly diagnosed or recurrent endometrial cancer in adults) showed a substantial similarity in incidence of the different subtypes of adverse events. Although this comparison is largely impaired by the difference setting of disease and the absence of radiotherapy in the other approved indication, it could be helpful for excluding an excess of toxicity in the claimed extension of indication in HNSCC.

2.5.2. Conclusions on clinical safety

The safety profile of pembrolizumab in combination with RT± cisplatin is considered manageable. When used in a combination therapy, pembrolizumab does not seem to be associated with excess toxicity and no new safety signals have been identified, despite the longer duration of treatment compared to SoC. Most of the AEs recorded can be attributed to the cytotoxic therapies (RT and cisplatin) associated to pembrolizumab and no signs of excess toxicity related to the combination therapy were recorded.

The analysis per-treatment phases did not show an excess toxicity. The higher exposure to pembrolizumab in the experimental arm did not affect the prosecution on the subsequent phases of treatments in most of patients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 46.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 46.0 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

In addition, Annex II.D has been updated as follows:

- With regards to the PAM related to KEYNOTE-204 final analysis (Hodgkin lymphoma indication), the Annex II condition due date has been extended from 4Q2025 to 4Q2026, due to slow event accrual to allow for the FA to be conducted in a timely fashion.
- The PAES related to MSI-H/dMMR indication has been deleted, given that it has been submitted and assessed by CHMP (VR/0000264560).

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the patient leaflet are minimal; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication is the following: *KEYTRUDA as monotherapy is indicated for the treatment of 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 whose tumours express PD-L1 with a CPS ≥ 1.*

3.1.2. Available therapies and unmet medical need

Head and neck cancer is the sixth most common cancer worldwide, mainly of squamous histology (HNSCC)[35]. Around half of patients with HNSCC are diagnosed at a locally advanced stage[36]. Locally advanced HNSCC can be resectable or unresectable. For patients for whom primary surgical treatment is recommended, the surgical option includes reconstruction plus risk-adapted postoperative RT or CRT, based on risk factors of locoregional recurrence. The 5-year OS rate of resectable locally advanced HNSCC is around 40-50%[37], underlining the research for new treatments that can improve survival outcomes. Neoadjuvant or adjuvant treatment beyond radiation with or without cisplatin, remains investigational to date.

3.1.3. Main clinical studies

The pivotal study supporting this application is KEYNOTE-689, a phase 3 randomized multicenter open-label study in adult patients with resectable non metastatic squamous cell carcinoma of the head and neck (stage III-IVA per AJCC 8th ed). A total of 714 patients were randomized to receive in the experimental arm (n=363) neoadjuvant therapy consisting in 2 cycles of pembrolizumab, then surgical resection and then adjuvant therapy with pembrolizumab in combination with SoC radiotherapy (RT) +/- cisplatin every 3 weeks (3 cycles) followed by pembrolizumab monotherapy (12 cycles) (approximate pembrolizumab treatment duration of 1 year overall). In the control arm (n=351) no neoadjuvant therapy was administered, patients had immediately surgery, followed by adjuvant therapy with SoC RT +/- cisplatin.

Stratification factors were primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx), tumour stage (III vs IVA), and PD-L1 status (TPS ≥50% vs <50%).

EFS per RECIST1.1 by BICR was the primary endpoint. Major pathological response (mPR) and OS were secondary endpoints, both adjusted for the multiplicity. Those endpoints were tested in the PD-L1 CPS≥10 population, then CPS≥1 population, and then in all participants.

The MAH has submitted the results of the Interim Analysis 1 (data cut-off 25 July 2024), with median survival follow-up 27.1 months (range 0.5, 66.5). At IA1, 4% of subjects in the pembrolizumab arm were still receiving active treatment.

3.2. Favourable effects

- At IA1, KEYNOTE-689 study showed statistically significant EFS improvement for the experimental arm compared with the control arm in all 3 populations analysed, with a trend of higher benefit with higher PD-L1 expression: all participants (HR: 0.73; 95% CI: 0.58, 0.92; p=0.00411), CPS≥1 (HR: 0.70; 95% CI: 0.55, 0.89; p=0.00140), CPS≥10 (HR: 0.66; 95% CI: 0.49, 0.88; p=0.00217). EFS events occurred in about 41% of the population.
- A reduction mostly in distant PD as EFS events is observed in the pembrolizumab arm, further supported by a positive trend in distant metastases-free survival (DMFS).

[35] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229-63.
[36] Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, risk factors, and prevention of head and neck squamous cell carcinoma. Med Sci. 2023 Jun 13;11:42.
[37] Machiels JP, Rene Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(11):1462-75.

- At IA1, a favourable trend in OS was observed for the experimental compared with the control arm. As for EFS, the benefit appears incremental with higher PD-L1 expression: all participants (HR: 0.76; 95% CI: 0.59, 0.98; nominal p=0.01529), CPS≥1 (HR: 0.72; 95% CI: 0.56, 0.94; nominal p=0.00666), CPS≥10 (HR: 0.72; 95% CI: 0.52, 0.98; p=0.01793). Although follow-up is still short, 35% of patients overall experienced an OS event.

3.3. Uncertainties and limitations about favourable effects

- The study design does not allow to disentangle the contribution of pembrolizumab to each treatment phase. It remains unclear whether both the neoadjuvant and adjuvant parts are necessary, and the study does not assess the optimised duration of adjuvant therapy. Therefore, the study results can only be interpreted within the context of a comprehensive peri-operative approach, including both neoadjuvant and adjuvant treatment for resectable, locally advanced HNSCC.
- Several post-hoc analyses exploring hypothetical conservative scenarios were conducted: the results show that the EFS HR estimates in KEYNOTE-689 may be affected by differences in EFS assessments between arms and by management of disease progression that did not preclude surgery in patients who were lost early after randomization, suggesting a likely potential overestimation of the pembrolizumab effect. Therefore, limitations in the study design and analyses need to be recognized, and caution is needed when interpreting the obtained EFS estimates.
- At IA1, OS did not reach statistical significance in the CPS≥10 population, therefore OS was not statistically tested in the CPS≥1 and overall population according to the pre-specified multiplicity strategy. The final OS data will be submitted post-approval as REC.
- It is not possible to exclude a detrimental effect with the use of pembrolizumab in patients with CPS<1 as compared to SoC: EFS HR 2.57 (0.50, 13.36), OS HR 1.73 (0.32, 9.54), no mPR. Acknowledging the limited sample size, such trend is considered biologically plausible being consistent with external data from trials of pembrolizumab in HNSCC (KEYNOTE-040, KEYNOTE-048, KEYNOTE-412) showing a predictive value of PD-L1 expression in HNSCC. The MAH restricted the indication to patients with PD-L1 CPS≥1 expression.

3.4. Unfavourable effects

- Although the use of pembrolizumab in association with RT + cisplatin was not associated with an increased toxicity or new safety signals, almost all patients enrolled in the trial experienced at least one AEs (96.4%); most of them were considered drug-related (81.4%). Differences in the incidence of drug-related AEs (>10%) affecting pembrolizumab were hypothyroidism (19.4% vs 1.9%) and stomatitis (52.2% vs 38.8%). The frequency of Grade 3-5 AEs and Grade 3-5 drug-related AEs was 76.2% and 44.6%, respectively. Although lower incidence rates were observed in the pembrolizumab arm compared to the SoC arm for AEs (165.9 events/100 person-months vs 304.3), drug-related AEs (63.4 events/100 person-months vs 137.7), Grade 3-5 AEs (28.6 events/100 person-months vs 63.1) Grade 3-5 drug-related AEs (9.5 vs 25.4) after adjusting for time of exposure, the risk of adverse events associated with treatment remains. The same consideration applies to the risk of SAEs and drug-related SAEs [SAEs: 49.6%; drug-related SAEs: 19.1%, respectively]. When adjusted for time of exposure the incidence rates were pembrolizumab 10.9 vs SoC 17.5 and drug-related SAEs: 2.8 vs 4.07. A descriptive, indirect comparison with other approved combinations of pembrolizumab and platinum-based

chemotherapies (for the treatment of resectable non-small cell lung carcinoma and newly diagnosed or recurrent endometrial cancer in adults) showed substantial similarity in the incidence of various subtypes of adverse events, supporting the absence of excess toxicity in the proposed extension of indication in HNSCC.

- Overall, 25 deaths were reported in the pembrolizumab arm, of which 4 were considered drug-related. The most frequently reported drug-related AEs resulting in death in the pembrolizumab group were COVID-19 pneumonia, death, pneumonitis and renal failure (0.3% each).
- The frequency of AEOSI in the pembrolizumab group was 43.8%, most of which were considered drug-related (35.5%). The most frequently reported (incidence ≥10%) AEOSI was hypothyroidism (24.7%); all of which were either Grade 1 or 2. AEOSI with an incidence rate between 10-5 % were hyperthyroidism (8.9% vs 3.2%) and pneumonitis (5.5% vs 0%). No cases of Grade > 3 of hyperthyroidism were reported, while 2 cases of Grade 4 (0.6%) and 1 case of Grade 5 (0.3%) pneumonitis were reported in the pembrolizumab arm. After adjusting for differences in treatment exposure, the difference between the two arms remains, although it was less pronounced (hypothyroidism 2.92 vs 1.65 events/100-person months, hyperthyroidism: 1.02 vs 0.87, pneumonitis 0.68 vs 0).

3.5. Uncertainties and limitations about unfavourable effects

Although the analysis of AEs by age category showed a higher proportion of participants aged ≥75 years who experienced death, discontinuation due to AEs, and discontinuation due to SAEs compared to those aged <65 years, the smaller number of participants aged 75 to 85 limits the interpretation of these observed age-related differences. In section 4.4 of the SmPC, a general warning for elderly patients over 75 years is already reflected.

3.6. Effects Table

Table 84. Effects Table for Keytruda monotherapy as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without concomitant cisplatin and then as monotherapy for adult patients with resectable locally advanced HNSCC in the CPS≥1 population (KEYNOTE-689, Interim Analysis 1, data cut-off 25 July 2024)

Effect	Short description	Unit	Treatment Pembro neoadj →surgery →pembro adj+ RT+/-cisplatin (n=347)	Control surgery→ RT+/-cisplatin (n=335)	Uncertainties / Strength of evidence	References
Favourable Effects						
EFS	Event free survival (per RECIST1.1 by BICR)	HR (95%CI)	CPS≥1: 0.70 (0.55, 0.89)		EFS statistically significant	CSR KN689
OS	Overall survival	HR (95%CI)	CPS≥1: 0.72 (0.56, 0.94)		OS not stat sign in CPS≥10, thus not tested in CPS≥1 and all participants	
Unfavourable Effects						
AEs	Grade 3-5 AEs Drug related 3-5 AEs	%	76.2% 44.6%	74% 44.9%	Toxicity reflecting the toxicity of each component, no new safety signals	CSR KN689
SAEs	SAEs Drug related SAEs		49.6% 19.1%	36.8% 10.5%		

Effect	Short description	Unit	Treatment Pembro neoadj →surgery →pembro adj+ RT+/-cisplatin (n=347)	Control surgery→ RT+/-cisplatin (n=335)	Uncertainties / Strength of evidence	References
Deaths	Deaths		6.9%	7.6%		

Abbreviations: AE: Adverse Event; SAE: Serious Adverse Event; all part. = all participants; CPS= combined positive score

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KEYNOTE-689 showed, at the first pre-specified interim analysis, a statistically and clinically significant improvement in EFS per RECIST 1.1 by BICR in all PD-L1-positive populations (CPS≥10 and CPS≥1) as well as in the overall population. OS was not statistically significant in the CPS≥10 population and was therefore not formally tested in the CPS≥1 and overall population. However, a favourable trend in OS was observed across all patient populations, acknowledging the still limited survival follow-up. The difference in mPR vs SoC also reached statistical significance, although the clinical relevance of the observed mPR rate remains questionable. Subgroup analyses showed consistent results across the pre-planned subgroups, with the exception of tumours located in the hypopharynx. However, in this small subgroup some imbalances in baseline characteristics and treatment pathways between arms could have contributed to the difference in outcomes observed, considering the lack of biological rationale to expect differential efficacy in the hypopharynx versus other sites. More importantly, KEYNOTE-689 results confirmed the predictive value of PD-L1 expression according to CPS score; in particular, a potential OS detriment in patients with CPS<1 could not be excluded. Although this was a very small subgroup (3.8% of the ITT population), the biological plausibility is supported by all prior pembrolizumab studies in HNSCC, and the indication was restricted to the PD-L1 CPS≥1 population.

In addition, as all patients in the pivotal study received cisplatin monotherapy concomitantly with RT, and cisplatin concomitantly with RT is recommended as SoC in this setting in ESMO guidelines, the wording of the final indication was revised to clarify this.

Several protocol amendments have impacted relevant aspects of this open-label study. In particular, a late amendment updated the EFS definition to exclude progressive disease that did not preclude surgery as an event. Reassuringly, the MAH stated that this amendment was done without any knowledge of treatment group-level results. KEYNOTE-689 included a neoadjuvant phase only in the experimental arm. Due to such study design, efficacy assessments were carried out at later time after randomization in the pembrolizumab arm compared with the control arm.

These factors, the timing of EFS assessment and the updated EFS definition, may have led to an overestimation of the observed benefit in EFS for pembrolizumab, and caution is needed when interpreting the obtained EFS estimates. However, OS results in the CPS≥1 population suggest a beneficial effect with pembrolizumab, although not formally statistically tested due to prespecified multiplicity rules. The low rate of censoring due to withdrawal or lost to follow-up observed in the control arm, which was comparable to that in the pembrolizumab arm, supports the robustness of the observed OS estimates. Considering that OS is a robust and clinically meaningful endpoint, these results partially alleviate the methodological concerns associated with the EFS endpoint. Based on available data, it is not expected that the OS trend will meaningfully change with longer follow-up. However, as OS has not been formally tested in the CPS≥1 population, and considering the early disease setting, the MAH will provide final OS results post-approval **(REC)**.

Overall, the safety profile of pembrolizumab in combination with RT +/-cisplatin is considered manageable. When used in combination therapy, no new safety signals were identified for the combination with RT + chemotherapy. The crude evaluation of the safety profile showed a similar incidence between the two arms of KN 689 in terms of AEs and drug-related AEs (regardless of grade) and a higher incidence in the pembrolizumab group of SAEs and drug-related SAEs. When the frequency of SAE and drug related SAE is adjusted for time of exposure, the incidence was lower in the pembrolizumab arm, but the value of exposure-adjusted toxicity assessments in a (neo)adjuvant setting like this is considered limited. In general, the high incidence of SAEs and drug-related SAEs are considered clinically relevant, although the benefit-risk balance in the sought indication is not considered negatively affected. The profile of AEOSI was in line with the known safety profile of pembrolizumab. Finally, the per-treatment phase analysis did not show an excess toxicity per single phase of treatment and can be considered consistent with the overall safety profile.

3.7.2. Balance of benefits and risks

KN-689 showed statistically significant and clinically relevant EFS improvement in the pembrolizumab arm compared with the control arm, although the magnitude of the EFS effect is likely to be overestimated due to methodological limitations. The observed favourable OS trend, while not formally statistically significant, provides supporting evidence and partially alleviates the concerns on the EFS estimation.

The toxicity of pembrolizumab was consistent with the overall known safety profile. Although the added toxicity is considered of clinical importance, overall, the safety profile of pembrolizumab in combination with RT+/-cisplatin is considered manageable.

In conclusion, the overall results of KN-689 support the sought indication of pembrolizumab as neoadjuvant/adjuvant treatment in resectable locally advanced HNSCC in the PD-L1 CPS≥1 population.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall benefit-risk profile of Keytruda as monotherapy for the treatment of resectable locally advanced HNSCC as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1 is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include, KEYTRUDA as monotherapy, for the treatment of resectable locally advanced head and neck squamous cell carcinoma (HNSCC) as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1, based on the results of study P689V01MK3475 (KEYNOTE-689); this is a Phase 3, randomised, open-label study evaluating pembrolizumab as neoadjuvant therapy and in combination with standard of care as adjuvant therapy for stage III or IVA, resectable, locoregionally advanced head and neck squamous cell carcinoma. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 46.0 has also been submitted. In addition, Annex II.D has been updated, and the MAH took the opportunity to introduce some minor editorial changes to the PI.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.