20 May 2021
EMA/331504/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0097

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
3L+	Third-line or later
5-FU	5-fluorouracil
AC	Adenocarcinoma
AE	Adverse event
AEOSI	Adverse event of special interest
ALT	Alanine aminotransferase
ASaT	All Subjects as Treated
BICR	Blinded independent central review
CDE	Center for Drug Evaluation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2019
CPS	Combined positive score
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	Deficient mismatch repair
DOR	Duration of response
EAC	Esophageal adenocarcinoma
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EGJ	Esophagogastric junction
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire in Oesophageal Cancer 18
EQ-5D	EuroQol 5-dimension
ESCC	Esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
HER-2	Human epidermal growth factor receptor 2
HR	Hazard ratio

Abbreviation	Definition
IA	Interim analysis
IFNγ	Interferon gamma
IgG4	Immunoglobulin G4
IL-2	Interleukin 2
ISS	Integrated summary of safety
ITT	Intention to treat
KM	Kaplan-Meier
LS	Least squares
MSI-H	Microsatellite instability-high
ORR	Objective response rate
OS	Overall survival
mAb	Monoclonal antibody
MedDRA	Medical Dictionary of Regulatory Activities
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung carcinoma
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand-1
PD-L2	Programmed cell death-1 ligand-2
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcome
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RSD	Reference Safety Dataset
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
SCC	Squamous cell carcinoma
SOP	Standard Operating procedures
TNFα	Tumor necrosis factor alpha
US	United States
VAS	Visual analogue scale
WBC	White blood cell

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 11 November 2020 an application for a variation.

The following variation was requested:

Variation requested		**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 and IIIB

Extension of indication to include in combination with chemotherapy, first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults for Keytruda, based on the results from the pivotal KEYNOTE-590 (KN590) trial, a Phase 3, randomized, double-blind, placebo-controlled, multisite study to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy (cisplatin and 5-FU) versus chemotherapy (cisplatin with 5-FU) as first line treatment in participants with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction; as a consequence sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version of the RMP (Version 30.1) has also been submitted.

The variation requested amendments to the Summary of Product Characteristics 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) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) was not yet completed as some measures were deferred.

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 did seek Scientific Advice at the CHMP on the design of KEYNOTE-590, the pivotal trial for this application (EMEA/H/SA/2437/19/2017/II). Questions referred to the study population, choice of comparator, proposed endpoints and statistical plan.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

2. Timetable	**Actual dates**
Submission date	11 November 2020
Start of procedure:	28 November 2020
CHMP Rapporteur Assessment Report	22 January 2021
CHMP Co-Rapporteur Assessment Report	22 January 2021
PRAC Rapporteur Assessment Report	26 January 2021
PRAC Outcome	11 February 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 February 2021
Request for supplementary information (RSI)	25 February 2021
CHMP Rapporteur Assessment Report	8 April 2021
CHMP members comments	12 April 2021
Updated CHMP Rapporteur Assessment Report	19 April 2021
Request for supplementary information (RSI)	23 April 2021
CHMP Rapporteur Assessment Report	6 May 2021
CHMP members comments	12 May 2021
Updated CHMP Rapporteur Assessment Report	N/A
The Oral explanation was held on:	18 May 2021
Opinion	20 May 2021

3. Scientific discussion

3.1. Introduction

Within the current type II variation, the MAH is seeking an extension of indication for pembrolizumab, in combination with chemotherapy, to the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults, based on the results from an analysis of the pivotal KEYNOTE-590 (KN590) trial.

3.1.1. Problem statement

Disease or condition

Locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults.

State the claimed the therapeutic indication

"KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults (see section 5.1)"

Epidemiology

In 2018, oesophageal cancer was the seventh most common cancer in terms of incidence (572,034 new cases) and the sixth leading cause of cancer-related death worldwide with 508,585 deaths. Over 77% of the new oesophageal cancer cases diagnosed worldwide occur in Asia, and incidence varies significantly between regions[1]. In most regions, including the US and Europe, males have a 2- to 3-fold higher incidence compared to females. In Western Europe, an estimated 13,938 new cases and 11,403 deaths are expected to occur in 2020[2].

Biologic features, aetiology and pathogenesis

Oesophageal cancers can be categorized into 2 main histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (AC). While SCC is the most common subtype of oesophageal cancer globally (84% of all cases) with the highest incidence rates in Eastern Asia and Eastern Africa, AC is the most common subtype in high-income countries, with the highest incidence rates in Northern Europe, North America, and Oceania[3]. SCC typically occurs in the proximal two-thirds of the oesophagus, whereas AC is found in the distal third of the oesophagus and at the EGJ. AC tumours of the EGJ are classified based on Siewert types[4]. Siewert type I tumours are adenocarcinomas whose epicenter is located 1 to 5 centimeters proximally from the anatomical line of the cardia[5]. As regards risk factors, smoking and alcohol consumption have been associated with SCC in western countries, while AC generally occurs in patients with gastro-oesophageal reflux and a higher risk has been recognised for obese patients.

Clinical presentation, diagnosis and stage/prognosis

Most patients are diagnosed at an advanced stage, and the prognosis for metastatic oesophageal cancer is generally poor, with an overall 5-year survival rate of 5%6. Treatment of advanced oesophageal cancer is largely palliative in intent.

[1] Global Cancer Observatory (GCO). Oesophagus: Globacon 2018. Lyon (France): International Agency for Research on Cancer (IARC); 2019 Mar. 2 p.
[2] Oesophagus - Global Cancer Observatory - IARC - https://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf
[3] Arnold M, Ferlay J, van Berge Henegouwen MI, Soerjomataram I. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69:1564-71.
[4] Ilson DH, van Hillegersberg R. Management of patients with adenocarcinoma or squamous cancer of the esophagus. Gastroenterology. 2018 Jan;154(2):437-51.
[5] Escrig Sos J, Gomez Quiles L, Maiocchi K. The 8th edition of the AJCCTNM classification: new contributions to the staging of esophagogastric junction cancer. Cir Esp. 2019;97(8):432-7.
[6] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan-Feb;70(1):7-30.

Management

For previously untreated patients with locally advanced unresectable or metastatic carcinoma of the oesophagus, NCCN and ESMO guidelines recommend first-line treatment with the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin). Some of the first-line treatments recommended and/or used for oesophageal cancer are based on evidence that is extrapolated from data from either gastric or gastroesophageal junction trials[7] [8] [9].

Triplet regimens with the addition of anthracycline or taxanes can also be considered in fit patients, although controversy remains as regards their clinical advantage. Taxane and platinum combinations can be also considered. In SCC, cisplatin-based combinations showed increased response rate but no survival gain compared with monotherapy; overall, results with palliative chemotherapy are worse than for AC tumours [7] [8] [9].

An overview on clinical efficacy of currently available treatments has been provided by the MAH in the table below:

Table 1: First-line Treatment Outcomes from Phase 1 and 2 Studies in Oesophageal Cancer

Treatment	Histology	No. of Patients	ORR (%)	PFS/TTP (months)	OS (months)	Reference
5-FU + alpha 2a-interferon	SCC + AC	21	25	n/a	n/a	{04LDGG}
Cisplatin + 5-FU	SCC	44	35	6.2	7.6	{04RYQR}
Cisplatin + 5-FU	SCC	36[a]	33	n/a	6.6	{046BQQ}
Cisplatin + 5-FU	SCC	30	30	3.6	5.5	{04KC0F}
Cisplatin + 5-FU	SCC	20	55	n/a	20.5	{04LDG2}
Cisplatin + 5-FU + leucovorin	SCC + AC	10	40	n/a	10.6	{04L90K}
Cisplatin + 5-FU + adriamycin	SCC	21	33	n/a	8.0	{04L90Y}
Cisplatin + 5-FU + cetuximab	SCC	32	34	5.9	9.5	{04KC0F}
Cisplatin + 5-FU + doxorubicin	SCC	41	44	5.0	10.1	{04L9F9}
Cisplatin + 5-FU + folinic acid + etoposide	SCC	68	34	n/a	9.5	{04LDG0}

[7] F. Lordick, C. Mariette, K. Haustermans, R. Obermannová and D. Arnold. Oesophageal Cancer: ESMO Clinical Practice Guidelines. Ann Oncol (2016) 27 (suppl 5): v50-v57
[8] K. Muro, F. Lordick, T. Tsushima et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer; a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol (2019); 30: 34–43.
[9] NCCN Guidelines Esophageal and Esophagogastric Junction Cancers version 2.2021

Cisplatin + capecitabine	SCC	45	58	4.7	11.2	{04L9FC}
Cisplatin + capecitabine	SCC	46	57	5.1	10.5	{04L9FF}
Cisplatin + paclitaxel	SCC + AC	20	40	8.0[b]	11.0[b]	{04LDFZ}
Cisplatin + paclitaxel	SCC + AC	59	52	n/a	n/a	{04LDG8}
Cisplatin + paclitaxel + nimotuzumab	SCC	56	52	10.8	20.2	{04LDFY}
Cisplatin + vinorelbine	SCC	71	34	3.6	6.8	{04L90P}
Oxaliplatin + 5-FU + leucovorin (FOLFOX)	SCC	56	23	4.4	7.7	{04LDH4}
Paclitaxel + capecitabine	SCC	48	58	6.7	13.2	{04L9FF}
Paclitaxel + carboplatin	SCC + AC	35	43	n/a	9	{04L90V}
Paclitaxel + nedaplatin	SCC + AC	36	44	6.1	10.3	{04L924}
Paclitaxel + nedaplatin	SCC	36	46	7.1	12.4	{04L9F8}

Abbreviations: 5-FU = 5-fluorouracil; AC = adenocarcinoma; n/a = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SCC = squamous cell carcinoma; TTP = time to progression.

[a] Number of eligible patients.

[b] Median PFS and OS were based on responding patients.

3.1.2. About the product

Keytruda (pembrolizumab) is a humanized mAb IgG4/kappa isotype directed against PD-1. By blocking the interaction between PD-1 and its ligands PD-L1/2, pembrolizumab enhances T cell lymphocyte activity with consequent stimulation of the immune-mediated anti-tumour activity. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not non-specifically activate T cells.

Pembrolizumab is currently approved in the EU for the treatment of melanoma, NSCLC, RCC, HNSCC, urothelial cancer, and cHL. Pembrolizumab has been approved both as monotherapy and in combination with other agents.

The scope of this variation is to include a new indication for Keytruda: in combination with chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults. The proposed indication is supported by the results from a single pivotal study, the KEYNOTE-590 (KN590) trial. A Phase 3, randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy (cisplatin and 5-FU) versus chemotherapy (cisplatin and 5-FU) as first line treatment in participants with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction. A total of 700 patients were randomized to one of the two treatment arms. A dosing regimen of 200 mg Q3W is recommended.

The CHMP accepted the following indication:

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express

PD-L1 with a CPS ⩾ 10.

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

Scientific Advice was obtained from the CHMP on 23 March 2017, with questions relating to the design elements of Study KN590, such as the study population, comparator, endpoints and statistical analysis plan.

- As regards inclusion/exclusion criteria, the CHMP noted the exclusion of locally advanced carcinoma that is resectable or potentially curable by radiation therapy, as determined by local investigators; in this regard, it was advised to carefully select study centres with adequate expertise in the management of oesophageal cancer (i.e. high-volume centres with experienced surgeons and multidisciplinary teams as recommended by guidelines) since this is known to impact on patient's clinical outcome. The Applicant did not comment on this aspect within the submitted application; however, information has been requested in view of the OS results as stratified by geographic region.

- Although the chosen comparator was deemed adequate, it was suggested to consider the addition of a third treatment arm to test pembrolizumab monotherapy based on study KN180 results. The MAH did not follow the advice; however, the completed KN181 trial testing pembrolizumab in monotherapy for the same indication after prior systemic therapy has provided evidence for lack of benefit on clinical outcomes of the immunotherapeutic agent alone.

- Among the proposed stratification factors, it was recommended to include PD-L1 status. The MAH did not follow the advice, however, clinical characteristics of patients as stratified by CPS cut-off levels (≥10 and <10) showed balanced treatment arms and good representation of the two subgroups (CPS ≥10 and <10) within the overall population was achieved providing unbiased result analysis and data interpretation.

- PFS as primary endpoint was considered acceptable if supported by a positive trend in OS. However, the CHMP highlighted that the magnitude of the effect in the overall population and in both biomarker positive and negative subgroups will be taken into account. In addition, to assess the overall clinical relevance of the results, the effect will also be considered in relation to the tolerability of the combination.

- On the statistical aspects of the study design, the need for compelling statistical significance based on a single pivotal trial was highlighted in support of the pursued extension of indication, and if superiority in PFS could not be provided, the exclusion of detrimental effect of treatment on mortality either in the interim or final analysis was requested to be shown.

3.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The assessment of KN590 data did not raise concern over GCP compliance leading to request for GCP inspection.

3.2. Non-clinical aspects

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

3.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to be metabolised in the body and biodegrade in 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 conducting Environmental Risk Assessment studies as the product and excipients are not expected to pose a significant risk to the environment.

3.2.2. Discussion and conclusion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient, an ERA justifying the lack of ERA studies is considered acceptable.

3.3. Clinical aspects

3.3.1. 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 the main clinical study

Table of All Clinical Trials

Study ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
3475-590 [Ref. 5.3.5.1: P590V01MK3475]	3	Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Denmark, France, Germany, Guatemala, Hongkong, Japan, Malaysia, Peru, Romania, Russia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, UK, USA	A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/ Metastatic Esophageal Carcinoma	Randomized, double-blind, parallel-group, active-controlled	Arm 1: pembrolizumab 200 mg IV Q3W plus cisplatin 80 mg/m^2 IV Q3W plus 5FU 800 mg/m^2/day continuous IV infusion on each Day 1 to Day 5 Q3W (total of 4000 mg/m^2 per 3-week cycle) Arm 2: Placebo IV Q3W plus cisplatin 80 mg/m^2 IV Q3W plus 5FU 800 mg/m^2/day continuous IV infusion on each Day 1 to Day 5 Q3W (total of 4000 mg/m^2 per 3-week cycle) Duration: Pembrolizumab/placebo: 35 administration or approximately 2 years Cisplatin capped at 6 doses 5FU per local standard. But not to exceed a maximum of 35 cycles.	Males/females Age: ≥18 participants with advanced/metastatic esophageal carcinoma	Pembrolizumab plus chemotherapy: 373 Chemotherapy: 376

The clinical development program of pembrolizumab in support of the pursued indication in oesophageal cancer is schematized below:

Table 3: clinical development program:

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-028 Ongoing Enrollment complete for oesophageal cohort	Phase 1 Multicenter, non-randomized, single-arm, multicohort	PD-L1 positive participants Cohort A4 of advanced/metastatic oesophageal cancer participants N=23	Pembrolizumab monotherapy (10 mg/kg Q2W)	ORR
KEYNOTE-180 Ongoing	Phase 2 Multicenter, non-randomized, single-arm, multicohort	Advanced/metastatic oesophageal cancer participants, 3L+ N=121	Pembrolizumab monotherapy (200 mg Q3W)	ORR
KEYNOTE-181 Ongoing	Phase 3 Multicenter, randomized, open label	Advanced/metastatic oesophageal cancer, 2L N=628	Pembrolizumab monotherapy (200 mg Q3W) or investigator's choice of paclitaxel, docetaxel, or irinotecan	OS
KEYNOTE-590 Ongoing	Phase 3 Multicenter, randomized, double-blind, placebo-controlled	Locally advanced unresectable or metastatic oesophageal cancer, 1L Target N=700	Pembrolizumab (200 mg Q3W) or placebo in combination with chemotherapy	OS, PFS
KEYNOTE-975 Ongoing	Phase 3 Multicenter, randomized, double-blind, placebo-controlled	cTX N + M0 or cT2-T4aNXM0 ESCC (as defined by AJCC 8th edition), Siewert Type I adenocarcinoma of the EGJ, or EAC Target N = 600	Pembrolizumab (200 mg Q3W, 8 cycles) and then 400 mg Q6W (5 cycles) with dCRT or placebo with dCRT	OS, EFS

3.3.2. Pharmacokinetics

Pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled in studies KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and EU SmPC.

Within the current application, the MAH provided PK data from KEYNOTE-181 (a Phase III randomized open-label study of single agent pembrolizumab vs. physicians' choice of single agent docetaxel, paclitaxel, or irinotecan in subjects with advanced/metastatic adenocarcinoma and squamous cell carcinoma of the oesophagus that have progressed after first-line standard therapy), which has a comparable patient population as KEYNOTE-590.

The results of systemic exposures are shown by tumour histology types, squamous cell carcinoma and adenocarcinoma.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in target population

A substantial characterization of the key clinical pharmacology and immunogenicity findings of pembrolizumab as monotherapy has been provided in previous submissions.

The updated clinical pharmacology results specific to this submission include:

• PK data from subjects with advanced/metastatic squamous cancer and adenocarcinomas of the oesophagus (ESO) (KEYNOTE-181)

• A comparison of KN181 observed PK data with reference model (TDPK) predicted PK.

Pembrolizumab PK data from KEYNOTE-181 study

PK samples with a 15 October 2018 visit cut-off date were measured for 318 subjects in KN181 ESO.

Table 4: Overview of pembrolizumab included in KN181 PK analysis

Study	Cohort/Part	Treatment	Cancer Type	Number of subjects providing PK [a]	Data cutoff
KN181	ESO	200 mg Q3W	ESO	318	15-Oct-2018

[a] unique subjects providing PK samples, not all subjects have Cycle 1 day 1 samples.

ESO: esophagus cancer
Data Source: 04VNRS: analysis-p181pkdm02

PK schedule in KN181 200 mg Q3W: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 6 and 8 and every 4 cycles (12 weeks) thereafter.

Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in ESO subjects from KN0181 are presented in the tables below:

Table 5: Overall PK results:

Overall PK Results

Summary Statistics of Pembrolizumab Predose (Ctrough) Serum Concentration Values Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KN181 Subjects

Predose (C_{trough})								
Cycle	NOM TAFD (Day)	N	GM (%CV) (µg/mL)	GM (SD) (µg/mL)	AM (SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 2 (Week 3)	21	274	14.5 (41)	14.5 (5.6)	15.6 (5.6)	2.98	15.0	39.1
Cycle 4 (Week 9)	63	158	28.2 (49.6)	28.2 (12.7)	31.0 (12.7)	3.87	30.8	73.7
Cycle 6 (Week 15)	105	106	35.3 (46.9)	35.3 (15.3)	38.6 (15.3)	8.54	36.0	87.3
Cycle 8 (Week 21)	147	76	40.3 (48.1)	40.3 (18.1)	44.2 (18.1)	10.5	40.8	99.5
Cycle 12 (Week 33)	231	41	47.4 (39.4)	47.4 (21.1)	51.0 (21.1)	22.4	45.9	120
Cycle 16 (Week 45)	315	26	46.3 (46.7)	46.3 (22.2)	50.7 (22.2)	16.8	47.1	121
Cycle 20 (Week 57)	399	15	45.2 (36.9)	45.2 (15.1)	47.7 (15.1)	18.7	44.8	74.5
Cycle 24 (Week 69)	483	13	44.8 (40.2)	44.8 (17.3)	47.9 (17.3)	21.2	44.8	78.8
Cycle 28 (Week 81)	567	10	45.5 (45.4)	45.5 (18.1)	49.0 (18.1)	18.5	51.3	70.7
Cycle 32 (Week 93)	651	3	59.4 (39.7)	59.4 (21.2)	62.2 (21.2)	38.5	68.5	79.5

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean;
%CV = Geometric Coefficient of Variation;
SD = Standard Deviation;
AM = Arithmetic Mean;
Results for time points with N ≥ 3.

Data Source: 04VNRS: analysis-p181pkdm02

PK Results by Tumor Histology Type

Summary Statistics of Pembrolizumab Predose (Ctrough) Serum Concentrations Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KN181 Subjects Stratified by Histology Type

NOMTAFD (day)	Cycle (week)	Adenocarcinoma		Squamous cell carcinoma	
		N	GM(%CV) (µg/mL)	N	GM(%CV) (µg/mL)
21	Cycle 2 (Week 3)	95	12.9 (35.1)	179	15.5 (42.3)
63	Cycle 4 (Week 9)	44	25.9 (43.6)	114	29.1 (51.6)
105	Cycle 6 (Week 15)	25	26.8 (57.9)	81	38.5 (39.2)
147	Cycle 8 (Week 21)	16	32.4 (52.3)	60	42.7 (45.3)
231	Cycle 12 (Week 33)	9	42.0 (27.2)	32	49.0 (41.9)
315	Cycle 16 (Week 45)	6	40.5 (30.3)	20	48.1 (50.8)
399	Cycle 20 (Week 57)			13	46.4 (38.6)
483	Cycle 24 (Week 69)	3	38.6 (32.7)	10	46.9 (42.6)
567	Cycle 28 (Week 81)			8	48.4 (49.3)
651	Cycle 32 (Week 93)			3	59.4 (39.7)

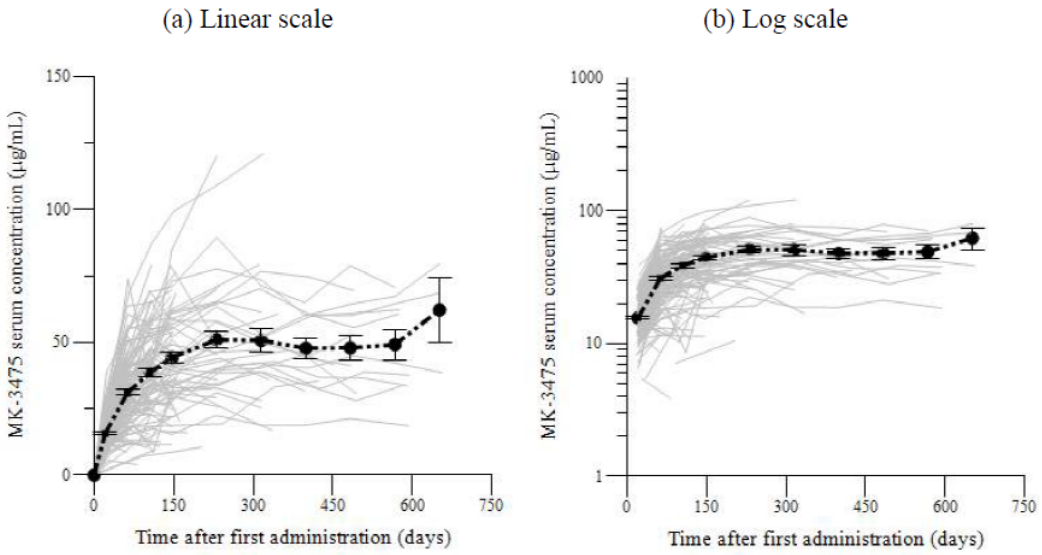
NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean;
%CV = Geometric Coefficient of Variation;
Results for time points with N ≥ 3.

Data Source: 04VNRS: analysis-p181pkdm02

The following figures show the individual and mean pre-dose concentration-time profiles:

Figure 1:

Individual and Arithmetic Mean Predose Serum Concentrations of Pembrolizumab Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KN181 Subjects (a) Linear scale, (b) Log scale



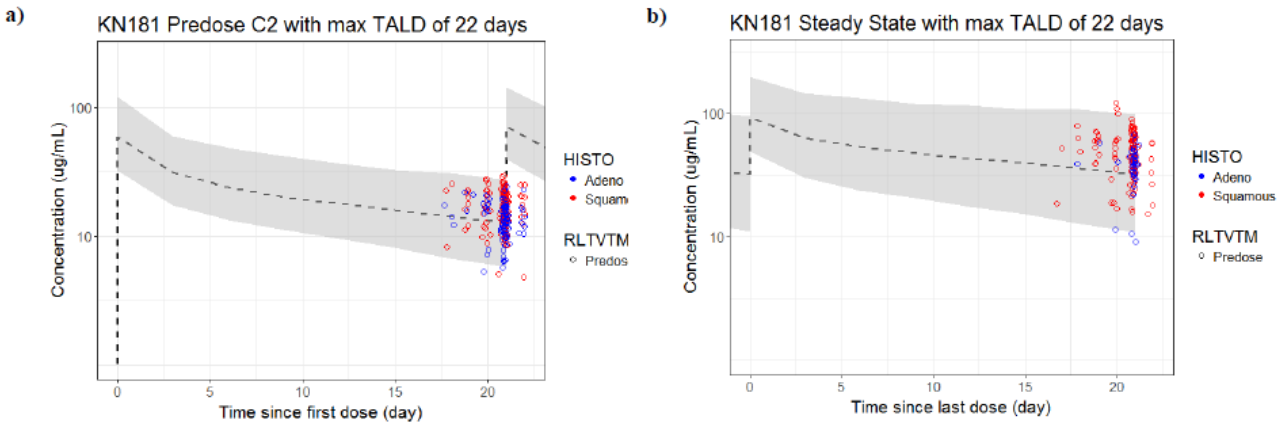
Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE. Actual times from CDR data were used for this analysis.

Data Source: 053SLR: analysis-p181pkdm02

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration at predose cycle 2 and at steady state with a time since last dose of maximum 22 days are illustrated in the following figure, stratified by histology type:

Figure 2:

Observed Concentration Data in KN181 Subjects Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen Stratified by Histology type



a) After 1st dose on log scale; b) At and after cycle 8 (21 weeks) on log scale. Blue symbols are individual observed data (Actual time) from subjects with adenocarcinoma (Adeno) in KN181; red symbols are individual observed data (Actual time) from subjects with squamous cell carcinoma (Squamous); black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval. RLTVTM = relative time; TALD = Time after last dose.

Data Source: 04VNRS: analysis-p181pkdm02

A comparison with other globally approved studies in different cancer indications (KEYNOTE-024 in NSCLC, KEYNOTE-045 and KEYNOTE-052 in UC, KEYNOTE-055 in HNSCC, KEYNOTE-087 in cHL, KEYNOTE-158 and KEYNOTE-164 in MSI-H) has been also provided, as shown in the following table and graph.

Table 6: Summary statistics of Observed pembrolizumab trough concentrations:

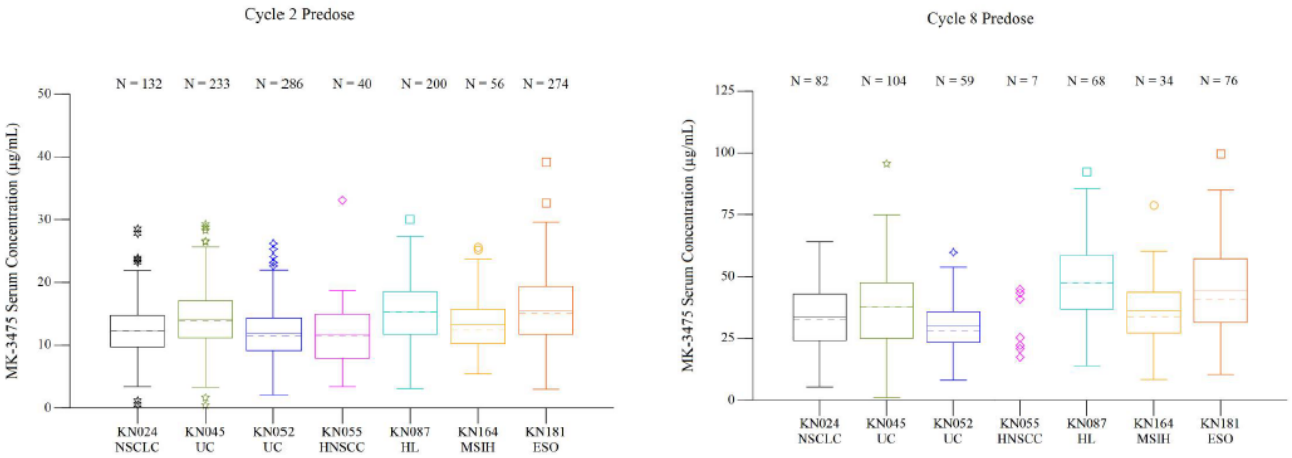
Summary Statistics of Observed Pembrolizumab Trough Concentrations at Cycle 2 and Cycle 8 (Steady-state) in Various Monotherapy Trials (KEYNOTE-024, -045, -052, -055, -087, -158, -164, and -181)

Time point	Study/Indication	N	GM(%CV) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 2 Predose	KN024 NSCLC	132	11.1 (54)	12.3 (5)	0.535	12.2	28.5
	KN045 UC	233	13.1 (47)	14.2 (5)	0.475	13.9	29.3
	KN052 UC	286	11.1 (42)	11.9 (4)	2.07	11.5	26.2
	KN055 HNSCC	40	10.7 (47)	11.8 (5)	3.45	11.6	33.1
	KN087 HL	200	14.4 (40)	15.4 (5)	3.06	15.3	30.0
	KN164 MSIH	56	12.5 (35)	13.2 (5)	5.44	12.4	25.6
	KN181 ESO	274	14.5 (41)	15.6 (6)	2.98	15.0	39.1
Cycle 8 Predose	KN024 NSCLC	82	30.6 (50)	33.6 (13)	5.26	32.7	64.1
	KN045 UC	104	33.4 (64)	37.8 (17)	1.13	37.5	95.6
	KN052 UC	59	28.0 (38)	29.9 (10)	8.15	27.9	59.8
	KN055 HNSCC	7	27.8 (41)	29.6 (11)	16.8	24.5	43.3
	KN087 HL	68	43.9 (43)	47.4 (17)	13.9	47.5	92.4
	KN164 MSIH	34	33.6 (43)	36.2 (14)	8.40	33.7	78.8
	KN181 ESO	76	40.3 (48)	44.2 (18)	10.5	40.8	99.5

GM = Geometric Mean; %CV = Geometric Coefficient of Variation; AM = Arithmetic Mean; SD = Standard Deviation; NSCLC = non-small cell lung cancer; UC = urothelial cancer; HNSCC = head and neck squamous cell carcinoma; HL = Hodgkin lymphoma; MSIH = micro satellite instability high cancer, colorectal cancer; ESO = esophageal cancer.

Figure 3:

Trough Pembrolizumab Concentrations at Cycle 2 and Cycle 8 (Steady-state) Pre-dose in Various Monotherapy Trials (KEYNOTE-024, -045, -052, -055, -087, -158, -164 and -181)



3.3.3. Pharmacodynamics

Mechanism of action

Pembrolizumab is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Dose regimen selection

Pembrolizumab is approved at a 2 mg/kg or 200 mg Q3W dosing regimen for multiple indications as monotherapy and in combination with small molecule or chemotherapy worldwide (e.g., melanoma, NSCLC, HNSCC, HL, UC, gastric cancer, MSI-H cancer, HCC and RCC).

Pembrolizumab is also approved at 400 mg Q6W in the EU for monotherapy and combination therapies indications.

A dosing regimen of 200 mg Q3W or 400 mg Q6W is recommended for pembrolizumab in the treatment of adult subjects with oesophageal cancer in combination with chemotherapy.

PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

Immunogenicity

No new ADA data are provided in this submission.

3.3.4. Discussion on clinical pharmacology

Clinical pharmacology results to support the extension of indication for Keytruda to include a new indication in oesophageal cancer are available from study KEYNOTE-181.

Based on the existing robust characterization of pembrolizumab PK, a comparison was conducted between the observed PK of pembrolizumab for the current indication in Oesophageal Cancer (ESO) and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024).

Based on the previous and current population PK analysis, the pembrolizumab PK profile is typical for a therapeutic mAb, with a low systemic clearance (0.25 L/day) and a low volume of distribution (6 L) at steady state, that is predicted to be achieved after approximately 16 weeks (for the intended dosing regimen of 200 mg Q3W). Elimination half-life (t1/2) is 22 days.

Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 6 and 8 and every 4 cycles (12 weeks) thereafter.

The observed concentrations in patients with advanced/metastatic squamous cell cancer and adenocarcinoma of the oesophagus treated with Pembrolizumab 200 mg Q3W generally fall within the range of predicted concentrations, both after first dose and at steady state.

The observed pembrolizumab serum concentration values at cycle 2 and cycle 8 are consistent with other globally approved studies in different cancer indications.

The MAH did not provide any further PK data for the 1L oesophageal study KN590 (in combo with chemotherapy) but only PK data of the 2L supportive study KN181 (in mono). The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently summarized in the USPI and in the EU SmPC. This low rate of immunogenicity has been shown to be consistent across tumour type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading. Based on the existing robust characterization of immunogenicity potential, alignment has been obtained with the US FDA and EMA that the current assessment of immunogenicity for pembrolizumab is adequate for non-adjuvant monotherapy settings.

Following the above outlined agreements, the MAH provided PK data from KEYNOTE-181 to demonstrate that pembrolizumab PK/exposures in oesophageal carcinoma are consistent with the PK from other indications that are approved in the EU.

3.3.5. Conclusions on clinical pharmacology

The observed concentration from study KN-181 falls within the 90% CI of the model predicted median concentration, independently of tumour histology (adenocarcinoma or squamous cell carcinoma).

3.4. Clinical efficacy

The efficacy data in this submission are based on a single study (KEYNOTE-590).

KEYNOTE-590 is an ongoing, Phase 3, randomized, double-blind, placebo-controlled, multisite study to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy (cisplatin and 5-FU) versus chemotherapy (cisplatin with 5-FU) as 1L treatment in participants with locally advanced unresectable metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction.

This submission is based on results from the IA for KEYNOTE-590 with a data cut-off date of 2 July 2020, which was after a minimum of 13 months of follow-up.

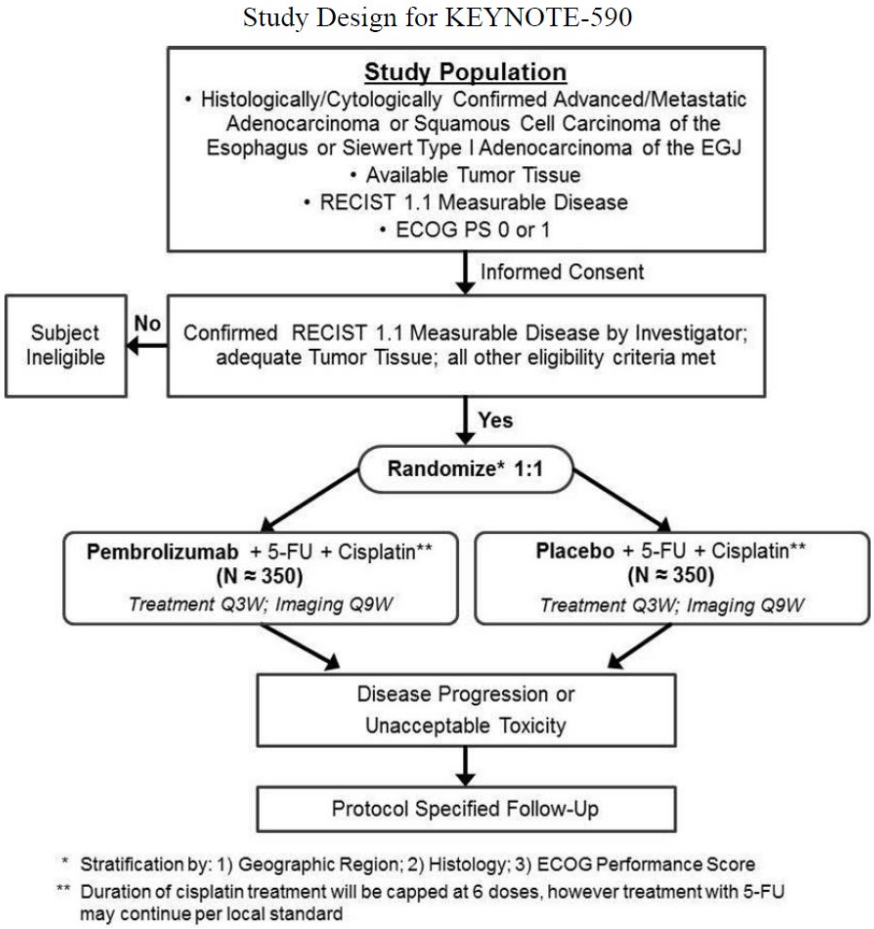
3.4.1. Dose response study(ies)

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

3.4.2. Main study(ies)

Title of Study

A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Oesophageal Carcinoma (KEYNOTE-590)



Methods

Study participants

Key inclusion criteria

1. Was ≥18 years of age on the day of signing informed consent.

2. Had histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ.

3. Had measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment.

4. Had an ECOG PS of 0 to 1.

5. Provided either a newly obtained or archival tissue sample for PD-L1 by IHC analysis.

Key exclusion criteria

1. Had locally advanced oesophageal carcinoma that was resectable or potentially curable with radiation therapy (as determined by local investigator). Subjects with Siewert type 1 adenocarcinoma of the EGJ with known HER-2/neu-positive tumours are not eligible.

2. Had previous therapy for advanced/metastatic adenocarcinoma or squamous cell cancer of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ.

3. Had a known additional malignancy that was progressing or required active treatment.

4. Had known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may have participated provided they met specific criteria.

5. Had an active autoimmune disease that had required systemic treatment in past 2 years.

6. Had a diagnosis of immunodeficiency or was receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment, or had a history of organ transplant, including allogeneic stem cell transplant.

7. Had a history of (non-infectious) pneumonitis that required steroids or had current pneumonitis.

8. Had an active infection requiring systemic therapy.

9. 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 or had previously participated in a pembrolizumab (MK-3475) clinical trial.

Treatments

Patients were randomised (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration.

Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Patients randomised to pembrolizumab were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Assessment of tumour status was performed every 9 weeks.

Objectives/Endpoints

Primary Objectives/Endpoints

- To compare OS between treatment arms in participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS >=10).

- To compare OS between treatment arms in participants with ESCC.

- To compare OS between treatment arms in participants whose tumours are PD-L1 biomarker-positive (CPS >=10).

- To compare OS between treatment arms in all participants.

- To compare PFS per RECIST 1.1, as determined by investigator, in participants with ESCC.

- To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms in participants whose tumours are PD-L1 biomarker-positive (CPS >=10).

-To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms in all participants.

The study was considered to have met its primary objective if at least one hypothesis about superiority of pembrolizumab in combination with chemotherapy compared with placebo plus chemotherapy is significant.

Secondary Objectives/Endpoints

Key secondary objectives/Endpoints

- To evaluate ORR per RECIST 1.1, as determined by investigator, between treatment arms in all participants.

Other secondary objectives/Endpoints

- To evaluate ORR per RECIST 1.1 as determined by investigator, between treatment arms in participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS >=10), in participants with ESCC, and in participants whose tumours are PD-L1 biomarker-positive (CPS >=10).

- To evaluate DOR per RECIST 1.1 as determined by investigator between treatment arms in participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS >=10), in participants whose tumours are PD-L1 biomarker-positive (CPS >=10), in participants with ESCC, and in all participants.

- To evaluate the safety and tolerability profile.

- To evaluate changes from baseline in HRQoL using the EORTC QLQ-C30 and EORTC QLQ-OES18 in all participants, in participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS >=10), in participants with ESCC, and in participants whose tumours are PD-L1 biomarker-positive (CPS >=10), treated with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

Exploratory Objectives/Endpoints

- To characterize PRO utilities using EQ-5D-5L questionnaire in all participants, in participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS >=10), in ESCC participants, and in participants whose tumours are PD-L1 biomarker-positive (CPS >=10) treated with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

- To evaluate PFS per irRECIST as determined by investigator between treatment arms in all participants and in participants whose tumours are PD-L1 biomarker-positive (CPS >=10), ESCC participants, and in ESCC participants whose tumours are PD-L1 biomarker-positive (CPS >=10).

- To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments. This could include the evaluation of MSI, WES, and/or GEP in available tumour tissue. Note: this is not applicable to China.

Sample size

The sample size and power calculations for PFS and OS assumed the following:

- PFS follows an exponential distribution with a median of 6 months for the control group.

- OS follows an exponential distribution with a median of 12 months for the control group.

- Enrollment period of 22 months

- An annual dropout rate of 5% for both PFS and OS

The sample size and power calculations were performed using R ("gsDesign" package).

The study was event-driven and originally planned to randomize approximately 700 subjects with 1:1 ratio into the two treatment groups: Pembrolizumab + Chemo and Placebo + Chemo.

One interim efficacy analysis was planned in this study, which is the main analysis for PFS, and an interim analysis for OS. A Lan-DeMets O'Brien-Fleming alpha-spending function was constructed to implement group sequential efficacy boundaries to control the Type I error for each OS hypothesis.

In the following the sample size calculation for the two primary hypotheses are listed:

1. With 460 PFS events, there was 62.2% power to detect a hazard ratio of 0.77 (pembrolizumab vs. Placebo) at alpha = 0.002% (one-sided) in subjects with PD-L1 CPS >= 10, assuming PFS follows an exponential distribution with a median of 6 months in the control arm. In the scenario that the PFS hypothesis is rejected in ESCC, the PFS test has 62.2% power to detect an HR of 0.7 at an α level of 0.002 in subjects with PD-L1 CPS ≥10. In the scenario that both of PFS hypotheses in ESCC and in PD-L1 CPS ≥10 are rejected, the PFS test has 76.8% power to detect an HR of 0.75 at an α level of 0.002 in all subjects. In the scenario that the PFS null hypotheses in all populations and all OS null hypotheses are rejected, the PFS test has 95.1% power to detect an HR of 0.75 at an α level of 0.025 in all subjects.

2. With 233 OS events and one interim analysis at approx. 86% of the target number of events, there was 84.5% power to detect a hazard ratio of 0.65 (pembrolizumab vs. Placebo) at alpha = 0.012% (one-sided) in ESCC subjects with PD-L1 CPS >= 10, assuming OS follows an exponential distribution with a median of 12 months in the control arm. Based on a target number of 455 events, the study has approximately 88.3% power at FA to detect an HR of 0.72 at an overall α level of 0.011 (1-sided) in ESCC subjects.

In the scenario that the OS hypothesis is rejected in ESCC with PD-L1 CPS ≥10 but is not rejected in ESCC, the OS test has approximately 89.9% power at FA to detect an HR of 0.65 at an overall α level of 0.006 (1-sided) in PD-L1 CPS ≥10. In the scenario that the OS hypothesis is rejected in ESCC but is not rejected in ESCC with PD-L1 CPS ≥10, the OS test has approximately 93.2% power at FA to detect an HR of 0.65 at an overall α level of 0.011 (1-sided) in PD-L1 CPS ≥10. In the scenario that the OS hypotheses in ESCC with PD-L1 CPS ≥10 and in ESCC are both rejected, the OS test has approximately 96.2% power at FA to detect an HR of 0.65 at an overall α level of 0.023 (1-sided) in PD-L1 CPS ≥10. In the scenario that OS hypotheses in ESCC with PD-L1 CPS ≥10, in ESCC, and in PD-L1 CPS ≥10 are all rejected, the OS test has approximately 94.2% power at FA to detect an HR of 0.75 at an overall α level of 0.023 (1-sided) in all subjects. In the scenario that OS hypotheses in all populations and all PFS null hypotheses are rejected, the OS test has approximately 94.6% power at FA to detect an HR of 0.75 at an overall α level of 0.025 (1-sided) in all subjects.

For both primary endpoints the enrolment period was assumed to be 22 months, the annual dropout rate was 5%, and the prevalence of ESCC with PD-L1 CPS ≥10 is 38%, PD-L1 CPS ≥10 is 51% (all subjects), and ESCC is 73%.

Based on 749 subjects with at least 10 months of follow-up, the power of the ORR testing at the allocated α=0.025 is approximately 98.7% to detect a 15-percentage point difference between an underlying 35% response rate in the control arm and a 50% response rate in the experimental arm.

Randomisation

Treatment randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects were assigned randomly in a 1:1 ratio to pembrolizumab + cisplatin + 5-FU (Arm 1) or placebo + cisplatin + 5-FU (Arm 2).

Treatment randomization was stratified according to the following factors:

1. Geographic region (Asia versus Rest of World)

2. Histology (adenocarcinoma versus squamous cell carcinoma)

3. ECOG performance status (0 versus 1)

After global cohort was recruited, further subjects from China were planned to be enrolled up to 106 subjects. This China Extension study was randomized in a 1:1 allocation with the same stratification factors as the global cohort. The randomization was implemented in IVRS.

Blinding (masking)

A double-blinding technique was used. Pembrolizumab or placebo treatment was blinded to the subject, study site personnel, and Sponsor personnel.

Statistical methods

Interim analysis

One interim analysis was planned in addition to the final analysis for this study. For the interim and final analyses, all randomized subjects were included. Results of the interim analysis were reviewed by the DMC.

Table 7: Summary of Interim and Final analyses strategy:

Table 15 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Subject Randomized	Primary Purpose of Analysis
IA	PFS in ESCC; PFS in PD-L1 CPS≥10; PFS in All subjects; OS in ESCC with PD-L1 CPS≥10; OS in ESCC; OS in PD-L1 CPS≥10; OS in All subjects	(1) Enrollment is complete with a minimum follow-up of 13 months and (2) ~ 460 investigator-assessed PFS events have been observed in ESCC and (3) ~391 deaths have occurred in ESCC At this time ~200 deaths are expected to have occurred in ESCC with PD-L1 CPS≥10 and ~ 267 deaths are expected to have occurred in PD-L1 CPS≥10	~35 months	• Final PFS analysis • Interim OS analysis
FA	OS in ESCC with PD-L1 CPS≥10; OS in PD-L1 CPS≥10; OS in ESCC; OS in All subjects	(1) A minimum follow-up of 9 months after IA and (2) ~233 deaths have occurred in ESCC with PD-L1 CPS≥10 and (3) ~ 455 deaths have occurred in ESCC. At this time ~311 deaths are expected to have occurred in PD-L1 CPS≥10	~44 months	• Final OS analysis
Abbreviations: FA = final analysis; IA = interim analysis; OS = overall survival; PFS = progression-free survival.				

Table 8: Censoring rules for primary and sensitivity analyses of PFS:

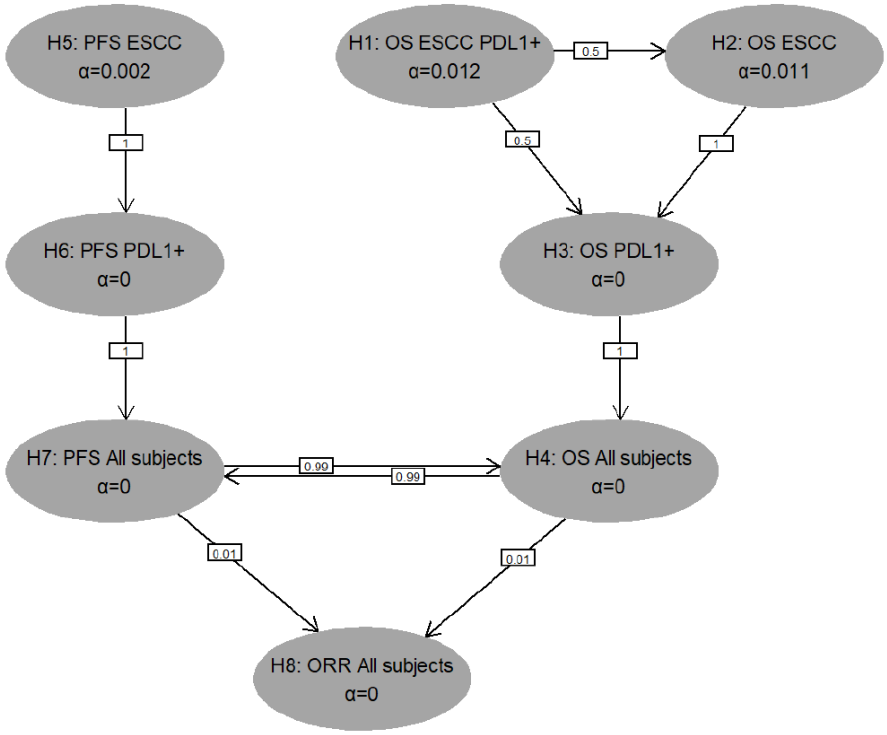
Table 11 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments, or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
Abbreviations: PD = progressive disease			

Multiplicity

The study uses the graphical method of Maurer and Bretz to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. Figure below shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis.

The weights for re-allocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses. The boundaries provided in this section are calculated based on the estimated number of events at each analysis, and the actual boundaries will be determined from the actual number of events observed at the time of the analyses, using the spending functions specified.



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

Figure 4: Multiplicity Diagram for type I Error control

The study will test PFS twice, at IA1 and at IA2. The initial alpha assigned to PFS in ESCC will be 0.002. If PFS hypothesis in ESCC subjects is rejected, the alpha will be reallocated to PFS in subjects with PD-L1 CPS ≥10. If PFS hypothesis in subjects with PD-L1 CPS ≥10 is also rejected, the alpha will be reallocated to PFS in all subjects. If all the OS null hypotheses are rejected, 0.99 of the initially allocated alpha i.e. 0.023 to OS hypotheses will be reallocated to test the PFS hypothesis in all subjects. Thus, if the PFS null hypotheses in the ESCC and the PDL1 CPS ≥10 populations are rejected and the OS hypothesis in all subjects is not rejected the PFS null hypothesis in all subjects may be tested at α=0.002. If the PFS null hypotheses in the ESCC and the PDL1 CPS ≥10 populations are rejected and all the OS hypotheses are rejected, the PFS null hypothesis in all subjects may be tested at α=0.025.

The following table shows the boundary properties for PFS in IA1 and IA2 for each of these α levels, as assuming the estimated numbers of events are analyzed. IA2 will be the final analysis for PFS. The PFS efficacy boundaries will be set using the Lan-DeMets spending function that approximates an O'Brien-Fleming boundary.

Note that the final row indicates the total power to reject the null hypothesis for PFS at each a level. Also, note that if the OS null hypothesis in all subjects is rejected at the final analysis, PFS in all subjects may be tested again with its updated bounds, considering the alpha reallocation from the OS hypothesis.

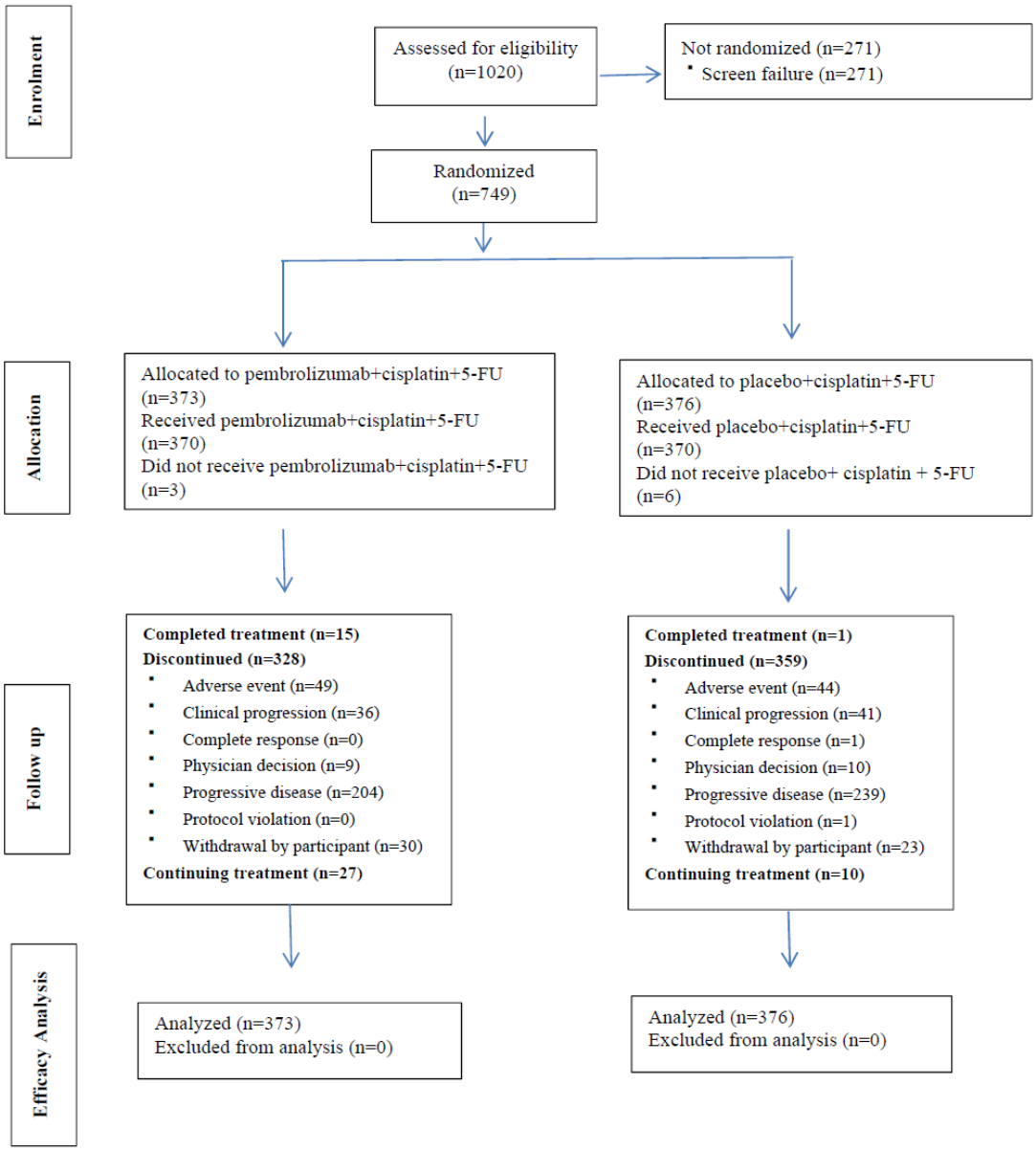
Table 8: Efficacy Boundaries and Properties for Progression Free Survival Analyses

Analysis for ESCC	Value	α=0.002	
IA (Final):100%* N = 547 Events: 460 Month: 35	Z	2.878	
	p (1-sided) [a]	0.002	
	HR at bound[b]	0.765	
	P(Cross) if HR=1[c]	0.002	
	P(Cross) if HR=0.7[d]	0.828	
Analysis for PD-L1 CPS ≥10	**Value**	**α=0.002**	
IA (Final):100%* N = 381 Events: 320 Month: 35	Z	2.878	
	p (1-sided) [a]	0.002	
	HR at bound[b]	0.725	
	P(Cross) if HR=1[c]	0.002	
	P(Cross) if HR=0.7[d]	0.622	
Analysis for All Subjects	**Value**	**α=0.002**	**α=0.025**
IA (Final):100%* N = 749 Events: 630 Month: 35	Z	2.878	1.960
	p (1-sided) [a]	0.002	0.025
	HR at bound[b]	0.795	0.855
	P(Cross) if HR=1[c]	0.002	0.025
	P(Cross) if HR=0.75[d]	0.768	0.951

Abbreviations: HR = hazard ratio; IA = interim OS analysis; PD-L1 = programmed cell death-ligand 1.
The number of events and timings are estimated approximately.
*Percentage of the target number of events at final analysis anticipated at interim analysis
[a] *p* (1-sided) is the nominal α for testing.
[b] HR at bound is the approximate HR required to reach an efficacy bound.
[c] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d] P(Cross if HR=0.xx) is the probability of crossing a bound under the alternative hypothesis.

Results

Participant flow



Abbreviations: 5-FU: 5-fluorouracil

Source: [**Table 14.1-1**, **Table 14.1-2**, **Table 10-1**]

Table 9: Disposition of Subjects (ITT Population)

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

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

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl]

271 of the 1020 screened patients (27%) were not randomized because eligibility criteria were not met. Most common reason was that diagnosis was not confirmed (n=51); however, also a relevant number of participants were screen failures because they did not have an ECOG PS of 0 or 1 (n=47) or adequate organ functions (n=42) or had a condition that might confound study evaluations (n=34). Ten (10) patients were not enrolled due to a known history or being positive hepatitis B or C.

A total of 9 of 749 randomized patients did not receive any study medication (n=3 in the pembrolizumab plus chemotherapy arm and n=6 in the chemotherapy arm).

Subsequent therapy

A similar proportion of patients, 43.5% and 47.8% of participants in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively received new oncological medication, mostly chemotherapeutics. A low proportion of 32 patients received subsequent therapy with a checkpoint inhibitor in the chemotherapy arm (8.5%); however, also 21 patients received immunotherapy after pembrolizumab plus chemotherapy treatment (5.6%).

Recruitment

A total of 1020 participants were screened and 749 were randomized (pembrolizumab plus chemotherapy: 373; chemotherapy: 376) across 168 global study centres in 26 countries.

Conduct of the study

Changes to the original study protocols and their respective rationale are detailed below:

Table 10-Protocol amendments:

Document	Date of Issue	Overall Rationale
Amendment 09 / Global	17-JUN-2020	Due to higher than expected discordance rate in assessment of progressive disease between BICR (blinded independent central review) and investigator and following input from the US regulatory agency on the statistical analyses plan, the protocol is amended as follows: (i) change in primary endpoint from PFS by BICR to investigator-assessed and (ii) elimination of one of the two planned efficacy interim analyses.
Amendment 08 / Global	03-JAN-2020	1. Based on results from the KN181 study, 3 primary objectives and corresponding hypotheses were added: OS in esophageal squamous cell carcinoma (ESCC) population; OS in ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10) population; and PFS in ESCC population. 2. Secondary objectives updated accordingly with respect to ORR and DOR endpoints in the ESCC and ESCC PD-L1 CPS ≥10 populations. Exploratory objectives were updated for PFS per irRECIST in the ESCC and ESCC PD-L1 CPS ≥10 populations. 3. Due to the short interval (~5 months) between the last subject enrolled in the Global Cohort (n=711) and in the China Extension Study (n=38), these 2 subject groups are merged into 1 "Global Study" for the primary analyses (N=749). 4. To include assessment of DOR, QoL (C30) and QoL (OES18) in all pre-specified populations. The statistical analyses plan is updated accordingly
Amendment 07 / Global	Not activated	N/A
Amendment 06 / France-specific	28-JAN-2019	Apply changes from Global Amendment 05 to France-specific Amendment 03.
Amendment 05 / Global	12-DEC-2018	To extend the enrollment period beyond the Global Cohort to achieve the required sample size of the China Cohort to investigate efficacy and safety in Chinese subjects.
Amendment 04 / China-specific	21-SEP-2018	Remove all sampling, analysis and objectives for exploratory biomarkers for subjects from China as these were not approved by HGRAC
Amendment 03 / France-specific	02-FEB-2018	Apply changes from Global Amendment 02 to France-specific Amendment 01.
Amendment 02 / Global	19-DEC-2017	Change primary biomarker from GEP to PD-L1; clarify 5-FU dosing; update statistical analysis plan; reduce PK/ADA sampling
Amendment 01 / France-specific	20-OCT-2017	To address French HA requests for monthly pregnancy tests and mandatory audiograms for cisplatin use
Original Protocol	14-MAR-2017	Not applicable

COVID-19-related Changes to the Conduct of the Study

There were no changes in the planned conduct of the study due to the COVID-19 pandemic. The Sponsor continued to follow its standard operating procedures (SOPs) for study conduct, monitoring, and oversight during the COVID-19 pandemic. A risk-based approach, consistent with recent Health Authority guidance on conducting clinical studies during the pandemic, was used to assess and mitigate the impact of the pandemic on study conduct in order to (1) assure the safety of study participants, study staff and health care providers, (2) maintain compliance with GCP principles, and (3) minimize risks to study data integrity. Contingency measures were implemented as per the Sponsor's SOP for exception and deviation management and as appropriate for the country, region and individual study site. Exceptions and deviations from SOPs were documented.

Clinical investigator study sites were advised to follow local and national guidance regarding the pandemic and to share any mitigation plans for study participant management with the IRB/EC and the Sponsor. Study sites were also advised to remain in contact with study participants to monitor for safety concerns, help ensure participants adhered to their study intervention schedule, and to keep participants informed of changes to the study and other study activities.

Measures implemented by the Sponsor to manage key aspects of study conduct during the pandemic are summarized below (implementation date shown in parentheses). Not all measures were implemented at all study sites due to differences in local conditions and impact of the pandemic.

Table 11: study conduct measures during COVID-19 pandemic

Process	Measure (Date Implemented)
Study site monitoring	• Modifications to the frequency of onsite and remote monitoring were allowed due to national and local travel restrictions and/or study site restrictions to onsite monitoring (21-MAR-2020). • Redacted/alternate methods for source data review and verification for critical data points in absence of remote access to electronic medical records were allowed under documented circumstances (06-MAR-2020). • Source data review and/or verification prior to database lock was /were waived for various countries and sites for this study (13-MAR-2020).
Protocol Deviations	• Study sites were queried as to the relationship of reported deviations to the COVID-19 pandemic; responses were documented (20-MAR-2020).
AE reporting	• COVID-19 infection was to be reported following the protocol's AE and SAE reporting instructions [Sec. 12].
Clinical supplies (including study intervention)	• An alternate location (eg, primary care center, pharmacy) for injectable and/or infusion administration of study intervention / other clinical supplies was allowed when participant travel was impacted, and administration could not be postponed (21-APR-2020).
Data management	• Alternative procedures were allowed for study sites using shared electronic devices to complete clinical outcome assessments (08-APR-2020). • Study sites were queried, and responses documented about the relationship of the following to the COVID-19 pandemic (08-APR-2020): o Missing participant study visits and data. o Participants who discontinued study intervention and/or the study.
Clinical laboratory and other facilities	• Alternate clinical laboratory facilities were allowed for collection of samples for study participants unable to visit the study site (16-APR-2020). • Alternate imaging facilities and delayed schedules for study-site and alternate facility imaging were allowed for protocol-required imaging (each to be reported as a protocol deviation) (24-MAR-2020).
Informed consent	• Oral confirmation of participant consent (eg, via telephone) was allowed when in-person discussion and signature was not possible (30-MAR-2020).

Missing participant study visits and/or data were queried as per the Sponsor's standard processes. As per the Sponsor's standard process, missing procedures and study visits were to be reported as protocol deviations for that participant. Procedures and study visits conducted outside protocol-defined windows were also to be reported as protocol deviations. Participants with protocol deviations due to the pandemic are described below.

Protocol deviations

Important protocol deviations ("those that may significantly impact the quality or integrity of key trial data or that may significantly affect a participant's rights, safety, or well-being") were reported for 60 participants in this study (6%). None of the important protocol deviations were considered to be clinically important ("deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety").

Table 12: Summary of Important Protocol Deviations

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		376		749	
With one or more important protocol deviations	29	(7.8)	31	(8.2)	60	(8.0)
With no important protocol deviations	344	(92.2)	345	(91.8)	689	(92.0)
Prohibited Medications	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Participant received radiation therapy for tumor control (with curative intent) while on treatment.	1	(0.3)	0	(0.0)	1	(0.1)
Safety Reporting	**25**	**(6.7)**	**28**	**(7.4)**	**53**	**(7.1)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	25	(6.7)	28	(7.4)	53	(7.1)
Study Intervention	**3**	**(0.8)**	**3**	**(0.8)**	**6**	**(0.8)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	3	(0.8)	3	(0.8)	6	(0.8)

Every subject is counted a single time for each applicable row and column.
Database Cutoff Date: 02JUL2020

Prematurely Unblinding

As of the data cut-off, there were 11 confirmed inadvertent unblinding events that were determined to not significantly impact the study blind, validity of site's data, or reliability of study results. However, there were 21 premature "emergency" unblinding events. Emergency unblinding is done at the discretion of the investigator in situations where unblinded information is needed to provide proper medical management for a study participant. These premature unblinding events had no impact on the data analyses per evaluation by the SQI process. Therefore, these participants were not excluded from the efficacy and safety analyses.

Baseline data

Table 13: Subject Characteristics (ITT)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		376		749	
Gender						
Male	306	(82.0)	319	(84.8)	625	(83.4)
Female	67	(18.0)	57	(15.2)	124	(16.6)
Age (Years)						
< 65	201	(53.9)	226	(60.1)	427	(57.0)
>= 65	172	(46.1)	150	(39.9)	322	(43.0)
Mean	62.8		62.0		62.4	
SD	9.8		9.2		9.5	
Median	64.0		62.0		63.0	
Range	28 to 94		27 to 89		27 to 94	
Race						
American Indian Or Alaska Native	9	(2.4)	12	(3.2)	21	(2.8)
Asian	201	(53.9)	199	(52.9)	400	(53.4)
Black Or African American	5	(1.3)	2	(0.5)	7	(0.9)
Multiple	5	(1.3)	9	(2.4)	14	(1.9)
American Indian Or Alaska Native, White	3	(0.8)	6	(1.6)	9	(1.2)
Black Or African American, White	2	(0.5)	3	(0.8)	5	(0.7)
White	139	(37.3)	139	(37.0)	278	(37.1)
Missing	14	(3.8)	15	(4.0)	29	(3.9)
Ethnicity						
Hispanic Or Latino	42	(11.3)	57	(15.2)	99	(13.2)
Not Hispanic Or Latino	315	(84.5)	296	(78.7)	611	(81.6)
Not Reported	2	(0.5)	1	(0.3)	3	(0.4)
Unknown	12	(3.2)	20	(5.3)	32	(4.3)
Missing	2	(0.5)	2	(0.5)	4	(0.5)
Region						
Asia	196	(52.5)	197	(52.4)	393	(52.5)
Rest of World	177	(47.5)	179	(47.6)	356	(47.5)
Primary Diagnosis						

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Squamous Cell Carcinoma of the Esophagus	274	(73.5)	274	(72.9)	548	(73.2)
Adenocarcinoma of the Esophagus	58	(15.5)	52	(13.8)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	41	(11.0)	50	(13.3)	91	(12.1)
Metastatic Staging						
M0	29	(7.8)	37	(9.8)	66	(8.8)
M1	344	(92.2)	339	(90.2)	683	(91.2)
Brain Metastasis						
Yes	1	(0.3)	2	(0.5)	3	(0.4)
No	372	(99.7)	374	(99.5)	746	(99.6)
Current Disease Stage						
IB	0	(0.0)	1	(0.3)	1	(0.1)
IIB	1	(0.3)	0	(0.0)	1	(0.1)
III	4	(1.1)	6	(1.6)	10	(1.3)
IIIA	4	(1.1)	5	(1.3)	9	(1.2)
IIIB	8	(2.1)	12	(3.2)	20	(2.7)
IIIC	12	(3.2)	13	(3.5)	25	(3.3)
IV	268	(71.8)	289	(76.9)	557	(74.4)
IVA	9	(2.4)	7	(1.9)	16	(2.1)
IVB	65	(17.4)	41	(10.9)	106	(14.2)
IVC	1	(0.3)	1	(0.3)	2	(0.3)
IVE	1	(0.3)	1	(0.3)	2	(0.3)
ECOG Performance Scale						
0	149	(39.9)	150	(39.9)	299	(39.9)
1	223	(59.8)	225	(59.8)	448	(59.8)
2	1	(0.3)	1	(0.3)	2	(0.3)
Histology						
Adenocarcinoma	99	(26.5)	102	(27.1)	201	(26.8)
Squamous Cell Carcinoma	274	(73.5)	274	(72.9)	548	(73.2)
Disease Status						
Metastatic	344	(92.2)	339	(90.2)	683	(91.2)
Unresectable - Locally Advanced	29	(7.8)	37	(9.8)	66	(8.8)
PD-L1 Status						
CPS >= 10	186	(49.9)	197	(52.4)	383	(51.1)
CPS < 10	175	(46.9)	172	(45.7)	347	(46.3)
Not evaluable	6	(1.6)	6	(1.6)	12	(1.6)
Missing	6	(1.6)	1	(0.3)	7	(0.9)
Database Cutoff Date: 02JUL2020						

Source: [P590V01MK3475: adam-adsl]

Numbers analysed

The primary efficacy analysis was based on the ITT population defined as all randomized participants. A total of 749 participants were included in the primary efficacy population, which is the Global Study population defined as all participants randomized in the study. The Global Study population included participants enrolled in the Global Cohort (n=711) and the China Extension Study (n=38). China Cohort has a separate analysis not in scope for this CSR.

Efficacy analyses were conducted in the populations identified as follows:

Study population

Table 14: study population:

	Pembrolizumab + SOC	SOC	Total
Subjects Randomized	373	376	749
Intention-to-Treat (ITT) Global Cohort	355	356	711
Intention-to-Treat (ITT) China Cohort	51	55	106
Intention-to-Treat (ITT) ESCC	274	274	548
Intention-to-Treat (ITT) PD-L1 CPS ≥ 10	186	197	383
Intention-to-Treat (ITT) ESCC PD-L1 CPS ≥ 10	143	143	286
All-Subjects-as-Treated (ASaT)	370	370	740
Database Cutoff Date: 02JUL2020.			

Source: [P590V01MK3475: adam-adsl]

Outcomes and estimation

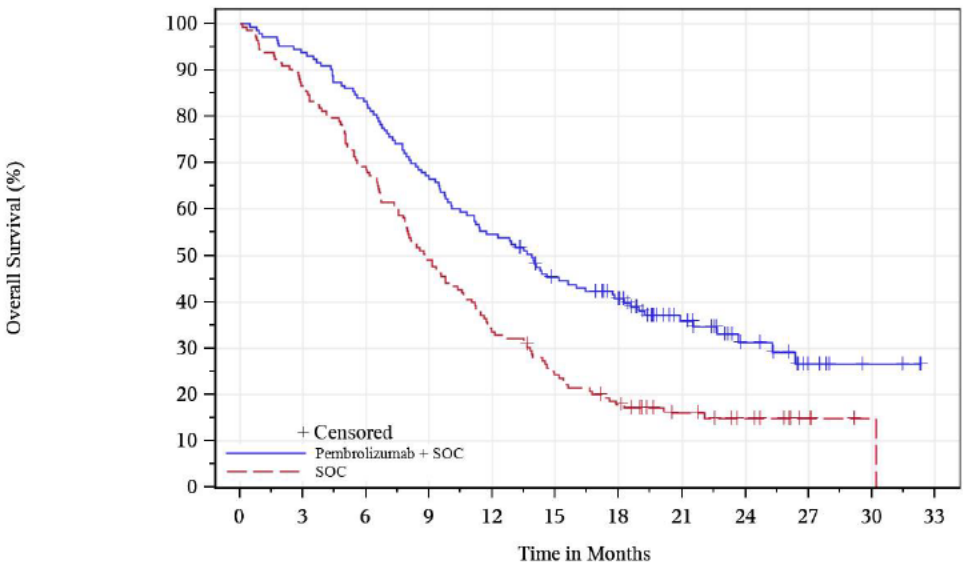
At this interim analysis (i.e. final for PFS and interim for OS), efficacy analyses were performed on PFS, OS, ORR, DOR, and PRO. As of the data cut-off (02 July 2020), the median follow-up time for participants was 12.6 months (range: 0.1-33.6 months) in the pembrolizumab plus chemotherapy group and 9.8 months (range: 0.1-33.6 months) in the chemotherapy group.

Primary endpoint

Overall Survival

Figure 5: Patients with ESCC whose tumours express PD-L1 CPS ≥10

Figure 11-1
Kaplan-Meier Estimates of Overall Survival
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	143	134	119	96	78	61	51	29	16	7	3	0
SOC	143	124	99	70	48	34	24	15	10	4	1	0

Table 11-1

Analysis of Overall Survival
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	143	94 (65.7)	1997.6	4.7	13.9 (11.1, 17.7)	54.5 (46.0, 62.3)
SOC	143	121 (84.6)	1505.6	8.0	8.8 (7.8, 10.5)	33.6 (26.0, 41.3)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.57 (0.43, 0.75)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

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

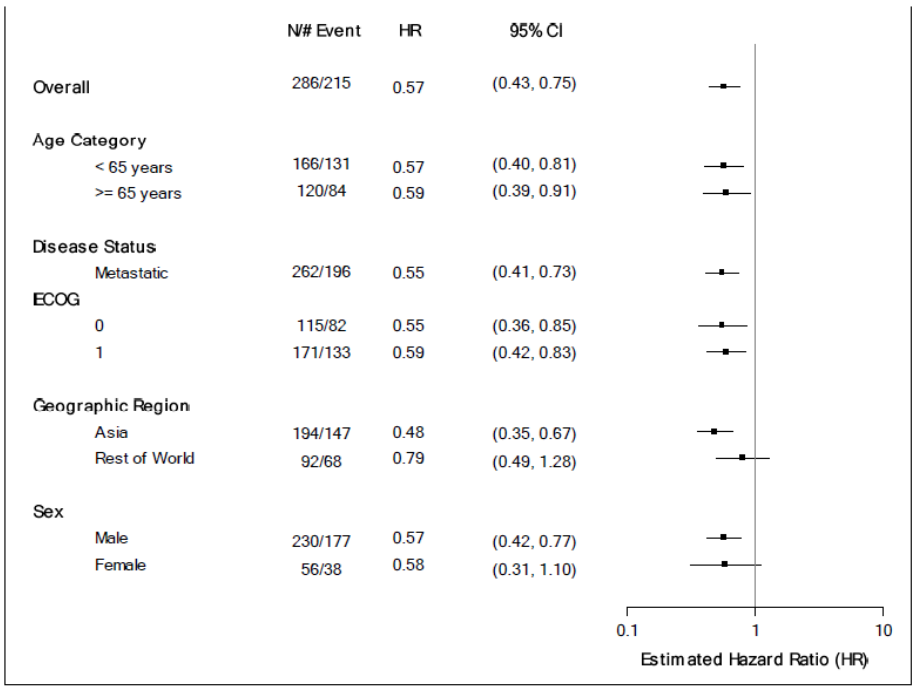
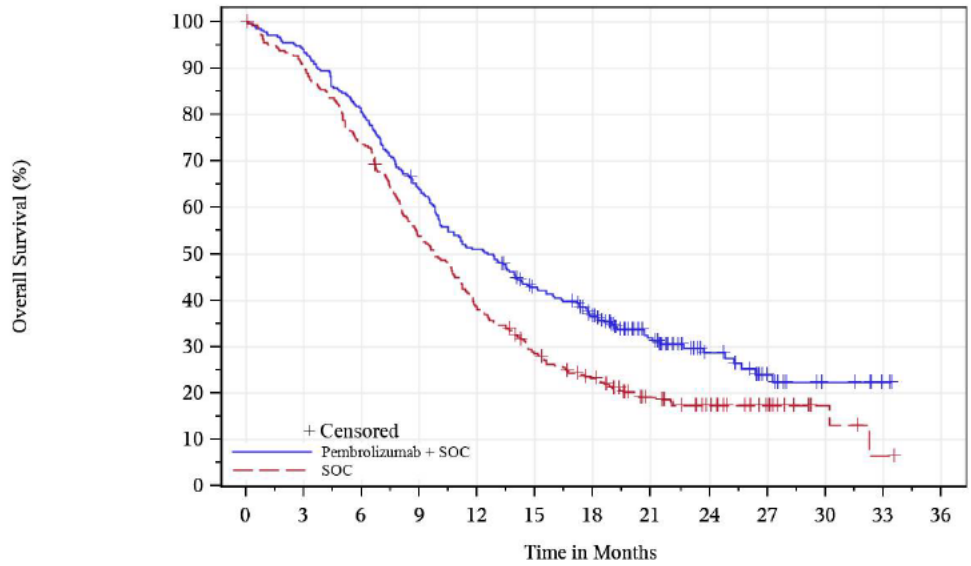


Figure 6: Patients with ESCC

Figure 11-3
Kaplan-Meier Estimates of Overall Survival
(Subjects with Squamous Cell Carcinoma, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	274	258	221	175	139	111	89	50	27	14	6	2	0
SOC	274	247	203	146	103	75	57	34	23	13	4	1	0

Analysis of Overall Survival
(Subjects with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	274	190 (69.3)	3667.2	5.2	12.6 (10.2, 14.3)	51.0 (44.9, 56.8)
SOC	274	222 (81.0)	3129.7	7.1	9.8 (8.6, 11.1)	37.9 (32.2, 43.7)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.72 (0.60, 0.88)	0.0006§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Forest Plot of OS Hazard Ratio by Subgroup Factor
(Subjects with Squamous Cell Carcinoma, ITT Population)

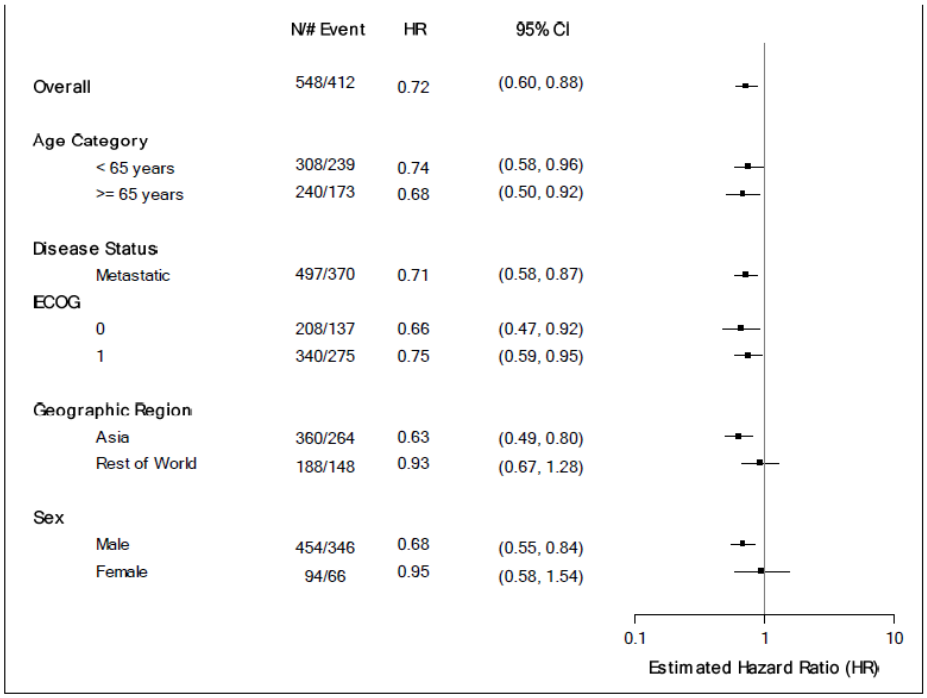
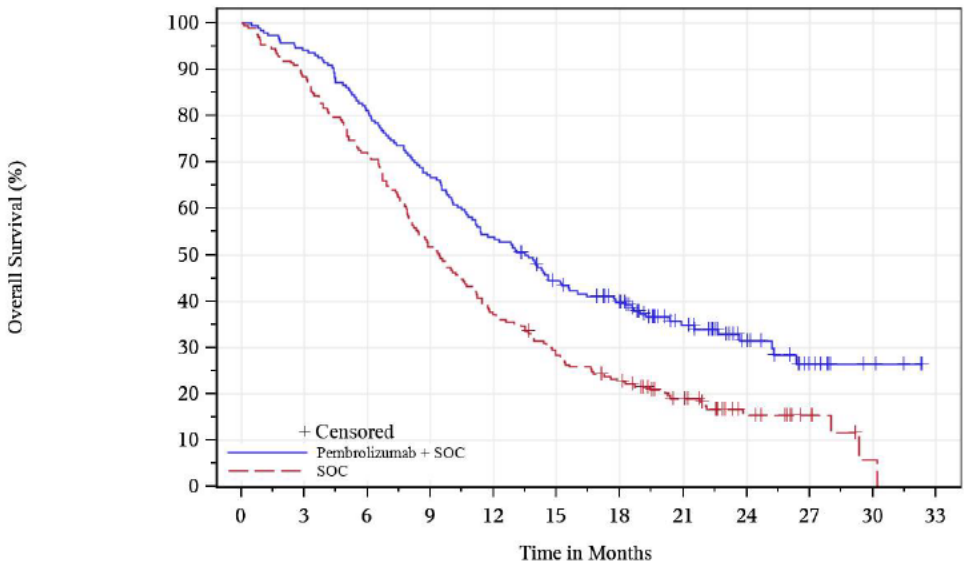


Figure 7: Patients whose tumours express PD-L1 CPS ≥10

PD-L1 CPS ≥ 10 was determined using the PD-L1 IHC 22C3 pharmDxTM kit.

Figure 11-3
Kaplan-Meier Estimates of Overall Survival
(Subjects with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

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

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

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

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

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

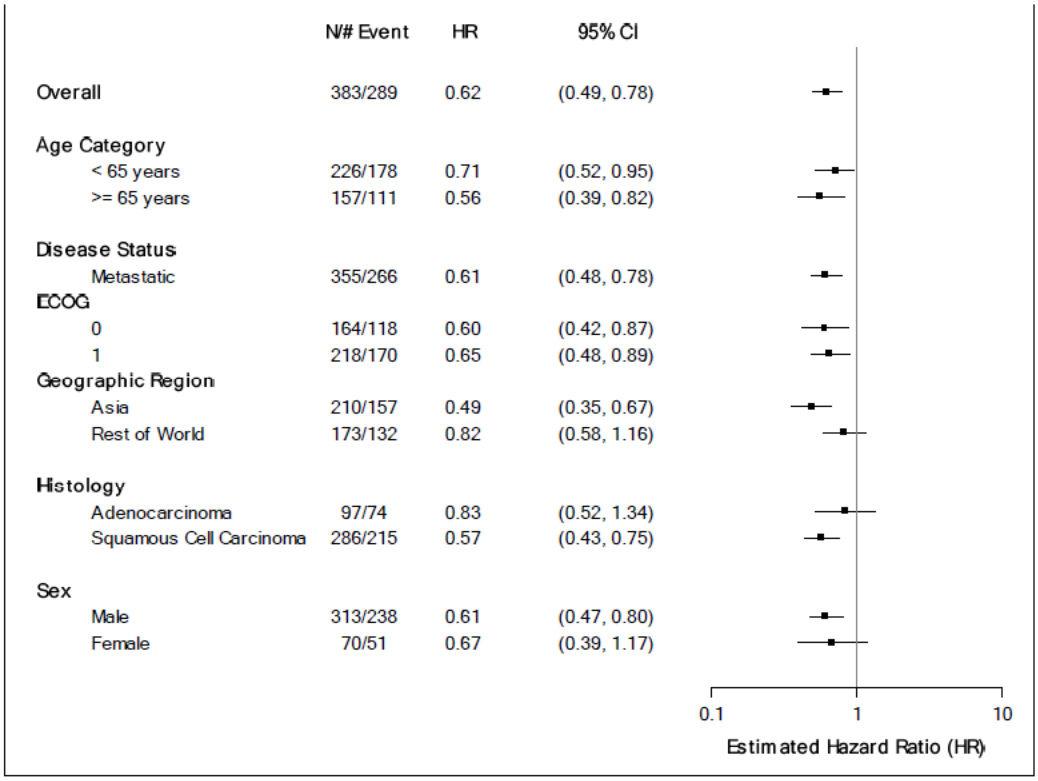
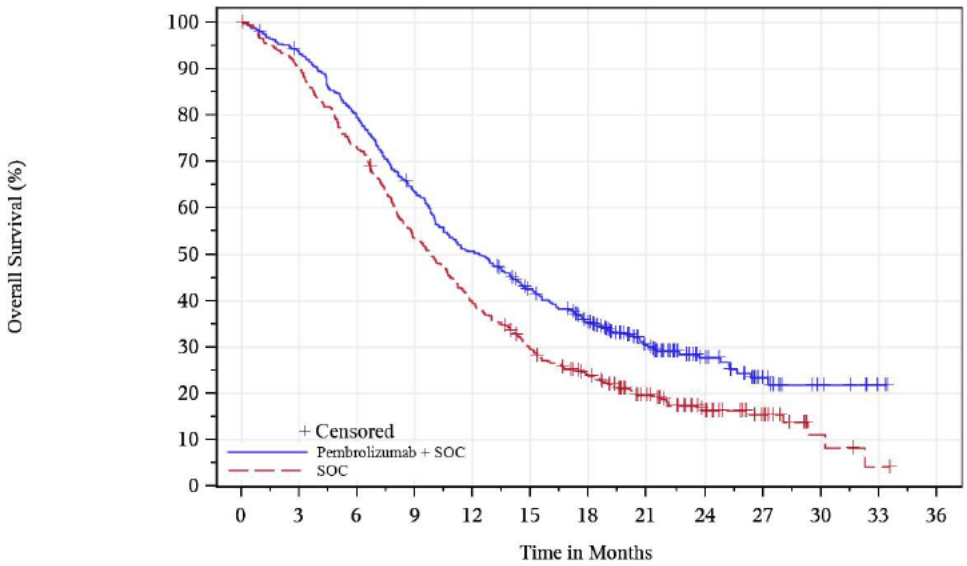


Figure 8: All comer patients

Figure 11-7
Kaplan-Meier Estimates of Overall Survival
(ITT Population)



Number of Subjects at Risk

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

Analysis of Overall Survival
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS [†] (Months) (95% CI)	OS Rate at Month 12 in % [†] (95% CI)
Pembrolizumab + SOC	373	262 (70.2)	4935.1	5.3	12.4 (10.5, 14.0)	50.6 (45.4, 55.6)
SOC	376	309 (82.2)	4301.2	7.2	9.8 (8.8, 10.8)	39.4 (34.4, 44.3)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value
Pembrolizumab + SOC vs. SOC					0.73 (0.62, 0.86)	<0.0001[§]

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Forest Plot of OS Hazard Ratio by Subgroup Factor
(ITT Population)

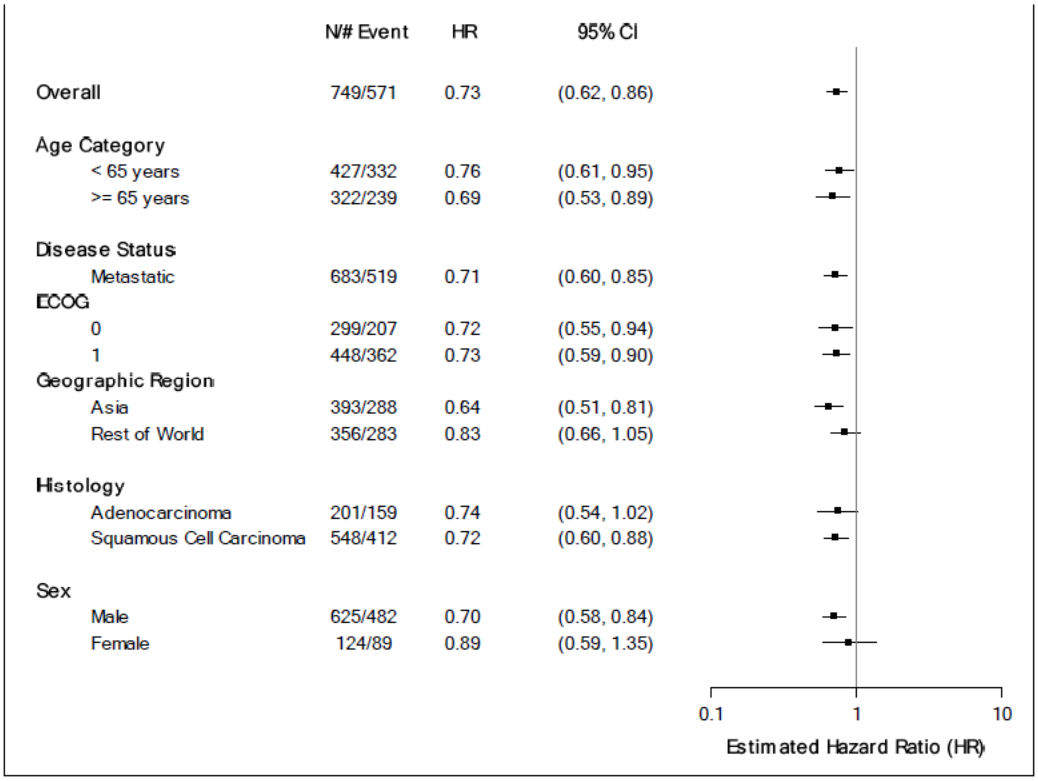
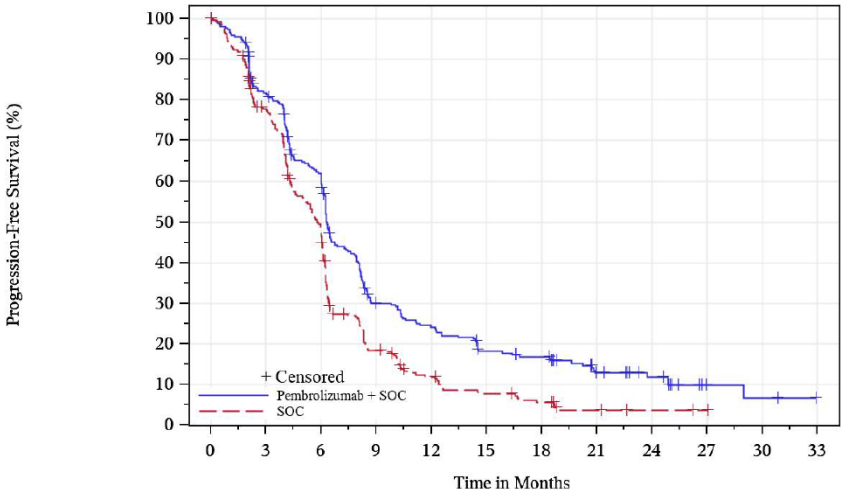


Figure 9: Progression Free Survival by Investigator

Patients with ESCC

Figure 11-9
Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(Subjects with Squamous Cell Carcinoma, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	274	211	156	71	57	41	35	19	13	3	2	0
SOC	274	205	127	45	26	16	11	5	2	1	0	0

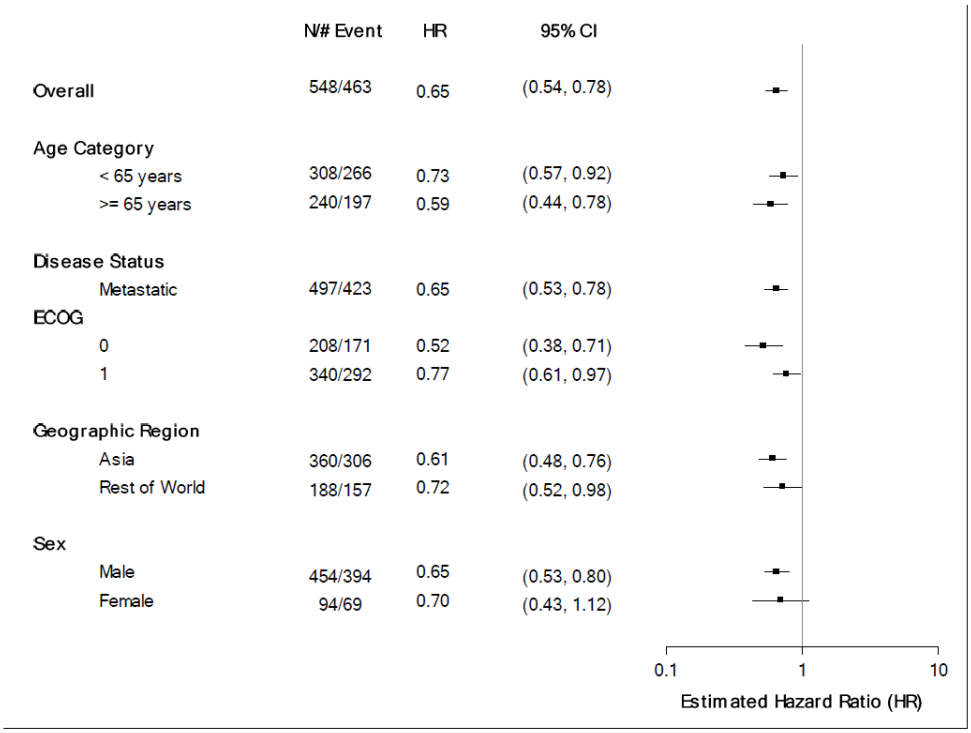
Table 11-9
Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(Subjects with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	274	219 (79.9)	2202.6	9.9	6.3 (6.2, 6.9)	62.1 (55.8, 67.7)
SOC	274	244 (89.1)	1645.9	14.8	5.8 (5.0, 6.1)	48.8 (42.6, 54.6)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.65 (0.54, 0.78)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

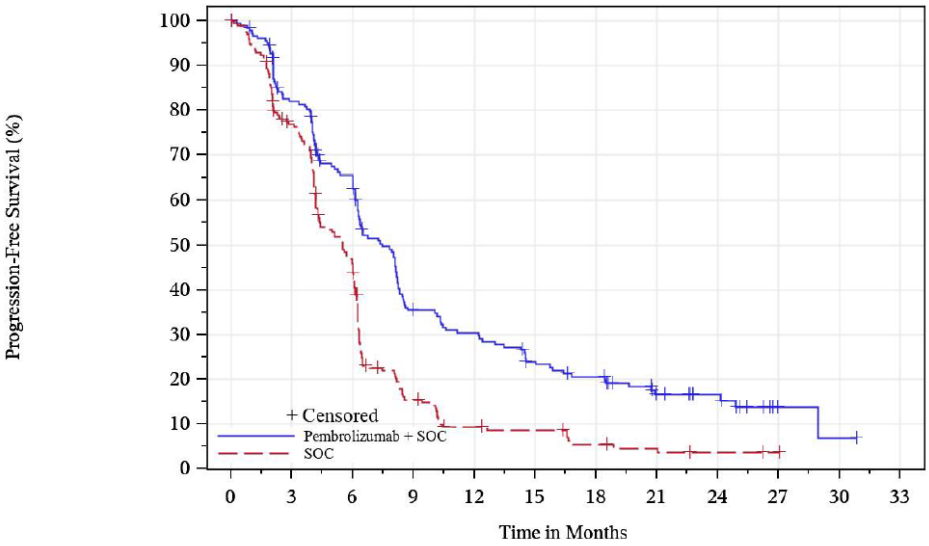
Figure 11-10
Forest Plot of PFS Hazard Ratio by Subgroup Factor
Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Subjects with Squamous Cell Carcinoma, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 10: Patients whose tumours express PD-L1 CPS ≥10

Figure 11-11
Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment p
RECIST 1.1
(Primary Censoring Rule)
(Subjects with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

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

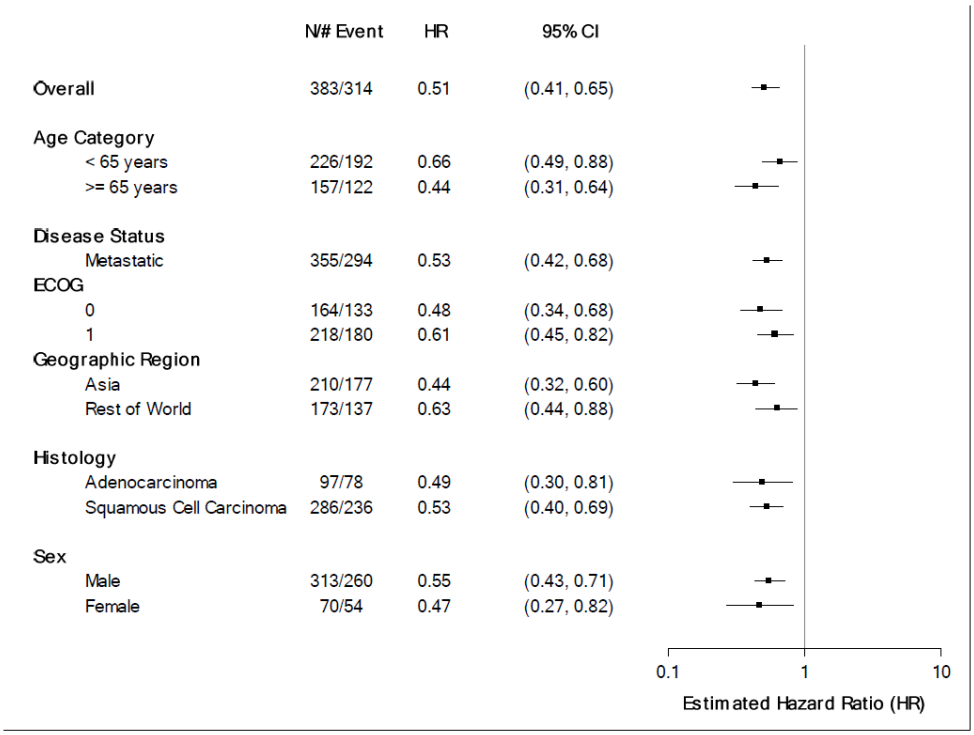
Table 11-11
Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(Subjects with PD-L1 CPS >= 10, ITT Population)

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

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

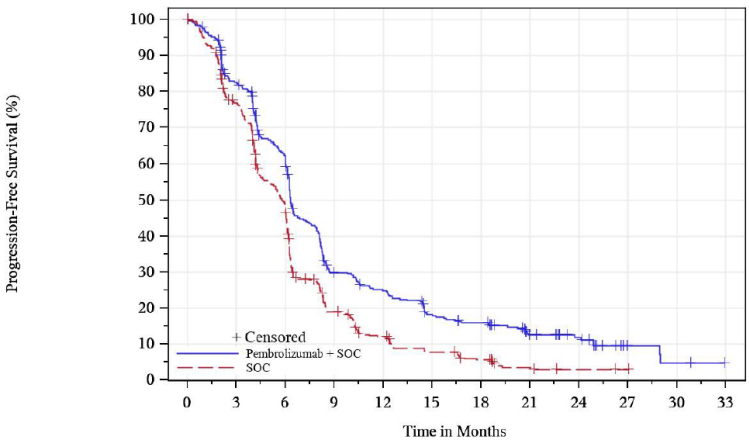
Figure 11-12
Forest Plot of PFS Hazard Ratio by Subgroup Factor
Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Subjects with PD-L1 CPS >= 10, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 11: All comer patients

Figure 11-13
Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	373	289	210	96	79	55	45	25	17	4	2	0
SOC	376	278	172	62	36	22	14	6	2	1	0	0

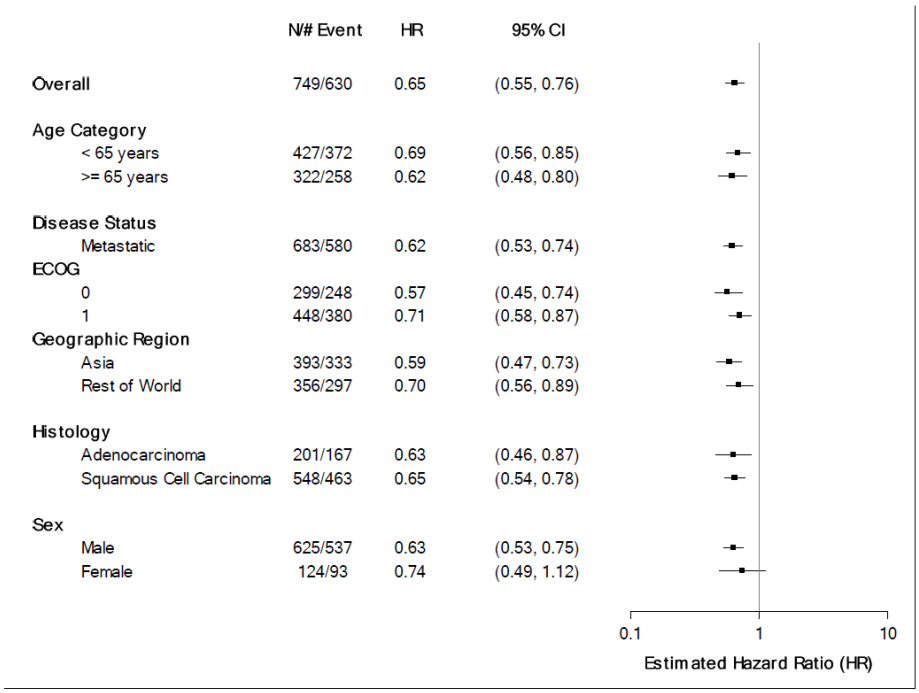
Table 11-13
Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(ITT Population)

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

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 11-14
Forest Plot of PFS Hazard Ratio by Subgroup Factor
Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(ITT Population)

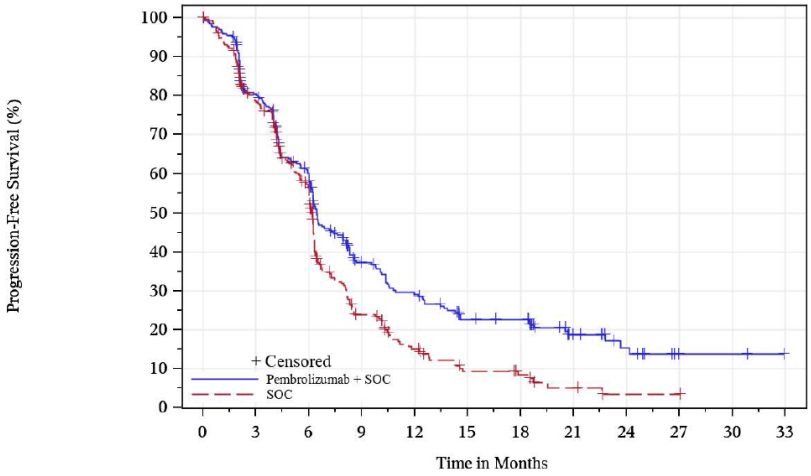


Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 12: Progression-free Survival by BICR primary endpoint

Patients with ESCC

Figure 14.2-23
Kaplan-Meier Estimates of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1
(Primary Censoring Rule)
(Subjects with Squamous Cell Carcinoma, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	274	204	145	74	57	39	36	16	9	2	2	0
SOC	274	203	133	46	24	12	9	4	1	1	0	0

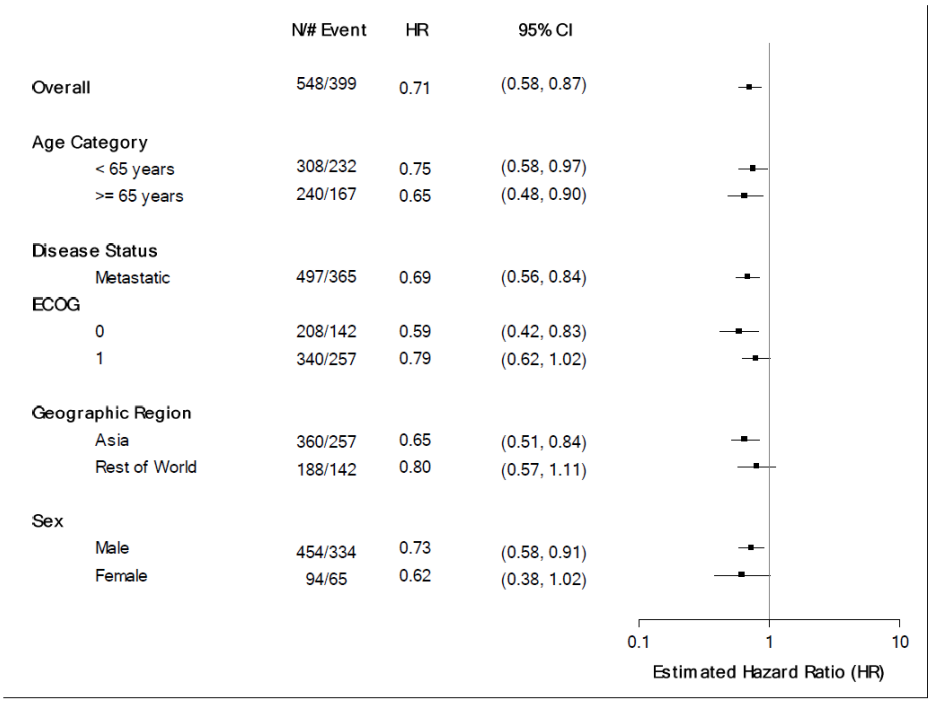
Table 14.2-33
Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1
(Primary Censoring Rule)
(Subjects with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	274	189 (69.0)	2123.2	8.9	6.4 (6.2, 7.9)	60.3 (54.0, 66.0)
SOC	274	210 (76.6)	1647.9	12.7	6.2 (6.0, 6.3)	56.5 (50.2, 62.3)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.71 (0.58, 0.87)	0.0004§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

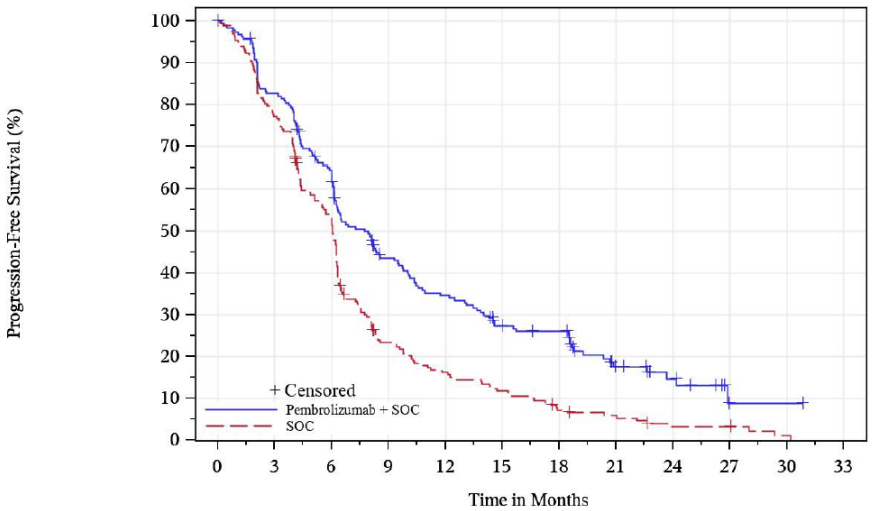
Forest Plot of PFS Hazard Ratio by Subgroup Factor
Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule)
(Subjects with Squamous Cell Carcinoma, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 13: Patients whose tumours express PD-L1 CPS ≥10

Kaplan-Meier Estimates of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1
(Sensitivity Censoring Rule 1)
(Subjects with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	186	152	116	73	58	42	37	16	9	1	1	0
SOC	197	152	102	42	29	21	12	9	4	4	1	0

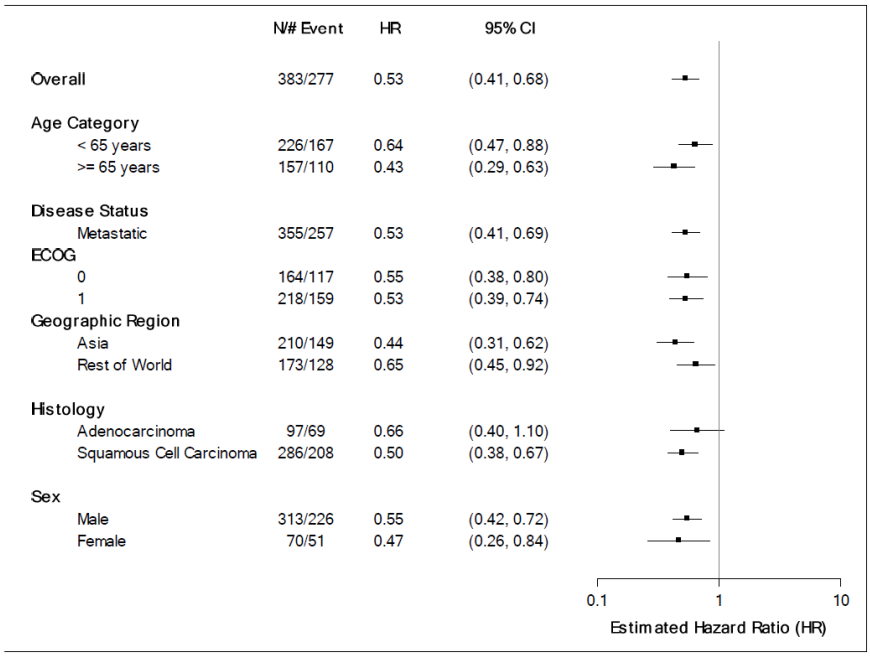
Table 14.2-39
Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1
(Sensitivity Censoring Rule 1)
(Subjects with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Month 6 in % [†] (95% CI)
Pembrolizumab + SOC	186	145 (78.0)	1772.7	8.2	7.8 (6.2, 9.5)	64.5 (57.1, 71.0)
SOC	197	186 (94.4)	1386.7	13.4	6.0 (5.1, 6.2)	53.0 (45.7, 59.7)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value
Pembrolizumab + SOC vs. SOC					0.60 (0.48, 0.75)	<0.0001[§]

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

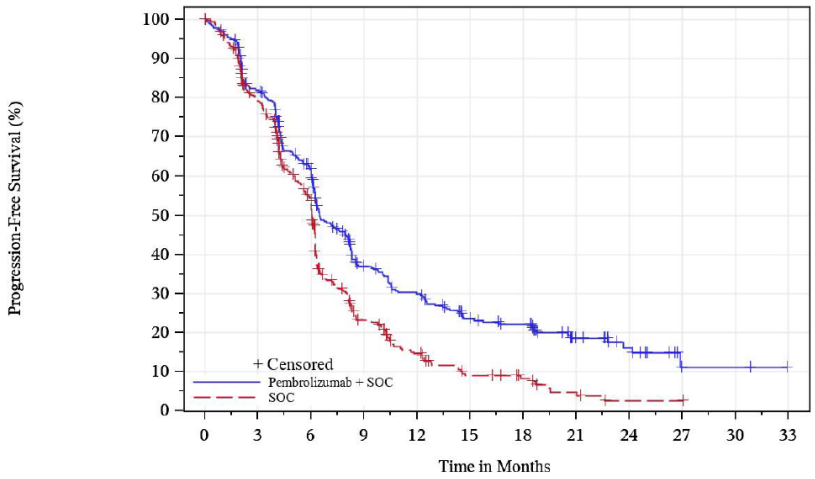
Figure 14.2-27
Forest Plot of PFS Hazard Ratio by Subgroup Factor
Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule)
(Subjects with PD-L1 CPS >= 10, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 14: All comer patients

Figure 14.2-11
Kaplan-Meier Estimates of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1
(Primary Censoring Rule)
(ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	373	285	200	101	80	54	46	22	12	2	2	0
SOC	376	280	174	60	32	16	11	5	1	1	0	0

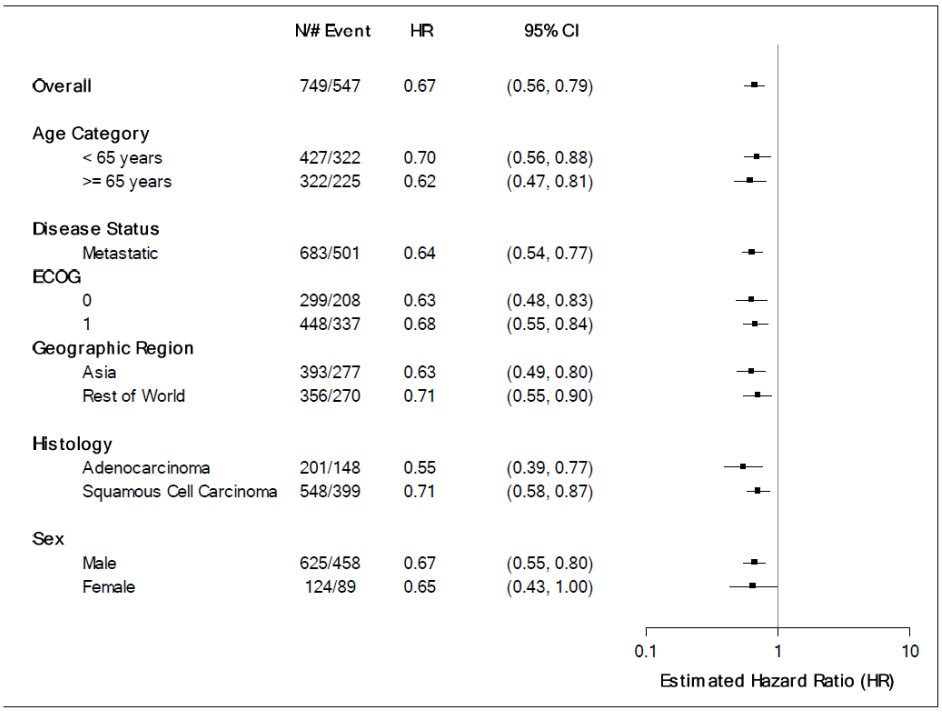
Table 14.2-16
Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1
(Primary Censoring Rule)
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Month 6 in % [†] (95% CI)
Pembrolizumab + SOC	373	256 (68.6)	2915.4	8.8	6.5 (6.2, 8.0)	61.8 (56.4, 66.7)
SOC	376	291 (77.4)	2216.4	13.1	6.0 (5.7, 6.2)	53.7 (48.3, 58.8)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value
Pembrolizumab + SOC vs. SOC					0.67 (0.56, 0.79)	<0.0001[§]

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Forest Plot of PFS Hazard Ratio by Subgroup Factor
Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule)
(ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Secondary Objectives

Objective response rate

Table 15: All comer patients (ITT population)

By investigator

Table 11-16
Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation
(ITT Population)

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

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

Table 16: By BICR

Table 14.2-49
Summary of Best Overall Response Based on Central Radiology Assessment per RECIST 1.1 with Confirmation
(ITT Population)

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Subjects in Population	373		376	
Complete Response (CR)	49	13.1	25	6.6
Partial Response (PR)	113	30.3	84	22.3
Best Overall Response (CR+PR)	**162**	**43.4**	**109**	**29.0**
Stable Disease (SD)	126	33.8	183	48.7
Disease Control (CR + PR + SD)	**288**	**77.2**	**292**	**77.7**
Progressive Disease (PD)	46	12.3	45	12.0
Not Evaluable (NE)	7	1.9	8	2.1
No Evidence of Disease (NED)	3	0.8	3	0.8
No Assessment	29	7.8	28	7.4

Responses are based on Central Radiology Assessment best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

Table 17: Patients with ESCC whose tumours express PD-L1 CPS ≥10

By investigators

Table 14.2-51
Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Subjects in Population	143		143	
Complete Response (CR)	10	7.0	3	2.1
Partial Response (PR)	63	44.1	37	25.9
Best Overall Response (CR+PR)	**73**	**51.0**	**40**	**28.0**
Stable Disease (SD)	43	30.1	69	48.3
Disease Control (CR + PR + SD)	**116**	**81.1**	**109**	**76.2**
Progressive Disease (PD)	16	11.2	20	14.0
Not Evaluable (NE)	2	1.4	0	0.0
No Assessment	9	6.3	14	9.8

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

By BICR

Table 14.2-53
Summary of Best Overall Response Based on Central Radiology Assessment per RECIST 1.1 with Confirmation
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Subjects in Population	143		143	
Complete Response (CR)	24	16.8	9	6.3
Partial Response (PR)	44	30.8	31	21.7
Best Overall Response (CR+PR)	**68**	**47.6**	**40**	**28.0**
Stable Disease (SD)	41	28.7	70	49.0
Disease Control (CR + PR + SD)	**109**	**76.2**	**110**	**76.9**
Progressive Disease (PD)	19	13.3	19	13.3
Not Evaluable (NE)	4	2.8	2	1.4
No Evidence of Disease (NED)	2	1.4	0	0.0
No Assessment	9	6.3	12	8.4

Responses are based on Central Radiology Assessment best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

Table 18: Patients with ESCC

By investigators

Table 14.2-55
Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation
(Subjects with Squamous Cell Carcinoma, ITT Population)

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Subjects in Population	274		274	
Complete Response (CR)	21	7.7	4	1.5
Partial Response (PR)	99	36.1	81	29.6
Best Overall Response (CR+PR)	**120**	**43.8**	**85**	**31.0**
Stable Disease (SD)	97	35.4	126	46.0
Disease Control (CR + PR + SD)	**217**	**79.2**	**211**	**77.0**
Progressive Disease (PD)	32	11.7	39	14.2
Not Evaluable (NE)	3	1.1	0	0.0
No Assessment	22	8.0	24	8.8

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

By BICR

Table 14.2-57
Summary of Best Overall Response Based on Central Radiology Assessment per RECIST 1.1 with Confirmation
(Subjects with Squamous Cell Carcinoma, ITT Population)

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Subjects in Population	274		274	
Complete Response (CR)	40	14.6	21	7.7
Partial Response (PR)	77	28.1	62	22.6
Best Overall Response (CR+PR)	**117**	**42.7**	**83**	**30.3**
Stable Disease (SD)	89	32.5	130	47.4
Disease Control (CR + PR + SD)	**206**	**75.2**	**213**	**77.7**
Progressive Disease (PD)	38	13.9	35	12.8
Not Evaluable (NE)	6	2.2	2	0.7
No Evidence of Disease (NED)	3	1.1	2	0.7
No Assessment	21	7.7	22	8.0

Responses are based on Central Radiology Assessment best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

Table 19: Patients whose tumours express PD-L1 CPS ≥10

By investigators

Table 14.2-59
Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation
(Subjects with PD-L1 CPS ≥ 10, ITT Population)

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

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

By BICR

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

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Subjects in Population	186		197	
Complete Response (CR)	30	16.1	11	5.6
Partial Response (PR)	57	30.6	46	23.4
Best Overall Response (CR+PR)	**87**	**46.8**	**57**	**28.9**
Stable Disease (SD)	57	30.6	98	49.7
Disease Control (CR + PR + SD)	**144**	**77.4**	**155**	**78.7**
Progressive Disease (PD)	24	12.9	23	11.7
Not Evaluable (NE)	5	2.7	3	1.5
No Evidence of Disease (NED)	2	1.1	0	0.0
No Assessment	11	5.9	16	8.1

Responses are based on Central Radiology Assessment best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

An analysis of the concordance of progression events assessed by investigator and BICR has been provided:

Concordance of Progression Events (Investigator vs. BICR)
(Pembrolizumab + SOC vs SOC) (ITT Population)

	Pembrolizumab + SOC	SOC	Total
Number of Subjects in Population	373	376	749
Investigator Assessment - PD	246	276	522
BICR Agreed	180 (73.2%)	194 (70.3%)	374 (71.6%)
BICR and Investigator agreed on time	111 (45.1%)	131 (47.5%)	242 (46.4%)
BICR has earlier time	54 (22.0%)	40 (14.5%)	94 (18.0%)
BICR has later time	15 (6.1%)	23 (8.3%)	38 (7.3%)
BICR Disagreed	66 (26.8%)	82 (29.7%)	148 (28.4%)
No BICR Assessment	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigator Assessment - Non PD	96	67	163
BICR Agreed	84 (87.5%)	50 (74.6%)	134 (82.2%)
BICR Disagreed	12 (12.5%)	17 (25.4%)	29 (17.8%)
No BICR Assessment	0 (0.0%)	0 (0.0%)	0 (0.0%)

PD: Progressive Disease.
BICR: Blinded Independent Central Review.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adintdt]

Duration of Response

Table 20: All comer patients

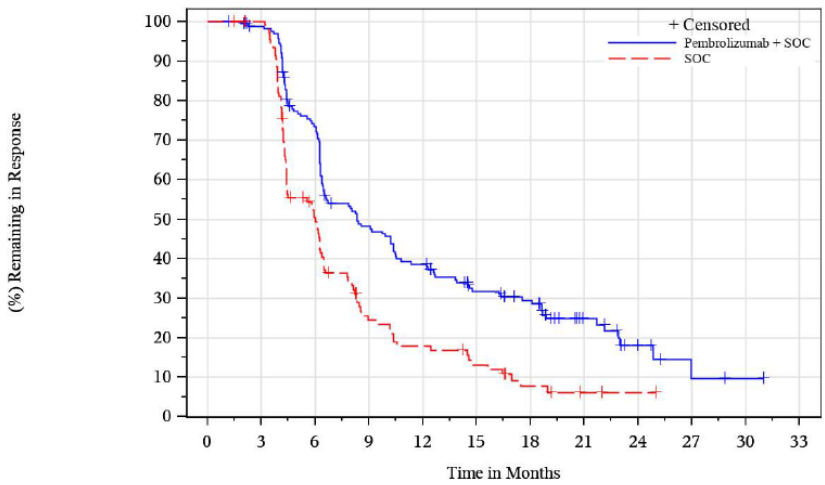
Table 11-20
Summary of Time to Response and Duration of Response
Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response
(ITT Population)

	Pembrolizumab + SOC (N=373)	SOC (N=376)
Number of subjects with response†	168	110
Time to Response† (months)		
Mean (SD)	2.3 (0.9)	2.4 (1.2)
Median (Range)	2.1 (1.1-8.3)	2.1 (1.3-12.6)
Response Duration‡ (months)		
Median (Range)	8.3 (1.2+ - 31.0+)	6.0 (1.5+ - 25.0+)
Number (%‡) of Subjects with Extended Response Duration:		
≥3 months	162 (98.8)	106 (100.0)
≥6 months	117 (73.5)	50 (50.4)
≥9 months	75 (48.2)	22 (24.5)
≥12 months	60 (38.6)	16 (17.8)
≥18 months	35 (29.4)	5 (7.7)
≥24 months	6 (18.1)	1 (6.1)

†Includes subjects with confirmed complete response or partial response.
‡From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 11-15
Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response
Based on Investigator Assessment per RECIST 1.1
(ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	168	162	117	75	60	43	35	16	6	2	1	0
SOC	110	106	50	22	16	11	5	2	1	0	0	0

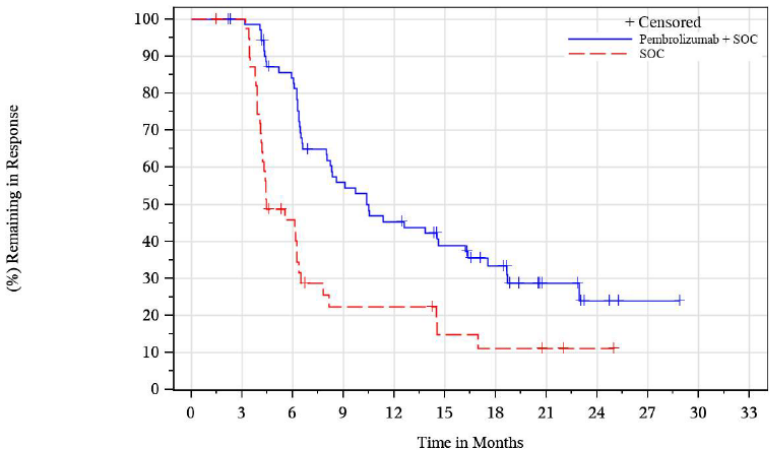
Table 21: Patients with ESCC whose tumours express PD-L1 CPS >=10

Table 11-21
Summary of Time to Response and Duration of Response
Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + SOC (N=143)	SOC (N=143)
Number of subjects with response[†]	73	40
Time to Response[†] (months)		
Mean (SD)	2.3 (0.9)	2.2 (0.6)
Median (Range)	2.1 (1.4-8.3)	2.1 (1.3-4.3)
Response Duration[‡] (months)		
Median (Range)	10.4 (2.2+ - 28.9+)	4.4 (1.5+ - 25.0+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	71 (100.0)	39 (100.0)
≥6 months	57 (84.2)	16 (45.9)
≥9 months	37 (55.9)	7 (22.3)
≥12 months	30 (45.3)	7 (22.3)
≥18 months	16 (33.3)	3 (11.1)
≥24 months	3 (23.9)	1 (11.1)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 02JUL2020

Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response
Based on Investigator Assessment per RECIST 1.1
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS >= 10, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	73	71	57	37	30	23	16	7	3	1	0	0
SOC	40	39	16	7	7	4	3	2	1	0	0	0

Table 22: Patients with ESCC

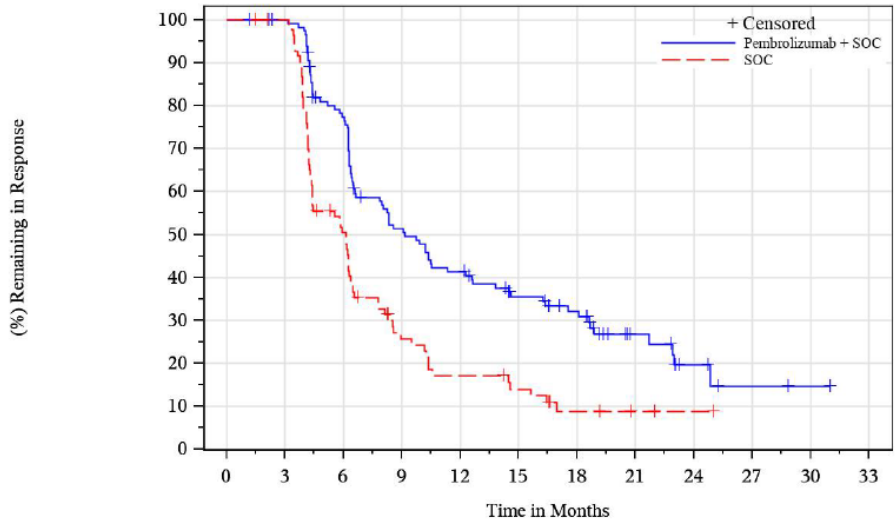
Table 11-22
Summary of Time to Response and Duration of Response
Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Subjects with Squamous Cell Carcinoma, ITT Population)

	Pembrolizumab + SOC (N=274)	SOC (N=274)
Number of subjects with response†	120	85
Time to Response† (months)		
Mean (SD)	2.2 (0.8)	2.3 (1.2)
Median (Range)	2.1 (1.1-8.3)	2.1 (1.3-12.6)
Response Duration‡ (months)		
Median (Range)	9.1 (1.2+ - 31.0+)	6.1 (1.5+ - 25.0+)
Number (%‡) of Subjects with Extended Response Duration:		
≥3 months	117 (100.0)	83 (100.0)
≥6 months	87 (77.5)	40 (50.4)
≥9 months	56 (51.4)	18 (25.6)
≥12 months	45 (41.3)	12 (17.1)
≥18 months	26 (32.1)	4 (8.7)
≥24 months	5 (19.6)	1 (8.7)

†Includes subjects with confirmed complete response or partial response.
‡From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 11-17
Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response
Based on Investigator Assessment per RECIST 1.1
(Subjects with Squamous Cell Carcinoma, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	120	117	87	56	45	34	26	12	5	2	1	0
SOC	85	83	40	18	12	9	4	2	1	0	0	0

Table 23: Patients whose tumours express PD-L1 CPS ≥10

Summary of Time to Response and Duration of Response
Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Subjects with PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + SOC (N=186)	SOC (N=197)
Number of subjects with response[†]	95	53
Time to Response[†] (months)		
Mean (SD)	2.3 (1.0)	2.3 (0.6)
Median (Range)	2.1 (1.4-8.3)	2.1 (1.3-4.3)
Response Duration[‡] (months)		
Median (Range)	10.4 (1.9 - 28.9+)	5.6 (1.5+ - 25.0+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	91 (98.9)	50 (100.0)
≥6 months	71 (80.2)	22 (47.7)
≥9 months	46 (52.9)	10 (23.2)
≥12 months	38 (43.7)	10 (23.2)
≥18 months	22 (33.4)	4 (10.4)
≥24 months	4 (24.0)	1 (7.8)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 11-18
Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response
Based on Investigator Assessment per RECIST 1.1
(Subjects with PD-L1 CPS >= 10, ITT Population)

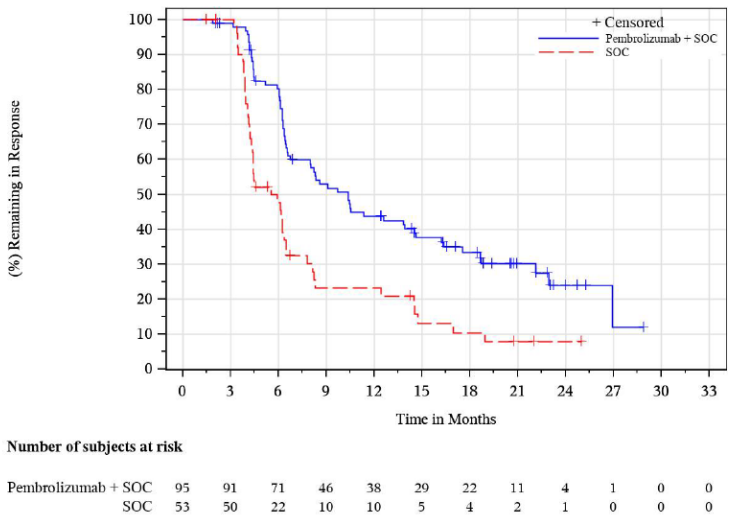
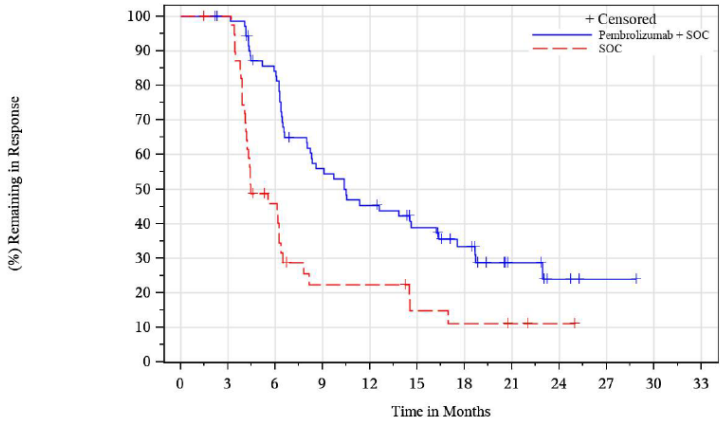


Figure 15: Patients with ESCC whose tumours express PD-L1 CPS ≥10

Figure 11-16
Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response Based on Investigator Assessment per RECIST 1.1
(Subjects with Squamous Cell Carcinoma and PD-L1 CPS >= 10, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	73	71	57	37	30	23	16	7	3	1	0	0
SOC	40	39	16	7	7	4	3	2	1	0	0	0

Patient-reported Outcomes-table 24:

Table 11-24
Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 18
(FAS Population)

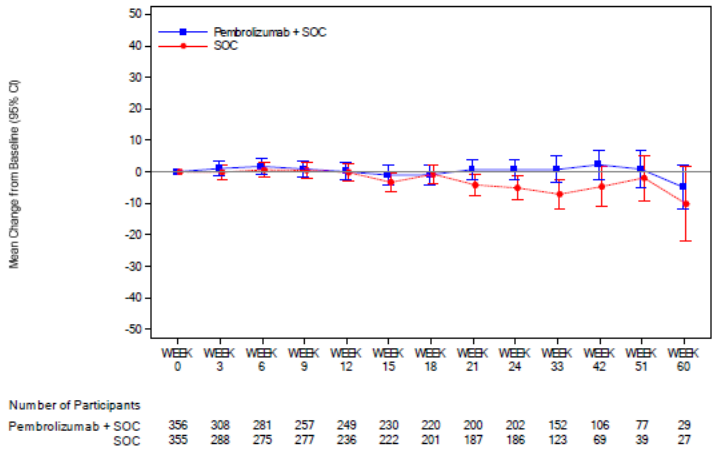
Treatment	Baseline		Week 18		Change from Baseline to Week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	356	64.37 (21.23)	225	65.00 (20.80)	366	-1.74 (-4.24, 0.75)
SOC	355	65.66 (20.06)	206	66.42 (18.59)	363	-1.64 (-4.21, 0.92)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	-0.10 (-3.40, 3.20)	0.9530

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group
(FAS Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adpro]

Analysis of Change from Baseline in OES-18 Dysphagia to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	355	33.18 (30.93)	224	29.27 (34.06)	366	-3.18 (-7.19, 0.82)
SOC	350	37.87 (32.82)	204	36.76 (35.43)	359	2.36 (-1.77, 6.49)
Pairwise Comparison					Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC					-5.54 (-10.93, -0.16)	0.0436

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Analysis of Change from Baseline in OES-18 Pain to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	355	15.43 (18.51)	224	10.02 (15.85)	366	-4.78 (-7.01, -2.56)
SOC	350	17.30 (20.03)	204	13.13 (17.79)	359	-1.85 (-4.14, 0.45)
Pairwise Comparison					Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC					-2.94 (-5.86, -0.02)	0.0487

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Analysis of Change from Baseline in OES-18 Reflux to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab + SOC	355	15.96 (21.78)	224	14.88 (19.95)	366	-0.22 (-2.81, 2.36)
SOC	350	16.10 (21.63)	204	16.09 (21.40)	359	0.71 (-1.96, 3.38)

Pairwise Comparison	Difference in LS Means[†] (95% CI)	p-Value[†]
Pembrolizumab + SOC vs. SOC	-0.93 (-4.36, 2.49)	0.5932

[†] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Ancillary Analyses

Participants whose tumours express PD-L1 CPS <10

Table 25: Subject Characteristics
(Subjects with PD-L1 CPS < 10, ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	175		172		347	
Gender						
Male	145	(82.9)	152	(88.4)	297	(85.6)
Female	30	(17.1)	20	(11.6)	50	(14.4)
Age (Years)						
< 65	98	(56.0)	95	(55.2)	193	(55.6)
>= 65	77	(44.0)	77	(44.8)	154	(44.4)
Mean	62.9		62.5		62.7	
SD	9.8		9.3		9.5	
Median	64.0		63.0		63.0	
Range	34 to 94		27 to 82		27 to 94	
Race						
American Indian Or Alaska Native	2	(1.1)	5	(2.9)	7	(2.0)
Asian	88	(50.3)	90	(52.3)	178	(51.3)
Black Or African American	3	(1.7)	1	(0.6)	4	(1.2)
Multiple	3	(1.7)	3	(1.7)	6	(1.7)
American Indian Or Alaska Native, White	2	(1.1)	3	(1.7)	5	(1.4)
Black Or African American, White	1	(0.6)	0	(0.0)	1	(0.3)
White	74	(42.3)	65	(37.8)	139	(40.1)
Missing	5	(2.9)	8	(4.7)	13	(3.7)
Ethnicity						
Hispanic Or Latino	22	(12.6)	27	(15.7)	49	(14.1)
Not Hispanic Or Latino	148	(84.6)	132	(76.7)	280	(80.7)
Not Reported	0	(0.0)	1	(0.6)	1	(0.3)
Unknown	5	(2.9)	12	(7.0)	17	(4.9)
Region						
Asia	85	(48.6)	89	(51.7)	174	(50.1)

Rest of World	90	(51.4)	83	(48.3)	173	(49.9)
Primary Diagnosis						
	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Squamous Cell Carcinoma of the Esophagus	121	(69.1)	126	(73.3)	247	(71.2)
Adenocarcinoma of the Esophagus	35	(20.0)	23	(13.4)	58	(16.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	19	(10.9)	23	(13.4)	42	(12.1)
Metastatic Staging						
M0	16	(9.1)	20	(11.6)	36	(10.4)
M1	159	(90.9)	152	(88.4)	311	(89.6)
Brain Metastasis						
Yes	1	(0.6)	1	(0.6)	2	(0.6)
No	174	(99.4)	171	(99.4)	345	(99.4)
Current Disease Stage						
IB	0	(0.0)	1	(0.6)	1	(0.3)
IIB	1	(0.6)	0	(0.0)	1	(0.3)
III	1	(0.6)	3	(1.7)	4	(1.2)
IIIA	3	(1.7)	2	(1.2)	5	(1.4)
IIIB	4	(2.3)	8	(4.7)	12	(3.5)
IIIC	7	(4.0)	6	(3.5)	13	(3.7)
IV	119	(68.0)	132	(76.7)	251	(72.3)
IVA	5	(2.9)	3	(1.7)	8	(2.3)
IVB	34	(19.4)	16	(9.3)	50	(14.4)
IVE	1	(0.6)	1	(0.6)	2	(0.6)
ECOG Performance Scale						
0	59	(33.7)	67	(39.0)	126	(36.3)
1	115	(65.7)	105	(61.0)	220	(63.4)
2	1	(0.6)	0	(0.0)	1	(0.3)
Histology						
Adenocarcinoma	54	(30.9)	46	(26.7)	100	(28.8)
Squamous Cell Carcinoma	121	(69.1)	126	(73.3)	247	(71.2)
Disease Status						
Metastatic	159	(90.9)	152	(88.4)	311	(89.6)
	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Unresectable - Locally Advanced	16	(9.1)	20	(11.6)	36	(10.4)
Database Cutoff Date: 02JUL2020						

Overall survival

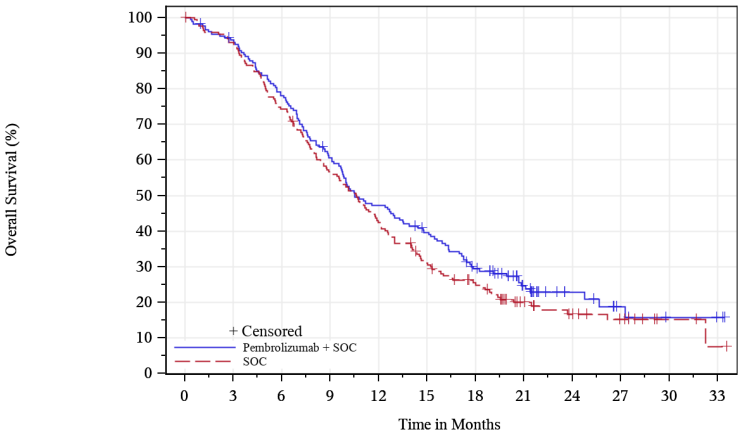


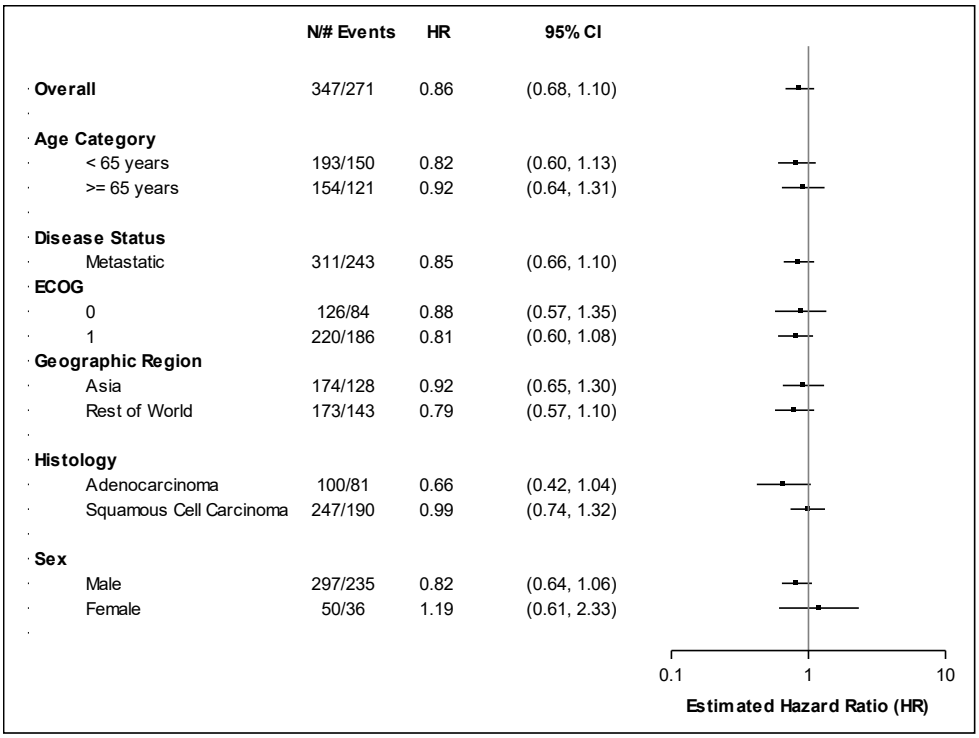
Figure 16: Kaplan-Meier Estimates of Overall Survival (Subjects with PD-L1 CPS < 10, ITT Population)

Table 2.7.3-esophageal3: 1
Analysis of Overall Survival
(Subjects with PD-L1 CPS < 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	175	132 (75.4)	2187.2	6.0	10.5 (9.7, 13.5)	47.3 (39.7, 54.5)
SOC	172	139 (80.8)	2024.8	6.9	10.6 (8.8, 12.0)	42.5 (35.0, 49.7)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.86 (0.68, 1.10)	0.1174§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

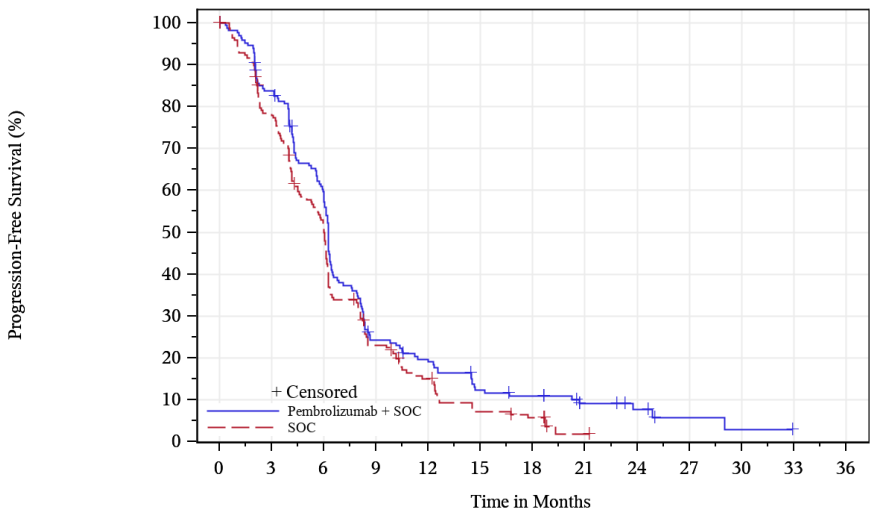
Source: [P590V01MK3475: adam-adsl; adtte]



Database Cutoff Date: 02JUL2020

Figure 17: Forest Plot of OS Hazard Ratio by Subgroup Factor (Subjects with PD-L1 CPS < 10, ITT Population)

Progression Free Survival



Number of Subjects at Risk

Pembrolizumab + SOC	175	138	96	38	29	18	15	8	5	2	1	0	0
SOC	172	130	85	36	22	10	7	1	0	0	0	0	0

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

Figure 18: Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule) (Subjects with PDL1 < 10, ITT Population)

Analysis of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1
(Primary Censoring Rule)
(Subjects with PD-L1 CPS < 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	175	148 (84.6)	1288.2	11.5	6.2 (6.0, 6.4)	19.0 (13.4, 25.5)
SOC	172	154 (89.5)	1084.1	14.2	6.0 (5.0, 6.2)	15.0 (10.0, 21.1)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.80 (0.64, 1.01)	0.0272§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1
(Subjects with PD-L1 CPS < 10, ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + SOC vs. SOC	
				Estimate (95% CI)†	p-Value††
Pembrolizumab + SOC	175	68	38.9 (31.6, 46.5)	6.8 (-3.3, 16.8)	0.0930
SOC	172	55	32.0 (25.1, 39.5)		

† Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Patients with adenocarcinoma of the oesophagus

Baseline Characteristics

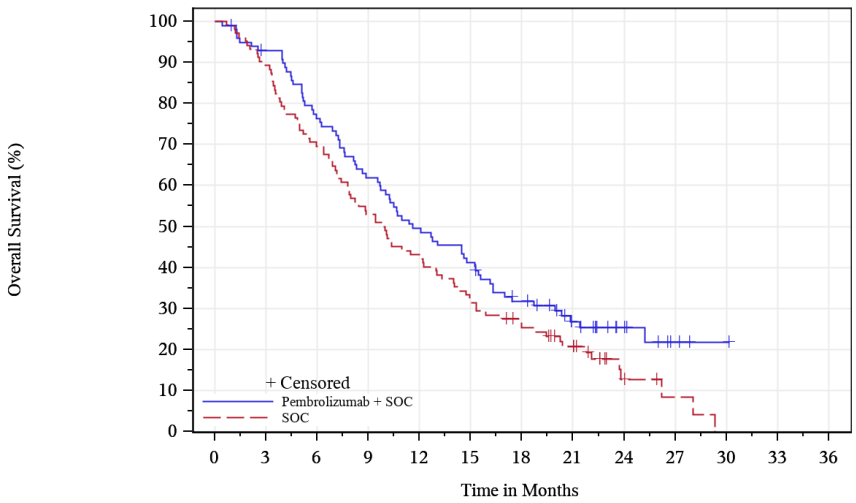
Table 26: Subject Characteristics (Subjects with Adenocarcinoma, ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	99		102		201	
Gender						
Male	84	(84.8)	87	(85.3)	171	(85.1)
Female	15	(15.2)	15	(14.7)	30	(14.9)
Age (Years)						
< 65	49	(49.5)	70	(68.6)	119	(59.2)
>= 65	50	(50.5)	32	(31.4)	82	(40.8)
Mean	62.3		59.1		60.7	
SD	11.9		10.2		11.2	
Median	65.0		59.5		62.0	
Range	28 to 83		27 to 79		27 to 83	
Race						

American Indian Or Alaska Native	3	(3.0)	3	(2.9)	6	(3.0)
Asian	18	(18.2)	18	(17.6)	36	(17.9)
Black Or African American	0	(0.0)	2	(2.0)	2	(1.0)
Multiple	2	(2.0)	4	(3.9)	6	(3.0)
American Indian Or Alaska Native, White	1	(1.0)	2	(2.0)	3	(1.5)
Black Or African American, White	1	(1.0)	2	(2.0)	3	(1.5)
White	69	(69.7)	70	(68.6)	139	(69.2)
Missing	7	(7.1)	5	(4.9)	12	(6.0)
Ethnicity						
Hispanic Or Latino	10	(10.1)	20	(19.6)	30	(14.9)
Not Hispanic Or Latino	82	(82.8)	73	(71.6)	155	(77.1)
Not Reported	0	(0.0)	1	(1.0)	1	(0.5)
Unknown	5	(5.1)	7	(6.9)	12	(6.0)
Missing	2	(2.0)	1	(1.0)	3	(1.5)
Region						
Asia	16	(16.2)	17	(16.7)	33	(16.4)
Rest of World	83	(83.8)	85	(83.3)	168	(83.6)
Primary Diagnosis						

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Adenocarcinoma of the Esophagus	58	(58.6)	52	(51.0)	110	(54.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	41	(41.4)	50	(49.0)	91	(45.3)
Metastatic Staging						
M0	8	(8.1)	7	(6.9)	15	(7.5)
M1	91	(91.9)	95	(93.1)	186	(92.5)
Brain Metastasis						
Yes	1	(1.0)	1	(1.0)	2	(1.0)
No	98	(99.0)	101	(99.0)	199	(99.0)
Current Disease Stage						
IB	0	(0.0)	1	(1.0)	1	(0.5)
III	1	(1.0)	0	(0.0)	1	(0.5)
IIIA	1	(1.0)	0	(0.0)	1	(0.5)
IIIB	4	(4.0)	3	(2.9)	7	(3.5)
IIIC	2	(2.0)	3	(2.9)	5	(2.5)
IV	69	(69.7)	84	(82.4)	153	(76.1)
IVA	2	(2.0)	1	(1.0)	3	(1.5)
IVB	18	(18.2)	9	(8.8)	27	(13.4)
IVC	1	(1.0)	0	(0.0)	1	(0.5)
IVE	1	(1.0)	1	(1.0)	2	(1.0)
ECOG Performance Scale						
0	46	(46.5)	45	(44.1)	91	(45.3)
1	52	(52.5)	56	(54.9)	108	(53.7)
2	1	(1.0)	1	(1.0)	2	(1.0)
Histology						
Adenocarcinoma	99	(100.0)	102	(100.0)	201	(100.0)
Disease Status						
Metastatic	91	(91.9)	95	(93.1)	186	(92.5)
Unresectable - Locally Advanced	8	(8.1)	7	(6.9)	15	(7.5)
Database Cutoff Date: 02JUL2020						

Overall Survival



Number of Subjects at Risk

Pembrolizumab + SOC	99	90	74	60	48	40	29	18	9	3	1	0	0
SOC	102	91	71	54	44	33	25	17	5	2	0	0	0

Database Cutoff Date: 02JUL2020

Figure 19: Kaplan-Meier Estimates of Overall Survival (Subjects with Adenocarcinoma, ITT Population)

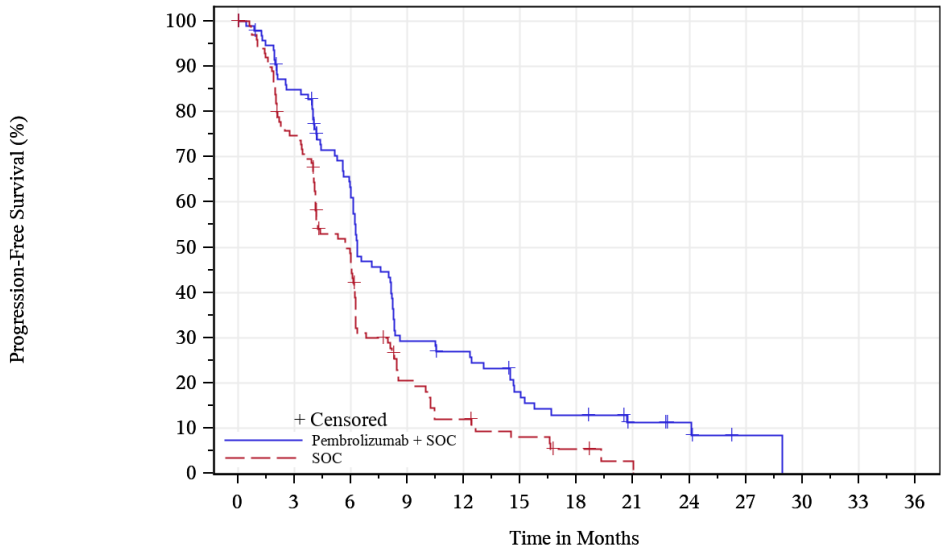
Table 14.2-184
Analysis of Overall Survival
(Subjects with Adenocarcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS [†] (Months) (95% CI)	OS Rate at Month 12 in % [†] (95% CI)
Pembrolizumab + SOC	99	72 (72.7)	1268.0	5.7	11.6 (9.7, 15.2)	49.5 (39.3, 59.0)
SOC	102	87 (85.3)	1171.4	7.4	9.9 (7.8, 12.3)	43.1 (33.4, 52.5)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value
Pembrolizumab + SOC vs. SOC					0.74 (0.54, 1.02)	0.0309[§]

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Progression Free Survival



Number of Subjects at Risk

Pembrolizumab + SOC	99	78	54	25	22	14	10	6	4	1	0	0	0
SOC	102	73	45	17	10	6	3	1	0	0	0	0	0

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020

Figure 20: Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule) (Subjects with Adenocarcinoma, ITT Population)

Table 14.2-186
Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(Subjects with Adenocarcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Month 12 in % [†] (95% CI)
Pembrolizumab + SOC	99	78 (78.8)	778.8	10.0	6.3 (6.0, 8.1)	27.0 (18.1, 36.6)
SOC	102	89 (87.3)	589.2	15.1	5.7 (4.1, 6.2)	12.0 (6.3, 19.9)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value
Pembrolizumab + SOC vs. SOC					0.63 (0.46, 0.87)	0.0019[§]

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Efficacy by histology and PD-L1 status is summarised in the following table:

Table 27: Efficacy by histology and PD-L1 status

	ESCC			AC	
	CPS ≥10 N=286	CPS <10 N=247		CPS ≥10 N=97	CPS <10 N=100
OS HR (95% CI)	0.57 (0.43, 0.75)	**0.99** (0.74, 1.32)		0.83 (0.52, 1.34)	**0.66** (0.42, 1.04)
PFS HR (95% CI)	0.53 (0.40, 0.69)	**0.83** (0.64, 1.11)		0.49 (0.30, 0.81)	**0.76** (0.49, 1.19)
ORR difference (95% CI)	22.8 (11.6, 33.4)	**2.7** (-9.2, 14.5)		27.5 (7.7, 45.6)	**19.8** (0.4, 37,4)

The Applicant was requested to provide the results (HR with 95% CIs by subgroup) of the following two models: (i) A model fitting the main factors treatment arm, geographic region, tumour histology, and PD-L1 status together with two-way interaction terms of treatment with one of the three remaining factors, and (ii) a model of treatment, PD-L1, histology, treatment*PDL1, Treatment * Histology, stratified by ECOG and geographic region.

Table 4 Comparison of Multivariate Cox Regression Models Using Likelihood Ratio Test (ITT Population)

Model Fit Statistics	Full Model	Simple Model	Likelihood Ratio Test Statistics†	p-value‡
-2 LOG L§ (With Covariates)	6610.11	6619.54	9.43	0.0931
Degree of Freedom	15	10	5	

† Likelihood ratio test statistics is the difference of -2 LOG L between full model and simple model, and it yields an approximate Chi-squared distribution.
‡ 1-sided p-value from Chi-squared test.
§ Log likelihood from Cox regression model.
Database Cutoff Date: 02JUL2020

Table 5 Multivariate Cox Regression Analysis for Overall Survival (ITT Population)

Region/Histology/PD-L1 Status	Treatment	N	Number of Events (%)	Hazard Ratio (95% CI)†
Asia/EAC/CPS>=10	P+SOC SOC	8 8	4 (50.0) 6 (75.0)	0.50 (0.31, 0.82)
Asia/EAC/CPS<10	P+SOC SOC	8 9	6 (75.0) 8 (88.9)	0.69 (0.43, 1.12)
Asia/SCC/CPS>=10	P+SOC SOC	96 98	61 (63.5) 86 (87.8)	0.57 (0.43, 0.75)
Asia/SCC/CPS<10	P+SOC SOC	77 80	55 (71.4) 59 (73.8)	0.78 (0.58, 1.05)
ROW/EAC/CPS>=10	P+SOC SOC	35 45	26 (74.3) 37 (82.2)	0.64 (0.44, 0.94)
ROW/EAC/CPS<10	P+SOC SOC	47 38	35 (74.5) 34 (89.5)	0.88 (0.61, 1.27)
ROW/SCC/CPS>=10	P+SOC SOC	47 46	33 (70.2) 36 (78.3)	0.72 (0.51, 1.03)
ROW/SCC/CPS<10	P+SOC SOC	43 45	36 (83.7) 38 (84.4)	0.99 (0.70, 1.41)

† Based on Cox regression model with Efron's method of tie handling, with covariates of treatment, PD-L1 status, tumor histology, geographic region, and all two-factor interactions.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 6 Interaction Tests from Multivariate Cox Regression Analysis (ITT Population)

Effect	Wald Chisquare Test Statistic	p-value†
Treatment	12.9248	0.0003
PD-L1	0.5462	0.4598
Histology	0.0290	0.8645
Treatment*PD-L1	3.3444	0.0674
Treatment*Histology	0.0108	0.9169

† 2-sided p-value from Wald's test based on a Cox regression model stratified by ECOG and geographic region.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 7 Multivariate Cox Regression Analysis for Overall Survival (ITT Population)

Histology/PD-L1 Status	Treatment	N	Number of Events (%)	Hazard Ratio (95% CI)†
EAC/CPS>=10	P+SOC	43	30 (69.8)	0.64 (0.45, 0.91)
	SOC	53	43 (81.1)	
EAC/CPS<10	P+SOC	55	41 (74.5)	0.87 (0.61, 1.25)
	SOC	47	42 (89.4)	
SCC/CPS>=10	P+SOC	143	94 (65.7)	0.63 (0.48, 0.81)
	SOC	144	122 (84.7)	
SCC/CPS<10	P+SOC	120	91 (75.8)	0.86 (0.66, 1.11)
	SOC	125	97 (77.6)	

† Based on Cox regression model with Efron's method of tie handling, stratified by ECOG and geographic region with covariates of treatment, PD-L1 status, tumor histology, interaction of treatment and PD-L1 status, and interaction of treatment and tumor histology.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

EU patient population

Baseline Characteristics

Table 28: Subject Characteristics in EU and Rest of World (ITT Population)

	EU		Ex-EU		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	114		635		749	
Gender						
Male	92	(80.7)	533	(83.9)	625	(83.4)
Female	22	(19.3)	102	(16.1)	124	(16.6)
Age (Years)						
< 65	68	(59.6)	359	(56.5)	427	(57.0)
>= 65	46	(40.4)	276	(43.5)	322	(43.0)
Mean	61.4		62.6		62.4	
SD	9.3		9.5		9.5	
Median	61.0		63.0		63.0	
Range	27 to 79		30 to 94		27 to 94	
Race						
American Indian Or Alaska Native	0	(0.0)	21	(3.3)	21	(2.8)
Asian	3	(2.6)	397	(62.5)	400	(53.4)
Black Or African American	0	(0.0)	7	(1.1)	7	(0.9)

Multiple	0	(0.0)	14	(2.2)	14	(1.9)
American Indian Or Alaska Native, White	0	(0.0)	9	(1.4)	9	(1.2)
Black Or African American, White	0	(0.0)	5	(0.8)	5	(0.7)
White	82	(71.9)	196	(30.9)	278	(37.1)
Missing	29	(25.4)	0	(0.0)	29	(3.9)
Ethnicity						
Hispanic Or Latino	3	(2.6)	96	(15.1)	99	(13.2)
Not Hispanic Or Latino	79	(69.3)	532	(83.8)	611	(81.6)
Not Reported	2	(1.8)	1	(0.2)	3	(0.4)
Unknown	26	(22.8)	6	(0.9)	32	(4.3)
Missing	4	(3.5)	0	(0.0)	4	(0.5)
Region						
Asia	0	(0.0)	393	(61.9)	393	(52.5)
Rest of World	114	(100.0)	242	(38.1)	356	(47.5)
Primary Diagnosis						

	EU		Ex-EU		Total	
	n	(%)	n	(%)	n	(%)
Squamous Cell Carcinoma of the Esophagus	66	(57.9)	482	(75.9)	548	(73.2)
Adenocarcinoma of the Esophagus	27	(23.7)	83	(13.1)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	21	(18.4)	70	(11.0)	91	(12.1)
Metastatic Staging						
M0	11	(9.6)	55	(8.7)	66	(8.8)
M1	103	(90.4)	580	(91.3)	683	(91.2)
Brain Metastasis						
Yes	0	(0.0)	3	(0.5)	3	(0.4)
No	114	(100.0)	632	(99.5)	746	(99.6)
Current Disease Stage						
IB	0	(0.0)	1	(0.2)	1	(0.1)
IIB	0	(0.0)	1	(0.2)	1	(0.1)
III	2	(1.8)	8	(1.3)	10	(1.3)
IIIA	0	(0.0)	9	(1.4)	9	(1.2)
IIIB	5	(4.4)	15	(2.4)	20	(2.7)
IIIC	4	(3.5)	21	(3.3)	25	(3.3)
IV	84	(73.7)	473	(74.5)	557	(74.4)
IVA	5	(4.4)	11	(1.7)	16	(2.1)
IVB	11	(9.6)	95	(15.0)	106	(14.2)
IVC	1	(0.9)	1	(0.2)	2	(0.3)
IVE	2	(1.8)	0	(0.0)	2	(0.3)
ECOG Performance Scale						
0	52	(45.6)	247	(38.9)	299	(39.9)
1	62	(54.4)	386	(60.8)	448	(59.8)
2	0	(0.0)	2	(0.3)	2	(0.3)
Histology						
Adenocarcinoma	48	(42.1)	153	(24.1)	201	(26.8)

Squamous Cell Carcinoma	66	(57.9)	482	(75.9)	548	(73.2)
Disease Status						
Metastatic	103	(90.4)	580	(91.3)	683	(91.2)
Unresectable - Locally Advanced	11	(9.6)	55	(8.7)	66	(8.8)

Subject Characteristics in EU and Rest of World
(ITT Population)

	EU		Ex-EU		Total	
	n	(%)	n	(%)	n	(%)
PD-L1 Status						
CPS >= 10	57	(50.0)	326	(51.3)	383	(51.1)
CPS < 10	56	(49.1)	291	(45.8)	347	(46.3)
Not evaluable	0	(0.0)	12	(1.9)	12	(1.6)
Missing	1	(0.9)	6	(0.9)	7	(0.9)
Database Cutoff Date: 02JUL2020						

Source: [P590V01MK3475: adam-adsl]

Overall Survival

Table 2.7.3-esophageal3: 1
Analysis of Overall Survival
(ITT Population, EU)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	61	44 (72.1)	830.5	5.3	11.4 (8.0, 17.2)	49.2 (36.2, 60.9)
SOC	53	45 (84.9)	610.0	7.4	11.0 (8.0, 13.3)	47.2 (33.4, 59.8)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.72 (0.47, 1.10)	0.0619§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

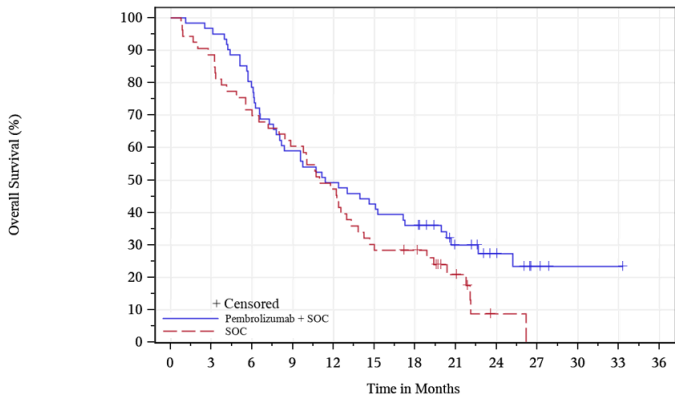
Source: [P590V01MK3475: adam-adsl; adtte]

In patients with PD-L1 CPS ≥ 10, the median OS was 11.4 months vs. 8.6 months with a HR of 0.6, and the 12 months OS rates was 48% vs. 35% in the pembrolizumab plus chemotherapy group [n=31] and chemotherapy group [n=26], respectively.

Median OS and 12 months OS rates are in favour of the pembrolizumab + chemotherapy group for European patients with CPS≥10 (OS HR 0.60). No clinically meaningful benefit could be observed for the EU population with CPS<10 (OS HR 0.85, median OS 9.7 vs. 12.6 months, 12 month OS rates 48.3% vs. 59.3% for pembrolizumab+chemotherapy vs chemotherapy, respectively).

The OS KM curves for European patients with PD-L1 CPS ≥10 and with PD-L1 CPS <10, are shown below:

Figure 5 Kaplan-Meier Estimates of Overall Survival (ITT Population, EU)

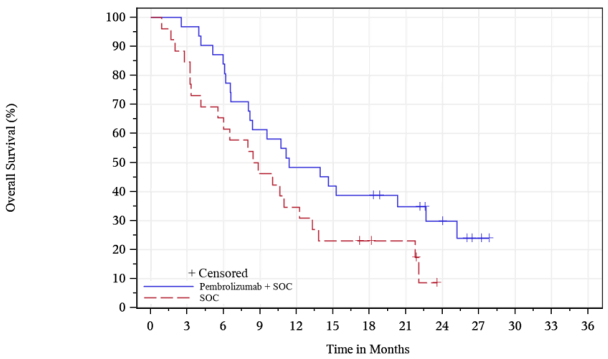


Number of Subjects at Risk

Pembrolizumab + SOC	61	59	48	36	30	26	22	13	8	3	1	1	0
SOC	53	47	38	32	25	16	14	7	1	0	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

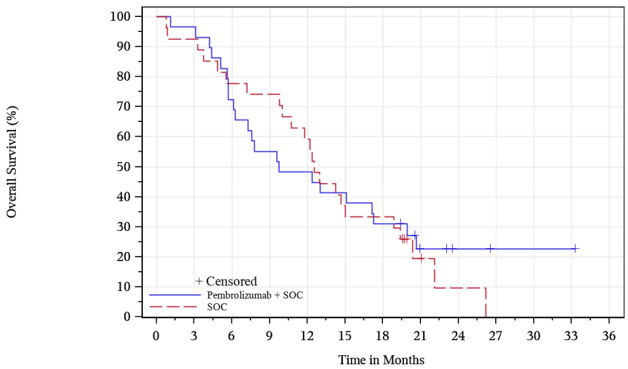
Figure 6 Kaplan-Meier Estimates of Overall Survival (Subjects with PD-L1 CPS >= 10, ITT Population, EU)



Number of Subjects at Risk

Pembrolizumab + SOC	31	30	26	19	15	13	12	9	6	2	0	0	0
SOC	26	22	17	12	9	6	5	4	0	0	0	0	0

Figure 7 Kaplan-Meier Estimates of Overall Survival (Subjects with PD-L1 CPS < 10, ITT Population, EU)



Number of Subjects at Risk

Pembrolizumab + SOC	29	28	21	16	14	12	9	4	2	1	1	1	0
SOC	27	25	21	20	16	10	9	3	1	0	0	0	0

In the EU subgroup the HR for OS 0.72 was in line with the results of the overall study population. However, despite limited numbers of EU participants, the benefit of pembrolizumab appears to be lower for patients with PD-L1 CPS <10 (OS HR 0.85, PFS HR 0.72) compared to CPS ≥10 (OS HR 0.6, PFS HR 0.48).

A PFS benefit was observed (HR 0.55) across all EU participants. This appeared also more pronounced for patients with PD-L1 CPS ≥10 (PFS HR 0.48) compared to patients with CPS <10 (PFS HR 0.72). There were no relevant differences between histology regarding the treatment effect of pembrolizumab in the EU population.

Ex-Asia Versus Asia Participant Population

Baseline Characteristics

Table 22: Subject Characteristics in Asia and Rest of World (ITT Population)

	Asia		Rest of World		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	393		356		749	
Gender						
Male	354	(90.1)	271	(76.1)	625	(83.4)

Female	39	(9.9)	85	(23.9)	124	(16.6)
Age (Years)						
< 65	216	(55.0)	211	(59.3)	427	(57.0)
>= 65	177	(45.0)	145	(40.7)	322	(43.0)
Mean	62.8		62.0		62.4	
SD	8.7		10.3		9.5	
Median	64.0		62.0		63.0	
Range	31 to 82		27 to 94		27 to 94	
Race						
American Indian Or Alaska Native	0	(0.0)	21	(5.9)	21	(2.8)
Asian	393	(100.0)	7	(2.0)	400	(53.4)
Black Or African American	0	(0.0)	7	(2.0)	7	(0.9)
Multiple	0	(0.0)	14	(3.9)	14	(1.9)
American Indian Or Alaska Native, White	0	(0.0)	9	(2.5)	9	(1.2)
Black Or African American, White	0	(0.0)	5	(1.4)	5	(0.7)
White	0	(0.0)	278	(78.1)	278	(37.1)
Missing	0	(0.0)	29	(8.1)	29	(3.9)
Ethnicity						
Hispanic Or Latino	1	(0.3)	98	(27.5)	99	(13.2)
Not Hispanic Or Latino	388	(98.7)	223	(62.6)	611	(81.6)
Not Reported	0	(0.0)	3	(0.8)	3	(0.4)
Unknown	4	(1.0)	28	(7.9)	32	(4.3)
Missing	0	(0.0)	4	(1.1)	4	(0.5)
Region						
Asia	393	(100.0)	0	(0.0)	393	(52.5)
Rest of World	0	(0.0)	356	(100.0)	356	(47.5)
Primary Diagnosis						

Subject Characteristics in Asia and Rest of World
(ITT Population)

	Asia		Rest of World		Total	
	n	(%)	n	(%)	n	(%)
Squamous Cell Carcinoma of the Esophagus	360	(91.6)	188	(52.8)	548	(73.2)
Adenocarcinoma of the Esophagus	17	(4.3)	93	(26.1)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	16	(4.1)	75	(21.1)	91	(12.1)
Metastatic Staging						
M0	30	(7.6)	36	(10.1)	66	(8.8)
M1	363	(92.4)	320	(89.9)	683	(91.2)
Brain Metastasis						
Yes	0	(0.0)	3	(0.8)	3	(0.4)
No	393	(100.0)	353	(99.2)	746	(99.6)
Current Disease Stage						
IB	0	(0.0)	1	(0.3)	1	(0.1)
IIB	1	(0.3)	0	(0.0)	1	(0.1)
III	4	(1.0)	6	(1.7)	10	(1.3)
IIIA	5	(1.3)	4	(1.1)	9	(1.2)
IIIB	6	(1.5)	14	(3.9)	20	(2.7)
IIIC	14	(3.6)	11	(3.1)	25	(3.3)
IV	291	(74.0)	266	(74.7)	557	(74.4)
IVA	5	(1.3)	11	(3.1)	16	(2.1)
IVB	66	(16.8)	40	(11.2)	106	(14.2)
IVC	1	(0.3)	1	(0.3)	2	(0.3)
IVE	0	(0.0)	2	(0.6)	2	(0.3)
ECOG Performance Scale						
0	157	(39.9)	142	(39.9)	299	(39.9)
1	236	(60.1)	212	(59.6)	448	(59.8)
2	0	(0.0)	2	(0.6)	2	(0.3)
Histology						
Adenocarcinoma	33	(8.4)	168	(47.2)	201	(26.8)
Squamous Cell Carcinoma	360	(91.6)	188	(52.8)	548	(73.2)
Disease Status						
Metastatic	363	(92.4)	320	(89.9)	683	(91.2)
Unresectable - Locally Advanced	30	(7.6)	36	(10.1)	66	(8.8)

Subject Characteristics in Asia and Rest of World
(ITT Population)

	Asia		Rest of World		Total	
	n	(%)	n	(%)	n	(%)
PD-L1 Status						
CPS >= 10	210	(53.4)	173	(48.6)	383	(51.1)
CPS < 10	174	(44.3)	173	(48.6)	347	(46.3)
Not evaluable	6	(1.5)	6	(1.7)	12	(1.6)
Missing	3	(0.8)	4	(1.1)	7	(0.9)
Database Cutoff Date: 02JUL2020						

Source: [P590V01MK3475: adam-adsl]

The MAH assessed whether the higher OS observed in participants from Asia were the result of differences in baseline characteristics, prior disease treatment or posttreatment antineoplastic therapy received between regions.

Table 23: Post-Trial Management (ITT Population)

	Asia Pembro + SOC		Asia SOC		Rest of World Pembro + SOC		Rest of World SOC		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	196		197		177		179		749	
Oncologic Drugs/Biologic										
Yes	105	(53.6)	107	(54.3)	58	(32.8)	70	(39.1)	340	(45.4)
No	91	(46.4)	90	(45.7)	119	(67.2)	109	(60.9)	409	(54.6)
Radiation										
Yes	27	(13.8)	18	(9.1)	1	(0.6)	6	(3.4)	52	(6.9)
No	169	(86.2)	179	(90.9)	176	(99.4)	173	(96.6)	697	(93.1)
Oncology Surgery										
Yes	11	(5.6)	10	(5.1)	8	(4.5)	1	(0.6)	30	(4.0)
No	185	(94.4)	187	(94.9)	169	(95.5)	178	(99.4)	719	(96.0)
Database Cutoff Date: 02JUL2020										

Age Category

Table 24: ITT Population Sizes by Age Categories

Age (Years)	ITT Population (N=749)		Subjects with Squamous Cell Carcinoma (N= 548)		Subjects with PD-L1 CPS>=10 (N= 383)		Subjects with Squamous Cell Carcinoma and PD-L1 CPS>=10 (N= 286)	
	Pembrolizumab+SOC	SOC	Pembrolizumab+SOC	SOC	Pembrolizumab+SOC	SOC	Pembrolizumab+SOC	SOC
<65	201	226	152	156	99	127	78	88
65 - 74	135	118	98	91	69	56	52	41
75 - 84	36	30	23	25	18	12	13	12
≥85	1	2	1	2	0	2	0	2
Database Cutoff Date: 02JUL2020								

Primary Efficacy Endpoint Results by Specific Age Category

Overall survival

Table 25: Efficacy Results for Overall Survival by Age Categories

Pembrolizumab + SOC vs. SOC	Age (Years)	ITT Population, Subjects with Squamous Cell Carcinoma and PD-L1 CPS>=10†	ITT Population, Subjects with Squamous Cell Carcinoma†	ITT Population, Subjects with PD-L1 CPS>=10†	ITT Population†
HR (95% CI)	<65	0.57 (0.40, 0.81)	0.74 (0.58, 0.96)	0.71 (0.52, 0.95)	0.76 (0.61, 0.95)
HR (95% CI)	65 - 74	0.55 (0.33, 0.91)	0.64 (0.45, 0.91)	0.52 (0.34, 0.80)	0.64 (0.48, 0.85)
HR (95% CI)	75 - 84	0.90 (0.36, 2.29)	0.93 (0.49, 1.76)	0.85 (0.36, 2.02)	0.98 (0.57, 1.69)

† Based on Cox regression model with treatment as a covariate.
Note: there were 3 participants with age >= 85 years and hence this category is not analyzed.
Database Cutoff Date: 02JUL2020

Progression free survival

Table 26: Efficacy Results for PFS by INV Per RECIST 1.1 by Age Categories (Primary Censoring Rule)

Pembrolizumab + SOC vs. SOC	Age (Years)	ITT Population, Subjects with Squamous Cell Carcinoma†	ITT Population, Subjects with PD-L1 CPS>=10†	ITT Population†
HR (95% CI)	<65	0.73 (0.57, 0.92)	0.66 (0.49, 0.88)	0.69 (0.56, 0.85)
HR (95% CI)	65 - 74	0.57 (0.41, 0.79)	0.45 (0.30, 0.67)	0.56 (0.42, 0.75)
HR (95% CI)	75 - 84	0.73 (0.39, 1.37)	0.50 (0.21, 1.19)	0.93 (0.54, 1.62)

† Based on Cox regression model with treatment as a covariate.
Note: there were 3 participants with age >= 85 years and hence this category is not analyzed.
Database Cutoff Date: 02JUL2020

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 27: Summary of Efficacy for trial KEYNOTE-590.

Title: A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Oesophageal Carcinoma (KEYNOTE-590)			
Study identifier	IND: 123,482; EudraCT: 2017-000958-19		
Design	Phase 3, randomized, double-blind, placebo-controlled,		
Hypothesis	Superiority		
Treatments groups	Pembrolizumab + SOC		pembrolizumab 200 mg Q3W + Cisplatin and 5-Fluorouracil 800 mg/m2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m2 per 3-week cycle) 373 randomized pts
	SOC		Placebo IV Q3W + Cisplatin and 5-Fluorouracil 800 mg/m2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m2 per 3-week cycle) 376 randomized pts
Endpoints and definitions	Co-Primary endpoint	OS	Time from randomization to death due to any cause
		PFS	Time from randomization to PD, based upon RECIST 1.1 by Investigator, or death, whichever occurred earlier

	Secondary endpoint	ORR DoR	proportion of subjects who have a CR or a PR by Investigator time from first documented evidence of CR or PR until disease progression or death
Database lock	30-JUL-2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + SOC	SOC
	Number of subject	373	376
	OS (median months)	12.4	9.8
	95% CI	10.5, 14	8.8, 10.8
	PFS (median months)	6.5	6
	95% CI	6.2, 8	5.7, 6.2
	ORR (CR+PR) (%) **DOR** (median months)	45 8.3 (1.2+ - 31)	29.3 6 (1.5 – 25)

Effect estimate per comparison	Co-Primary endpoint	Pembrolizumab + SOC vs SOC	OS
		HR	0.73
		95% CI	0.62, 0.86
		P-value	<0.0001
	Co-Primary endpoint	Pembrolizumab + SOC vs SOC	PFS
		HR	0.67
		95% CI	0.56, 0.79
		P-value	<0.0001

3.4.3. Discussion on clinical efficacy

In support of this application, data are presented from the pivotal KEYNOTE-590 (KN590) trial, an ongoing Phase 3, randomized, double-blind, placebo-controlled, multisite study to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy (cisplatin and 5-FU) versus chemotherapy (cisplatin with 5-FU) alone as first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults.

Design and conduct of clinical studies

The study design of KEYNOTE-590 study can be considered overall appropriate to support a MA in the sought indication, although several methodological aspects were raised.

The inclusion/exclusion criteria define a study population characterised by relatively fit patients (ECOG 0-1) with an advanced disease status (unresectable or metastatic tumours) and who were treatment-naïve. Overall, the study is representative of the population for which palliative chemotherapy is indicated as

front-line approach. Recruitment occurred in centres with adequate expertise in the management of oesophageal cancer, i.e. high-volume centres with experienced surgeons and multidisciplinary teams, as recommended by CHMP at the time of the provided Scientific Advice.

EMA Scientific Advice on the design of KEYNOTE-590 was given on 23 March 2017. At that time, study KEYNOTE-180 in 3L+ oesophageal cancer was still ongoing and only preliminary results from the phase I trial KEYNOTE-028 in PD-L1 positive (CPS ≥1%) patients were available (n=23; ORR of 40% reported according to investigator assessment with responses observed only in GEP-positive patients). Based on these data, the CHMP recommended to wait for KEYNOTE-180 study results before starting recruitment of KEYNOTE-590, in order to make an informed decision on the definition of a biomarker as stratification factor and on the possible addition of a pembrolizumab monotherapy arm in the KN590 study design (possibly in a biomarker selected population).

The MAH did not follow the advice to include PD-L1 status as a stratification factor. KN590 enrolment started before biomarker analyses from KN180 were available. However, it was required that subjects had to provide a tissue sample for biomarker analysis at enrolment.

The MAH opted not to include a pembrolizumab monotherapy arm. KN028 ORR data as reported by an independent assessment from a database cut-off date as of 31 January 2018 were 18.2%. Available study outcomes from KN180 (ORR in CPS ≥10 population 13.8% and 21.5% in KN180 and KN181, respectively) further support that the omission of a monotherapy arm can be considered acceptable in the 1L setting.

Pembrolizumab was used at the 200 mg Q3W dose which was approved in both monotherapy and chemotherapy combined regimens across different indications; this is considered acceptable. The chosen comparator (cisplatin and 5-FU) is deemed adequate and in line with current clinical recommendations. Although being the most widely used chemotherapy combination, several other options are currently contemplated by clinical guidelines in the treatment of advanced oesophageal cancer. Oxaliplatin in combination with 5-FU or capecitabine are also recommended as preferred regimens in the current NCCN guideline and would be expected to be used in clinical practice. In addition, three drug regimens (including docetaxel or epirubicin) are recommended and used for medically fit patients. The broad indication (in combination with platinum and fluoropyrimidine based chemotherapy) and the proposed extrapolation from the combination (cisplatin with 5-FU) are accepted as a large difference in the benefit/risk between different platinum compound would not be reasonably expected. Oxaliplatin is used as an alternative treatment option in relation to safety. A reference to section 5.1 of the SmPC is included in the indication (section 4,1) in order to reflect the drug regimens used in the study.

The study recruited 749 patients with both histologies: squamous cell cancer (ESCC) and adenocarcinoma (AC) of the oesophagus. Enrolment of patients with adenocarcinoma of the gastroesophageal junction (EGJ) were restricted to Siewert I tumours (as reflected in section 5.1 of the SmPC). The exclusion of HER-2 positive EGJ AC patients is endorsed by the CHMP, as the standard treatment for these patients includes trastuzumab in addition to chemotherapy.

Stratification factors included geographic region (Asia versus Rest of World), tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1). PD-L1 expression status was expected to be assessed by IHC, which is in line with routine clinical practice, and was quantified by means of the CPS score. Recruitment was not stratified by CPS, contrary to the Scientific Advice provided by the CHMP that underlined a generally expected variability of response to treatment based on PD-L1 status. Among primary endpoints, PD-L1-based subgroup analyses were conducted although restricted to the CPS≥10 stratum while the CPS<10 category was tested in a non pre-specified exploratory analysis. Comparison between treatment arms within the CPS≥10 and its complementary (CPS<10) subgroup showed balanced clinical and disease characteristics. The lack of stratification by PD-L1 status is not cause of concern in the current application.

The assumptions made for median PFS (6 months) and median OS (12 months) in the control arm are in line with the available historical data of chemotherapy in 1L setting and support the sample size calculation.

The original protocol was revised with 9 Amendments in total. Among the most relevant modifications, the change in biomarkers from GEP assayed in a central laboratory to PD-L1 tested in a local facility (Amendment n.02, 19-DEC-2017) based on recommendations from emerging data in KN180 trial showing a prevalence of PD-L1 in oesophageal cancer of approximately 45% using CPS ≥10, and the utility of this level of expression across a range of PD-L1 CPS cut points in identifying responders to pembrolizumab. The amendment was adopted relatively early (i.e. nine months after the original protocol); moreover, the study aimed at recruiting "all comers" and stratification was regardless of biomarkers. Therefore, this is not considered problematic in terms of data collection and analysis.

In the original protocol, the study had PFS per RECIST1.1 by BICR and OS, both in "all comers" (ITT population) and in subjects with GEP-biomarker positive tumours (later changed to PD-L1 biomarker positive tumours; Amendment n.2), as dual primary endpoints. With Amendment n.8 (03-JAN-2020), the OS analysis within the ESCC tumour subtype, the ESCC tumour with CPS ≥10, and the PFS analysis in the ESCC population were implemented, driven by data analysed from study KN181. The study was considered to have met its primary objective if at least one of the above hypotheses was statistically significant. At the time of the amendment n. 8, recruitment was completed with a total of 749 subjects enrolled in a 1:1 ratio in the pembrolizumab and control arm. One of the two interim analysis (IA) originally planned was removed with Amendment 9 (17-JUN-2020). They were originally planned to be conducted at 448 PFS events in patients with ESCC after approximately32 months (IA1), and at 487 PFS events in patients with ESCC after approx. 40 months (IA2). With amendment No. 9 these two interim analyses were combined to one analysis after 460 investigator-assessed PFS events in patients with ESCC after approx. 35 months. This change was justified by input from the FDA.

The overall Type I error was controlled at 2.5% (1-sided), with 1.2% initially allocated to OS in ESCC with PD-L1 CPS ≥10, 1.1% to OS in ESCC, 0 to OS in PD-L1 CPS ≥10, 0 to OS in all subjects, 0.2% to PFS in ESCC, 0 to PFS in PD-L1 CPS ≥10, and 0 to PFS in all subjects.

Finally, with Amendment n. 9 (17-JUN-2020), the MAH has also replaced the original BICR-based PFS analysis with Investigator-based analysis in view of a higher than expected discordance rate between Investigator and BICR response evaluation (26%). A sensitivity analysis testing PFS results based on BICR-assessment was in agreement with the Investigator-based results. Censoring of PFS-events led to less than expected PFS-events assessed by BICR. Sensitivity analysis were conducted to assess PFS and ORR as determined by BICR, which demonstrated overall similar results with these of investigator assessment and support the assumption that the B/R assessment is not seriously impacted by this change. Sensitivity analyses were conducted by BICR within the ITT population and by subgroup analysis. Given the differences in treatment effect on OS by geographic location, which did not emerge in the PFS assessment, it was questioned whether a different approach in PFS result analysis was possibly undertaken in Asia and Rest of World relatively to the centralised assessment. The higher than expected discordance rate observed in the overall population was generally consistent across Asia and ROW regions; no differences between areas were noted.

Overall, statistical methods appeared not controversial. The rate of protocol deviations was similar in both arms and no concern is raised over possible impact of protocol deviations on efficacy results.

Efficacy data and additional analyses

The MAH presented the results of the interim analysis (i.e. final for PFS) of study KN-590 (data cut-off date of 02-JUL-2020) based on the ITT population, as defined by all randomized patients (i.e. a total of 749 patients, 373 in pembrolizumab plus chemotherapy, 376 in the chemotherapy arm), with a median

follow-up of 12.6 months (range: 0.1-33.6 months) in the pembrolizumab plus chemotherapy group and 9.8 months (range: 0.1-33.6 months) in the chemotherapy group.

Baseline characteristics as well as demographics appear well balanced between treatment arms in the ITT population, although a higher prevalence of subjects aged ≥65 years populated the experimental arm (46.1% vs 39.9%); distribution of histology, region, ECOG score and PD-L1 expression were all similar between groups. Diversity in both geographical localization (Asia and Rest of World, 52.5% vs 47.5% respectively) and PD-L1 score (CPS≥10 vs <10, 51.1% vs 46.3% respectively with 1.5% not evaluable and 0.9% missing) was well represented. The study population was mainly composed of male participants (83.4% vs 16.6%), metastatic status was prevailing over unresectable tumours (91.2% vs 8.8%), and the majority of patients harboured squamous cell carcinoma histology (73.2% SCC vs 26.8% adenocarcinoma). However, the age distribution of the study population (with only 43.3% ≥ 65 years) is not considered representative and rather reflects the eligibility criteria only allowing patients in good performance status (ECOG PS 0 or 1) and with adequate organ function. Only a small proportion of patients was included with locally advanced/non-metastatic disease (n=66; 8.8%). Even though PD-L1 status did not constitute a stratification factor, the distribution of clinical variables across the trial groups when analysed by CPS score (i.e. ESCC and PD-L1 CPS ≥10, PD-L1 positive tumours) as well as the assessment of baseline characteristics within the ESCC group showed a balanced diversity in treatment arms.

51.1% of all participants had tumours that expressed PD-L1 CPS ≥10. This proportion was balanced between treatment arms (49.9% vs. 52.4% for Pembro+Chemo vs. Chemo, respectively). In KEYNOTE-590, the prevalence in PD-L1 CPS ≥10 was also generally similar between oesophageal squamous cell (52%) and adenocarcinoma (48%) .

In participants with ESCC and PD-L1 CPS ≥10, pembrolizumab as add-on to chemotherapy provided a statistically significant improvement in OS compared with chemotherapy alone (HR: 0.57; 95% CI: 0.43, 0.75; p<0.0001, which is below the p-value crossing boundary of 0.0067 for statistical significance) with a 5 month gain in median OS in the experimental arm relatively to control (13.9 months vs 8.8 months, respectively). A total of 215 events have occurred within this group at this stage, which accounts for a 92.5% of the expected total events assumed at FA. Therefore, data can be considered mature. The subgroup analysis reveals consistency of results across patient pre-specified categories (age, sex, disease status, ECOG score), although a higher magnitude of effect was reached in Asia (OS HR:0.48; 95% CI: 0.35, 0.67) compared to Rest of World (OS HR:0.79; 95% CI: 0.49, 1.28).

Within the entire ESCC group regardless of PD-L1 score, the positive effect of pembrolizumab on OS was attenuated in magnitude but remains statistically significant compared to control (HR: 0.72; 95% CI: 0.60, 0.88; p<0.0006). Variability of response by geographic region (Asia HR: 0.63; 95% CI: 0.49, 0.80; Rest of World HR:0.93; 95% CI: 0.67, 1.28) can be observed and a differential extent of benefit emerges also between sexes, the two geographic regions can be considered numerically adequate for statistical evaluation and well represented although two third of the total ESCC tumours were localised in Asia.

As part of exploratory analyses, the MAH presented efficacy data in the adenocarcinoma subtype. As expected, the majority of cases were localised in Rest of World (83.6% vs 16.4% in Asia); this is the only notable difference in baseline characteristics compared to the ESCC participants. A survival advantage with pembrolizumab was observed also in the adenocarcinoma group, although with a highest degree of variability of response as reflected by a wider CI (HR: 0.74; 95% CI: 0.54, 1.02; p<0.0006 Overall, histology did not appear to be the most relevant driver for a different treatment effect of pembrolizumab. Results for patients with ESCC and adenocarcinoma by PD-L1 status were provided. Interpretation of data is hampered by the limited patient numbers, especially in the smaller subgroup of patients with adenocarcinoma, the fact that these data represent a subgroup analysis of a subgroup and randomization was not stratified for both histology and PD-L1 expression status. OS results for patients with ESCC and

CPS<10 indicated no benefit for the addition of pembrolizumab (OS HR 0.99). In the subgroup of patients with adenocarcinoma, OS data appear not reliable; the OS benefit for adenocarcinoma patients was more pronounced in the PD-L1 CPS <10 than their counterpart CPS ≥10 subpopulation (OS HR 0.66 vs. 0.83) which lacks biological plausibility and is not consistent with literature data for CPI in oesophageal-gastric adenocarcinoma; finally, by analysing the data with one Cox-proportional hazards model fitting two-way interactions of treatment with histology and PD-L1 status instead of performing subgroup analyses, the larger treatment effect for PD-L1 negative patients reverse to smaller treatment effects in comparison to PD-L1 positive patients. Although acknowledging that results of these models need to be interpreted with caution, as they were not pre-specified, the more powerful analysis is reasoned by the fact that all patients are included in this model fit and more covariates can be considered as confounders. The results of this model show homogeneous results in treatment effects for the PD-L1 negative population, meaning that for both histologies patients with CPS<10 have larger OS hazard ratios than patients with CPS≥10. This was also in line with results for PFS and ORR that showed a more pronounced treatment effect for adenocarcinoma patients with CPS≥10 compared to patients with CPS <10.

The analysis of efficacy within the totality of PD-L1 positive tumours including both the squamous and adenocarcinoma subtype showed advantage of pembrolizumab plus chemotherapy vs control in terms of OS (HR: 0.62; 95% CI: 0.49, 0.78; p<0.0001) with a 5 month gain in median OS in the experimental arm relative to control (13.5 months vs 9.4 months, respectively). However, results stratification by histology demonstrated a higher efficacy of pembrolizumab in the squamous histology (HR: 0.57; 95% CI: 0.43, 0.75) compared to adenocarcinoma (HR: 0.83; 95% CI: 0.52, 1.34); the geographic location impacted point estimates favouring Asia (HR: 0.49; 95% CI: 0.35, 0.67) over Rest of World (HR: 0.82; 95% CI: 0.58, 1.16). Similarly to the observation reported for the ESCC group, Asia was the prevailing region within this group (63.3% vs 36.7% in Rest of World).

Efficacy data in complementary CPS<10 tumours have been presented as exploratory analysis. CHMP had highlighted the necessity to account for biomarker status when planning stratification and analyses strategy and emphasised that "at the time of assessment, the magnitude of the effect in the overall population and in both biomarker positive and negative subgroups will be taken into account" (procedure EMEA/H/SA/2437/19/2017/II). Within this category of patients, the CI of overall survival HR crossed 1 (HR: 0.86; 95% CI: 0.68, 1.10) and no gain in median OS was observed (10.5 vs 10.6 months). Overall, data confirm that response is PD-L1-dependent, as previously observed in other indications as well as in the oesophageal second line setting (KEYNOTE-181). Unlike the CPS≥10 population, in the CPS<10 group the effect of the combination pembrolizumab+chemotherapy was overall marginal compared to chemotherapy alone. The OS HR was 0.86 (95% CI: 0.68, 1.10). Median OS (10.5 vs 10.6 months) as well as OS rates at 12 and 18 months (differences 4.8% and 3.9%) were similar between the two treatment groups. Given the biological plausibility of a target-dependent response, the net advantage of pembrolizumab as add-on to chemotherapy does not appear convincing in this patient subgroup that represented a significant proportion (46%) of the ITT population.

In the ITT population encompassing all histologies and PD-L1 status, pembrolizumab demonstrated superiority on OS relative to control (HR: 0.73; 95% CI: 0.62, 0.86; p<0.0001) with a 3 months gain in median OS (12.4 vs 9.8 months in control). With a total of 571 events reported at this IA, the trial reached 91% data maturity (627 events expected at FA). Among the pre-specified subgroup analysis, a different performance for pembrolizumab can be recognised by geographic location (Asia HR:0.64; 95% CI: 0.51, 0.81; Rest of World HR:0.83; 95% CI: 0.66, 1.05), while consistency has been shown across the remaining clinical categories.

In comparing the baseline characteristics between Asia and Rest of World, it emerges a higher prevalence of male participants (90.1% vs 76.1%), squamous cell carcinoma (91.6% vs 52.8%) and tumours with CPS ≥10 (53.4% vs 48.6%) in the former group. However, differences in magnitude of effect by geographic location persists in the individual analysis of the ESCC and CPS ≥10 subcategories. No differences emerged

between geographic area in terms of patient characteristics or study conduct or patient management that could possibly justify the observed better response to treatment in Asians; furthermore, no inadequacy in study recruitment emerged across study centres. In the European population, a non-statistically significant survival advantage of pembrolizumab over control can be observed (HR 0.72; 95% CI 0.47, 1.10; p=ns); hence a favourable trend for efficacy can be concluded upon, although the limited sample size is not expected to provide statistical power. As for all participants, the benefit of pembrolizumab appears to be associated with PD-L1 expression. Median OS and 12 months OS rates are in favour of the chemotherapy group for European patients with CPS <10.

The Investigator-Based PFS Analysis showed superiority of pembrolizumab plus chemotherapy versus chemotherapy alone within the ESCC population (HR:0.65; 95% CI:0.54, 0.78; p<0.0001), PD-L1 positive group (HR:0.51; 95% CI:0.41, 0.65; p<0.0001) and ITT population (HR:0.65; 95% CI:0.55, 0.76; p<0.0001). Unlike OS, PFS results were consistent across all pre-specified patient categories, including geographic location. The BICR-based assessment was overall consistent with local analysis showing advantage of pembrolizumab over control in terms of PFS across the different patient groups, namely the ESCC population (HR:0.71; 95% CI:0.58, 0.87; p<0.0004), PD-L1 positive group (HR:0.60; 95% CI:0.48, 0.75; p<0.0001) and ITT population (HR:0.67; 95% CI:0.56, 0.79; p<0.0001). Among the exploratory analyses, results in patients with CPS<10 showed no clinically meaningful advantage of pembrolizumab + chemotherapy over chemotherapy alone (HR: 0.80; 95% CI: 0.64, 1.01; p=0.02 with a gain of only 0.2 months in PFS median vs control). A beneficial effect was observed in adenocarcinoma patients (HR=0.63, 95% CI: 0.46,0.87; p=0.0019 and gain in 1.4 months in median PFS).

Histology (AC vs ESCC) was one of the stratification factors. In participants with AC, baseline characteristics were generally similar between arms and consistent with the all comer patient population. A higher proportion of patients in the pembrolizumab plus chemotherapy group were ≥65 years of age (50.5% vs 31.4%) in the adenocarcinoma population. As expected, fewer patients with adenocarcinoma were from Asia (16.4%) compared with all participants (52.5%).

For all comer patients, the treatment benefit of pembrolizumab + chemotherapy was similar for patients with adenocarcinoma and patients with squamous carcinoma of the oesophagus.

Overall, patients appeared to benefit from the addition of pembrolizumab regardless of histology; however to enable a complete assessment of efficacy by PD-L1 expression status and histology, the MAH provided also PFS and ORR results for patients with ESCC and adenocarcinoma by PD-L1 status (CPS <10 and CPS ≥10).

PFS and ORR data indicate a trend towards a lower treatment effect in the PD-L1 negative population.

Available study data with checkpoint inhibitors suggest a predictive value of PD-L1 expression status for gastro-esophageal adenocarcinoma (Study ONO-4538-12: Opdivo in metastatic gastric cancer, KEYNOTE-059: Keytruda in ≥3L gastric or GE junction carcinoma, KEYNOTE-061: Keytruda in 2L gastric cancer, study KEYNOTE-181: Keytruda in 2L oesophageal cancer, study KEYNOTE-062: Keytruda in 1L gastric cancer).

The MAH provided analyses intended to disentangle the interaction effects of the Geographic Region, ESCC/AC patients, and PD-L1 positive/negative patients with the treatment effect.

The results of the Cox regression analysis show that there is an interaction effect of treatment with PD-L1.

The results (HR with 95% CIs by subgroup) of the following two models were provided: (i) A model fitting the main factors treatment arm, geographic region, tumour histology, and PD-L1 status together with two-way interaction terms of treatment with one of the three remaining factors, and (ii) a model of treatment, PD-L1, histology, treatment*PDL1, Treatment * Histology, stratified by ECOG and geographic region.

Contrary to the subgroup analyses, patients with CPS≥10 show more beneficial effects from treatment than patients with CPS<10 for both histologies ESCC and adenocarcinoma (estimates for HR 0.86 and 0.87 for SCC and AC, respectively).The beneficial treatment effect for patients with CPS<10 could not be confirmed.

Discordance between Investigator- and BICR-based assessment emerged in the evaluation of ORR. Within the ITT population, ORR (CR+PR) was judged similarly by Investigators (45% vs 29.3% in pembrolizumab and control arm, respectively) and centralised analysis (43.4% vs 29% in pembrolizumab and control arm, respectively). A sensitivity analysis testing PFS results based on BICR-assessment was in agreement with the Investigator-based results.

Available data for patients ≥75 years (n=69; 9% of study population) suggest that these elderly patients do not derive a benefit by the addition of pembrolizumab to chemotherapy (OS HR 0.98, PFS HR 0.93) in the overall study population. A total of 32 patients aged ≥ 75 years for PD-L1 CPS ≥ 10 were enrolled in KEYNOTE 590 (18 in the pembrolizumab combination and 14 in the control). Taking also the considerably worse toxicity profile for patients ≥75 years into account, information about limited efficacy and safety data is included in section 4.4 and 5.1 of the SmPC.

Overall, a trend towards a lower OS benefit was also observed for female subjects (OS HR 0.89 [0.59, 1.35] compared to male subjects (OS HR 0.7 [0.58, 0.84]. For female subjects whose tumours express CPS ≥10, OS HR was 0.67 (n=70; 95% CI 0.39, 1.17). Although conclusions are limited by even smaller numbers in this biomarker selected female subgroups, results are reassuring for female patients with CPS ≥10.

The double blinded nature of the study vs placebo makes interpretation of PRO result unbiased. No differences were observed between treatment arms in the baseline global health status/QoL scores; also, changes from baseline in global health status/QoL scores evaluated at week 18 were similar between pembrolizumab plus chemotherapy (LS mean: -1.74 points [95% CI: -4.24, 0.75]) and chemotherapy alone (LS means of -0.10 points (95% CI: -3.40, 3.20); the variation on this parameter at week 18 can be considered not clinically significant (<-10% cut-off). The OES-18 scores for Dysphagia, Pain and Reflux were all comparable between experimental and control arm.

3.4.4. Conclusions on the clinical efficacy

In KEYNOTE-590, statistically significant OS, PFS and ORR results were demonstrated in the overall study population with oesophageal or gastroesophageal junction carcinoma. In patients whose tumours express PD-L1 CPS<10, although the experimental arm carried a numerical advantage in the OS and PFS HRs compared to the control group (0.86 and 0.80, respectively), no gain in median survivals was achieved with the combined therapy vs chemotherapy alone (10.5 vs 10.6 months for OS and 6.0 vs 6.1 months for PFS, in the experimental and control arm, respectively). A clinically meaningful benefit for the addition of pembrolizumab to chemotherapy could not be shown for subjects whose tumours express PD-L1 CPS <10.

3.5. Clinical safety

Introduction

The safety profile of pembrolizumab in combination with chemotherapy (cisplatin and 5-fluorouracil) for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus and gastroesophageal junction (Siewert type 1) is from the ongoing double-blind placebo-controlled phase 3 study KEYNOTE-590, which is the pivotal for this application. Safety analyses are

presented by treatment group (pembrolizumab/placebo + cisplatin and 5-fluorouracil),using the ASaT population (those who received at least 1 dose of study medication) as of the data cut-off of 02-JUL-2020.

Adverse events (AEs) were coded using MedDRA Version 23.0 and reported according to NCI CTCAE Version 4.03.

In addition, the safety profile of pembrolizumab in combination with chemotherapy observed in KEYNOTE-590 has been compared to the established safety profile for pembrolizumab monotherapy in all approved indications (Reference Safety Dataset, RSD) and in participants with advanced/metastatic oesophageal cancer in ≥2L (KEYNOTE-028 [Cohort A4], KEYNOTE-180, and KEYNOTE-181). The following 4 datasets are thus presented:

Table 28: Safety Datasets

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-590 pembrolizumab + chemotherapy	(N=370): Safety data from participants with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction adenocarcinoma (Siewert type 1) who received pembrolizumab in combination with chemotherapy in KEYNOTE-590.	KN590 Data for MK-3475 + Chemotherapy	Pembrolizumab plus chemotherapy group[1]
KEYNOTE-590 chemotherapy	(N=370): Safety data from participants with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction adenocarcinoma (Siewert type 1) who received placebo in combination with chemotherapy in KEYNOTE-590	KN590 Data for Placebo + Chemotherapy	Chemotherapy group[2]
Pembrolizumab Oesophageal Monotherapy	(N=458): Pooled safety data from participants with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction adenocarcinoma (Siewert type 1) treated with pembrolizumab monotherapy in KEYNOTE-028 (Cohort A4), KEYNOTE-180, and KEYNOTE-181.	Pembrolizumab Oesophageal Monotherapy	Pembrolizumab oesophageal monotherapy group[3]
Pembrolizumab monotherapy reference safety	(N=5884): Pooled safety data from participants treated with pembrolizumab monotherapy, including 2076 participants with advanced melanoma from KEYNOTE-001, -002, -006, and -054; 2022 participants with NSCLC from KEYNOTE-001, -010, -024, and -042; 909 participants with HNSCC from KEYNOTE-012, -040, -048, and -055; 241 participants from HL in KEYNOTE-013 and -087, and 636 participants from bladder cancer in KEYNOTE-045 and -052.	Reference Safety Dataset for MK-3475	Pembrolizumab monotherapy RSD[4]

Abbreviations: HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; N=number; NSCLC=non-small cell lung cancer; RSD=reference safety dataset.
[1] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
[2] Includes all subjects who received at least one dose of chemotherapy in KN590.
[3] Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028.
[4] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010.

Patient exposure

Table 29: Summary of Drug Exposure (ASaT Population)

	KN590 Data for	KN590 Data for	Pooled Oesophageal	Reference Safety

	Pembrolizumab + Chemotherapy[††] (N=370)	Placebo + Chemotherapy[¶¶] (N=370)	Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=458)	Dataset for Pembrolizumab Monotherapy[§§] (N=5884)
Duration On Therapy (month)				
Mean	7.7	5.8	4.1	7.3
Median	5.68	5.11	2.10	4.86
SD	6.84	4.76	5.27	6.79
Range	0.03 to 26.02	0.10 to 26.58	0.03 to 24.38	0.03 to 32.46
Number of cycle				
Mean	11.0	8.5	6.9	11.6
Median	8.00	7.00	4.00	8.00
SD	9.35	6.43	7.97	10.17
Range	1.00 to 35.00	1.00 to 35.00	1.00 to 51.00	1.00 to 59.00

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

[‡‡] Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012-HNSCC, KN013-Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)

Database Cutoff date for Oesophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018, KN590: 02JUL2020)

Table 30: Drug Exposure by Duration (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††] (N=370)			KN590 Data for Placebo + Chemotherapy[¶¶] (N=370)			Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=458)			Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	370	(100.0)	(237.9)	370	(100.0)	(179.8)	458	(100.0)	(157.9)	5,884	(100.0)	(3,555.3)
>=1 m	326	(88.1)	(236.4)	325	(87.8)	(178.5)	349	(76.2)	(154.0)	5,033	(85.5)	(3,527.1)
>=3 m	269	(72.7)	(226.0)	260	(70.3)	(167.3)	182	(39.7)	(128.5)	3,620	(61.5)	(3,291.8)
>=6m	167	(45.1)	(186.9)	131	(35.4)	(117.3)	83	(18.1)	(92.6)	2,612	(44.4)	(2,926.0)
>=12m	79	(21.4)	(126.6)	39	(10.5)	(53.3)	39	(8.5)	(62.0)	1,281	(21.8)	(1,915.3)

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

[‡‡] Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012-HNSCC, KN013-Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)

Database Cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018, KN590: 02JUL2020)

Table 31: Table: Summary of Drug Administration by Regimen Component (ASaT Population)

Number of Cycles	Pembrolizumab + SOC (N = 370)			SOC (N = 370)		
	Pembrolizumab n (%)	Cisplatin n (%)	5-Fluorouracil n (%)	Placebo (Unspecified) n (%)	Cisplatin n (%)	5-Fluorouracil n (%)
>=1	370 (100.0)	369 (99.7)	370 (100.0)	370 (100.0)	370 (100.0)	370 (100.0)
>=2	339 (91.6)	335 (90.5)	337 (91.1)	337 (91.1)	331 (89.5)	333 (90.0)
>=3	321 (86.8)	314 (84.9)	316 (85.4)	317 (85.7)	312 (84.3)	314 (84.9)
>=4	292 (78.9)	282 (76.2)	289 (78.1)	285 (77.0)	274 (74.1)	282 (76.2)
>=5	267 (72.2)	245 (66.2)	262 (70.8)	265 (71.6)	241 (65.1)	260 (70.3)
>=6	240 (64.9)	206 (55.7)	232 (62.7)	235 (63.5)	205 (55.4)	227 (61.4)
>=7	213 (57.6)	0 (0.0)	138 (37.3)	204 (55.1)	0 (0.0)	135 (36.5)
>=8	194 (52.4)	0 (0.0)	126 (34.1)	176 (47.6)	0 (0.0)	116 (31.4)
>=9	175 (47.3)	0 (0.0)	107 (28.9)	139 (37.6)	0 (0.0)	94 (25.4)
>=10	143 (38.6)	0 (0.0)	84 (22.7)	111 (30.0)	0 (0.0)	75 (20.3)
>=11	132 (35.7)	0 (0.0)	74 (20.0)	97 (26.2)	0 (0.0)	68 (18.4)
>=12	116 (31.4)	0 (0.0)	62 (16.8)	86 (23.2)	0 (0.0)	60 (16.2)
>=13	105 (28.4)	0 (0.0)	54 (14.6)	72 (19.5)	0 (0.0)	48 (13.0)
>=14	96 (25.9)	0 (0.0)	50 (13.5)	59 (15.9)	0 (0.0)	36 (9.7)
>=15	88 (23.8)	0 (0.0)	43 (11.6)	53 (14.3)	0 (0.0)	32 (8.6)
>=16	82 (22.2)	0 (0.0)	39 (10.5)	42 (11.4)	0 (0.0)	25 (6.8)
>=17	80 (21.6)	0 (0.0)	38 (10.3)	40 (10.8)	0 (0.0)	23 (6.2)
>=18	76 (20.5)	0 (0.0)	38 (10.3)	35 (9.5)	0 (0.0)	19 (5.1)
>=19	70 (18.9)	0 (0.0)	36 (9.7)	26 (7.0)	0 (0.0)	13 (3.5)
>=20	66 (17.8)	0 (0.0)	33 (8.9)	26 (7.0)	0 (0.0)	12 (3.2)
>=21	57 (15.4)	0 (0.0)	28 (7.6)	21 (5.7)	0 (0.0)	10 (2.7)
>=22	52 (14.1)	0 (0.0)	25 (6.8)	21 (5.7)	0 (0.0)	10 (2.7)
>=23	50 (13.5)	0 (0.0)	24 (6.5)	18 (4.9)	0 (0.0)	8 (2.2)
>=24	48 (13.0)	0 (0.0)	23 (6.2)	17 (4.6)	0 (0.0)	8 (2.2)
>=25	45 (12.2)	0 (0.0)	21 (5.7)	12 (3.2)	0 (0.0)	6 (1.6)
>=26	45 (12.2)	0 (0.0)	19 (5.1)	9 (2.4)	0 (0.0)	5 (1.4)
>=27	41 (11.1)	0 (0.0)	17 (4.6)	8 (2.2)	0 (0.0)	5 (1.4)
>=28	38 (10.3)	0 (0.0)	16 (4.3)	6 (1.6)	0 (0.0)	4 (1.1)
>=29	34 (9.2)	0 (0.0)	16 (4.3)	5 (1.4)	0 (0.0)	4 (1.1)
>=30	30 (8.1)	0 (0.0)	13 (3.5)	5 (1.4)	0 (0.0)	4 (1.1)
>=31	28 (7.6)	0 (0.0)	13 (3.5)	5 (1.4)	0 (0.0)	4 (1.1)
>=32	22 (5.9)	0 (0.0)	9 (2.4)	4 (1.1)	0 (0.0)	3 (0.8)
>=33	18 (4.9)	0 (0.0)	9 (2.4)	4 (1.1)	0 (0.0)	3 (0.8)
>=34	15 (4.1)	0 (0.0)	8 (2.2)	2 (0.5)	0 (0.0)	2 (0.5)
=35	14 (3.8)	0 (0.0)	8 (2.2)	2 (0.5)	0 (0.0)	2 (0.5)
Mean	10.8	4.7	8.0	8.4	4.7	7.1
SD	9.3	1.7	7.2	6.4	1.8	5.4
Median	8.0	6.0	6.0	7.0	6.0	6.0
Range	1 to 35	1 to 6	1 to 35	1 to 35	1 to 6	1 to 35
Database Cutoff Date: 02JUL2020						

Source: [P590V01MK3475: adam-adsl; adexsum]

Table 32: Summary of drug exposure by component (ASaT population)

Number of Cycles	KN590 Data for Pembrolizumab + Chemotherapy†† (N = 370)		KN590 Data for Placebo + Chemotherapy¶¶ (N = 370)	Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡ (N = 458)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N = 5884)
	Cisplatin n (%)	Pembrolizumab n (%)	Cisplatin n (%)	Pembrolizumab n (%)	Pembrolizumab n (%)
>=1	369 (99.7)	370 (100.0)	370 (100.0)	458 (100.0)	5884 (100.0)
>=2	335 (90.5)	339 (91.6)	331 (89.5)	412 (90.0)	4977 (84.6)
>=3	314 (84.9)	321 (86.8)	312 (84.3)	347 (75.8)	4534 (77.1)
>=4	282 (76.2)	292 (78.9)	274 (74.1)	249 (54.4)	3960 (67.3)
>=5	245 (66.2)	267 (72.2)	241 (65.1)	205 (44.8)	3558 (60.5)
>=6	206 (55.7)	240 (64.9)	205 (55.4)	173 (37.8)	3178 (54.0)
>=7	0 (0.00)	213 (57.6)	0 (0.00)	135 (29.5)	2855 (48.5)
Mean	4.7	10.8	4.7	6.9	10.5
SD	1.7	9.3	1.8	7.9	10.4
Median	6.0	8.0	6.0	4.0	6.0
Range	1 to 6	1 to 35	1 to 6	1 to 51	1 to 59

Each subject is counted once on each applicable cycle category row.

†† Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

¶¶ Includes all subjects who received at least one dose of chemotherapy in KN590.

‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028.

§§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012-HNSCC, KN013-Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)

Database Cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018, KN590: 02JUL2020)

Adverse events

Table 33: Adverse Event Summary (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	370	(100.0)	368	(99.5)	437	(95.4)	5,690	(96.7)
with no adverse event	0	(0.0)	2	(0.5)	21	(4.6)	194	(3.3)
with drug-related[†] adverse events	364	(98.4)	360	(97.3)	281	(61.4)	4,132	(70.2)
with toxicity grade 3-5 adverse events	318	(85.9)	308	(83.2)	245	(53.5)	2,829	(48.1)
with toxicity grade 3-5 drug-related adverse events	266	(71.9)	250	(67.6)	80	(17.5)	913	(15.5)
with serious adverse events	205	(55.4)	204	(55.1)	180	(39.3)	2,266	(38.5)
with serious drug-related adverse events	117	(31.6)	97	(26.2)	56	(12.2)	656	(11.1)
who died	28	(7.6)	38	(10.3)	39	(8.5)	312	(5.3)
who died due to a drug-related adverse event	9	(2.4)	5	(1.4)	6	(1.3)	39	(0.7)
discontinued any drug due to an adverse event	90	(24.3)	74	(20.0)	55	(12.0)	790	(13.4)
discontinued Pembrolizumab or placebo	54	(14.6)	45	(12.2)	55	(12.0)	790	(13.4)
discontinued any chemotherapy	75	(20.3)	69	(18.6)	55	(12.0)	790	(13.4)
discontinued all drugs	23	(6.2)	28	(7.6)	55	(12.0)	790	(13.4)
discontinued any drug due to a drug-related adverse event	72	(19.5)	43	(11.6)	27	(5.9)	410	(7.0)
discontinued Pembrolizumab or placebo	35	(9.5)	15	(4.1)	27	(5.9)	410	(7.0)
discontinued any chemotherapy	58	(15.7)	42	(11.4)	27	(5.9)	410	(7.0)
discontinued all drugs	16	(4.3)	10	(2.7)	27	(5.9)	410	(7.0)
discontinued any drug due to a serious adverse event	58	(15.7)	47	(12.7)	44	(9.6)	572	(9.7)
discontinued Pembrolizumab or placebo	47	(12.7)	43	(11.6)	44	(9.6)	572	(9.7)
discontinued any chemotherapy	43	(11.6)	41	(11.1)	44	(9.6)	572	(9.7)
discontinued all drugs	21	(5.7)	27	(7.3)	44	(9.6)	572	(9.7)
discontinued any drug due to a serious drug-related adverse event	38	(10.3)	17	(4.6)	18	(3.9)	245	(4.2)
discontinued Pembrolizumab or placebo	29	(7.8)	14	(3.8)	18	(3.9)	245	(4.2)
discontinued any chemotherapy	25	(6.8)	16	(4.3)	18	(3.9)	245	(4.2)
discontinued all drugs	14	(3.8)	10	(2.7)	18	(3.9)	245	(4.2)

[†] 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.

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

[‡‡] Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012-HNSCC, KN013-Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)

Database Cutoff date for Oesophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018, KN590: 02JUL2020)

Table 34: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (ASaT Population)

	Event Count and Rate (Events/100 person-months)[†]			
	KN590 Data for Pembrolizumab + Chemotherapy[††]	KN590 Data for Placebo + Chemotherapy[¶¶]	Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy[‡‡]	Reference Safety Dataset for Pembrolizumab Monotherapy[§§]
Number of subjects exposed	370	370	458	5884
Total exposure[‡] in person-months	3198.57	2516.83	2340.50	47883.80
Total events (rate)				
adverse events	7383 (230.82)	6733 (267.52)	3421 (146.17)	61600 (128.64)
drug-related[§] adverse events	4661 (145.72)	4167 (165.57)	795 (33.97)	19283 (40.27)
toxicity grade 3-5 adverse events	1141 (35.67)	1105 (43.90)	571 (24.40)	6162 (12.87)
toxicity grade 3-5 drug-related adverse events	722 (22.57)	642 (25.51)	116 (4.96)	1374 (2.87)
serious adverse events	399 (12.47)	379 (15.06)	294 (12.56)	4094 (8.55)
serious drug-related adverse events	179 (5.60)	154 (6.12)	68 (2.91)	916 (1.91)
adverse events leading to death	31 (0.97)	38 (1.51)	39 (1.67)	319 (0.67)
drug-related adverse events leading to death	9 (0.28)	5 (0.20)	6 (0.26)	39 (0.08)
adverse events resulting in drug discontinuation	116 (3.63)	84 (3.34)	55 (2.35)	863 (1.80)
drug-related adverse events resulting in drug discontinuation	89 (2.78)	49 (1.95)	27 (1.15)	448 (0.94)
serious adverse events resulting in drug discontinuation	69 (2.16)	52 (2.07)	44 (1.88)	609 (1.27)
serious drug-related adverse events resulting in drug discontinuation	44 (1.38)	19 (0.75)	18 (0.77)	259 (0.54)

[†] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[‡] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[§] 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.

A pooled safety data from studies of pembrolizumab plus chemotherapy in approved indications (NSCLC: KEYNOTE-021, KEYNOTE-189, and KEYNOTE-407; HNSCC: KEYNOTE-048) is also provided below:

Table 35: Adverse event summary (subjects in ASaT population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]		KN021 + KN048 + KN189 + KN407 Data[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		1,067	
with one or more adverse events	370	(100.0)	368	(99.5)	1,057	(99.1)
with no adverse event	0	(0.0)	2	(0.5)	10	(0.9)
with drug-related[†] adverse events	364	(98.4)	360	(97.3)	1,010	(94.7)
with toxicity grade 3-5 adverse events	318	(85.9)	308	(83.2)	800	(75.0)
with toxicity grade 3-5 drug-related adverse events	266	(71.9)	250	(67.6)	612	(57.4)
with serious adverse events	205	(55.4)	204	(55.1)	576	(54.0)
with serious drug-related adverse events	117	(31.6)	97	(26.2)	328	(30.7)
who died	28	(7.6)	38	(10.3)	96	(9.0)
who died due to a drug-related adverse event	9	(2.4)	5	(1.4)	32	(3.0)
discontinued drug due to an adverse event	90	(24.3)	74	(20.0)	331	(31.0)
discontinued drug due to a drug-related adverse event	72	(19.5)	43	(11.6)	249	(23.3)
discontinued drug due to a serious adverse event	58	(15.7)	47	(12.7)	217	(20.3)
discontinued drug due to a serious drug-related adverse event	38	(10.3)	17	(4.6)	140	(13.1)

[†] 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.
[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.
[§§] Includes all subjects who received at least one dose of Pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189 and KN407.
Database cutoff date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN048: 25FEB2019)
Database cutoff date for Esophageal (KN590: 02JUL2020)

Source: [ISS: adam-adsl; adae]

All adverse events

Table 36: Subjects with adverse events (incidence ≥ 10% in one or more treatment groups) by decreasing frequency of preferred term (ASaT population)

	KN590 Data for	KN590 Data for	Pooled	Reference Safety

	Pembrolizumab + Chemotherapy[††]		Placebo + Chemotherapy[¶¶]		Oesophageal Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	370	(100.0)	368	(99.5)	437	(95.4)	5,690	(96.7)
with no adverse events	0	(0.0)	2	(0.5)	21	(4.6)	194	(3.3)
Nausea	249	(67.3)	232	(62.7)	87	(19.0)	1,213	(20.6)
Anaemia	187	(50.5)	208	(56.2)	77	(16.8)	836	(14.2)
Decreased appetite	164	(44.3)	141	(38.1)	109	(23.8)	1,136	(19.3)
Fatigue	149	(40.3)	126	(34.1)	110	(24.0)	1,884	(32.0)
Constipation	148	(40.0)	149	(40.3)	85	(18.6)	995	(16.9)
Neutrophil count decreased	139	(37.6)	111	(30.0)	4	(0.9)	37	(0.6)
Diarrhoea	135	(36.5)	123	(33.2)	61	(13.3)	1,200	(20.4)
Vomiting	126	(34.1)	117	(31.6)	61	(13.3)	732	(12.4)
Stomatitis	100	(27.0)	95	(25.7)	10	(2.2)	144	(2.4)
Neutropenia	97	(26.2)	90	(24.3)	0	(0.0)	49	(0.8)
White blood cell count decreased	97	(26.2)	69	(18.6)	4	(0.9)	57	(1.0)
Weight decreased	87	(23.5)	90	(24.3)	49	(10.7)	561	(9.5)
Blood creatinine increased	79	(21.4)	78	(21.1)	15	(3.3)	256	(4.4)
Hyponatraemia	68	(18.4)	77	(20.8)	26	(5.7)	345	(5.9)
Hypokalaemia	67	(18.1)	71	(19.2)	25	(5.5)	270	(4.6)
Platelet count decreased	62	(16.8)	62	(16.8)	9	(2.0)	73	(1.2)
Asthenia	60	(16.2)	45	(12.2)	55	(12.0)	666	(11.3)
Dysphagia	60	(16.2)	63	(17.0)	60	(13.1)	174	(3.0)
Cough	59	(15.9)	56	(15.1)	65	(14.2)	1,148	(19.5)
Mucosal inflammation	59	(15.9)	68	(18.4)	7	(1.5)	92	(1.6)
Hiccups	56	(15.1)	53	(14.3)	5	(1.1)	25	(0.4)
Alopecia	55	(14.9)	39	(10.5)	4	(0.9)	87	(1.5)
Pyrexia	55	(14.9)	44	(11.9)	45	(9.8)	746	(12.7)
Pneumonia	54	(14.6)	52	(14.1)	49	(10.7)	433	(7.4)
Insomnia	49	(13.2)	44	(11.9)	36	(7.9)	429	(7.3)
Malaise	48	(13.0)	43	(11.6)	22	(4.8)	115	(2.0)
Rash	44	(11.9)	26	(7.0)	32	(7.0)	904	(15.4)
Hypothyroidism	40	(10.8)	24	(6.5)	49	(10.7)	651	(11.1)
Dysgeusia	38	(10.3)	32	(8.6)	10	(2.2)	110	(1.9)
Neuropathy peripheral	37	(10.0)	37	(10.0)	13	(2.8)	116	(2.0)
Dyspnoea	36	(9.7)	30	(8.1)	48	(10.5)	989	(16.8)
Hypoalbuminaemia	35	(9.5)	49	(13.2)	20	(4.4)	187	(3.2)
Pruritus	31	(8.4)	12	(3.2)	38	(8.3)	1,060	(18.0)
Headache	30	(8.1)	25	(6.8)	23	(5.0)	711	(12.1)
Thrombocytopenia	28	(7.6)	37	(10.0)	5	(1.1)	89	(1.5)
Abdominal pain	27	(7.3)	20	(5.4)	48	(10.5)	480	(8.2)
Back pain	26	(7.0)	31	(8.4)	50	(10.9)	662	(11.3)
Arthralgia	22	(5.9)	10	(2.7)	24	(5.2)	851	(14.5)

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

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

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

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

Table 37: Exposure-adjusted adverse events by observation period (including multiple occurrences of events) (incidence ≥10% in one or more treatment groups) (ASaT population)

Observation period of drug exposure	Event Count and Rate (Events/100 person-months) †							
	Pembrolizumab + SOC				SOC			
	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of subjects exposed‡	370	302	210	85	370	295	190	45
Total exposure§ person-months	1029.73	762.13	773.55	633.17	1022.83	715.99	569.80	208.21
Total events (rate)	2956(287.07)	1015(133.18)	373(48.22)	177(27.95)	2760(269.84)	951(132.82)	337(59.14)	80(38.42)
AE Category								
Blood and lymphatic system disorders	339(31.1)	146(46.9)	37(21.2)	14(24.2)	354(33.1)	133(41.4)	40(20.3)	19(26.6)
Anaemia	180(31.8)	67(33.5)	30(21.9)	11(23.3)	200(33.3)	70(35.9)	26(19.4)	13(43.4)
Neutropenia	130(32.6)	60(83.5)	3(45.0)	0(0)	124(35.3)	41(47.9)	11(26.5)	4(12.6)
Thrombocytopenia	29(23.1)	19(48.7)	4(13.0)	3(28.6)	30(25.4)	22(53.5)	3(13.6)	2(20.3)
Endocrine disorders	13(10.6)	14(18.9)	16(30.7)	3(31.6)	15(23.8)	6(24.9)	6(45.6)	0(0)
Hypothyroidism	13(10.6)	14(18.9)	16(30.7)	3(31.6)	15(23.8)	6(24.9)	6(45.6)	0(0)
Gastrointestinal disorders	1015(43.3)	276(33.6)	115(18.2)	62(25.6)	958(45.4)	249(35.0)	110(27.4)	28(30.7)
Constipation	156(41.0)	49(31.9)	23(19.8)	10(29.9)	157(52.3)	35(36.3)	13(23.5)	4(22.8)
Diarrhoea	144(34.5)	42(21.3)	30(18.1)	17(23.0)	138(47.4)	31(29.6)	14(20.1)	8(27.0)
Dysphagia	34(19.6)	13(11.9)	17(16.8)	12(28.2)	27(14.0)	24(20.0)	24(27.9)	4(39.5)
Nausea	384(51.1)	94(43.2)	26(15.0)	18(28.3)	383(50.3)	94(47.5)	29(33.6)	4(29.3)
Stomatitis	126(53.2)	31(59.5)	5(20.7)	2(16.2)	120(60.0)	10(13.2)	14(20.2)	6(30.8)
Vomiting	171(44.4)	47(51.0)	14(27.4)	3(18.3)	133(36.4)	55(46.7)	16(46.2)	2(229.5)
General disorders and administration site conditions	393(36.9)	123(29.6)	56(17.0)	32(25.7)	338(39.3)	108(36.3)	46(30.0)	11(33.6)
Asthenia	55(25.3)	17(14.3)	17(11.7)	16(20.3)	45(33.8)	17(35.6)	7(30.0)	3(33.3)
Fatigue	159(42.4)	48(39.6)	14(18.6)	8(36.9)	143(48.9)	29(38.0)	13(30.8)	2(26.0)
Malaise	56(45.7)	18(56.7)	3(42.9)	1(35.9)	42(39.0)	19(60.6)	1(7.8)	2(77.5)
Mucosal inflammation	81(44.6)	21(32.3)	9(20.0)	3(20.7)	75(36.3)	23(25.3)	20(35.1)	2(21.1)
Pyrexia	42(24.8)	19(24.2)	13(22.7)	4(58.8)	33(27.2)	20(39.3)	5(27.5)	2(50.9)
Infections and infestations	23(15.9)	22(32.9)	6(10.4)	8(22.5)	17(11.8)	26(33.2)	14(34.2)	2(24.2)
Pneumonia	23(15.9)	22(32.9)	6(10.4)	8(22.5)	17(11.8)	26(33.2)	14(34.2)	2(24.2)
Investigations	527(32.3)	224(49.0)	55(22.3)	23(29.0)	477(33.0)	214(55.1)	39(35.7)	6(44.3)
Blood creatinine increased	66(23.7)	38(29.9)	18(20.2)	9(22.6)	67(30.3)	36(41.4)	8(18.8)	5(42.7)
Neutrophil count decreased	187(34.4)	80(75.1)	10(24.1)	4(27.7)	163(34.6)	71(72.2)	8(49.5)	0(0)
Platelet count decreased	60(27.4)	38(61.9)	5(25.9)	1(25.4)	76(34.4)	29(58.0)	4(40.9)	0(0)
Weight decreased	71(44.1)	15(31.2)	6(15.9)	4(55.1)	61(27.2)	35(37.4)	14(41.6)	1(54.6)
White blood cell count decreased	143(33.4)	53(46.6)	16(27.5)	5(36.4)	110(36.0)	43(72.2)	5(71.2)	0(0)
Metabolism and nutrition disorders	365(38.9)	123(41.1)	44(24.0)	13(18.9)	342(35.3)	138(40.0)	49(29.9)	10(28.2)
Decreased appetite	207(46.7)	52(39.7)	19(21.3)	7(34.5)	168(42.5)	48(33.4)	24(31.2)	5(34.8)
Hypoalbuminaemia	22(23.6)	17(47.1)	4(35.4)	1(21.6)	36(26.1)	21(35.6)	8(25.7)	2(17.7)
Hypokalaemia	72(34.2)	30(47.9)	9(29.0)	2(9.8)	71(32.1)	35(54.7)	5(15.9)	3(30.7)
Hyponatraemia	64(33.4)	24(34.6)	12(23.0)	3(12.8)	67(31.4)	34(43.2)	12(49.1)	0(0)
Nervous system disorders	47(29.8)	26(34.9)	11(40.3)	2(69.6)	43(27.7)	24(35.6)	10(45.1)	1(15.1)
Dysgeusia	35(54.0)	7(53.2)	1(6.8)	2(69.6)	32(72.6)	3(83.7)	0(0)	0(0)
Neuropathy peripheral	12(12.9)	19(30.9)	10(80.1)	0(0)	11(9.9)	21(32.9)	10(45.1)	1(15.1)
Psychiatric disorders	41(40.5)	6(12.9)	11(34.0)	1(13.5)	40(41.3)	11(38.9)	4(39.6)	1(27.7)
Insomnia	41(40.5)	6(12.9)	11(34.0)	1(13.5)	40(41.3)	11(38.9)	4(39.6)	1(27.7)
Respiratory, thoracic and mediastinal disorders	117(38.5)	35(30.4)	13(11.6)	13(30.0)	118(45.1)	33(39.3)	13(32.8)	2(33.2)
Cough	37(25.9)	17(24.7)	6(8.2)	9(30.7)	35(27.9)	17(30.8)	10(29.6)	2(33.2)
Hiccups	80(49.7)	18(39.0)	7(18.0)	4(28.7)	83(60.9)	16(55.6)	3(51.3)	0(0)
Skin and subcutaneous tissue disorders	76(43.7)	20(26.7)	9(12.0)	6(25.7)	58(49.3)	9(31.0)	6(30.8)	0(0)
Alopecia	53(96.7)	2(230.8)	0(0)	0(0)	34(61.8)	6(105.5)	0(0)	0(0)
Rash	23(19.3)	18(24.3)	9(12.0)	6(25.7)	24(38.4)	3(12.8)	6(30.8)	0(0)

† Event rate per 100 person-month of exposure=event count *100/person-month of exposure.
‡ Number of subjects exposed to drug at the start of indicated time interval.
§ Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 02JUL2020

Drug-related adverse events

Table 38: Subjects with drug-related adverse events (incidence ≥ 5% in one or more treatment groups) by decreasing frequency of preferred term (ASaT population)

	KN590 Data for Pembrolizumab + Chemotherapy††	KN590 Data for Placebo + Chemotherapy¶¶	Pooled Oesophageal Safety Dataset for Pembrolizumab	Reference Safety Dataset for Pembrolizumab Monotherapy§§

					Monotherapy‡‡			
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	364	(98.4)	360	(97.3)	281	(61.4)	4,132	(70.2)
with no adverse events	6	(1.6)	10	(2.7)	177	(38.6)	1,752	(29.8)
Nausea	233	(63.0)	220	(59.5)	25	(5.5)	535	(9.1)
Decreased appetite	145	(39.2)	119	(32.2)	32	(7.0)	461	(7.8)
Anaemia	143	(38.6)	162	(43.8)	9	(2.0)	202	(3.4)
Fatigue	135	(36.5)	107	(28.9)	50	(10.9)	1,170	(19.9)
Neutrophil count decreased	135	(36.5)	109	(29.5)	3	(0.7)	26	(0.4)
Vomiting	110	(29.7)	99	(26.8)	11	(2.4)	198	(3.4)
Diarrhoea	97	(26.2)	85	(23.0)	24	(5.2)	630	(10.7)
Neutropenia	96	(25.9)	88	(23.8)	0	(0.0)	30	(0.5)
Stomatitis	96	(25.9)	93	(25.1)	5	(1.1)	71	(1.2)
White blood cell count decreased	89	(24.1)	69	(18.6)	3	(0.7)	28	(0.5)
Blood creatinine increased	67	(18.1)	70	(18.9)	6	(1.3)	68	(1.2)
Platelet count decreased	61	(16.5)	56	(15.1)	3	(0.7)	32	(0.5)
Mucosal inflammation	59	(15.9)	65	(17.6)	2	(0.4)	48	(0.8)
Alopecia	51	(13.8)	39	(10.5)	2	(0.4)	46	(0.8)
Constipation	50	(13.5)	63	(17.0)	6	(1.3)	155	(2.6)
Asthenia	45	(12.2)	35	(9.5)	26	(5.7)	363	(6.2)
Malaise	43	(11.6)	39	(10.5)	12	(2.6)	45	(0.8)
Weight decreased	43	(11.6)	47	(12.7)	2	(0.4)	137	(2.3)
Hiccups	40	(10.8)	33	(8.9)	0	(0.0)	9	(0.2)
Hypothyroidism	38	(10.3)	22	(5.9)	42	(9.2)	565	(9.6)
Dysgeusia	34	(9.2)	32	(8.6)	3	(0.7)	60	(1.0)
Hypokalaemia	34	(9.2)	41	(11.1)	0	(0.0)	36	(0.6)
Peripheral sensory neuropathy	34	(9.2)	29	(7.8)	1	(0.2)	29	(0.5)
Tinnitus	33	(8.9)	25	(6.8)	1	(0.2)	5	(0.1)
Hyponatraemia	32	(8.6)	40	(10.8)	6	(1.3)	59	(1.0)
Neuropathy peripheral	32	(8.6)	32	(8.6)	4	(0.9)	41	(0.7)
Rash	29	(7.8)	18	(4.9)	24	(5.2)	676	(11.5)
Thrombocytopenia	25	(6.8)	33	(8.9)	1	(0.2)	41	(0.7)
Leukopenia	24	(6.5)	28	(7.6)	0	(0.0)	29	(0.5)
Pruritus	23	(6.2)	8	(2.2)	23	(5.0)	836	(14.2)
Hypomagnesaemia	21	(5.7)	14	(3.8)	0	(0.0)	32	(0.5)
Lymphocyte count decreased	21	(5.7)	20	(5.4)	7	(1.5)	47	(0.8)
Dehydration	20	(5.4)	16	(4.3)	3	(0.7)	33	(0.6)
Pneumonitis	20	(5.4)	0	(0.0)	21	(4.6)	223	(3.8)
Hyperthyroidism	19	(5.1)	2	(0.5)	15	(3.3)	219	(3.7)
Aspartate aminotransferase increased	18	(4.9)	19	(5.1)	18	(3.9)	220	(3.7)
Arthralgia	11	(3.0)	4	(1.1)	10	(2.2)	437	(7.4)

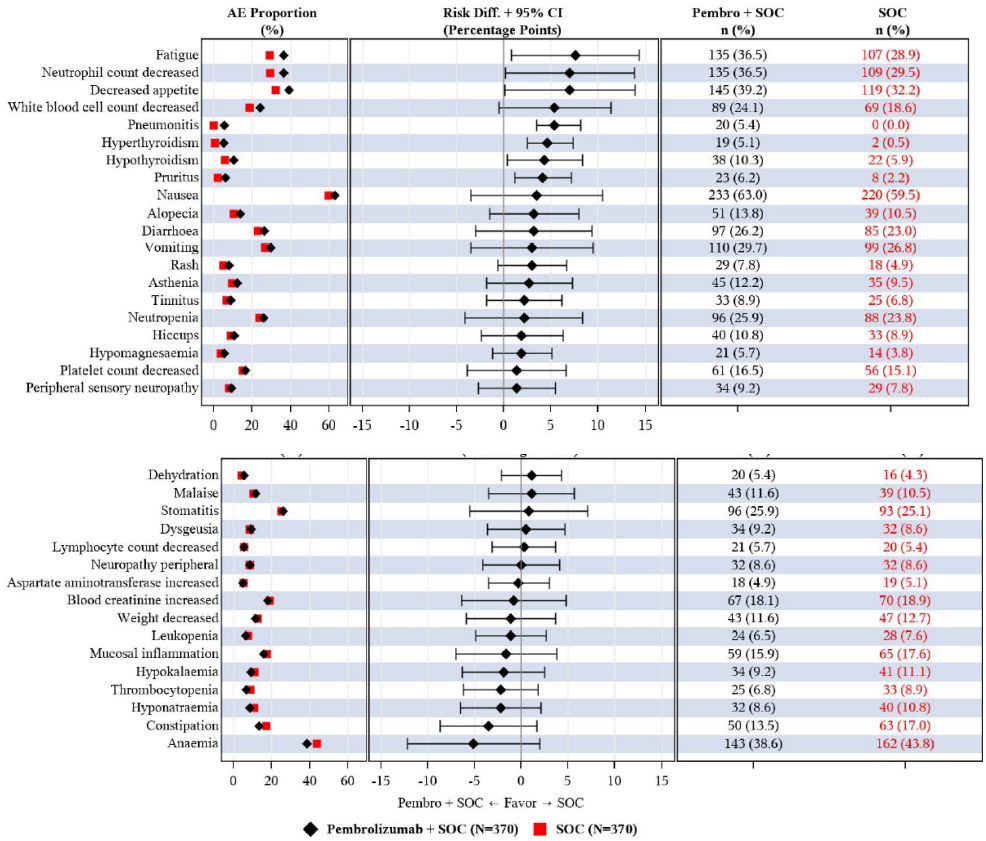


Figure 21: Between-treatment Comparisons in Drug-related Adverse Events Selected Adverse Events (>=5% Incidence) and Sorted by Risk Difference (ASaT Population)

All Grade 3 to 5 Adverse Events

Table 39: Subjects With Adverse Events by Maximum Toxicity Grade (extract)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	370	(100.0)	368	(99.5)	437	(95.4)	5,690	(96.7)
Grade 1	7	(1.9)	3	(0.8)	58	(12.7)	757	(12.9)
Grade 2	45	(12.2)	57	(15.4)	134	(29.3)	2,104	(35.8)
Grade 3	219	(59.2)	210	(56.8)	174	(38.0)	2,165	(36.8)
Grade 4	71	(19.2)	60	(16.2)	32	(7.0)	353	(6.0)
Grade 5	28	(7.6)	38	(10.3)	39	(8.5)	311	(5.3)
with no adverse events	0	(0.0)	2	(0.5)	21	(4.6)	194	(3.3)

Table 40: Subjects With Grade 3-5 Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	318	(85.9)	308	(83.2)	245	(53.5)	2,829	(48.1)

with no adverse events	52	(14.1)	62	(16.8)	213	(46.5)	3,055	(51.9)
Neutrophil count decreased	89	(24.1)	64	(17.3)	2	(0.4)	8	(0.1)
Anaemia	63	(17.0)	81	(21.9)	31	(6.8)	233	(4.0)
Neutropenia	54	(14.6)	61	(16.5)	0	(0.0)	15	(0.3)
Hyponatraemia	45	(12.2)	41	(11.1)	11	(2.4)	153	(2.6)
Pneumonia	35	(9.5)	35	(9.5)	31	(6.8)	242	(4.1)
White blood cell count decreased	34	(9.2)	18	(4.9)	1	(0.2)	4	(0.1)
Dysphagia	29	(7.8)	26	(7.0)	20	(4.4)	30	(0.5)
Fatigue	29	(7.8)	25	(6.8)	9	(2.0)	144	(2.4)
Nausea	27	(7.3)	26	(7.0)	5	(1.1)	50	(0.8)
Vomiting	27	(7.3)	20	(5.4)	6	(1.3)	42	(0.7)
Hypokalaemia	24	(6.5)	32	(8.6)	4	(0.9)	58	(1.0)
Stomatitis	21	(5.7)	14	(3.8)	0	(0.0)	9	(0.2)
Decreased appetite	15	(4.1)	20	(5.4)	15	(3.3)	74	(1.3)
Weight decreased	11	(3.0)	19	(5.1)	6	(1.3)	30	(0.5)
Platelet count decreased	7	(1.9)	20	(5.4)	1	(0.2)	8	(0.1)

Table 41: Exposure-Adjusted Grade 3-5 Adverse Events (Including Multiple Occurrences of Events) (Incidence ≥5% in One or More Treatment Groups) (ASaT Population)

	Event Count and Rate (Events/100 person-year) [†]	
	Pembrolizumab + SOC	SOC
Number of Subjects exposed[‡]	370	370
Total exposure[§] person-years	266.55	209.74
Total events (rate)	653(244.98)	616(293.70)
AE Category		
Blood and lymphatic system disorders	153(57.4)	181(86.3)
Anaemia	70(26.3)	96(45.8)
Neutropenia	83(31.1)	85(40.5)
Gastrointestinal disorders	118(44.3)	92(43.9)
Dysphagia	33(12.4)	28(13.4)
Nausea	30(11.3)	27(12.9)
Stomatitis	22(8.3)	16(7.6)
Vomiting	33(12.4)	21(10.0)
General disorders and administration site conditions	33(12.4)	31(14.8)
Fatigue	33(12.4)	31(14.8)
Infections and infestations	37(13.9)	39(18.6)
Pneumonia	37(13.9)	39(18.6)
Investigations	211(79.2)	156(74.4)
Neutrophil count decreased	145(54.4)	93(44.3)
Platelet count decreased	7(2.6)	23(11.0)
Weight decreased	11(4.1)	19(9.1)
White blood cell count decreased	48(18.0)	21(10.0)
Metabolism and nutrition disorders	101(37.9)	117(55.8)
Decreased appetite	15(5.6)	25(11.9)
Hypokalaemia	32(12.0)	41(19.6)
Hyponatraemia	54(20.3)	51(24.3)

[†] Event rate per 100 person-year of exposure=event count *100/person-year of exposure.
[‡] Number of subjects exposed to drug at the start of indicated time interval.
[§] Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.
Grades are based on NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 02JUL2020

Adverse Drug Reactions

The MAH has updated section 4.8 of the SmPC to include the population of Oesophageal Cancer patients receiving Keytruda in combination with chemotherapy (study KEYNOTE-590) into the current chemotherapy combination Reference Safety Dataset which includes all chemotherapy combination indications approved in the EU. Table below serves as support for the updates made to SmPC Section 4.8.

Adverse Reactions in Patients Treated with Pembrolizumab in Combination with Chemotherapy

		Combination Therapy (N=1437)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Very common	Pneumonia	13.4% (193)	124
Blood and lymphatic system disorders			
Very common	Anaemia	51.1% (735)	267
Very common	Neutropenia	29.2% (420)	237
Very common	Thrombocytopenia	19.4% (279)	92
Common	Febrile neutropenia	5.8% (83)	82
Common	Leukopenia	7.9% (113)	39
Common	Lymphopenia	1.7% (25)	8
Uncommon	Eosinophilia	0.3% (4)	1
Immune system disorders			
Common	Infusion Reactions[a]	2.9% (42)	10
Endocrine disorders			
Very common	hypothyroidism	11.5% (165)	3
Common	Hyperthyroidism[b]	5.4% (78)	2
Uncommon	Hypophysitis[c]	0.8% (11)	4
Uncommon	Adrenal Insufficiency[d]	0.6% (9)	4
Uncommon	Thyroiditis[e]	0.4% (6)	1
Metabolism and nutrition disorders			
Very common	Hyponatraemia	10.5% (151)	89
Very common	Hypokalaemia	13.0% (187)	64
Very common	Decreased appetite	33.6% (483)	42
Common	Hypocalcaemia	5.5% (79)	15
Uncommon	Type 1 Diabetes Mellitus	0.2% (3)	3
Psychiatric disorders			
Very common	Insomnia	11.0% (158)	0
Nervous system disorders			
Very common	Dizziness	11.9% (171)	5
Very common	Neuropathy peripheral	10.7% (154)	4
Very common	Headache	11.9% (171)	3
Common	Dysgeusia	9.1% (131)	1
Common	Lethargy	1.7% (25)	0
Uncommon	Encephalitis	0.1% (2)	2
Uncommon	Epilepsy	0.3% (5)	2
Rare	Guillain-Barre Syndrome	0.07% (1)	1
Eye disorders			
Common	Dry eye	3.2% (46)	0
Cardiac disorders			
Common	cardiac arrhythmia (including atrial fibrillation)[f]	4.0% (58)	18
Uncommon	Myocarditis[g]	0.1% (2)	2
Uncommon	Pericardial effusion	0.3% (4)	2
Rare	Pericarditis	0.07% (1)	1
Vascular disorders			
Common	Hypertension	6.6% (95)	41
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	16.5% (237)	36
Very common	Cough	20.9% (300)	4
Common	Pneumonitis[h]	6.0% (86)	36
Gastrointestinal disorders			
Very common	Nausea	54.9% (789)	63
Very common	Diarrhoea	33.1% (476)	60
Very common	Vomiting	28.2% (405)	56
Very common	abdominal pain[i]	13.6% (195)	13
Very common	Constipation	36.7% (527)	6
Common	Colitis[j]	3.1% (44)	22

Common	Dry mouth	4.7% (68)	1
Uncommon	Pancreatitis[k]	0.4% (6)	3
Uncommon	gastrointestinal ulceration[l]	0.4% (6)	1
Hepatobiliary disorders			
Common	Hepatitis[m]	1.3% (19)	18
Skin and subcutaneous tissue disorders			
Very common	rash[n]	20.8% (299)	3
Very common	Alopecia	17.3% (248)	1
Very common	pruritus[o]	13.9% (200)	1
Common	Severe Skin Reactions[p]	1.7% (25)	23
Common	Dry skin	5.6% (81)	0
Common	Erythema	3.7% (53)	0
Common	Dermatitis	1.0% (15)	0
Uncommon	Psoriasis	0.8% (11)	3
Uncommon	vitiligo[q]	0.8% (12)	0
Uncommon	Eczema	0.7% (10)	0
Uncommon	Dermatitis acneiform	0.6% (9)	0
Uncommon	Papule	0.1% (2)	0
Uncommon	lichenoid keratosis	0.1% (2)	0
Rare	Hair colour changes	0.07% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[r]	18.5% (266)	18
Very common	Arthralgia	12.2% (176)	9
Common	myositis[s]	6.4% (92)	6
Common	Pain in extremity	7.1% (102)	1
Common	arthritis[t]	2.2% (31)	0
Uncommon	tenosynovitis[u]	0.3% (5)	1
Renal and urinary disorders			
Common	Acute kidney injury	5.6% (81)	31
Uncommon	Nephritis[v]	0.9% (13)	8

General disorders and administration site conditions			
Very common	Fatigue	39.1% (562)	99
Very common	Asthenia	18.1% (260)	58
Very common	Pyrexia	17.0% (245)	7
Very common	oedema[w]	17.0% (244)	6
Common	Influenza like illness	2.5% (36)	0
Common	Chills	2.2% (31)	0
Investigations			
Very common	Blood creatinine increased	15.3% (220)	12
Common	Aspartate aminotransferase increased	9.2% (132)	15
Common	Hypercalcaemia	2.8% (40)	13
Common	Alanine aminotransferase increased	9.5% (137)	12
Common	Blood alkaline phosphatase increased	3.8% (54)	3
Common	Blood bilirubin increased	1.3% (18)	1

Uncommon	Amylase increased	0.6% (8)	3

Every subject is counted a single time for each applicable row.
a. Infusion Reactions (anaphylactic reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, infusion related reaction)
b. Hyperthyroidism (basedow's disease, hyperthyroidism)
c. Hypophysitis (hypophysitis, hypopituitarism)
d. Adrenal Insufficiency (addison's disease, adrenal insufficiency)
e. Thyroiditis (autoimmune thyroiditis, thyroiditis)
f. cardiac arrhythmia (including atrial fibrillation) (arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, atrioventricular block second degree, electrocardiogram qt prolonged, extrasystoles, heart rate irregular, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, ventricular arrhythmia, ventricular extrasystoles)
g. Myocarditis (autoimmune myocarditis, myocarditis)
h. Pneumonitis (interstitial lung disease, pneumonitis)
i. abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper)
j. Colitis (autoimmune colitis, colitis, colitis microscopic, enterocolitis)
k. Pancreatitis (pancreatitis, pancreatitis acute)
l. gastrointestinal ulceration (duodenal ulcer, gastric ulcer)
m. Hepatitis (autoimmune hepatitis, hepatitis, immune-mediated hepatitis)
n. rash (genital rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular)
o. pruritus (pruritus, urticaria)
p. Severe Skin Reactions (dermatitis bullous, dermatitis exfoliative generalised, pruritus, rash, rash maculo-papular, rash pruritic, toxic skin eruption)
q. vitiligo (skin hypopigmentation, vitiligo)
r. musculoskeletal pain (back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness)
s. myositis (myalgia, myopathy, polymyalgia rheumatica)
t. arthritis (arthritis, joint effusion, joint swelling, polyarthritis)
u. tenosynovitis (synovitis, tendonitis, tenosynovitis)
v. Nephritis (autoimmune nephritis, nephritis, tubulointerstitial nephritis)
w. oedema (eyelid oedema, face oedema, fluid retention, generalised oedema, lip oedema, localised oedema, oedema, oedema peripheral, periorbital oedema)
Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN407 and KN590.
Database cutoff date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN048: 25FEB2019)
Database Cutoff date for Esophageal (KN590: 02JUL2020)

Serious adverse event/deaths/other significant events

Serious adverse events

Table 42: Subjects with serious adverse events up to 90 days of last dose by decreasing incidence in KEYNOTE-590 (incidence ≥2% in one or more treatment groups) (ASaT population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more serious adverse events	205	(55.4)	204	(55.1)
with no serious adverse events	165	(44.6)	166	(44.9)
Pneumonia	38	(10.3)	32	(8.6)
Dysphagia	17	(4.6)	13	(3.5)
Pneumonitis	12	(3.2)	0	(0.0)
Acute kidney injury	11	(3.0)	6	(1.6)
Pneumonia aspiration	11	(3.0)	7	(1.9)
Febrile neutropenia	9	(2.4)	13	(3.5)
Vomiting	9	(2.4)	6	(1.6)
Dehydration	6	(1.6)	8	(2.2)
Platelet count decreased	5	(1.4)	10	(2.7)
Anaemia	3	(0.8)	10	(2.7)

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 02JUL2020

Table 43: Subjects with serious adverse events up to 90 days of last dose (incidence ≥ 5% in one or more treatment groups) by decreasing frequency of preferred term (ASaT population)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	205	(55.4)	204	(55.1)	180	(39.3)	2,266	(38.5)
with no adverse events	165	(44.6)	166	(44.9)	278	(60.7)	3,618	(61.5)
Pneumonia	38	(10.3)	32	(8.6)	30	(6.6)	246	(4.2)

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

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

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

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

Table 44: Subjects With <u>Drug-related</u> Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	117	(31.6)	97	(26.2)	56	(12.2)	656	(11.1)
with no adverse events	253	(68.4)	273	(73.8)	402	(87.8)	5,228	(88.9)

The most frequently reported drug-related SAEs (≥2%) in the pembrolizumab plus chemotherapy group and the chemotherapy group of KN590 study were: pneumonia (3.5% vs 0.8%), pneumonitis (3.2% vs 0.0%), febrile neutropenia (2.4% vs 3.2%), acute kidney injury (2.2% vs 1.4%), vomiting (2.2% vs 1.6%), and platelet count decreased (1.4% vs 2.2%).

<u>Deaths Due to Adverse Events</u>

Table 45: Subjects With Adverse Events Resulting in Death Up to 90 Days of Last Dose (Incidence > 0% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population) (extract)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	28	(7.6)	38	(10.3)	39	(8.5)	312	(5.3)
with no adverse events	342	(92.4)	332	(89.7)	419	(91.5)	5,572	(94.7)
Pneumonia	6	(1.6)	10	(2.7)	4	(0.9)	36	(0.6)
Pneumonia aspiration	3	(0.8)	2	(0.5)	6	(1.3)	8	(0.1)
Pulmonary sepsis	3	(0.8)	0	(0.0)	0	(0.0)	2	(0.0)

Death	2	(0.5)	7	(1.9)	5	(1.1)	42	(0.7)
Acute kidney injury	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.1)
Acute myocardial infarction	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Acute respiratory failure	1	(0.3)	1	(0.3)	1	(0.2)	5	(0.1)
COVID-19	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cardio-respiratory arrest	1	(0.3)	0	(0.0)	1	(0.2)	4	(0.1)
Clostridium difficile colitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Febrile neutropenia	1	(0.3)	1	(0.3)	0	(0.0)	1	(0.0)
Hepatic failure	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.1)
Interstitial lung disease	1	(0.3)	1	(0.3)	0	(0.0)	1	(0.0)
Multiple organ dysfunction syndrome	1	(0.3)	1	(0.3)	0	(0.0)	5	(0.1)
Oesophageal fistula	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Oesophagobronchial fistula	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(0.3)	0	(0.0)	3	(0.7)	8	(0.1)
Pulmonary embolism	1	(0.3)	0	(0.0)	0	(0.0)	10	(0.2)
Sudden cardiac death	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Upper gastrointestinal haemorrhage	1	(0.3)	2	(0.5)	0	(0.0)	1	(0.0)
Aspiration	0	(0.0)	1	(0.3)	0	(0.0)	3	(0.1)
Cardiac arrest	0	(0.0)	2	(0.5)	0	(0.0)	9	(0.2)
Cerebral haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Cerebrovascular accident	0	(0.0)	1	(0.3)	2	(0.4)	5	(0.1)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.3)	2	(0.4)	0	(0.0)
Haematemesis	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	1	(0.3)	0	(0.0)	17	(0.3)
Sepsis	0	(0.0)	3	(0.8)	1	(0.2)	9	(0.2)
Tracheal haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)

NOTE: The PT "death" was reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term in a participant with comorbidities and confounding factors that led to death.

Adverse event of special interest (AEOSI)

AEOSI are immune-related events and IRRs associated with pembrolizumab (list of MK-3475 AEOSI Preferred Terms Version 18, 05-MAY-2020).

Table 46: Adverse Event Summary for AEOSI (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	95	(25.7)	43	(11.6)	106	(23.1)	1,474	(25.1)
with no adverse event	275	(74.3)	327	(88.4)	352	(76.9)	4,410	(74.9)
with drug-related[†] adverse events	91	(24.6)	35	(9.5)	95	(20.7)	1,281	(21.8)
with toxicity grade 3-5 adverse events	26	(7.0)	8	(2.2)	27	(5.9)	381	(6.5)
with toxicity grade 3-5 drug-related adverse events	25	(6.8)	6	(1.6)	26	(5.7)	331	(5.6)
with serious adverse events	30	(8.1)	7	(1.9)	29	(6.3)	381	(6.5)
with serious drug-related adverse events	28	(7.6)	5	(1.4)	27	(5.9)	337	(5.7)
who died	2	(0.5)	1	(0.3)	4	(0.9)	11	(0.2)
who died due to a drug-related adverse event	2	(0.5)	1	(0.3)	4	(0.9)	11	(0.2)
discontinued any drug due to an adverse event	16	(4.3)	2	(0.5)	19	(4.1)	232	(3.9)
discontinued Pembrolizumab or placebo	14	(3.8)	2	(0.5)	19	(4.1)	232	(3.9)
discontinued any chemotherapy	6	(1.6)	1	(0.3)	19	(4.1)	232	(3.9)
discontinued all drugs	3	(0.8)	0	(0.0)	19	(4.1)	232	(3.9)
discontinued any drug due to a drug-related adverse event	16	(4.3)	2	(0.5)	19	(4.1)	228	(3.9)
discontinued Pembrolizumab or placebo	14	(3.8)	2	(0.5)	19	(4.1)	228	(3.9)
discontinued any chemotherapy	6	(1.6)	1	(0.3)	19	(4.1)	228	(3.9)
discontinued all drugs	3	(0.8)	0	(0.0)	19	(4.1)	228	(3.9)
discontinued any drug due to a serious adverse event	12	(3.2)	2	(0.5)	12	(2.6)	156	(2.7)
discontinued Pembrolizumab or placebo	11	(3.0)	2	(0.5)	12	(2.6)	156	(2.7)

discontinued any chemotherapy	4	(1.1)	1	(0.3)	12	(2.6)	156	(2.7)
discontinued all drugs	2	(0.5)	0	(0.0)	12	(2.6)	156	(2.7)
discontinued any drug due to a serious drug-related adverse event	12	(3.2)	2	(0.5)	12	(2.6)	154	(2.6)
discontinued Pembrolizumab or placebo	11	(3.0)	2	(0.5)	12	(2.6)	154	(2.6)
discontinued any chemotherapy	4	(1.1)	1	(0.3)	12	(2.6)	154	(2.6)

Table 47: Subjects With Adverse Events of Special Interest (AEOSI) By AEOSI Category and Preferred Term (ASaT Population) (extract, PT incidence > 0% in the KN590 pembrolizumab + chemotherapy arm)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	95	(25.7)	43	(11.6)	106	(23.1)	1,474	(25.1)
with no adverse events	275	(74.3)	327	(88.4)	352	(76.9)	4,410	(74.9)
Adrenal Insufficiency	**4**	**(1.1)**	**2**	**(0.5)**	**1**	**(0.2)**	**47**	**(0.8)**
Adrenal insufficiency	4	(1.1)	2	(0.5)	1	(0.2)	42	(0.7)
Colitis	**8**	**(2.2)**	**6**	**(1.6)**	**7**	**(1.5)**	**110**	**(1.9)**
Colitis	6	(1.6)	4	(1.1)	5	(1.1)	95	(1.6)
Autoimmune colitis	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.1)
Enterocolitis	1	(0.3)	2	(0.5)	2	(0.4)	8	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**4**	**(0.1)**
Hepatitis	**5**	**(1.4)**	**0**	**(0.0)**	**7**	**(1.5)**	**56**	**(1.0)**
Hepatitis	3	(0.8)	0	(0.0)	0	(0.0)	24	(0.4)
Autoimmune hepatitis	2	(0.5)	0	(0.0)	6	(1.3)	25	(0.4)
Hyperthyroidism	**21**	**(5.7)**	**3**	**(0.8)**	**18**	**(3.9)**	**247**	**(4.2)**
Hyperthyroidism	20	(5.4)	3	(0.8)	18	(3.9)	247	(4.2)
Basedow's disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypophysitis	**3**	**(0.8)**	**0**	**(0.0)**	**3**	**(0.7)**	**36**	**(0.6)**
Hypopituitarism	2	(0.5)	0	(0.0)	2	(0.4)	14	(0.2)
Hypophysitis	1	(0.3)	0	(0.0)	1	(0.2)	22	(0.4)
Hypothyroidism	**40**	**(10.8)**	**24**	**(6.5)**	**50**	**(10.9)**	**652**	**(11.1)**
Hypothyroidism	40	(10.8)	24	(6.5)	49	(10.7)	651	(11.1)
Infusion Reactions	**6**	**(1.6)**	**4**	**(1.1)**	**4**	**(0.9)**	**138**	**(2.3)**
Infusion related reaction	4	(1.1)	0	(0.0)	4	(0.9)	56	(1.0)
Hypersensitivity	2	(0.5)	2	(0.5)	0	(0.0)	47	(0.8)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Myocarditis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**5**	**(0.1)**
Myositis	**1**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.4)**	**19**	**(0.3)**
Myopathy	1	(0.3)	0	(0.0)	0	(0.0)	4	(0.1)
Nephritis	**1**	**(0.3)**	**2**	**(0.5)**	**3**	**(0.7)**	**23**	**(0.4)**
Tubulointerstitial nephritis	1	(0.3)	1	(0.3)	0	(0.0)	11	(0.2)
Pancreatitis	**2**	**(0.5)**	**1**	**(0.3)**	**1**	**(0.2)**	**18**	**(0.3)**
Pancreatitis	2	(0.5)	1	(0.3)	1	(0.2)	14	(0.2)
Pneumonitis	**23**	**(6.2)**	**2**	**(0.5)**	**24**	**(5.2)**	**264**	**(4.5)**
Pneumonitis	21	(5.7)	0	(0.0)	21	(4.6)	242	(4.1)
Interstitial lung disease	2	(0.5)	2	(0.5)	3	(0.7)	22	(0.4)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**10**	**(0.2)**
Severe Skin Reactions	**4**	**(1.1)**	**2**	**(0.5)**	**4**	**(0.9)**	**97**	**(1.6)**
Rash maculo-papular	4	(1.1)	1	(0.3)	0	(0.0)	16	(0.3)
Pruritus	1	(0.3)	0	(0.0)	0	(0.0)	12	(0.2)
Thyroiditis	**1**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.4)**	**58**	**(1.0)**

Thyroiditis	1	(0.3)	0	(0.0)	2	(0.4)	41	(0.7)
Type 1 Diabetes Mellitus	**1**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.7)**	**20**	**(0.3)**
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)	2	(0.4)	16	(0.3)
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**21**	**(0.4)**
Every subject is counted a single time for each applicable row and column.								

Table 48: Subjects With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade (ASaT Population) (extract)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	95	(25.7)	43	(11.6)	106	(23.1)	1,474	(25.1)
Grade 1	26	(7.0)	16	(4.3)	20	(4.4)	367	(6.2)
Grade 2	43	(11.6)	19	(5.1)	59	(12.9)	726	(12.3)
Grade 3	24	(6.5)	7	(1.9)	18	(3.9)	325	(5.5)
Grade 4	0	(0.0)	0	(0.0)	5	(1.1)	45	(0.8)
Grade 5	2	(0.5)	1	(0.3)	4	(0.9)	11	(0.2)
with no adverse events	275	(74.3)	327	(88.4)	352	(76.9)	4,410	(74.9)

Table 49: Summary of Outcome for Subjects With AEOSI (ASaT Population) (extract)

		KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	Outcome	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population		370		370		458		5884	
With one or more AEOSI	**Overall**	**95**	**(25.7)**	**43**	**(11.6)**	**106**	**(23.1)**	**1474**	**(25.1)**
	Fatal	2	(2.1)	1	(2.3)	4	(3.8)	11	(0.7)
	Not Resolved	41	(43.2)	15	(34.9)	57	(53.8)	693	(47.0)
	Resolving	12	(12.6)	7	(16.3)	10	(9.4)	97	(6.6)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)	27	(1.8)
	Sequelae	2	(2.1)	0	(0.0)	1	(0.9)	33	(2.2)
	Resolved	38	(40.0)	20	(46.5)	34	(32.1)	613	(41.6)

Hypothyroidism: most AEOSI events for hypothyroidism were considered drug related (10.3%), were all Grade 1 or 2; at the time of data cut-off, 57.5% were not resolved, 12.5% were considered resolving and 27.5% resolved. Only 1 out of 46 subjects with hypothyroidism received corticosteroids.

Pneumonitis: pneumonitis occurred in 23 participants in the pembrolizumab plus chemotherapy group (6.2%), and most of those events were considered drug related (5.9%). Almost half were grade 2 in severity (G1 0.8%, G2 3%, G3 1.9%, G4 0%, G5 0.5%). The median time to onset for the AEOSI pneumonitis in the pembrolizumab + chemotherapy group compared with pembrolizumab monotherapy RSD was longer (149 vs 106 days) and lasted longer (median episode duration 216 vs 58 days). Most of the patients experiencing were treated with corticosteroids (78.3%), starting usually at high (≥40 mg/day prednisone or equivalent) dose (68%). Events were mostly considered resolving (21.7%) or resolved (47.8%) at the time of data cut-off, while 21.7% were not resolved.

In the 23 patients with pneumonitis in the pembrolizumab plus chemotherapy group, 3 (all G2) had prior thoracic radiation. In the 2 participants in the chemotherapy group who had pneumonitis, 1 (G1) had prior thoracic radiation. The small number of participants with pneumonitis who had prior thoracic radiation precludes clinically meaningful conclusions about the role of prior radiation in the events.

Hyperthyroidism: most AEOSI events for hyperthyroidism were considered drug related (5.4%), the majority were Grade 1 or 2 in severity, and at the time of data cut-off, the majority (66.7%) were considered resolved.

Laboratory findings

In KEYNOTE-590 study, the most frequently reported (≥5%) laboratory abnormalities were similar in the pembrolizumab plus chemotherapy group and the chemotherapy group, and the majority were CTCAE Grade 1 to 2 toxicity. The largest between-treatment difference (>5%) in laboratory abnormalities (all grades) between the pembrolizumab plus chemotherapy compared with the chemotherapy were: ALT increased (23.2% vs 17.7%), calcium decreased (43.8% vs 37.6%), calcium increased (7.5% vs 12.6%), and phosphate decreased (36.9% vs 30.5%). There was 1 participant in each treatment arm of KN590 who met the specified threshold of abnormal hepatic tests (i.e., AST or ALT ≥3x the upper limit of normal (ULN) and total bilirubin ≥2x ULN and alkaline phosphatase <2× ULN).

The following Grade 3 to 4 laboratory abnormalities were reported with an incidence ≥5% and were higher (≥5% point difference) in the pembrolizumab plus chemotherapy group compared with the pembrolizumab monotherapy RSD: Haemoglobin decreased (20.9% vs 6.4%), leukocytes decreased (20.9% vs 0.8%), lymphocytes decreased (22.3% vs 11.0%), neutrophils decreased (43.3% vs 1.9%), potassium decreased (11.9% vs 2.3%), and sodium decreased (19.2% vs 8.3%). Those are consistent with the established safety profiles of the chemotherapies.

In the pool of patients treated with pembrolizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 33.0% for neutrophils decreased, 25.5% for lymphocytes decreased, 20.3% for haemoglobin decreased, 19.3% for leucocytes decreased, 13.9% for sodium decreased, 10.8% for platelets decreased, 9.7% for phosphate decreased, 8.4% for potassium decreased, 7.6% for glucose increased, 3.9% for AST increased, 3.8% for potassium increased, 3.7% for calcium decreased, 3.6% for ALT increased, 3.1% for creatinine increased, 3.0% for albumin decreased, 2.2% for calcium increased, 1.6% for alkaline phosphatase increased, 1.2% for bilirubin increased, 0.8% for glucose decreased, and 0.4% for sodium increased (see section 4.8 of the SmPC).

Safety in special populations

Age

Table 50: Adverse Event Summary by Age Category (<65, ≥65 Years) (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††				KN590 Data for Placebo + Chemotherapy¶¶				Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡				Reference Safety Dataset for Pembrolizumab Monotherapy§§			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	201		169		221		149		242		216		3,385		2,499	
with one or more adverse events	201	(100.0)	169	(100.0)	220	(99.5)	148	(99.3)	233	(96.3)	204	(94.4)	3,268	(96.5)	2,422	(96.9)
with no adverse event	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.7)	9	(3.7)	12	(5.6)	117	(3.5)	77	(3.1)
with drug-related† adverse events	200	(99.5)	164	(97.0)	213	(96.4)	147	(98.7)	145	(59.9)	136	(63.0)	2,366	(69.9)	1,766	(70.7)
with toxicity grade 3-5 adverse events	171	(85.1)	147	(87.0)	182	(82.4)	126	(84.6)	132	(54.5)	113	(52.3)	1,505	(44.5)	1,324	(53.0)
with toxicity grade 3-5 drug-related adverse events	143	(71.1)	123	(72.8)	143	(64.7)	107	(71.8)	37	(15.3)	43	(19.9)	456	(13.5)	457	(18.3)
with serious adverse events	107	(53.2)	98	(58.0)	121	(54.8)	83	(55.7)	94	(38.8)	86	(39.8)	1,182	(34.9)	1,084	(43.4)
with serious drug-related adverse events	60	(29.9)	57	(33.7)	51	(23.1)	46	(30.9)	27	(11.2)	29	(13.4)	346	(10.2)	310	(12.4)
who died	15	(7.5)	13	(7.7)	21	(9.5)	17	(11.4)	17	(7.0)	22	(10.2)	144	(4.3)	168	(6.7)
who died due to a drug-related adverse event	4	(2.0)	5	(3.0)	1	(0.5)	4	(2.7)	1	(0.4)	5	(2.3)	21	(0.6)	18	(0.7)
discontinued any drug due to an adverse event	41	(20.4)	49	(29.0)	34	(15.4)	40	(26.8)	29	(12.0)	26	(12.0)	399	(11.8)	391	(15.6)
discontinued Pembrolizumab or placebo	24	(11.9)	30	(17.8)	24	(10.9)	21	(14.1)	29	(12.0)	26	(12.0)	399	(11.8)	391	(15.6)
discontinued any chemotherapy	35	(17.4)	40	(23.7)	31	(14.0)	38	(25.5)	29	(12.0)	26	(12.0)	399	(11.8)	391	(15.6)
discontinued all drugs	10	(5.0)	13	(7.7)	14	(6.3)	14	(9.4)	29	(12.0)	26	(12.0)	399	(11.8)	391	(15.6)
discontinued any drug due to a drug-related adverse event	34	(16.9)	38	(22.5)	18	(8.1)	25	(16.8)	12	(5.0)	15	(6.9)	207	(6.1)	203	(8.1)
discontinued Pembrolizumab or placebo	14	(7.0)	21	(12.4)	9	(4.1)	6	(4.0)	12	(5.0)	15	(6.9)	207	(6.1)	203	(8.1)
discontinued any chemotherapy	29	(14.4)	29	(17.2)	18	(8.1)	24	(16.1)	12	(5.0)	15	(6.9)	207	(6.1)	203	(8.1)
discontinued all drugs	7	(3.5)	9	(5.3)	7	(3.2)	3	(2.0)	12	(5.0)	15	(6.9)	207	(6.1)	203	(8.1)
discontinued any drug due to a serious adverse event	27	(13.4)	31	(18.3)	24	(10.9)	23	(15.4)	25	(10.3)	19	(8.8)	287	(8.5)	285	(11.4)
discontinued Pembrolizumab or placebo	19	(9.5)	28	(16.6)	23	(10.4)	20	(13.4)	25	(10.3)	19	(8.8)	287	(8.5)	285	(11.4)
discontinued any chemotherapy	20	(10.0)	23	(13.6)	20	(9.0)	21	(14.1)	25	(10.3)	19	(8.8)	287	(8.5)	285	(11.4)
discontinued all drugs	8	(4.0)	13	(7.7)	14	(6.3)	13	(8.7)	25	(10.3)	19	(8.8)	287	(8.5)	285	(11.4)
discontinued any drug due to a serious drug-related adverse event	18	(9.0)	20	(11.8)	8	(3.6)	9	(6.0)	9	(3.7)	9	(4.2)	123	(3.6)	122	(4.9)
discontinued Pembrolizumab or placebo	10	(5.0)	19	(11.2)	8	(3.6)	6	(4.0)	9	(3.7)	9	(4.2)	123	(3.6)	122	(4.9)
discontinued any chemotherapy	13	(6.5)	12	(7.1)	8	(3.6)	8	(5.4)	9	(3.7)	9	(4.2)	123	(3.6)	122	(4.9)
discontinued all drugs	5	(2.5)	9	(5.3)	7	(3.2)	3	(2.0)	9	(3.7)	9	(4.2)	123	(3.6)	122	(4.9)

† 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.

Table 51: Adverse Event Summary by Age Category (<65, 65-74, 75-84, ≥85 Years) (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††								KN590 Data for Placebo + Chemotherapy¶¶							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	201		132		36		1		221		117		30		2	
with one or more adverse events	201	(100.0)	132	(100.0)	36	(100.0)	1	(100.0)	220	(99.5)	116	(99.1)	30	(100.0)	2	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.9)	0	(0.0)	0	(0.0)
with drug-related† adverse events	200	(99.5)	128	(97.0)	36	(100.0)	0	(0.0)	213	(96.4)	115	(98.3)	30	(100.0)	2	(100.0)
with toxicity grade 3-5 adverse events	171	(85.1)	111	(84.1)	35	(97.2)	1	(100.0)	182	(82.4)	100	(85.5)	24	(80.0)	2	(100.0)
with toxicity grade 3-5 drug-related adverse events	143	(71.1)	92	(69.7)	31	(86.1)	0	(0.0)	143	(64.7)	83	(70.9)	22	(73.3)	2	(100.0)
with serious adverse events	107	(53.2)	69	(52.3)	28	(77.8)	1	(100.0)	121	(54.8)	67	(57.3)	15	(50.0)	1	(50.0)
with serious drug-related adverse events	60	(29.9)	36	(27.3)	21	(58.3)	0	(0.0)	51	(23.1)	35	(29.9)	10	(33.3)	1	(50.0)
who died	15	(7.5)	3	(2.3)	9	(25.0)	1	(100.0)	21	(9.5)	13	(11.1)	3	(10.0)	1	(50.0)
who died due to a drug-related adverse event	4	(2.0)	1	(0.8)	4	(11.1)	0	(0.0)	1	(0.5)	1	(0.9)	2	(6.7)	1	(50.0)
discontinued any drug due to an adverse event	41	(20.4)	33	(25.0)	15	(41.7)	1	(100.0)	34	(15.4)	28	(23.9)	11	(36.7)	1	(50.0)
discontinued Pembrolizumab or placebo	24	(11.9)	16	(12.1)	13	(36.1)	1	(100.0)	24	(10.9)	14	(12.0)	6	(20.0)	1	(50.0)
discontinued any chemotherapy	35	(17.4)	25	(18.9)	14	(38.9)	1	(100.0)	31	(14.0)	26	(22.2)	11	(36.7)	1	(50.0)
discontinued all drugs	10	(5.0)	4	(3.0)	8	(22.2)	1	(100.0)	14	(6.3)	9	(7.7)	5	(16.7)	0	(0.0)
discontinued any drug due to a drug-related adverse event	34	(16.9)	26	(19.7)	12	(33.3)	0	(0.0)	18	(8.1)	16	(13.7)	8	(26.7)	1	(50.0)
discontinued Pembrolizumab or placebo	14	(7.0)	11	(8.3)	10	(27.8)	0	(0.0)	9	(4.1)	2	(1.7)	3	(10.0)	1	(50.0)
discontinued any chemotherapy	29	(14.4)	19	(14.4)	10	(27.8)	0	(0.0)	18	(8.1)	15	(12.8)	8	(26.7)	1	(50.0)
discontinued all drugs	7	(3.5)	2	(1.5)	7	(19.4)	0	(0.0)	7	(3.2)	1	(0.9)	2	(6.7)	0	(0.0)
discontinued any drug due to a serious adverse event	27	(13.4)	17	(12.9)	13	(36.1)	1	(100.0)	24	(10.9)	15	(12.8)	7	(23.3)	1	(50.0)
discontinued Pembrolizumab or placebo	19	(9.5)	14	(10.6)	13	(36.1)	1	(100.0)	23	(10.4)	13	(11.1)	6	(20.0)	1	(50.0)
discontinued any chemotherapy	20	(10.0)	10	(7.6)	12	(33.3)	1	(100.0)	20	(9.0)	13	(11.1)	7	(23.3)	1	(50.0)
discontinued all drugs	8	(4.0)	4	(3.0)	8	(22.2)	1	(100.0)	14	(6.3)	8	(6.8)	5	(16.7)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	18	(9.0)	10	(7.6)	10	(27.8)	0	(0.0)	8	(3.6)	4	(3.4)	4	(13.3)	1	(50.0)
discontinued Pembrolizumab or placebo	10	(5.0)	9	(6.8)	10	(27.8)	0	(0.0)	8	(3.6)	2	(1.7)	3	(10.0)	1	(50.0)
discontinued any chemotherapy	13	(6.5)	4	(3.0)	8	(22.2)	0	(0.0)	8	(3.6)	3	(2.6)	4	(13.3)	1	(50.0)
discontinued all drugs	5	(2.5)	2	(1.5)	7	(19.4)	0	(0.0)	7	(3.2)	1	(0.9)	2	(6.7)	0	(0.0)

	Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡								Reference Safety Dataset for Pembrolizumab Monotherapy§§							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	242		166		49		1		3,385		1,737		663		99	
with one or more adverse events	233	(96.3)	154	(92.8)	49	(100.0)	1	(100.0)	3,268	(96.5)	1,678	(96.6)	646	(97.4)	98	(99.0)
with no adverse event	9	(3.7)	12	(7.2)	0	(0.0)	0	(0.0)	117	(3.5)	59	(3.4)	17	(2.6)	1	(1.0)
with drug-related† adverse events	145	(59.9)	104	(62.7)	32	(65.3)	0	(0.0)	2,366	(69.9)	1,224	(70.5)	467	(70.4)	75	(75.8)
with toxicity grade 3-5 adverse events	132	(54.5)	80	(48.2)	32	(65.3)	1	(100.0)	1,505	(44.5)	891	(51.3)	373	(56.3)	60	(60.6)
with toxicity grade 3-5 drug-related adverse events	37	(15.3)	29	(17.5)	14	(28.6)	0	(0.0)	456	(13.5)	311	(17.9)	128	(19.3)	18	(18.2)
with serious adverse events	94	(38.8)	58	(34.9)	28	(57.1)	0	(0.0)	1,182	(34.9)	719	(41.4)	315	(47.5)	50	(50.5)
with serious drug-related adverse events	27	(11.2)	20	(12.0)	9	(18.4)	0	(0.0)	346	(10.2)	213	(12.3)	85	(12.8)	12	(12.1)
who died	17	(7.0)	13	(7.8)	9	(18.4)	0	(0.0)	144	(4.3)	103	(5.9)	54	(8.1)	11	(11.1)
who died due to a drug-related adverse event	1	(0.4)	2	(1.2)	3	(6.1)	0	(0.0)	21	(0.6)	12	(0.7)	5	(0.8)	1	(1.0)
discontinued any drug due to an adverse event	29	(12.0)	16	(9.6)	10	(20.4)	0	(0.0)	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)
discontinued Pembrolizumab or placebo	29	(12.0)	16	(9.6)	10	(20.4)	0	(0.0)	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)
discontinued any chemotherapy	29	(12.0)	16	(9.6)	10	(20.4)	0	(0.0)	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)
discontinued all drugs	29	(12.0)	16	(9.6)	10	(20.4)	0	(0.0)	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)
discontinued any drug due to a drug-related adverse event	12	(5.0)	8	(4.8)	7	(14.3)	0	(0.0)	207	(6.1)	135	(7.8)	62	(9.4)	6	(6.1)
discontinued Pembrolizumab or placebo	12	(5.0)	8	(4.8)	7	(14.3)	0	(0.0)	207	(6.1)	135	(7.8)	62	(9.4)	6	(6.1)
discontinued any chemotherapy	12	(5.0)	8	(4.8)	7	(14.3)	0	(0.0)	207	(6.1)	135	(7.8)	62	(9.4)	6	(6.1)
discontinued all drugs	12	(5.0)	8	(4.8)	7	(14.3)	0	(0.0)	207	(6.1)	135	(7.8)	62	(9.4)	6	(6.1)
discontinued any drug due to a serious adverse event	25	(10.3)	11	(6.6)	8	(16.3)	0	(0.0)	287	(8.5)	174	(10.0)	100	(15.1)	11	(11.1)
discontinued Pembrolizumab or placebo	25	(10.3)	11	(6.6)	8	(16.3)	0	(0.0)	287	(8.5)	174	(10.0)	100	(15.1)	11	(11.1)
discontinued any chemotherapy	25	(10.3)	11	(6.6)	8	(16.3)	0	(0.0)	287	(8.5)	174	(10.0)	100	(15.1)	11	(11.1)
discontinued all drugs	25	(10.3)	11	(6.6)	8	(16.3)	0	(0.0)	287	(8.5)	174	(10.0)	100	(15.1)	11	(11.1)
discontinued any drug due to a serious drug-related adverse event	9	(3.7)	4	(2.4)	5	(10.2)	0	(0.0)	123	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)
discontinued Pembrolizumab or placebo	9	(3.7)	4	(2.4)	5	(10.2)	0	(0.0)	123	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)
discontinued any chemotherapy	9	(3.7)	4	(2.4)	5	(10.2)	0	(0.0)	123	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)
discontinued all drugs	9	(3.7)	4	(2.4)	5	(10.2)	0	(0.0)	123	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)

Table 52: Adverse Event Summary for Elderly Subjects by Age in KN590 (ASaT Population)

	Age (Years)							
	Pembrolizumab + SOC							
	< 65		65 - 74		75 - 84		85+	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	201		132		36		1	
with one or more adverse events	201	(100.0)	132	(100.0)	36	(100.0)	1	(100.0)
who died	15	(7.5)	3	(2.3)	9	(25.0)	1	(100.0)
with serious adverse events	107	(53.2)	69	(52.3)	28	(77.8)	1	(100.0)
discontinued due to an adverse event	41	(20.4)	33	(25.0)	15	(41.7)	1	(100.0)
CNS (confusion/extrapyramidal)	14	(7.0)	9	(6.8)	2	(5.6)	0	(0.0)
AE related to falling	6	(3.0)	9	(6.8)	6	(16.7)	0	(0.0)
CV events	50	(24.9)	46	(34.8)	12	(33.3)	0	(0.0)
Cerebrovascular events	3	(1.5)	3	(2.3)	1	(2.8)	0	(0.0)
Infections	81	(40.3)	57	(43.2)	14	(38.9)	0	(0.0)

	Age (Years)							
	SOC							
	< 65		65 - 74		75 - 84		85+	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	221		117		30		2	
with one or more adverse events	220	(99.5)	116	(99.1)	30	(100.0)	2	(100.0)
who died	21	(9.5)	13	(11.1)	3	(10.0)	1	(50.0)
with serious adverse events	121	(54.8)	67	(57.3)	15	(50.0)	1	(50.0)
discontinued due to an adverse event	34	(15.4)	28	(23.9)	11	(36.7)	1	(50.0)
CNS (confusion/extrapyramidal)	12	(5.4)	14	(12.0)	0	(0.0)	0	(0.0)
AE related to falling	13	(5.9)	11	(9.4)	3	(10.0)	0	(0.0)
CV events	55	(24.9)	40	(34.2)	5	(16.7)	1	(50.0)
Cerebrovascular events	8	(3.6)	5	(4.3)	3	(10.0)	0	(0.0)
Infections	80	(36.2)	53	(45.3)	14	(46.7)	2	(100.0)

AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 02JUL2020.

Table 53: Adverse Event Summary (ASaT Population, <u>Age ≥75</u>)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	37		32	
with one or more adverse events	37	(100.0)	32	(100.0)
with no adverse event	0	(0.0)	0	(0.0)

with drug-related† adverse events	36	(97.3)	32	(100.0)
with toxicity grade 3-5 adverse events	36	(97.3)	26	(81.3)
with toxicity grade 3-5 drug-related adverse events	31	(83.8)	24	(75.0)
with non-serious adverse events	36	(97.3)	32	(100.0)
with serious adverse events	29	(78.4)	16	(50.0)
with serious drug-related adverse events	21	(56.8)	11	(34.4)
who died	10	(27.0)	4	(12.5)
who died due to a drug-related adverse event	4	(10.8)	3	(9.4)
discontinued drug due to an adverse event	16	(43.2)	12	(37.5)
discontinued drug due to a drug-related adverse event	12	(32.4)	9	(28.1)
discontinued drug due to a serious adverse event	14	(37.8)	8	(25.0)
discontinued drug due to a serious drug-related adverse event	10	(27.0)	5	(15.6)

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

Grades are based on NCI CTCAE version 4.03.

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

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

Database Cutoff Date: 02JUL2020

Table 54: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (ASaT Population, Age ≥ 75)

	Event Count and Rate (Events/100 person-years)†			
	Pembrolizumab + SOC		SOC	
Number of Subjects exposed	37		32	
Total exposure‡ in person-years	17.65		17.33	
Total events (rate)				
adverse events	688	(3898.92)	485	(2798.88)
drug-related§ adverse events	402	(2278.15)	324	(1869.77)
toxicity grade 3-5 adverse events	146	(827.39)	99	(571.32)
toxicity grade 3-5 drug-related adverse events	93	(527.03)	61	(352.02)
serious adverse events	64	(362.69)	40	(230.84)
serious drug-related adverse events	37	(209.68)	19	(109.65)
adverse events resulting in dose modification‖	124	(702.71)	93	(536.69)
adverse events leading to death	11	(62.34)	4	(23.08)
drug-related adverse events leading to death	4	(22.67)	3	(17.31)
adverse events resulting in drug discontinuation	18	(102.01)	14	(80.79)
drug-related adverse events resulting in drug discontinuation	12	(68.00)	11	(63.48)
serious adverse events resulting in drug discontinuation	16	(90.67)	9	(51.94)
serious drug-related adverse events resulting in drug discontinuation	10	(56.67)	6	(34.63)

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

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

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

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

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

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

Database Cutoff Date: 02JUL2020

Pooled safety data of pembrolizumab plus chemotherapy from KEYNOTE-590 and studies of other approved indications in combination with chemotherapy (NSCLC: KEYNOTE-021, KEYNOTE-189, and

KEYNOTE-407; HNSCC: KEYNOTE-048) versus chemotherapy alone is provided by age groups in the tables below:

Table 55: Adverse Event Summary by Age for Elderly Subjects (ASaT Population)

	KN021 + KN048 + KN189 + KN407 + KN590 Data for Pembrolizumab + Chemotherapy††								KN021 + KN048 + KN189 + KN407 + KN590 Data for Chemotherapy§§							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	759	(100.0)	550	(100.0)	124	(100.0)	4	(100.0)	671	(100.0)	416	(100.0)	111	(100.0)	3	(100.0)
with one or more adverse events	754	(99.3)	546	(99.3)	123	(99.2)	4	(100.0)	668	(99.6)	410	(98.6)	109	(98.2)	3	(100.0)
who died	48	(6.3)	46	(8.4)	26	(21.0)	4	(100.0)	48	(7.2)	39	(9.4)	13	(11.7)	1	(33.3)
with serious adverse events	380	(50.1)	317	(57.6)	80	(64.5)	4	(100.0)	311	(46.3)	210	(50.5)	60	(54.1)	1	(33.3)
discontinued‡ due to an adverse event	186	(24.5)	179	(32.5)	52	(41.9)	4	(100.0)	115	(17.1)	92	(22.1)	27	(24.3)	1	(33.3)
CNS (confusion/extrapyramidal)	63	(8.3)	61	(11.1)	15	(12.1)	0	(0.0)	49	(7.3)	38	(9.1)	10	(9.0)	0	(0.0)
AE related to falling	54	(7.1)	62	(11.3)	18	(14.5)	0	(0.0)	39	(5.8)	49	(11.8)	11	(9.9)	0	(0.0)
CV events	193	(25.4)	176	(32.0)	39	(31.5)	2	(50.0)	154	(23.0)	118	(28.4)	26	(23.4)	1	(33.3)
Cerebrovascular events	20	(2.6)	19	(3.5)	9	(7.3)	0	(0.0)	23	(3.4)	15	(3.6)	5	(4.5)	0	(0.0)
Infections	392	(51.6)	324	(58.9)	61	(49.2)	1	(25.0)	308	(45.9)	212	(51.0)	62	(55.9)	3	(100.0)

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
†† Includes all subjects who received at least one dose of Pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN407 and KN590.
§§ Includes all subjects who received at least one dose of chemotherapy in KN021-A/C/G, KN048, KN189, KN407 and KN590.
Database cutoff date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN048: 25FEB2019)
Database cutoff date for Esophageal (KN590: 02JUL2020)

Table 2: Adverse Event Summary by Age Category (<65, 65-74, 75+ Years) (Subjects in ASaT Population)

	KN021 + KN048 + KN189 + KN407 + KN590 Data for Pembrolizumab + Chemotherapy††						KN021 + KN048 + KN189 + KN407 + KN590 Data for Chemotherapy§§					
	<65		65-74		75+		<65		65-74		75+	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	759		550		128		671		416		114	
with one or more adverse events	754	(99.3)	546	(99.3)	127	(99.2)	668	(99.6)	410	(98.6)	112	(98.2)
with no adverse event	5	(0.7)	4	(0.7)	1	(0.8)	3	(0.4)	6	(1.4)	2	(1.8)
with drug-related† adverse events	724	(95.4)	529	(96.2)	121	(94.5)	630	(93.9)	393	(94.5)	108	(94.7)
with toxicity grade 3-5 adverse events	584	(76.9)	425	(77.3)	109	(85.2)	502	(74.8)	316	(76.0)	93	(81.6)
with toxicity grade 3-5 drug-related adverse events	448	(59.0)	349	(63.5)	81	(63.3)	383	(57.1)	251	(60.3)	74	(64.9)
with serious adverse events	380	(50.1)	317	(57.6)	84	(65.6)	311	(46.3)	210	(50.5)	61	(53.5)
with serious drug-related adverse events	208	(27.4)	188	(34.2)	49	(38.3)	140	(20.9)	107	(25.7)	25	(21.9)
who died	48	(6.3)	46	(8.4)	30	(23.4)	48	(7.2)	39	(9.4)	14	(12.3)
who died due to a drug-related adverse event	15	(2.0)	15	(2.7)	11	(8.6)	8	(1.2)	9	(2.2)	5	(4.4)
discontinued drug due to an adverse event	186	(24.5)	179	(32.5)	56	(43.8)	115	(17.1)	92	(22.1)	28	(24.6)
discontinued drug due to a drug-related adverse event	150	(19.8)	134	(24.4)	37	(28.9)	72	(10.7)	59	(14.2)	20	(17.5)
discontinued drug due to a serious adverse event	118	(15.5)	111	(20.2)	46	(35.9)	72	(10.7)	54	(13.0)	20	(17.5)
discontinued drug due to a serious drug-related adverse event	82	(10.8)	69	(12.5)	27	(21.1)	33	(4.9)	23	(5.5)	11	(9.6)

† 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.
†† Includes all subjects who received at least one dose of Pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN407 and KN590.
§§ Includes all subjects who received at least one dose of chemotherapy in KN021-A/C/G, KN048, KN189, KN407 and KN590.
Database cutoff date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN048: 25FEB2019)
Database cutoff date for Esophageal (KN590: 02JUL2020)

Gender

Table 57: Adverse Event Summary by Gender (Male, Female) (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††				KN590 Data for Placebo + Chemotherapy¶¶				Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡				Reference Safety Dataset for Pembrolizumab Monotherapy§§			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	305		65		314		56		392		66		3,887		1,997	
with one or more adverse events	305	(100.0)	65	(100.0)	312	(99.4)	56	(100.0)	372	(94.9)	65	(98.5)	3,756	(96.6)	1,934	(96.8)
with no adverse event	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	20	(5.1)	1	(1.5)	131	(3.4)	63	(3.2)
with drug-related† adverse events	300	(98.4)	64	(98.5)	306	(97.5)	54	(96.4)	236	(60.2)	45	(68.2)	2,710	(69.7)	1,422	(71.2)
with toxicity grade 3-5 adverse events	259	(84.9)	59	(90.8)	256	(81.5)	52	(92.9)	211	(53.8)	34	(51.5)	1,894	(48.7)	935	(46.8)
with toxicity grade 3-5 drug-related adverse events	217	(71.1)	49	(75.4)	207	(65.9)	43	(76.8)	68	(17.3)	12	(18.2)	630	(16.2)	283	(14.2)
with serious adverse events	168	(55.1)	37	(56.9)	169	(53.8)	35	(62.5)	157	(40.1)	23	(34.8)	1,534	(39.5)	732	(36.7)
with serious drug-related adverse events	93	(30.5)	24	(36.9)	80	(25.5)	17	(30.4)	47	(12.0)	9	(13.6)	448	(11.5)	208	(10.4)
who died	23	(7.5)	5	(7.7)	31	(9.9)	7	(12.5)	35	(8.9)	4	(6.1)	221	(5.7)	91	(4.6)
who died due to a drug-related adverse event	8	(2.6)	1	(1.5)	3	(1.0)	2	(3.6)	5	(1.3)	1	(1.5)	25	(0.6)	14	(0.7)
discontinued any drug due to an adverse event	75	(24.6)	15	(23.1)	62	(19.7)	12	(21.4)	46	(11.7)	9	(13.6)	529	(13.6)	261	(13.1)
discontinued Pembrolizumab or placebo	44	(14.4)	10	(15.4)	38	(12.1)	7	(12.5)	46	(11.7)	9	(13.6)	529	(13.6)	261	(13.1)
discontinued any chemotherapy	64	(21.0)	11	(16.9)	57	(18.2)	12	(21.4)	46	(11.7)	9	(13.6)	529	(13.6)	261	(13.1)
discontinued all drugs	20	(6.6)	3	(4.6)	21	(6.7)	7	(12.5)	46	(11.7)	9	(13.6)	529	(13.6)	261	(13.1)
discontinued any drug due to a drug-related adverse event	60	(19.7)	12	(18.5)	35	(11.1)	8	(14.3)	21	(5.4)	6	(9.1)	278	(7.2)	132	(6.6)
discontinued Pembrolizumab or placebo	29	(9.5)	6	(9.2)	11	(3.5)	4	(7.1)	21	(5.4)	6	(9.1)	278	(7.2)	132	(6.6)
discontinued any chemotherapy	50	(16.4)	8	(12.3)	34	(10.8)	8	(14.3)	21	(5.4)	6	(9.1)	278	(7.2)	132	(6.6)
discontinued all drugs	15	(4.9)	1	(1.5)	6	(1.9)	4	(7.1)	21	(5.4)	6	(9.1)	278	(7.2)	132	(6.6)
discontinued any drug due to a serious adverse event	48	(15.7)	10	(15.4)	39	(12.4)	8	(14.3)	37	(9.4)	7	(10.6)	386	(9.9)	186	(9.3)
discontinued Pembrolizumab or placebo	37	(12.1)	10	(15.4)	36	(11.5)	7	(12.5)	37	(9.4)	7	(10.6)	386	(9.9)	186	(9.3)
discontinued any chemotherapy	39	(12.8)	4	(6.2)	33	(10.5)	8	(14.3)	37	(9.4)	7	(10.6)	386	(9.9)	186	(9.3)
discontinued all drugs	18	(5.9)	3	(4.6)	20	(6.4)	7	(12.5)	37	(9.4)	7	(10.6)	386	(9.9)	186	(9.3)
discontinued any drug due to a serious drug-related adverse event	32	(10.5)	6	(9.2)	13	(4.1)	4	(7.1)	14	(3.6)	4	(6.1)	167	(4.3)	78	(3.9)
discontinued Pembrolizumab or placebo	23	(7.5)	6	(9.2)	10	(3.2)	4	(7.1)	14	(3.6)	4	(6.1)	167	(4.3)	78	(3.9)
discontinued any chemotherapy	24	(7.9)	1	(1.5)	12	(3.8)	4	(7.1)	14	(3.6)	4	(6.1)	167	(4.3)	78	(3.9)
discontinued all drugs	13	(4.3)	1	(1.5)	6	(1.9)	4	(7.1)	14	(3.6)	4	(6.1)	167	(4.3)	78	(3.9)

ECOG

Table 58: Adverse Event Summary by ECOG Status Category (0, 1) (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††				KN590 Data for Placebo + Chemotherapy¶¶				Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡				Reference Safety Dataset for Pembrolizumab Monotherapy§§			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		221		146		223		178		279		2,761		2,931	
with one or more adverse events	148	(100.0)	221	(100.0)	146	(100.0)	221	(99.1)	169	(94.9)	267	(95.7)	2,671	(96.7)	2,835	(96.7)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	9	(5.1)	12	(4.3)	90	(3.3)	96	(3.3)
with drug-related† adverse events	146	(98.6)	217	(98.2)	145	(99.3)	214	(96.0)	124	(69.7)	156	(55.9)	2,085	(75.5)	1,940	(66.2)
with toxicity grade 3-5 adverse events	120	(81.1)	197	(89.1)	114	(78.1)	193	(86.5)	77	(43.3)	167	(59.9)	1,112	(40.3)	1,605	(54.8)
with toxicity grade 3-5 drug-related adverse events	100	(67.6)	165	(74.7)	93	(63.7)	156	(70.0)	27	(15.2)	53	(19.0)	410	(14.8)	471	(16.1)
with serious adverse events	70	(47.3)	134	(60.6)	72	(49.3)	131	(58.7)	58	(32.6)	121	(43.4)	872	(31.6)	1,294	(44.1)
with serious drug-related adverse events	33	(22.3)	84	(38.0)	33	(22.6)	63	(28.3)	25	(14.0)	31	(11.1)	311	(11.3)	325	(11.1)
who died	5	(3.4)	23	(10.4)	10	(6.8)	28	(12.6)	8	(4.5)	31	(11.1)	79	(2.9)	217	(7.4)
who died due to a drug-related adverse event	3	(2.0)	6	(2.7)	1	(0.7)	4	(1.8)	2	(1.1)	4	(1.4)	14	(0.5)	25	(0.9)
discontinued any drug due to an adverse event	31	(20.9)	59	(26.7)	32	(21.9)	42	(18.8)	16	(9.0)	39	(14.0)	304	(11.0)	452	(15.4)
discontinued Pembrolizumab or placebo	15	(10.1)	39	(17.6)	15	(10.3)	30	(13.5)	16	(9.0)	39	(14.0)	304	(11.0)	452	(15.4)
discontinued any chemotherapy	26	(17.6)	49	(22.2)	31	(21.2)	38	(17.0)	16	(9.0)	39	(14.0)	304	(11.0)	452	(15.4)
discontinued all drugs	4	(2.7)	19	(8.6)	8	(5.5)	20	(9.0)	16	(9.0)	39	(14.0)	304	(11.0)	452	(15.4)
discontinued any drug due to a drug-related adverse event	28	(18.9)	44	(19.9)	22	(15.1)	21	(9.4)	13	(7.3)	14	(5.0)	193	(7.0)	200	(6.8)
discontinued Pembrolizumab or placebo	10	(6.8)	25	(11.3)	5	(3.4)	10	(4.5)	13	(7.3)	14	(5.0)	193	(7.0)	200	(6.8)
discontinued any chemotherapy	23	(15.5)	35	(15.8)	21	(14.4)	21	(9.4)	13	(7.3)	14	(5.0)	193	(7.0)	200	(6.8)
discontinued all drugs	4	(2.7)	12	(5.4)	3	(2.1)	7	(3.1)	13	(7.3)	14	(5.0)	193	(7.0)	200	(6.8)
discontinued any drug due to a serious adverse event	17	(11.5)	41	(18.6)	14	(9.6)	33	(14.8)	10	(5.6)	34	(12.2)	198	(7.2)	350	(11.9)
discontinued Pembrolizumab or placebo	14	(9.5)	33	(14.9)	13	(8.9)	30	(13.5)	10	(5.6)	34	(12.2)	198	(7.2)	350	(11.9)
discontinued any chemotherapy	11	(7.4)	32	(14.5)	12	(8.2)	29	(13.0)	10	(5.6)	34	(12.2)	198	(7.2)	350	(11.9)
discontinued all drugs	3	(2.0)	18	(8.1)	7	(4.8)	20	(9.0)	10	(5.6)	34	(12.2)	198	(7.2)	350	(11.9)
discontinued any drug due to a serious drug-related adverse event	12	(8.1)	26	(11.8)	5	(3.4)	12	(5.4)	8	(4.5)	10	(3.6)	106	(3.8)	130	(4.4)
discontinued Pembrolizumab or placebo	9	(6.1)	20	(9.0)	4	(2.7)	10	(4.5)	8	(4.5)	10	(3.6)	106	(3.8)	130	(4.4)
discontinued any chemotherapy	7	(4.7)	18	(8.1)	4	(2.7)	12	(5.4)	8	(4.5)	10	(3.6)	106	(3.8)	130	(4.4)
discontinued all drugs	3	(2.0)	11	(5.0)	3	(2.1)	7	(3.1)	8	(4.5)	10	(3.6)	106	(3.8)	130	(4.4)

Region

Table 59: Adverse Event Summary by Region (EU, Ex-EU) (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††				KN590 Data for Placebo + Chemotherapy¶¶				Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡				Reference Safety Dataset for Pembrolizumab Monotherapy§§			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	60		310		50		320		144		314		2,092		3,792	
with one or more adverse events	60	(100.0)	310	(100.0)	49	(98.0)	319	(99.7)	140	(97.2)	297	(94.6)	2,014	(96.3)	3,676	(96.9)
with no adverse event	0	(0.0)	0	(0.0)	1	(2.0)	1	(0.3)	4	(2.8)	17	(5.4)	78	(3.7)	116	(3.1)
with drug-related† adverse events	59	(98.3)	305	(98.4)	49	(98.0)	311	(97.2)	77	(53.5)	204	(65.0)	1,430	(68.4)	2,702	(71.3)
with toxicity grade 3-5 adverse events	54	(90.0)	264	(85.2)	41	(82.0)	267	(83.4)	75	(52.1)	170	(54.1)	960	(45.9)	1,869	(49.3)
with toxicity grade 3-5 drug-related adverse events	38	(63.3)	228	(73.5)	28	(56.0)	222	(69.4)	21	(14.6)	59	(18.8)	317	(15.2)	596	(15.7)
with serious adverse events	42	(70.0)	163	(52.6)	28	(56.0)	176	(55.0)	61	(42.4)	119	(37.9)	796	(38.0)	1,470	(38.8)
with serious drug-related adverse events	16	(26.7)	101	(32.6)	10	(20.0)	87	(27.2)	11	(7.6)	45	(14.3)	241	(11.5)	415	(10.9)
who died	3	(5.0)	25	(8.1)	3	(6.0)	35	(10.9)	14	(9.7)	25	(8.0)	109	(5.2)	203	(5.4)
who died due to a drug-related adverse event	1	(1.7)	8	(2.6)	0	(0.0)	5	(1.6)	2	(1.4)	4	(1.3)	12	(0.6)	27	(0.7)
discontinued any drug due to an adverse event	19	(31.7)	71	(22.9)	13	(26.0)	61	(19.1)	17	(11.8)	38	(12.1)	267	(12.8)	523	(13.8)
discontinued Pembrolizumab or placebo	11	(18.3)	43	(13.9)	4	(8.0)	41	(12.8)	17	(11.8)	38	(12.1)	267	(12.8)	523	(13.8)
discontinued any chemotherapy	16	(26.7)	59	(19.0)	13	(26.0)	56	(17.5)	17	(11.8)	38	(12.1)	267	(12.8)	523	(13.8)
discontinued all drugs	3	(5.0)	20	(6.5)	3	(6.0)	25	(7.8)	17	(11.8)	38	(12.1)	267	(12.8)	523	(13.8)
discontinued any drug due to a drug-related adverse event	16	(26.7)	56	(18.1)	10	(20.0)	33	(10.3)	5	(3.5)	22	(7.0)	151	(7.2)	259	(6.8)
discontinued Pembrolizumab or placebo	6	(10.0)	29	(9.4)	2	(4.0)	13	(4.1)	5	(3.5)	22	(7.0)	151	(7.2)	259	(6.8)
discontinued any chemotherapy	14	(23.3)	44	(14.2)	10	(20.0)	32	(10.0)	5	(3.5)	22	(7.0)	151	(7.2)	259	(6.8)
discontinued all drugs	3	(5.0)	13	(4.2)	2	(4.0)	8	(2.5)	5	(3.5)	22	(7.0)	151	(7.2)	259	(6.8)
discontinued any drug due to a serious adverse event	11	(18.3)	47	(15.2)	5	(10.0)	42	(13.1)	15	(10.4)	29	(9.2)	193	(9.2)	379	(10.0)
discontinued Pembrolizumab or placebo	9	(15.0)	38	(12.3)	4	(8.0)	39	(12.2)	15	(10.4)	29	(9.2)	193	(9.2)	379	(10.0)
discontinued any chemotherapy	8	(13.3)	35	(11.3)	4	(8.0)	37	(11.6)	15	(10.4)	29	(9.2)	193	(9.2)	379	(10.0)
discontinued all drugs	3	(5.0)	18	(5.8)	3	(6.0)	24	(7.5)	15	(10.4)	29	(9.2)	193	(9.2)	379	(10.0)
discontinued any drug due to a serious drug-related adverse event	7	(11.7)	31	(10.0)	2	(4.0)	15	(4.7)	3	(2.1)	15	(4.8)	89	(4.3)	156	(4.1)
discontinued Pembrolizumab or placebo	5	(8.3)	24	(7.7)	2	(4.0)	12	(3.8)	3	(2.1)	15	(4.8)	89	(4.3)	156	(4.1)
discontinued any chemotherapy	5	(8.3)	20	(6.5)	2	(4.0)	14	(4.4)	3	(2.1)	15	(4.8)	89	(4.3)	156	(4.1)
discontinued all drugs	3	(5.0)	11	(3.5)	2	(4.0)	8	(2.5)	3	(2.1)	15	(4.8)	89	(4.3)	156	(4.1)

Safety related to drug-drug interactions and other interactions

No new drug-drug interaction data are available.

Immunogenicity

No new immunogenicity data are available.

Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation

Table 60: adverse event summary-treatment discontinuation

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Oesophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
discontinued any drug due to an adverse event	90	(24.3)	74	(20.0)	55	(12.0)	790	(13.4)
discontinued Pembrolizumab or placebo	54	(14.6)	45	(12.2)	55	(12.0)	790	(13.4)
discontinued any chemotherapy	75	(20.3)	69	(18.6)	55	(12.0)	790	(13.4)
discontinued all drugs	23	(6.2)	28	(7.6)	55	(12.0)	790	(13.4)
discontinued any drug due to a drug-related adverse event	72	(19.5)	43	(11.6)	27	(5.9)	410	(7.0)
discontinued Pembrolizumab or placebo	35	(9.5)	15	(4.1)	27	(5.9)	410	(7.0)
discontinued any chemotherapy	58	(15.7)	42	(11.4)	27	(5.9)	410	(7.0)
discontinued all drugs	16	(4.3)	10	(2.7)	27	(5.9)	410	(7.0)
discontinued any drug due to a serious adverse event	58	(15.7)	47	(12.7)	44	(9.6)	572	(9.7)
discontinued Pembrolizumab or placebo	47	(12.7)	43	(11.6)	44	(9.6)	572	(9.7)
discontinued any chemotherapy	43	(11.6)	41	(11.1)	44	(9.6)	572	(9.7)
discontinued all drugs	21	(5.7)	27	(7.3)	44	(9.6)	572	(9.7)
discontinued any drug due to a serious drug-related adverse event	38	(10.3)	17	(4.6)	18	(3.9)	245	(4.2)
discontinued Pembrolizumab or placebo	29	(7.8)	14	(3.8)	18	(3.9)	245	(4.2)
discontinued any chemotherapy	25	(6.8)	16	(4.3)	18	(3.9)	245	(4.2)
discontinued all drugs	14	(3.8)	10	(2.7)	18	(3.9)	245	(4.2)

Table 61: Subjects With Adverse Events Resulting in Any Treatment Discontinuation (ASaT Population) (extract)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
with one or more adverse events	90	(24.3)	74	(20.0)	55	(12.0)	790	(13.4)
with no adverse events	280	(75.7)	296	(80.0)	403	(88.0)	5,094	(86.6)
Pneumonia	10	(2.7)	9	(2.4)	4	(0.9)	31	(0.5)
Blood creatinine increased	8	(2.2)	11	(3.0)	0	(0.0)	1	(0.0)
Acute kidney injury	4	(1.1)	2	(0.5)	1	(0.2)	6	(0.1)
Pneumonitis	6	(1.6)	0	(0.0)	7	(1.5)	96	(1.6)

Table 62: Subjects With Adverse Events Resulting in Treatment Interruption (ASaT Population) (extract)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶		Pooled Esophageal Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	370		370		458		5,884	
Treatment interruption of ANY drugs:								
with one or more adverse events	262	(70.8)	242	(65.4)	128	(27.9)	1,492	(25.4)
Treatment interruption of ALL drugs:								
with one or more adverse events	186	(50.3)	180	(48.6)	128	(27.9)	1,492	(25.4)
Treatment interruption of pembrolizumab/placebo:								
with one or more adverse events	247	(66.8)	234	(63.2)	128	(27.9)	1,492	(25.4)

The most common AE leading to treatment interruption was neutropenia.

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2018 through 03-SEP-2019. No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country. Within the period reviewed, 3,776,415 dosage units were sold in post-authorisation setting (cumulatively 7,684,671). The cumulative post-marketing exposure of the previous PSUR was approximately 99,173 patient-years of treatment with pembrolizumab.

From clinical trials, a total of 32,845 serious adverse events were reported cumulatively. From post-authorisation sources, a total of 53,255 adverse reactions were reported cumulatively (36,092 spontaneous; 17,163 solicited). Of these, 15,653 reactions were considered non-serious and 37,602 reactions were classified as serious (20,439 spontaneous; 17,163 solicited). During the period under

review, there were 8,569 serious spontaneous; 5,703 non-serious spontaneous and 6,139 serious solicited. The most frequently reported serious adverse reactions during the period under review are malignant neoplasm progression, death and known immune-related adverse reactions such as colitis, hepatitis, pneumonitis/interstitial lung disease, thyroid disorders and adrenal insufficiency.

3.5.1. Discussion on clinical safety

Data from the primary analysis of the pivotal study KEYNOTE-590 (KN590) with data cut-off of 02-JUL-2020 were submitted.

The median duration of exposure to therapy was similar between the two arms of KN590 study (5.7 vs 5.1 months). The median number of cycles of pembrolizumab in the experimental arm of KN590 were doubled compared to the oesophageal monotherapy dataset (8 vs 4), which can be explained by the more advanced setting of the studies included in the pooled dataset. Treatment with 5-FU may have continued beyond 6 cycles per local standard up to 35 cycles: median number of 5-FU cycles were 6 in both arms of KN590, as this was balanced no impact on efficacy or safety results are expected.

Regarding the **summary of adverse events**, no major relevant differences are observed between pembrolizumab + platinum/5-FU vs placebo + platinum-5-FU, also after adjusting for exposure. The noted exception is that more patients discontinued any drug due to drug-related AEs (19.5% vs 11.6%) and drug-related SAEs (10.3% vs 4.6%) in the pembrolizumab combination arm, and a small difference of the discontinuation rate is maintained after exposure adjustment. In addition, the observed incidence of related SAEs (31.6% vs 26.2%) and drug-related Grade 3-5 AEs (71.9% vs 67.6%) was higher for the pembrolizumab chemo combo, as well as few more deaths due to drug-related AEs were observed (9 vs 5 deaths, i.e. 2.4% vs 1.4%).

As expected, the toxicity in the pembrolizumab + chemotherapy arm of KN590 study was worse compared to pembrolizumab monotherapy in the oesophageal dataset and in the RSD.

To better contextualize KN590 safety data with respect to the overall toxicity of pembrolizumab given with chemotherapy, a pooled safety dataset representing the established safety profile for pembrolizumab plus platinum-based chemotherapy in currently EU approved indications was provided (KN-021, KN-189, KN-407 and KN-048 studies). KN-590 appears to have a quite similar summary of adverse events, with the exception of a higher incidence of Grade 3-5 (85-9% vs 75%) and drug-related grade 3-5 AEs (71.9% vs 57.4%). However, since a higher incidence is also noted in the placebo+chemotherapy arm of KN-590, this could be related to backbone chemotherapy and baseline disease.

In KN590 a comparison of the frequencies of the most common **AEs** by treatment group showed high incidences of nausea, anaemia, decreased appetite and constipation in both arms (>40%). Higher rates of fatigue, WBC count decreased, neutrophil count decreased, rash, hypothyroidism and pruritus were observed in the pembrolizumab + chemotherapy group than in the chemotherapy group, and remained higher even after adjustment for exposure, with the exception of fatigue and neutrophil count decreased. Severe skin reactions and hypothyroidism are known AEOSI for pembrolizumab. The differences in safety profile observed between the pembrolizumab + chemotherapy arm of KN590 and the monotherapy datasets are consistent with the established safety profiles of the chemotherapies administered.

Regarding **drug-related AEs** pembrolizumab + chemotherapy could be regarded as comparable to placebo+chemotherapy; differences (>3%) were detected for neutrophil count decreased and white blood cell count decreased toxicities with higher incidences in the pembrolizumab+chemotherapy arm; anaemia was reported with higher rates in the placebo+chemotherapy arm. When comparing the pembrolizumab + chemotherapy KN590 Dataset with the monotherapy RSD, the rates for drug-related AEs were overall significantly higher, as expected.

In both arms, most of the AEs were **Grade 3-5**, with similar rate in both arms (85.9% vs 86.2%). Neutrophil count decreased, anemia, neutropenia and hyponatremia were the most common G3-5 AEs in both arms (≥10%). Despite the higher incidence of WBC and neutrophil count decrease in the pembrolizumab + chemotherapy arm, observed also after adjustment for exposure, rates of febrile neutropenia were comparable between the 2 groups (3.2% vs 4.1%). As expected, G3-5 AEs occurred more frequently when pembrolizumab was administered with chemotherapy than as a single agent (85.9% vs 48.1% in the RSD), and reflected the known safety profile of the cytotoxic agents and the underlying oesophageal disease.

Drug-related Grade 3 to 5 AEs occurred also at similar rate in the two treatment arms (71.9% vs 67.6%). The most frequently reported drug-related Grade 3 to 5 AEs in both treatment arms were decreased neutrophil count, neutropenia and anaemia. The rate of drug-related grade 3-5 febrile neutropenia was similar between arms (3% vs 3.8%), with one death due to febrile neutropenia in each arm. A total of 7 cases (1.9%) of grade 3-5 drug-related pneumonitis occurred in the pembrolizumab combination arm, vs none in the control. This incidence is however similar to the pembrolizumab monotherapy safety datasets (1.3%) and therefore can be considered consistent with the known pembrolizumab safety profile. Compared to the monotherapy safety datasets, the overall incidence of drug-related Grade 3 to 5 AEs was substantially higher in the pembrolizumab plus chemotherapy group (71.9% vs 15.5% in the RSD).

The overall incidence of **SAEs** was approximately 55% in both treatment groups of KN590 study, pneumonia being the most common SAE in both arms (10.3% vs 8.6%); although at higher incidence in the pembrolizumab + chemotherapy group, reassuringly no difference is observed when pneumonia is adjusted for exposure (15 vs 17.2 Events/100 person-year). **Drug-related SAE** by investigator also occurred at a similar incidence in the two arms (31.6% vs 26.2%), but were numerically higher compared to the RSD, which seems to generally reflect the course of the chemotherapy (cisplatin and 5-fluorouracil) and the underlying disease.

It is noted that incidence of **acute kidney injury** SAE was almost doubled in the pembrolizumab + chemotherapy group compared to the chemotherapy group of KN590 study (3% vs 1.6%), as well as Grade 3-5 events (2.7% vs 1.9%), including one fatal grade 5 event (vs none in the SOC). Acute kidney injury lead also more frequently to treatment discontinuation in the experimental arm (1.1% vs 0.5%). Acute kidney injury is reported as a common ADR in section 4.8 of the SmPC, which is considered sufficient at this stage based on the data provided. Narratives for the 13 cases (8 in the pembro combo and 5 in the control arm of KN590) of acute kidney injury were reviewed, all (except of 1 fatal event in the pembrolizumab and chemotherapy arm) were Grade 2-3 and often resolved or resolving. All events were considered related to cisplatin. Incidences are too small and the difference in incidences between the control and the pembrolizumab + chemotherapy arm is not clear enough to allow any conclusions about potential additive effects of pembrolizumab on the known renal toxicities of cisplatin.

The overall incidence of **AEs resulting in death** was not worse with the combination pembrolizumab + chemotherapy compared to chemotherapy alone (28 vs 38 patients, 7.6% vs 10.3%). The most frequently reported AEs leading to death in the pembrolizumab combination arm were related to respiratory infections (pneumonia, pneumonia aspiration, and pulmonary sepsis). Pneumonia was the most common cause of death in the chemotherapy arm as well. The overall incidence of AEs resulting in death in the pembrolizumab + chemotherapy group (7.6%) was higher than that of the pembrolizumab monotherapy RSD (5.3%), but similar to the oesophageal monotherapy dataset (8.5%); in this latter dataset, again respiratory infections (pneumonia aspiration and pneumonia) were the most frequent cause of death, which appeared to be related to the underlying oesophageal disease.

Deaths considered **drug-related** by the investigator were 9 vs 5 (2.4% vs 1.4%) in the pembrolizumab + chemotherapy vs chemotherapy arm of KN590 study. Although drug-related death has been observed at higher incidence in the experimental arm, such difference appears negligible after adjustment for exposure

(0.28 vs 0.20 event/100 person-month), which is reassuring. In most of the cases, it is difficult to clearly attribute the events to one or the other drug of the combination.

The most common AEOSI categories (≥5%) in the pembrolizumab plus chemotherapy group were hypothyroidism, pneumonitis, and hyperthyroidism, having similar incidences to the pembrolizumab monotherapy RSD. The majority of AEOSI reported in the pembrolizumab + chemotherapy group were mild to moderate (Grade 1 or 2). There were two cases of fatal AEOSI (pneumonitis and interstitial lung disease, vs 1 patient in the control arm who died due for pneumonitis).

The rate of **pneumonitis** was 6.2% for the combination (vs 0.5% in the chemotherapy arm), higher than what was reported with pembrolizumab alone (5.2% in the oesophageal dataset and 4.5% in the RSD), which were also more severe. The exposure-adjusted rate of pneumonitis showed a similar event rate compared to pembrolizumab monotherapy oesophageal dataset, the latter slightly higher than the monotherapy RSD, possibly related to the oesophageal localization of the disease than of the combination in itself. Due to the small number of patients with pneumonitis who had prior thoracic RT, it is not possible to draw meaningful conclusion about the role of prior thoracic RT in the risk of pneumonitis.

No new safety concerns based on **laboratory abnormalities** were reported in the pembrolizumab plus chemotherapy group, and differences observed between pembrolizumab combination and pembrolizumab monotherapy are consistent with the established safety profile of the chemotherapy drugs administered.

While the incidence of AEs (24.3% vs 20%) and SAEs (15.7% vs 12.7%) leading to **treatment discontinuation** was higher in the pembrolizumab + chemotherapy arm vs chemotherapy, the difference between arms is reduced when adjusted for exposure. Pneumonia, blood creatinine increase, pneumonitis and acute kidney injury were the most common AEs leading to treatment discontinuation in the pembrolizumab + chemotherapy group.

Most of the patients in the pembrolizumab + chemotherapy group had **treatment interruption** of <u>any</u> treatment due to AEs (70.8% vs 65.4%), and almost half of the subjects in both arms interrupted <u>all</u> treatment drugs.

Safety profile by subgroups: The AE profile according to **age** in the pembrolizumab plus chemotherapy group was generally similar between participants who were <65 years and ≥65 years, with the exception of discontinuation due to AE/SAE which occurred more frequently in the older age group, although the same trend is observed also in the chemotherapy arm.

When safety is analysed by age groups (<65, 65-74, 75-84, 85+), in the pembrolizumab + chemotherapy arm an increased percentage of patients who experienced Grade 3-5 AEs, SAE, death due to AEs and discontinuation in the 75-84 age group is observed compared to younger patients. The same trend is seen in the chemotherapy arm only for death due to drug-related AEs and treatment discontinuation. The toxicity of the pembrolizumab combination in patients aged 75-84 appears to be overall higher compared to the same age group of the chemotherapy arms (G3-5 AEs and drug-related AEs, SAE and drug-related SAE, death due to AE, discontinuation due to SAE and drug-related SAE, as well as slight increase in CNS and AE related to falling, CV and cerebrovascular events, infections).

In KEYNOTE 590, **patients aged ≥75 years** reported higher incidences (>10% difference) of Grade 3 to 5 AEs (84% vs. 75%), SAEs (78% vs. 50%), drug-related SAE (57% vs. 34%), deaths (27% vs. 13%), discontinuations due to SAEs (38% vs. 25%) and discontinuations due to drug-related SAEs (27% vs. 16%) in the pembrolizumab plus chemotherapy group compared to the chemotherapy group. Even in exposure adjusted analyses higher event rates were reported for pneumonitis (23 vs. 0 events/100 person year), pneumonia (45 vs. 12 events), neutrophil count decreased (96 vs. 35 events), diarrhea (40 vs. 6 events), vomiting (18 vs. 6 events), hyponatremia (74 vs. 35 events) and hypophosphatemia (23 vs. 0 events). Higher events for exposure-adjusted SAEs in the combination arm were reported for example for the SOCs gastrointestinal disorders (57 vs. 17 events/100 person year), infections and infestations (74 vs. 56

events), metabolism and nutrition disorders (51 vs. 12 events), and respiratory, thoracic and mediastinal disorders (62 vs. 17 events). In conclusion, data from KN-590 study showed a clear trend towards an increased toxicity for patients aged ≥75 years thus raising concern over the tolerability of pembrolizumab + chemotherapy combination in the elderly.

This increased risk of AEs in the elderly should be considered in the context of an expected lower benefit with higher age (see clinical efficacy). The limited sample size is acknowledged, however as the median age of patients with oesophageal cancer is approximately 68 years, the B/R in elderly is of special importance. As a result, it is considered clinically relevant to inform physicians in the SmPC (leaving room to treat especially fit patients despite the nominal age).

The tolerability of pembrolizumab combined with chemotherapy in patients aged ≥ 75 was questioned also in the assessment of previously approved combinations of pembrolizumab plus platinum-based chemotherapy in HNSCC and NSCLC (see EPAR var II/60 and II/65). However, the limited number of subjects in this age category in KN590 as well as in previous clinical trials hampered definitive conclusion. A pooled safety analysis of KN590 with pivotal studies for the EU approved combo indications (KN021, KN189, KN407 and KN048) included 128 vs 114 patients 75 years and older in the pembrolizumab combination vs chemotherapy, respectively, representing approximately 9% of the overall population. A trend toward higher incidence of overall toxicity by class of age is observed in the pembrolizumab combination pooled arm, although the same trend is present also in the chemotherapy group. When comparing each class of age (<65, 65-74, >=75) in both arms, overall a higher toxicity is evident with the addition of Keytruda to the combination.

Acknowledging the limited number, no meaningful differences in the overall AE profile between male and female participants are observed.

The AE profile based on **region** (EU vs Ex-EU) did not show relevant differences, although with the limitations of interpretability of the small sample size in the EU.

3.5.2. Conclusions on clinical safety

The combination of pembrolizumab + chemotherapy did not widely worsen the overall toxicity of chemotherapy alone. The safety profile of the combination reflected the established safety profiles of the chemotherapy administered (cisplatin and 5-Fluoruracil) and of pembrolizumab monotherapy. Toxicities could be mainly attributed to the chemotherapy regimen and the underlying disease. AEOSI were similar to the established safety profile for pembrolizumab monotherapy. Data from KEYNOTE-590 study showed a trend towards an increased toxicity for patients aged ≥75 years, thus raising concern over the tolerability of pembrolizumab + chemotherapy combination in the elderly. No new safety concerns were identified.

3.5.3. 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.

3.6. Risk management plan

The MAH submitted an updated RMP version 30.0 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 30.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 30.0 with the following content:

Safety concerns

Table 63: List of safety concerns

List of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

The list of the safety specifications remains unchanged. No new safety concerns have been identified from the submitted data supporting the new indication.

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab. Routine pharmacovigilance activities are sufficient to address the risk of Keytruda in all approved indications.

Risk minimisation measures

Table 64: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Table 64: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trials (KN087, KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

The risk minimisation measures remain unchanged and sufficient to mitigate the risks in all approved indications.

3.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, and 5.1, 5.2 and 5.3 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly. Minor updates are also included in Annex II of the Product Information.

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

3.7.1. 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:

- no significant changes are made to the package leaflet; in particular, the key messages for the safe use of the medicinal product are not impacted.

- the design, layout and format of the package leaflet will not be affected.

4. Benefit-Risk Balance

4.1.1. Disease or condition

Unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults.

The CHMP adopted an extension of indication for KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, in the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10.

4.1.2. Available therapies and unmet medical need

Currently, the management of inoperable locally advanced and/or metastatic (stage IV) disease is palliative in intent, with different chemotherapy-based options being indicated as first-line option in fit patients. For HER-2 negative adenocarcinoma (AC) tumours, doublet combinations of platinum (cisplatin, oxaliplatin, or carboplatin) and fluoropyrimidines (5-FU or capecitabine) are generally used; triplet regimens with the addition of anthracycline or taxanes can also be considered, although controversy remains as regards their clinical advantage. In HER-2 positive AC tumours, trastuzumab in addition to cisplatin and 5-fluorouracil or cisplatin and capecitabine is indicated. In SCC, cisplatin-based combinations showed increased response rate but no survival gain compared with monotherapy; overall, results with palliative chemotherapy are worse than AC tumours (for references see section 3.1.1.)

4.1.3. Main clinical studies

KEYNOTE-590 is an ongoing, Phase 3, randomized, double-blind, placebo-controlled, multisite study to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy (cisplatin and 5-FU) versus chemotherapy (cisplatin with 5-FU) as 1L treatment in participants with locally advanced unresectable metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction

4.2. Favourable effects

In participants with ESCC and PD-L1 CPS ≥10, pembrolizumab as add-on to chemotherapy provided a statistically significant improvement in OS compared with chemotherapy alone (HR:0.57; 95% CI: 0.43, 0.75; p<0.0001)

Within the entire ESCC group regardless of PD-L1 score, the positive effect of pembrolizumab on OS was attenuated in magnitude but remains statistically significant compared to control (HR:0.72; 95% CI: 0.60, 0.88; p<0.0006).

OS analysis in the adenocarcinoma subtype showed superiority of pembrolizumab + chemotherapy vs control (HR:0.74; 95% CI: 0.54, 1.02; p<0.0006).

Within the totality of PD-L1 positive tumours pembrolizumab plus chemotherapy was more advantageous than control in terms of OS (HR:0.62; 95% CI: 0.49, 0.78; p<0.0001).

Within the ITT population encompassing all histologies and PD-L1 status, pembrolizumab demonstrated superiority on OS relative to control (HR:0.73; 95% CI: 0.62, 0.86; p<0.0001) with a 3 month gain in median OS (12.4 vs 9.8 months in control).

Investigator-Based Analysis showed superiority of pembrolizumab plus chemotherapy versus chemotherapy alone within the ESCC population (HR:0.65; 95% CI:0.54, 0.78; p<0.0001), PD-L1 positive group (HR:0.51; 95% CI:0.41, 0.65; p<0.0001) and ITT population (HR:0.65; 95% CI:0.55, 0.76; p<0.0001).

Within the ITT population, ORR (CR+PR) was judged similarly by Investigators (45% vs 29.3% in pembrolizumab and control arm, respectively) and centralised analysis (43.4% vs 29% in pembrolizumab and control arm, respectively).

4.3. Uncertainties and limitations about favourable effects

- The benefit in the overall study population was driven by the biomarker positive subgroup. No clinically meaningful benefit was observed for subjects whose tumours express PD-L1 CPS <10 (n=347).

CPS <10:	OS HR 0.86 (95% CI 0.68, 1.10)	median OS 10.5 vs. 10.6 months
	PFS HR 0.8 (95% CI 0.64, 1.01)	median PFS 6.2 vs. 6.0 months
	ORR difference 6.8%	38.9% vs. 32.0%

- Elderly patients ≥75 years do not derive an obvious benefit (n=69; OS HR 0.98, PFS HR 0.93) in the overall study population. Data are limited in patients ≥ 75 years for pembrolizumab in chemotherapy combination in patients with oesophageal carcinoma as reflected in section 4.2 of the SmPC.

4.4. Unfavourable effects

The most common AEs (incidence ≥ 40%) in both arms were nausea, anemia, decreased appetite, fatigue and constipation. Higher rates of fatigue, WBC count decreased, neutrophil count decreased, rash, hypothyroidism and pruritus were observed in the pembrolizumab + chemotherapy group than in the chemotherapy group, and remained higher even after adjustment for exposure, with the exception of fatigue and neutrophil count decreased.

The rate of **Grade 3 to 5 AEs** in KEYNOTE-590 was similar in both arms (85.9% vs 86.2%). Neutrophil count decreased, anemia, neutropenia and hyponatremia were the most common G3-5 AEs (incidence ≥10%). Reassuringly, rates of febrile neutropenia were comparable between the 2 groups (3.2% vs 4.1%).

The overall incidence of **SAEs** was approximately 55% in both treatment groups of KN590 study, being pneumonia the most common SAE in both arms (10.3% vs 8.6%). The largest difference between treatment arms was noted for the SAE pneumonitis (3.2% vs 0%).

The overall incidence of **AEs resulting in death** was 7.6% vs 10.3%. The most frequently reported AEs leading to death were related to respiratory infections in both arms of KN590 as well as in the oesophageal pembrolizumab monotherapy dataset, which is possibly related to the oesophageal site of the tumour.

Drug-related deaths according to the investigator were 9 vs 5 (2.4% vs 1.4%), although such difference appears negligible after adjustment for exposure (0.28 vs 0.20 event/100 person-month)

The incidence of **AEOSI** in the pembrolizumab plus chemotherapy group was 25.7%. The most common AEOSI categories (≥5%) in the pembrolizumab plus chemotherapy group were hypothyroidism, pneumonitis, and hyperthyroidism. Grade 3 to 5 AEOSI occurred in 7% of participants, including 2 fatal cases (pneumonitis and interstitial lung disease).

Treatment discontinuation occurred in 24.3% vs 20% due to AEs and in 15.7% vs 12.7% due to SAEs in the pembrolizumab + chemotherapy arm vs chemotherapy, respectively. The difference between arms

is reduced when adjusted for exposure. Pneumonia, blood creatinine increase, pneumonitis and acute kidney injury were the most common AEs leading to treatment discontinuation.

Data from KN-590 study showed a clear trend towards an increased toxicity for patients aged ≥75 years, thus raising concern over the tolerability of pembrolizumab + chemotherapy combination in the elderly. This is also relevant in the context of an expected lower benefit with higher age (see clinical efficacy). The limited sample size is acknowledged, however as the median age of patients with oesophageal cancer is considered to be 68 years, the B/R in elderly is of special importance (see sections 4.4 and 5.1 of the SmPC).

4.5. Uncertainties and limitations about unfavourable effects

None

4.6. Effects Table

Table 65: Effects Table for KEYTRUDA in combination with platinum and fluoropyrimidine based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma with PD-L1 status CPS≥10 in adults (KEYNOTE-590 study, data cut-off: 02-JUL-2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (CPS≥10)						
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	13.5 (11.1,15.6)	9.4 (8.0,10.7)	Study double-blind, consistent results between INV and independent assessment of PFS Response was PD-L1 dependent. Trend for lower treatment effect for ex-Asian population, elderly ≥75 years and female subpopulation.	CSR KN-590
			HR 0.62 (95% CI 0.49, 0.78) P<0.0001			
PFS	duration of survival without progression from randomization to PD or death whichever occurred first	months (95% CI)	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)		
			HR 0.51 (95% CI 0.41, 0.65) P<0.0001			
ORR	Confirmed CR + PR	% (95% CI)	51.1 (43.7, 58.5)	26.9 (20.8, 33.7)		
DoR	Duration of CR/PR until documented PD	months (range)	10.4 (1.9, 28.9+)	5.6 (1.5+, 25+)		
Unfavourable Effects						
AE summary	AE	%	100	99.5	No major relevant worsening of the toxicity compared to chemotherapy alone.	CSR KN-590
	drug related AE		98.4	97.3		
	G3-5 AE		85.9	83.2		
	drug related G3-5 AE		71.9	67.6		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	SAE		55.4	55.1	Safety of the combination consistent with the established safety profile of the chemotherapy (cisplatin+5 FU) and pembrolizumab. No new safety concern identified. Worse toxicity in elderly, (⩾75 years) compared to chemotherapy and to the combination in younger age.	
	drug related SAE		31.6	26.2		
	death due to AE		7.6	10.3		
	death due to drug related AE		2.4	1.4		
	discontinuation of any drug due to AE		24.3	20		
	discontinuation of any drug due to drug related AE		19.5	11.6		
	discontinuation of any drug due to SAE		15.7	12.7		
	discontinuation of any drug due to drug related SAE		10.3	4.6		
AEOSI	hypothyroidism		10.8	6.5		
	pneumonitis		6.2	0.5		
	hyperthyroidism		5.7	0.8		

Abbreviations: AE: adverse event; SAE: serious adverse event; AEOSI: adverse event of special interest.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The combination of pembrolizumab + cisplatin/5-fluorouracil provided a clinically and statistically significant advantage on primary and secondary outcomes over chemotherapy alone in the ITT population. However, these results were driven by the treatment effect of pembrolizumab in the biomarker positive subgroup and the observed benefit for subjects whose tumours express PD-L1 CPS <10, representing approximately half of the study population, cannot be regarded as clinically meaningful.

The combination pembrolizumab + cisplatin/5-fluoruracil causes an increase in toxicity as the typical AE of checkpoint inhibition do not overlap with the toxicity of chemotherapy. As chemotherapy in itself is already rather toxic the increase toxicity by the combination is not reflected in simple metrics such as patients with SAE or higher grade AE. Nonetheless, higher toxicity rates were reported for nearly all categories in the pembrolizumab/chemo combination compared to the chemotherapy control or the pembrolizumab monotherapy reference data; however, no new safety concerns were identified. For elderly patients (≥75 years) increased toxicity is noted compared to chemotherapy alone.

4.7.2. Balance of benefits and risks

Study KEYNOTE-590 demonstrated a clinically relevant advantage in OS, PFS and ORR of pembrolizumab in combination with cisplatin/5-fluoruracil compared to chemotherapy alone in the first line treatment of advanced/metastatic oesophageal cancer patients. However, the observed benefit in the large CPS<10 subgroup is not considered to outweigh the increased toxicity that is associated with the add-on therapy.

4.7.3. Additional considerations on the benefit-risk balance

Considerations regarding the benefit in the PD-L1 CPS<10 subgroup:

The treatment benefit of pembrolizumab in the overall study population is driven by the subgroup of patients with high PD-L1 expression status. For participants whose tumours express PD-L1 CPS <10, the OS HR was 0.86 (95% CI: 0.68, 1.10). Median OS (10.5 vs 10.6 months) as well as OS rates at 12 and 18 months

(differences 4.8% and 3.9%) were similar between the two treatment groups. OS KM curves illustrate that the OS curve of the combination therapy lies only marginally above the chemotherapy arm and a small separation is shown only from months 11 onwards. Taken together, the OS curves indicate that only uncertain or little survival advantage by the addition of pembrolizumab to the combination therapy. This is also reflected by the OS events: n=132 (75.4%) in the pembrolizumab + chemotherapy arm compared to n=139 (80.8%) in the placebo + chemotherapy arm. The difference in ORR rate was 6.8% in the PD-L1 <10 subgroup (difference in patient numbers with response n=13 for the 175 patients in the PD-L1 <10 population). A clinically meaningful benefit could neither be shown regarding PFS (HR 0.8; 95% CI 0.64, 1.01) in the PD-L1 <10 subgroup; Median PFS is 6.2 vs 6.0 months, the difference in the PFS rate is 4% at 12 and 18 months. For comparison, in subjects with PD-L1 CPS ≥10, the OS HR was 0.62, the PFS HR was 0.51 and the difference in ORR was 24%.

It is acknowledged that efficacy analyses in the PD-L1 CPS <10 population were not prespecified and PD-L1 expression was not included as stratification factor. Nonetheless, biomarker negative patients represent nearly half of the study population, the distribution of PD-L1 expression status was balanced between treatment arms and the difference in treatment effect in both biomarker subgroups is biologically plausible in view of the MoA and consistent considering the known predictive value based on previous study results in gastroesophageal cancer. The CHMP had highlighted the necessity to account for biomarker status when planning stratification and analyses strategy and emphasised that "at the time of assessment, the magnitude of the effect in the overall population and in both biomarker positive and negative subgroups will be taken into account" (procedure EMEA/H/SA/2437/19/2017/II).

The overall evidence appears to suggest that indeed only very few patients would benefit from the addition of pembrolizumab to the already toxic chemotherapy combination. In this context, the rather vulnerable and in clinical practise mostly elderly patient population and the palliative treatment setting should be considered. Exposing all patients to the additional toxicity of pembrolizumab when only half of the patient population would be expected to benefit with a reasonable probability is not considered justified. The B/R would be judged differently in a situation, where the experimental therapy could be applied as an alternative treatment and with a possibly different safety profile providing further treatment options for individual treatment decisions.

To conclude, the add-on nature of the proposed treatment inevitably carries increased toxicity to patients, which are even more compelling in elderly people. Within the setting of a combined therapy, the uncertainties around the add-on efficacy is a critical aspect to conclude on a favourable B/R ratio. In this case, the uncertainties in efficacy relatively to increased toxicity, render the benefit/risk balance unfavourable in the CPS<10 group.

4.8. Conclusions

The overall B/R of Keytruda in combination with platinum-and fluoropyrimidine-based chemotherapy for the 1L treatment of patients with advanced oesophageal or EGJ carcinoma is positive for the biomarker positive subgroup PD-L1 CPS≥10.

5. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 28 out of 31 votes, 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 in combination with platinum and fluoropyrimidine based chemotherapy, first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10, based on the results from the pivotal KEYNOTE-590 (KN590) trial. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Minor updates are also included in Annex II of the Product Information. Version of the RMP (Version 31.0) has also been submitted.

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 Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Divergent position to the majority recommendation is appended to this report.

6. APPENDIX

1. APPENDIX Divergent position dated 20 May 2021.

APPENDIX

DIVERGENT POSITION DATED 20 May 2021

DIVERGENT POSITION DATED 20 May 2021

Keytruda EMEA/H/C/003820/II/0097

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the following restricted new indication for Keytruda: in combination with platinum and fluoropyrimidine based chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10.

The reason for divergent opinion was the following:

Within the ITT population, encompassing patients irrespective of PD-L1 expression, the add on of pembrolizumab to chemotherapy demonstrated superiority on OS relative to chemotherapy alone (HR:0.73; 95% CI: 0.62, 0.86; p<0.0001). Therefore, the pivotal trial for this application was positive on the primary endpoint in the all-comer population.

In the subgroup of patients with CPS<10, the OS HR was 0.86 (95%CI 0.68-1.10). The size of this subgroup does not allow for an independent establishment of efficacy with statistical certainty. However, the reality of an effect is supported by a PFS HR of 0.8 (95%CI 0.64-1.01) and a modest increase in objective response rate. While the addition of Keytruda to chemotherapy does increase toxicity, this is considered moderate and manageable.

Thus, a positive B/R has been demonstrated in the full study population.

Given these circumstances, we do not support the decision to limit the indication to patients with a CPS score ≥10.

Hillege Johann Lodewijk

Dunder Kristina

Concha Prieto Yerro