EMA/CHMP/128687/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0072

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	01 Mar 2019	01 Mar 2019	☐
☐	CHMP Co-Rapporteur Assessment Report	25 Apr 2019	26 Apr 2019	☐
☐	CHMP Rapporteur Assessment Report	25 Apr 2019	26 Apr 2019	☐
☐	PRAC Rapporteur Assessment Report	02 May 2019	30 Apr 2019	☐
☐	PRAC members comments	07 May 2019	07 May 2019	☐
☐	Updated PRAC Rapporteur Assessment Report	08 May 2019	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	16 May 2019	16 May 2019	☐
☐	CHMP members comments	20 May 2019	20 May 2019	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2019	23 May 2019	☐
☐	Request for supplementary information	29 May 2019	03 June 2019	☐
	Submission of MAH's responses	19 Jul 2019	19 Jul 2019	
☐	Re-start of procedure:	22 Jul 2019	22 Jul 2019	☐
☐	CHMP Rapporteur(s) (Joint) Assessment Report	20 Aug 2019	22 Aug 2019	☐
☐	PRAC Rapporteur Assessment Report	23 Aug 2019	n/a	☐
☐	PRAC members comments	28 Aug 2019	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	29 Aug 2019	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	05 Sep 2019	n/a	☐
☐	CHMP members comments	09 Sep 2019	09 Sep 2019	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 Sep 2019	n/a	☐
☐	2nd Request for supplementary information	19 Sep 2019	19 Sep 2019	☐
	Submission of MAH's responses	15 Oct 2019	15 Oct 2019	
☐	Re-start of procedure:	16 Oct 2019	16 Oct 2019	☐
☐	CHMP Rapporteur(s) (Joint) Assessment Report	30 Oct 2019	31 Oct 2019	☒
☐	CHMP members comments	04 Nov 2019	n/a	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 Nov 2019	n/a	☐
☒	3rd Request for supplementary information	14 Nov 2019	14 Nov 2019	☐

Procedure resources	
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Table of contents

List of abbreviations

Abbreviation	Definition
1L	First-line chemotherapy (participants who have not received any prior chemotherapy)
2L	Second-line chemotherapy (participants who have received 1prior chemotherapy)
2L+	Second-line or later chemotherapy (participants who have received 1 or more prior chemotherapies)
3L+	Third-line or later chemotherapy (participants who have received 2 or more prior chemotherapies)
5-FU	5-fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
AEOSI	Adverse event of special interest
ASaT	All Subjects as Treated; for KEYNOTE-180: all subjects who received at least one dose of pembrolizumab
BICR	Blinded Independent Central Radiology Review
CD	Cluster of differentiation
cHL	Classical Hodgkin Lymphoma
CI	Confidence interval
CL	Clearance
CPS	Combined positive score
CR	Complete response
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DOR	Duration of response
EAC	Oesophageal/esophageal adenocarcinoma, includes adenocarcinoma of the EGJ
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EGJ	Oesophagogastric junction
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-EOS18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire in Oesophageal Cancer 18
EQ-5D	EuroQoL-5 dimensions
ESCC	Oesophageal squamous cell carcinoma
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio

Abbreviation	Definition
ICF	Informed consent form
IHC	Immunohistochemistry
ITT	Intention-to-Treat
KM	Kaplan-Meier
LS	Least squares
mAb	Monoclonal antibodies
MSI	Advanced microsatellite instability
NSCLC	Nonsmall cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease/disease progression
PD-1	Programmed cell death
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death-1 ligand-2
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcomes
PS	Performance Status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
R/M	Recurrent/metastatic
RSD	Reference Safety Dataset
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SOC	Standard of care
USA/US	United States of America
VAS	Visual analog scale
Vc	Volume of distribution

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 12 February 2019 an application for a variation.

The following changes were proposed:

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 a new indication for Keytruda as monotherapy, for the "*treatment of recurrent locally advanced or metastatic oesophageal cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have received prior systemic therapy*", based on the results from KEYNOTE-181; an international, randomized, open-label Phase 3 trial of pembrolizumab versus the investigator's choice of paclitaxel, docetaxel, or irinotecan in participants with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus, or advanced/metastatic Siewert type I adenocarcinoma of the oesophagogastric junction; as a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to include editorial corrections to the updated version of the RMP (Version 25.1) submitted with this application.

The requested variation proposed 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(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

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

The PDCO issued an opinion on compliance for the PIP P/0043/2018.

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 applicant 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 received Scientific Advice from the CHMP on 23 March 2017 (EMA/CHMP/SAWP/172550/2017). This pertained to the design of the proposed 1L oesophageal cancer study (KN590), no Scientific Advice was requested for KEYNOTE-181.

2. Scientific discussion

2.1. Introduction

This application concerns an extension of indication for Keytruda as monotherapy for the "*treatment of recurrent locally advanced or metastatic oesophageal cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have received prior systemic therapy*".

Pembrolizumab

Keytruda (pembrolizumab, MK-3475) is a humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using a mAb can result in activation of antitumor T cells and subsequent tumor regression. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. 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 nonspecifically activate T cells. The PD-1 pathway, especially the PD-1 receptor-ligand interaction, represents a major immune-control switch that may be engaged by ligands expressed in the tumor microenvironment to overcome active antitumor-specific T cell immune surveillance.

Keytruda is approved in EU for melanoma, NSCLC (both monotherapy and in combination with chemotherapy), refractory classical Hodgkin lymphoma, urothelial carcinoma, second-line HNSCC and adjuvant melanoma (application for 1L HNSCC and 1L RCC ongoing).

Clinical studies are being conducted in these tumor types, as well as in several other advanced solid tumor indications and hematologic malignancies.

Esophageal cancer

According to GLOBOCAN 2018, esophageal cancer ranks seventh in terms of incidence (572,000 new cases) and sixth in mortality overall (509,000 deaths), and is estimated to be responsible for an estimated 1 in every 20 cancer deaths in 2018. Oesophageal cancers are histologically classified as Esophageal Squamous cell Carcinoma (ESCC) or Esophageal Adenocarcinoma (EAC). The distribution of histology types varies between different geographic regions: ESCC is notably common in south-east and central Asia. EAC is most prevalent in Northern and Western Europe, North America, and Oceania. EAC represents the majority of esophageal cancer cases in high-income countries, with excess body weight and gastroesophageal reflux disease among the key risk factors.

Metastatic oesophageal cancer is a fatal disease, with an overall 5-year survival rate of 3.4% [Zhang Y, World J Gastroenterol 2013].

Current therapies for Esophageal Cancer

Cytotoxic chemotherapies have remained the mainstay for treatment of metastatic oesophageal cancer for many years. Global guidelines provide recommendations on preferred 1L, 2L, and subsequent systemic treatment for patients with oesophageal cancer. For previously untreated patients (1L), combination chemotherapies are routinely used. Although there are some differences among global guidelines, in general guidelines are consistent and recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), which provides moderate benefit but high toxicity. Taxanes or epirubicin are sometimes used in combination with fluoropyrimidine and platinum agents (Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2016; Pan-Asian adapted ESMO Clinical Practice Guidelines for the

management of patients with metastatic oesophageal cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MSO, SSO and TOS, 2019; NCCN Clinical Practice Guidelines in Oncology: esophageal and esophagogastric junction cancers, version 1.2019)

The value of palliative chemotherapy is less proved in ESCC. Treatment guidelines for EAC were extrapolated from gastric cancer studies, despite the differences in biology between gastric and oesophageal cancers. For patients with human epidermal growth factor receptor 2 (HER2) positive EAC, based on the results of ToGA trial the guidelines recommend the addition of trastuzumab to first-line chemotherapy.

Several regimens were evaluated as 2L treatments for advanced or metastatic oesophageal cancer [see Table below. The ESMO and NCCN treatment guidelines include docetaxel, paclitaxel, and irinotecan, which show marginal benefit (median OS ranging from 4.0 months to 8.1 months and ORR ranging from 0% to 28.0%).

Table: Second-line Treatment Outcomes from Studies in Oesophageal Cancer

Treatment Drug	Histology (n)	Study Design	Patients in Study	ORR (%)	Median TTP/PFS (months)	Median OS (months)	Reference
Docetaxel	EAC (22)	Non-randomised Phase 2	22 (7 who received prior chemotherapy but not paclitaxel)	0[a]	1.4[a]	4[a]	Heath EI, et al. Invest New Drugs 2002
Paclitaxel	ESCC (31)	Non-randomised Phase 2	31	19.4	2.5 (PFS)	6.1	Shirakawa T, et al. Cancer Chemother Pharmacol 2014
Docetaxel	ESCC (132)	Non-randomised Phase 2	132	5.3	2.3 (PFS)	5.5	Shirakawa T, et al. Cancer Chemother Pharmacol 2014
Docetaxel	ESCC (46), EAC (1), and Other (2)	Non-randomised Phase 2	49	16	NR	8.1	K, et al. Ann Oncol 2004
Docetaxel	ESCC (21) and EAC (10)	Non-randomised Interventional Study	31	28	NR	NR	Metges J, et al. Proc ASCO Meeting, Abs.635 2001
Docetaxel	ESCC (28)	Retrospective Single Arm Study	28	18	2.1 (PFS)	5.1	Yamazaki K, et al. Int J Clin Oncol 2008
Irinotecan	ESCC (7) and EAC (7)	Non-randomised Phase 2	14	15	2 (PFS)	5	Burkart C, et al. Anticancer Res

							2007
Paclitaxel	ESCC (16) and EAC (71)	Randomised Phase 2[b]	87 (43 in paclitaxel only arm)	12[c]	2.6 (PFS)[c]	6.5[c]	Cohen SJ, et al. Proc ASCO Meeting, Abs.4020 2014
Paclitaxel	ESCC (3) and EAC (11)	Non-randomised Phase 2	14	0	NR	NR	Anderson SE, et al. Cancer Invest 2003

Abbreviations: EAC=oesophageal adenocarcinoma; ESCC=esophageal squamous cell carcinoma; IGF-IR=insulin-like growth factor receptor; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTP=time to progression.
[a] The data are for patients who received prior chemotherapy but not paclitaxel.
[b] This was a randomised Phase 2 study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab. Median PFS and OS for the cixutumumab arm were 2.3 and 6.4 months, respectively. The response rate was 14%.
[c] Data are for the paclitaxel only arm.

On July 30, 2019, FDA approved pembrolizumab for patients with recurrent, locally advanced or metastatic, squamous cell carcinoma of the esophagus whose tumors express PD-L1 with CPS≥10, with disease progression after one or more prior lines of systemic therapy.

Best supportive care is always indicated for patients with unresectable, locally advanced, recurrent or metastatic disease. The goal is to relieve symptoms and may result in prolongation of life, improvement of nutritional status, and improvement of quality of life: dysphagia, obstruction, bleeding, pain, nausea and vomiting are the most relevant signs and symptoms associated with esophageal cancer that are expected to impact on patients' status.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

- Tabular overview of clinical studies conducted with pembrolizumab monotherapy (pivotal trial highlighted by the Assessors)

Study ID / Status	Study Type/Design	Study Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-028 Ongoing	Phase 1 Multicentre, non-randomised, 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 Multicentre, non-randomised, single-arm, multicohort	Advanced/metastatic oesophageal cancer participants, 3L N=121	Pembrolizumab monotherapy (200 mg Q3W)	ORR
KEYNOTE-181 Ongoing	Phase 3 Multicentre, randomised, single-arm	Advanced/metastatic oesophageal cancer, 2L N=628	Pembrolizumab monotherapy (200 mg Q3W) or investigator's choice of paclitaxel, docetaxel, or irinotecan	OS

Abbreviations: 2L=second line; 3L=third line; ORR=objective response ratio or rate; OS=Overall survival; PFS=Progression-free survival; Q2W=once every 2 weeks; Q3W=once every 3 weeks.

2.3.2. Pharmacokinetics

Clinical pharmacology results to support the Extension of Indication for Keytruda to include a new indication in Oesophageal Cancer are available from the pivotal study KEYNOTE-181.

The updated clinical pharmacology results specific to this submission include:

- PK data of pembrolizumab at 200 mg Q3W obtained from subjects with advanced/metastatic squamous cancer and adenocarcinomas of the esophagus (ESO)(KEYNOTE-181)
- A comparison of KN181 observed PK data with reference model (TDPK) predicted PK.

Pharmacokinetic in target population

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

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.

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). This analysis is presented in the PK report (Report 04VNRS).

New data related to characterization of pharmacokinetics of pembrolizumab as monotherapy for the treatment of recurrent locally advanced or metastatic oesophageal cancer in adults whose tumours

express PD-L1 with a CPS ≥10 and who have received prior systemic therapy and a characterization of immunogenicity in this setting have been presented in this submission.

Pembrolizumab PK data from KEYNOTE-181 study

PK samples were collected and measured for 318 subjects in KN0181 ESO (200 mg Q3W).

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.

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]

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

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)	GM (SD)	AM (SD)	Min	Median	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

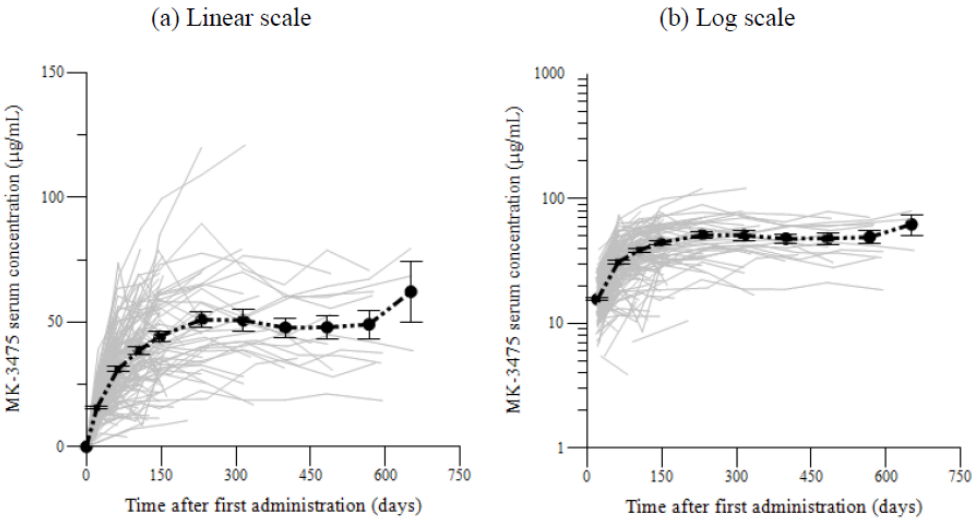
NOMTAFD (day)	Cycle (week)	Adenocarcinoma		Squamous cell carcinoma	
		N	GM(%CV) (µg/mL)	N	GM(%CV) (µg/mL)
21	Cycle 2 (Week 3)	95	12.9 (35.1)	179	15.5 (42.3)
63	Cycle 4 (Week 9)	44	25.9 (43.6)	114	29.1 (51.6)
105	Cycle 6 (Week 15)	25	26.8 (57.9)	81	38.5 (39.2)
147	Cycle 8 (Week 21)	16	32.4 (52.3)	60	42.7 (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:

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

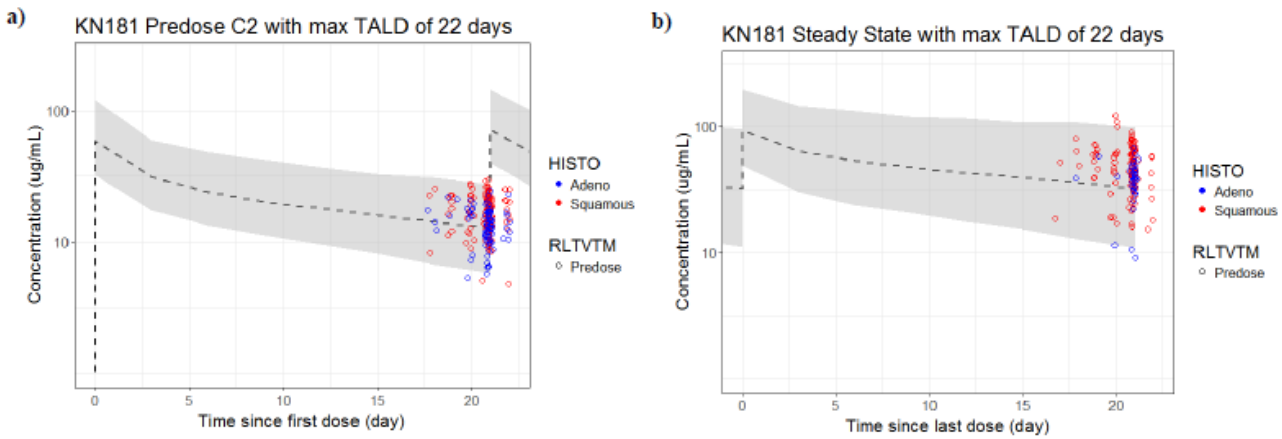


Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE. Actual times from CDR data were used for this analysis.

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:

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]

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.

A comparison of the observed PK data (trough and peak concentrations at each evaluated cycle) demonstrated a consistency in exposure between subjects with esophageal cancer treated with pembrolizumab 200 mg Q3W in monotherapy and subjects with other tumour type (trials in NSCLC, UC, HNSCC, HL, and MSI-H) treated with the same monotherapy regimen.

2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA 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.

Primary and secondary pharmacology

Dose regimen

A dosing regimen of 200 mg Q3W is recommended for pembrolizumab in the treatment of adult subjects with esophageal cancer. The pembrolizumab dosing regimen selected for KN181 was based upon the collective clinical experience of pembrolizumab monotherapy across multiple tumor types.

The dose regimen intended for treatment of esophageal cancer patients is 200mg Q3W, the same as for treatment of NSCLC, HL, HNSCC and urothelial carcinoma. Exposure response analyses of efficacy were not conducted.

Immunogenicity

The existing immunogenicity assessment for pembrolizumab is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment emergent ADA (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 EU SmPC. This low rate of immunogenicity has been shown to be consistent across tumor type and no clinical consequences have been observed in the subjects with a positive immunogenicity reading.

Immunogenicity evaluation for study KEYNOTE-181

An immunogenicity evaluation has been performed using data from study KN181, pembrolizumab monotherapy (200 mg pembrolizumab Q3W), including subjects with advanced/metastatic squamous cell cancer and adenocarcinoma of the esophagus. ADA samples were available from 321 subjects. A subset of the subjects was not assessable for drug-induced immunogenicity because the subjects were not treated with pembrolizumab (N=7) or only a pre-treatment ADA sample was available (N=20).
The remaining 294 subjects were included in the immunogenicity assessment.

Overview of Subjects Included in the Immunogenicity Analysis after Pembrolizumab Monotherapy, 200 mg Pembrolizumab Q3W (KN181)

Study	Indication	Subjects		
		Subjects providing ADA Samples	**Subjects Dosed with Pembrolizumab**	**Assessable Subjects** Subjects Dosed with Pembrolizumab and Post Treatment Samples
Pembrolizumab Combination Therapy				
KN181	Squamous cell carcinoma	202	198	189
	Adenocarcinoma of the esophagus	119	116	105
	Total	321	314	294

Data source [0544CD: analysis-p181pkada01]

The table below presents an overview of the immunogenicity status of all assessable subjects.
To evaluate immunogenicity, the overall immunogenicity was defined as the proportion of emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

Summary of Subject Immunogenicity Results after Pembrolizumab Monotherapy, 200 mg Pembrolizumab Q3W (KN181)

Stratified by indication			
Immunogenicity status	**Total**	**Squamous cell carcinoma**	**Adenocarcinoma**
Assessable subjects[a]	294	189	105
Inconclusive subjects[b]	11	7	4
Evaluable subjects[c]	**283**	**182**	**101**
Negative[d]	267 (94.3%)	171 (94.0%)	96 (95.0%)
Non-Treatment emergent positive[d]	5 (1.8%)	3 (1.6%)	2 (2.0%)
Neutralizing negative	5 (1.8%)	3 (1.6%)	2 (2.0%)
Neutralizing positive	0	0	0
Treatment emergent positive[d]	11 (3.9%)	8 (4.4%)	3 (3.0%)
Neutralizing negative	11 (3.9%)	8 (4.4%)	3 (3.0%)
Neutralizing positive	0	0	0

a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.

Data source [0544CD: analysis-p181pkada01]

The observed incidence of treatment emergent ADA in evaluable subjects with advanced/metastatic squamous cell cancer and adenocarcinoma of the esophagus is 3.9% (11 out of 283), based on 11 subjects with treatment emergent positive, 5 with non-treatment emergent positive and 267 with negative immunogenicity status.
None of the positive subjects, had antibodies with neutralizing capacity, yielding an incidence of treatment emergent neutralizing positive subjects of 0%.

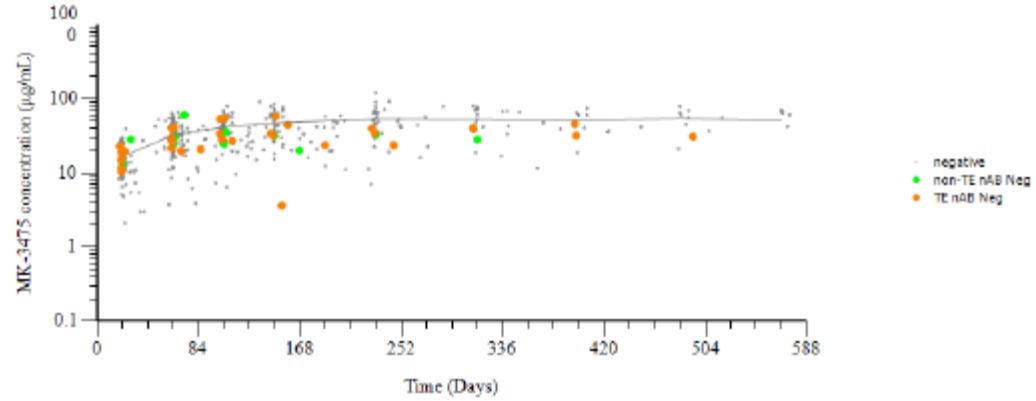
The incidence of treatment-emergent ADA to pembrolizumab in subjects with advanced/metastatic squamous cell cancer and adenocarcinoma of the esophagus treated with pembrolizumab was ~3.9% (11 out of 283 total evaluable samples) that is comparable to the overall incidence in the monotherapy setting in other tumors.
The incidence of treatment emergent neutralizing positive subjects is 0% as none of the positive subjects, had antibodies with neutralizing capacity.

Impact of ADA on Pembrolizumab Exposure

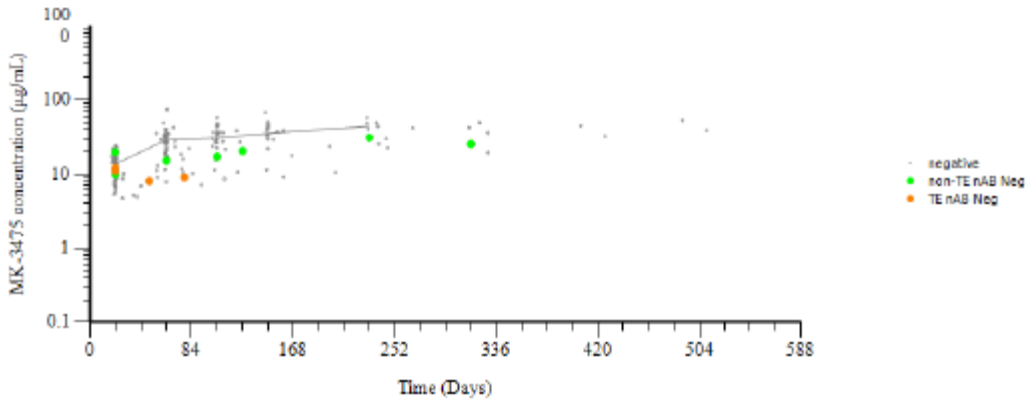
The effect of ADA on pembrolizumab levels, for the subjects with ADA positive samples, is compared with the subjects treated with the same regimen that only have ADA negative samples.
For all of the ADA positive subjects (5 non-treatment emergent and 11 treatment emergent), the pembrolizumab exposure was comparable to that for subjects with only ADA negative samples treated with the same regimen.

Effect of ADA on Pembrolizumab Exposure, for Subjects Treated with 200 mg Pembrolizumab Q3W (KN181)

A: Squamous cell carcinoma



B: Adeno carcinoma



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded.

Individual pembrolizumab concentrations for the ADA negative subjects (grey dot), mean value of the negative subjects (grey line), non-treatment emergent neutralizing negative subjects (green dot) and treatment emergent neutralizing negative subjects (orange dot).

If a subject is determined to be ADA positive (TE or non-TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

Data source [0544CD: analysis-p181pkada01]

2.3.4. PK/PD modelling

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

2.3.5. Discussion on clinical pharmacology

No dose finding study was conducted for pembrolizumab monotherapy for treatment of esophageal cancer. The recommended dose and schedule of pembrolizumab monotherapy is the same as that approved for 1L NSCLC, cHL, HNSCC and urothelial carcinoma monotherapy: 200 mg IV infusion over 60 minutes Q3W. This is considered acceptable.

No updated popPK analysis was presented. Clinical pharmacology results to support the Extension of Indication for Keytruda to include a new indication in Oesophageal Cancer are available from the pivotal 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).

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 esophagus treated with Pembrolizumab 200 mg Q3W generally fall within the range of predicted concentrations, both after first dose and at steady state.

A comparison of the observed PK data (trough and peak concentrations at each evaluated cycle) demonstrated a consistency in exposure between subjects with esophageal cancer treated with pembrolizumab 200 mg Q3W in monotherapy and subjects with other tumour type (trials in NSCLC, UC, HNSCC, HL, and MSI-H) treated with the same monotherapy regimen.

The incidence of treatment-emergent ADA to pembrolizumab in subjects with advanced/metastatic squamous cell cancer and adenocarcinoma of the esophagus treated with pembrolizumab was ~3.9% (11 out of 283 total evaluable samples) that is comparable to the overall incidence in the monotherapy setting in other tumors.

The incidence of treatment emergent neutralizing positive subjects is 0% as none of the positive subjects, had antibodies with neutralizing capacity.

For all of the ADA positive subjects (5 non-treatment emergent and 11 treatment emergent), the pembrolizumab exposure was comparable to that for subjects with only ADA negative samples treated with the same regimen.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics and immunogenicity of pembrolizumab has been sufficiently investigated for the extension of the indication of pembrolizumab 200 mg every 3 weeks for treatment of esophageal cancer.

The observed concentration from study KEY-181 fall within the 90% CI of the model predicted median concentration.

The incidence of treatment-emergent ADA to pembrolizumab in subjects with advanced/metastatic squamous cell cancer and adenocarcinoma of the esophagus was comparable to the overall incidence in other tumors.

2.4. Clinical efficacy

The scope of this variation is to include a new indication for Keytruda as monotherapy for the treatment of recurrent locally advanced or metastatic oesophageal cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have received prior systemic therapy.

The proposed indication is based on the results of KEYNOTE-181 Study, an ongoing, randomised (1:1), multi-site, open-label, Phase 3 study of pembrolizumab versus SOC (investigator's choice of paclitaxel, docetaxel, or irinotecan) in participants with advanced/metastatic EAC or ESCC, or advanced/metastatic Siewert type I adenocarcinoma of the EGJ who have progressed after first-line standard therapy.

The primary endpoint was OS, in participants with ESCC, in participants with tumours expressing PD-L1 CPS≥10, and in all participants. The key secondary efficacy endpoints were PFS and ORR in all participants. Additional secondary efficacy endpoints included PFS and ORR in the other two study populations (participants with tumours expressing PD-L1 CPS ≥10 and participants with ESCC) and DOR in all 3 analysis populations (PD-L1 CPS ≥10, ESCC, and all).

Results from other two studies, providing additional evidence of efficacy for pembrolizumab monotherapy in oesophageal cancer, were provided as supportive. The studies are:

- KEYNOTE-028 (Cohort 4A, n=22), a Phase 1b proof-of-concept study of participants with previously treated esophageal cancer treated with pembrolizumab monotherapy,
- KEYNOTE-180 (n=121) an on-going, single-arm Phase 2 study of pembrolizumab monotherapy in participants with esophageal cancer that have had at least two prior lines of therapy (3L+ advanced/metastatic oesophageal cancer, regardless of histology or biomarker status).

No pooled efficacy analyses were conducted based on KEYNOTE-181, KEYNOTE-180, and KEYNOTE-028 because KEYNOTE-180 and KEYNOTE-028 were single arm studies with participants with substantially more advanced stages of disease (different lines of therapy).

2.4.1. Dose response study(ies)

No specific dose-response studies have been performed for esophageal cancer population. Pembrolizumab has been administered at a fixed dose regimen of 200 mg Q3W to subjects in all trials, with the exception of cohort A4 in KN028 who received pembrolizumab at 10 mg/kg Q2W.

Pembrolizumab was initially approved for advanced melanoma at 2 mg/kg Q3W. Subsequent approvals for adult subjects were at 200 mg Q3W dosing regimens for multiple other indications. The choice of the switch to the flat dose was based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe (see Section 4.3.2).

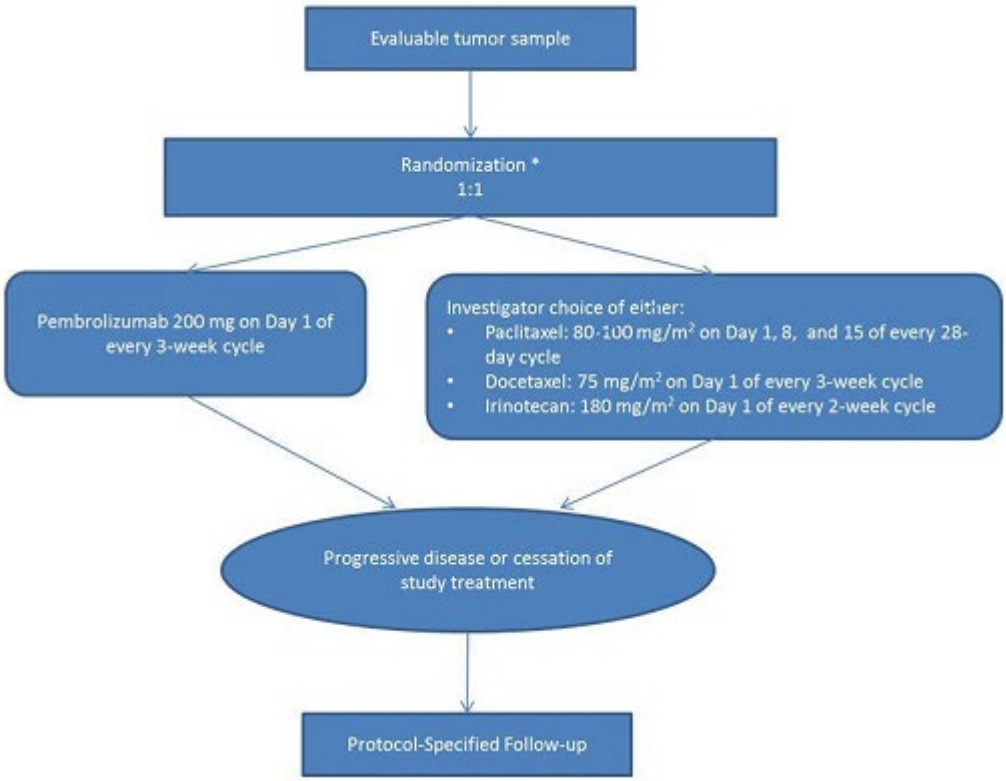
2.4.2. Main study

Title: *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 ESOPHAGUS THAT HAVE PROGRESSED AFTER FIRST-LINE STANDARD THERAPY (KEYNOTE-181)

Methods

Figure: Study design



KEYNOTE-181 is a Phase 3 randomized, multi-center, open-label study of pembrolizumab versus investigator's choice of paclitaxel, docetaxel, or irinotecan in participants with advanced/metastatic adenocarcinoma (EAC) or squamous cell carcinoma of the Oesophagus (ESCC), or advanced/metastatic Siewert type I adenocarcinoma of the esophagogastric junction (EGJ). Investigator's choice of treatment was determined prior to randomization.

Participants were required to have been previously treated with one line of chemotherapy (2L) and were also required to provide a tumor sample for PD-L1 immunohistochemistry. 628 participants (314 participants in each arm) were randomised and stratified by tumour histology and geographic region (Asia including China, Japan, Korea, Hong Kong, Taiwan, Malaysia, Thailand, Singapore versus ex-Asia including Europe/Israel/North America, Australia, South America).

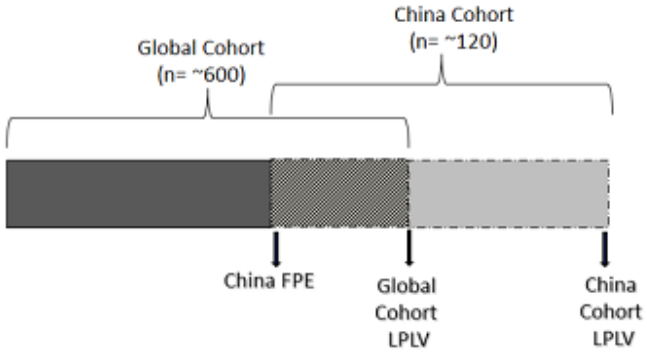
Treatment was to continue until one of the following occurred: PD, unacceptable adverse event, intercurrent illness, withdrawal of consent, investigator's decision, pregnancy, noncompliance, or administrative reasons. Participants in the pembrolizumab arm could receive up to 35 cycles (approximately 2 years).

Tumour assessments were performed every 9 weeks (+/- 7 days). Following verification of PD by RECIST 1.1, treatment decisions were made by irRECIST to account for the tumor response pattern observed with pembrolizumab intervention (eg, tumor flare).

Participants receiving SOC were not allowed to cross-over to the pembrolizumab arm during the study.

The study enrolled two periods: global and China extension enrollment. Participants enrolled during the global enrolment period are the focus of this submission.

Figure: China Enrollment Strategy (excerpt from Protocol Amendment No. 4)



FPE: First patient enrolled, LPLV: Last patient last visit

Assessor´s note: The figure is understood in a way that in the overlapping part of the cohorts, Chinese as well as non-Chinese patients were to be enrolled.

FPE: First patient enrolled, LPLV: Last patient last visit

The figure is understood in a way that in the overlapping part of the cohorts, Chinese as well as non-Chinese patients were to be enrolled.

Study participants

Key inclusion criteria were:

- ≥ 18 years of age on the day of signing informed consent.
- Histologically or cytologically-confirmed diagnosis of adenocarcinoma or squamous cell carcinoma of the esophagus or Siewert type I adenocarcinoma of the EGJ (defined as adenocarcinomas of the lower esophagus with the center located within 1cm to 5cm above the anatomic EGJ).
    - a. Subjects with Siewert type 1 adenocarcinoma of the EGJ with HER -2/neu negative tumors are eligible. Subjects with HER2/neu positive tumors, or those with an unknown tumor status, need to match the following:
        - If HER2/neu positive, subject must have documentation of disease progression on a prior line of therapy containing trastuzumab.
        - Subjects with unknown status must have their HER2/neu status determined locally. If HER2/neu negative, the subject will be eligible. If HER2/neu positive, the subject must have documentation of disease progression on a prior line of therapy containing trastuzumab.
- Have metastatic disease or locally advanced, unresectable disease. Subjects with direct invasion into adjacent organs such as the aorta or trachea (T4b disease) should be closely evaluated for bleeding risk prior to enrolment and a sponsor consultation before enrollment is required.
- Have a life expectancy of greater than 3 months.

- Have measurable disease based on RECIST 1.1 as determined by local site investigator/radiology assessment.
- Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
- Have experienced documented radiographic or clinical disease progression on one previous line of standard therapy. This study will only include second-line subjects. Second-line subjects are defined as those who have progressed during or after receiving at least one dose of standard therapy given in a first line setting.
    - Treatment with curative intent, including neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using standard of care agents or definitive chemoradiation, will count as a line of therapy if disease progression occurs during treatment or within 6 months of cessation of treatment.
- Provide either a newly obtained or archival tissue sample for intratumoral immune-related GEP analysis and PD-L1 by immunohistochemistry analysis.
- Adequate organ function

Key exclusion criteria were:

- Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Known central nervous system (CNS) metastases and/or carcinomatous meningitis (includes past history or current metastasis).
- Has received prior anti-cancer monoclonal antibody (mAb), chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1. However, a period of more than 2 weeks may be used if indicated both clinically and due to concern between possible negative interactions between prior therapy and study therapy. Subjects must have recovered from adverse events due to a previously administered agent to baseline toxicity grade or to grade 1 or less prior to enrollment.
- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or if the subject has previously participated in Merck pembrolizumab (MK-3475) clinical trials.
- Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb).
- Documented objective radiographic or clinical disease progression during or after receiving more than 1 line of therapy.
- Known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include curatively treated basal cell and squamous cell carcinoma of the skin and/or curatively resected in situ cervical and/or breast cancers and in situ or intramucosal pharyngeal cancer.

- Has received a live vaccine within 30 days of planned start of pembrolizumab.
- Has a known history of Human Immunodeficiency Virus (HIV) infection.
- Has known history of or is positive for hepatitis B (hepatitis B surface antigen reactive) or known active hepatitis C (hepatitis C virus RNA or hepatitis C antibody is detected).
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Active infection requiring systemic therapy.
- Experienced weight loss > 10% over approximately 2 months prior to first dose of study therapy.
- Has clinically apparent ascites or pleural effusion by physical exam. (Note that small amount of ascites which is only detectable on imaging studies is allowed.)

In the most recent AJCC staging classification (8th edition 2017) the esophagogastric junction (EGJ) was redefined: adenocarcinomas with epicenters no more than 2 cm into the gastric cardia are staged as esophageal adenocarcinomas, and those extending further are staged as stomach cancers. Thus, Siewert II adenocarcinomas (centered within 1 cm of the EGJ) are also considered as oesophageal cancer.

The change of the AJCC staging classification was introduced in 2017 after start of the study. Information that the study population did not include Siewert II EGJ adenocarcinoma has been included in section 5.1 of the SmPC.

The requirement of prior treatment with trastuzumab for HER2+ Siewert I ADC patients is endorsed, since the standard treatment includes trastuzumab in addition to chemotherapy according to ESMO guidelines.

The availability of tissue sample for biomarker analysis was requested; however, patients were eligible regardless of biomarker status and patients were not stratified according to biomarker status (that was changed from GEP to PD-L1 expression during the conduct of the study, see below).

Treatments

The study treatments are outlined in the table below

Study Intervention	Dose	Dose Frequency	Route of Administration	Regimen/ Intervention Period	Use
Pembrolizumab (MK-3475)	200 mg	Every 3 weeks	IV infusion	Day 1 of each 21-day (3-week) cycle	Experimental
Paclitaxel	80-100 mg/m^2	3 weeks on, 1 week off	IV infusion	Days 1, 8, and 15 of each 28-day (4-week) cycle	Active comparator
Docetaxel	75 mg/m^2	Every 3 weeks	IV infusion	Day 1 of each 21-day (3-week) cycle	Active comparator
Irinotecan	180 mg/m^2	Every 2 weeks	IV infusion	Day 1 of each 14-day (2-week) cycle	Active comparator

Study intervention was to begin within 3 days of randomization or as close as possible to the date on which the participant was allocated/assigned.

Local label was to be followed for dose modifications of paclitaxel, docetaxel and irinotecan. Dose modification decisions were to be documented in the subject's study records and in the case report form.

Subjects who started therapy with paclitaxel, docetaxel, or irinotecan could not switch to one of the other chemotherapies. Subjects who permanently discontinue treatment with paclitaxel, docetaxel, or irinotecan were continued to be monitored in the trial.

The choice of chemotherapeutic agents and the dose regimens can be considered acceptable as comparator.

Objectives

Primary Objectives

To compare overall survival:

- in all subjects
- in participants with squamous cell carcinoma of the esophagus (ESCC)
- in subjects with PD-L1 CPS ≥10.

The study is considered to have met its primary objective if pembrolizumab is superior to investigator's choice of paclitaxel, docetaxel, or irinotecan in any one of the three primary objectives.

Secondary Objectives

To evaluate the PFS and ORR per RECIST 1.1 assessed by central vendor review in all subjects, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.

Additional Secondary Objectives

- To evaluate the PFS and ORR per RECIST 1.1 assessed by central vendor review in subjects with squamous cell carcinoma of the esophagus and subjects with PD-L1 CPS ≥10, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.
- To evaluate the safety and tolerability profile of pembrolizumab in all subjects, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.

Exploratory Objectives

- To evaluate PFS per irRECIST assessed by blinded central vendor review in all subjects when treated with pembrolizumab 200 mg Q3W compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.
- To evaluate efficacy by GEP expression.
- To explore the concordance of PD-L1 in archival compared to newly obtained tumor tissue.
- To evaluate score change of health related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-OES18 from baseline among subjects when treated with pembrolizumab 200 mg Q3W compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.
- To characterize utilities using EuroQol EQ-5D among subjects when treated with pembrolizumab 200 mg Q3W compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.

- To explore the relationship between genetic variation and response to the treatment administered. Variation across the human genome are planned to be analyzed for association with clinical data collected in this study.

Overall survival is endorsed as a clinically meaningful objective and considered appropriate in view of the poor prognosis of the patients with advanced/metastatic oesophageal cancer.

However, the multiple changes of the primary analysis in this open-label study are seen as critical (please refer also to statistical methods and conduct of the study).

Efficacy by GEP was downgraded from primary to exploratory objective. This is not (really) endorsed and makes the confirmatory evidence of the pivotal study questionable (as it does not only confirm "known" hypothesis but changed a lot).

Outcomes/endpoints

Primary efficacy endpoint is overall survival (OS), defined as the time from randomization to death due to any cause, evaluated in subjects with ESCC, in subjects with PD-L1 CPS≥10, and in all subjects. Subjects without documented death at the time of the final analysis are censored at the date of the last follow-up.

Secondary efficacy endpoints are:

- Progression-free survival (PFS) – RECIST 1.1 by central imaging vendor review in all subjects. PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on central imaging vendor review or death due to any cause, whichever occurs first.

- Objective Response Rate (ORR) – RECIST 1.1 by central imaging vendor review in all subjects. ORR is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR)

Additional secondary efficacy endpoints included DOR in all 3 analysis populations (PD-L1 CPS =10, ESCC, and all).

Exploratory efficacy endpoints are:

- Progression-free survival (PFS) – RECIST 1.1 by investigator assessment and irRECIST assessed by central imaging vendor;

- Objective Response Rate (ORR) – RECIST 1.1 by investigator assessment,

PRO endpoints are:

As part of the exploratory analyses, subjects provided information regarding their health-related quality of life (HRQoL) via the following assessment tools: EORTC QLQ -C30 and QLQ-OES18, eEuroQol-5D (EQ-5D) questionnaires.

PD-L1 Expression Analyses

With Amendment 4 (03-Aug-2017), GEP was replaced as key biomarker by CPS. The MAH outlined that the determination of PD-L1 CPS≥10 as the biomarker for KEYNOTE-181 was made strictly outside of KEYNOTE-181, by using data from KEYNOTE-180 prior to conducting any analysis of KEYNOTE-181 (please refer to "conduct of the study" below for history of changes of the original GEP biomarker to PD-L1).

Excerpt from "Merck Esophageal Cancer Trials – Role of PD-L1 Biomarker"

Based on analysis of data from Merck KN0121 and KN0282 clinical trials, pembrolizumab efficacy evaluation by GEP status (immune-related gene expression profile) was initially included in the primary objectives for KN180 and KN181. However, based on emerging data from KN180, KN181 was amended to remove the GEP assessment from the primary objectives. Instead, pembrolizumab efficacy evaluation by PD-L1 expression (CPS ≥10) has been added to the primary objectives of KN181.

- **PD-L1 Assay** – Cutpoint Finalization

A CPS≥1 cutpoint was pre-specified to assess PD-L1 positive/negative status in KN180. CPS is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Additionally, since KN180 was a training set for identifying a PD-L1 cutpoint (CPS≥1 or higher PD-L1 cutpoints) that optimally enriches pembrolizumab responders relative to non-responders in esophageal cancer, pathologists were instructed to record CPS values precisely across the dynamic range of PD-L1 expression.

The KN180 trial enrolled 121 subjects (3L), all with evaluable PD-L1 data. Eleven of those subjects were considered confirmed responders (partial or complete responders) via RECIST v1.1 (central review) at the time of the analysis (cutoff date 17 JUL 2017). Some evidence for an association between CPS score and higher probability of response was observed (one-sided p-values: p = 0.022 logistic regression, p = 0.171 rank sum test). Figure 1 displays the ROC curve with the location of the CPS 1, 10, and 20 points and their associated (Specificity, Sensitivity) labelled. The area under the ROC curve was 0.59 with 95% confidence interval of (0.35, 0.82).

Figure 1: ROC curve for CPS in 121 subjects from KN180

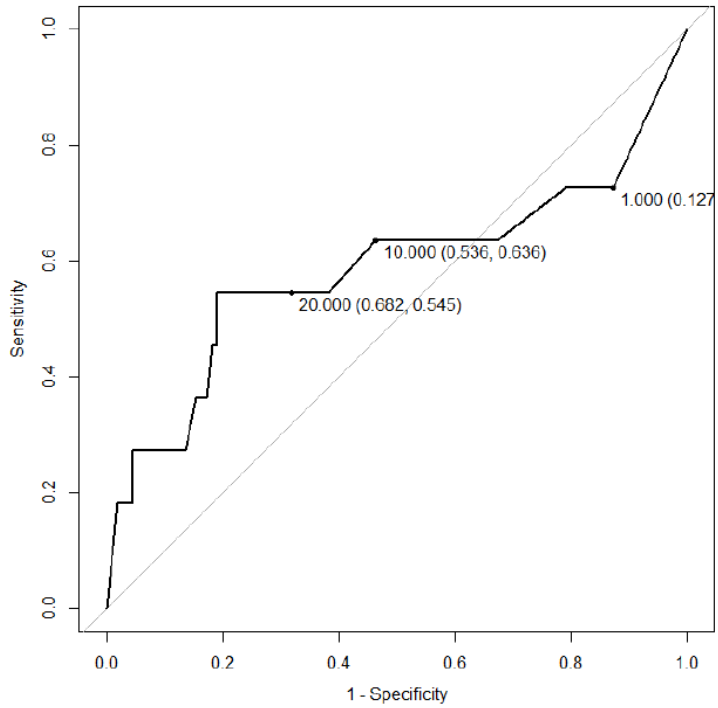


Table 1 shows various performance measures for CPS cutpoints 1, 10, and 20.

Table 1: Performance Measures for Several CPS Cutpoints in KN180 (N=121)

	CPS Cutpoint		
Performance Measure:	**≥1**	**≥10**	**≥20**
%PPV/NPV	7.7/82.4	12.1/93.7	14.6/93.8
%Sens./Spec.	72.7/12.7	63.6/53.6	54.5/68.2
%Prevalence	86.0	47.9	33.9
PPV: response rate at or above cutpoint NPV: non-response rate below cutpoint Prevalence: percent of patients with tumors score at or above cutpoint			

The pre-specified cutpoint of CPS≥1 demonstrated no enrichment of response in this population of esophageal cancer patients (7.7%, 8/104) compared with the overall response in the all subjects population of 9.1% (11/121 subjects). At CPS≥10, ORR increased to 12.1% (7/58). As shown in Table 1, while the ORR was similar at CPS≥20, there was a drop in sensitivity (one additional responding subject was not captured using CPS≥20 (n=5 responders not captured) relative to CPS≥10 (n=4 responders not captured) and prevalence compared to CPS≥10. At CPS≥32, the cutpoint which corresponds to the Youden index, while the PPV (22.2%) was higher compared to CPS≥10, the sensitivity and prevalence were lower, 54.5% and 22.3% respectively.

Taken together, the PPV, sensitivity and prevalence evident with use of the CPS≥10 cutpoint argue for further use of this assay and cutpoint in esophageal cancer trials with pembrolizumab. Table 2 represents a summary of the best overall response (with confirmation) based on central imaging assessment per RECIST 1.1 using the CPS≥10 cutpoint.

Table 2: Best response summary data for the CPS≥10 cutpoint in KN180

	PD-L1 CPS≥10 (N=58)		PD-L1 CPS<10 (N=63)	
	N (%)	95% CI[†]	N (%)	95% CI[†]
Objective Response	7 (12.1)	(5.0, 23.3)	4 (6.3)	(1.8, 15.5)
Stable Disease (SD)	14 (24.1)	(13.9, 37.2)	12 (19.0)	(10.2, 30.9)
[†] Based on binomial exact confidence interval method Database Cutoff Date: 17JUL2017				

The rationale for the selection of the CPS≥10 cutpoint is in principle understood. The main driver is the prevalence, which reflects the potential patient population to be treated after approval. Other criteria such as the Youden index and positive and negative predictive values would result in a different choice (at or above CPS ≥ 20).

Altogether, the predictive accuracy of CPS is limited in the given patient population with a rather low AUC and poor sensitivity and specificity for the potential cutpoints (1, 10 and 20). For CPS≥10 based on the KN180 data, neither sensitivity (64%) and specificity (54%) nor predictive values (PPV = 12.1%, NPV = 93.7%) could be considered adequate to fulfil the expectations for a particularly suitable biomarker. Additionally, as can be seen from the ROC curve, data seems to be too sparse (with only 11 responders out of 121 subjects) to properly define adequate cutpoints.

The presented analysis further focused on a surrogate endpoint (objective response) to define the cutpoint, while patient relevant endpoints such as PFS or even better OS were not used.

Finally, the value of 3L esophageal cancer for the determination of a biomarker cutoff in 2L esophageal cancer is to be questioned. As a consequence, the biomarker is not considered to be optimally chosen in the present patient population. Other cutoffs might provide a better separation of responders and non-responders.

- **GEP data** in KN180:

Of the 121 subjects enrolled in the trial, 118 subjects were evaluated for GEP status against objective response. Table 3 and Table 4 show the breakdown of the 11 responders using the two pre-specified cutpoints for the GEP. Evidence of a difference in response rates between the GEP groups was observed for both cutpoints ('GEP low' vs. 'GEP intermediate or high' and 'GEP low or intermediate' vs. 'GEP high'). The evaluation of the continuous GEP scores also showed evidence of an association with probability of response (one-sided p-values: p = 0.026 logistic regression, p = 0.040 rank sum test), with an ROC curve with AUC of 0.66 with 95% CI of (0.49, 0.83).

Table 3: Breakdown of Response Status by the -1.540 cutpoint for the GEP

	GEP Low (N=67)		GEP Intermediate or High (N=51)	
	N (%)	95% CI†	N (%)	95% CI†
Objective Response	4 (6.0)	(1.7, 14.6)	7 (13.7)	(5.7, 26.3)

† Based on binomial exact confidence interval method.
Only assessed for subjects who have at least one scan or died or discontinued.
GEP Intermediate or High: GEP Score ≥-1.540; GEP Low: GEP Score <-1.540
Data Cutoff Date: 17JUL2017

Table 4: Breakdown of Response Status by the -0.945 cutpoint for the GEP

	GEP Low or Intermediate (N=94)		GEP High (N=24)	
	N (%)	95% CI†	N (%)	95% CI†
Objective Response	6 (6.4)	(2.4, 13.4)	5 (20.8)	(7.1, 42.2)

† Based on binomial exact confidence interval method.
Only assessed for subjects who have at least one scan or died or discontinued.
GEP High: GEP Score ≥-0.945; GEP Intermediate or Low: GEP Score <-0.945
Data Cutoff Date: 17JUL2017

From a clinical standpoint, while GEP enriches for pembrolizumab responders, its enrichment profile at the lower cut-off, in terms of increasing the ORR as compared to all-comers, is comparable to PD-L1. From a technical standpoint, the number of clinical sample slides required to perform the GEP assay

proved to be much greater than anticipated in our development program. For example, although half of samples required 3 or fewer slides, 31% of samples required nine slides. This is in contrast to the PD-L1 assay, which routinely requires only 3 slides. Given that having adequate tissue is often a challenge in clinical development and may also likely be in subsequent clinical practice, the GEP assay may lead to, not infrequently, delay in results and/or no results due to specimen shortage. Finally, PD-L1 is an established biomarker and is widely used globally. Access to the test or the IHC technology has not been an issue in the commercialization of the PD-L1 IHC pharmDx assay. GEP on the other hand is a less mature technology in clinical practice globally. Merck is concerned that the limited commercial footprint of the instrumentation could limit access to pembrolizumab if physicians would like to perform a biomarker test prior to treatment selection. Due to these technical and commercial limitations with GEP testing, the esophageal program is prioritizing development of the PD-L1 assay rather than the GEP for esophageal cancer.

Thus, based on these considerations, the KN181 clinical protocol has been amended to remove the GEP assessment from the primary objective of the trial. Instead, evaluation of pembrolizumab efficacy based on PD-L1 expression has been added to the primary objective of the trial. Similar changes are being made to KN590 (1L Study).

The performance of the GEP (immune-related gene expression profile) as a biomarker with the lower cutoff ('GEP low' vs. 'GEP intermediate or high') was similar to the biomarker "PD-L1 expression" with the CPS>10 cutoff. Overall, GEP was the better prognostic biomarker in Study KN180 (AUC = 0.66 vs. 0.59 for CPS). The higher cutoff ('GEP low or intermediate' vs. 'GEP high') performed considerably better in predicting responders (ORR 20.8% vs. 6.4% [with n=24 v. n=94] for high vs. low or intermediate GEP values, respectively); however it is assumed that the low prevalence for "GEP high" might have been a relevant reason not to pursue this cutoff in the further clinical development.

As the Applicant pointed out the decision to further proceed with the PD-L1 biomarker was mainly based on commercial reasons and technical issues (high number of tumour tissue slides needed in approximately one third of samples).

- Use of **PD-L1 Assay** in esophageal cancer

For the development of pembrolizumab, PD-L1 expression in tumour cells and inflammatory cells within pre-treatment tumour tissue samples was characterised by immunohistochemistry (Dako PD-L1 IHC 22C3 pharmDx for KEYNOTE-181 and KEYNOTE-180 and QualteK for KEYNOTE-028). "The PD-L1 IHC 22C3 pharmDx assay is FDA approved (P150013) as a companion diagnostic in selecting PD-L1 positive NSCLC and gastric or gastroesophageal junction adenocarcinoma patients for KEYTRUDA, and is also being used in other pembrolizumab clinical programs. Assay details have also been submitted in IDE G140139 for NSCLC, IDE G140139 S002 for gastric cancer and PMA/sPMA (P150013) for NSCLC and gastric cancer. PD-L1 IHC 22C3 pharmDx assay reagents, including those that will be used in the esophageal cancer trials, are manufactured under GMP conditions." (Excerpt from Ref. 0522SV; "Merck Esophageal Cancer Trials – Role of PD-L1 Biomarker").

- **CPS Scoring Method Details**

As mentioned above, samples from the Merck esophageal cancer clinical trials are being assessed for PD-L1 expression using the CPS method. CPS is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Samples will be considered to have PD-L1 expression in esophageal cancer if CPS≥10. There could be examples where CPS can exceed 100 (e.g. 100% of tumor cells positive and additional positive MICs). In this case, the CPS value will default to 100.

Figure 2 and Figure 3 include representative staining of the PD-L1 IHC 22C3 pharmDx kit in esophageal cancer specimens; both photos are at 20X magnification. PD-L1 staining is evidenced by the presence of the brown chromogen. The blue color is the counterstain (hematoxylin).

Figure 2: Squamous Cell Carcinoma with PD-L1 expression

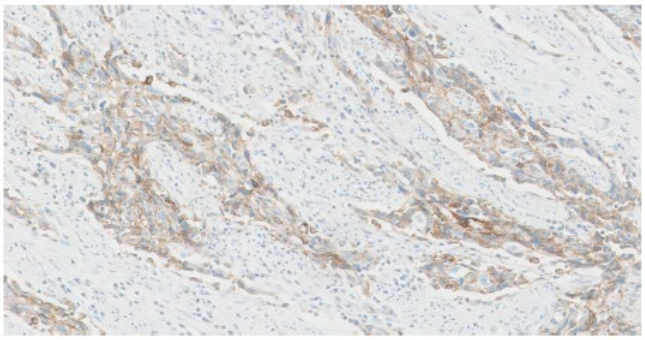
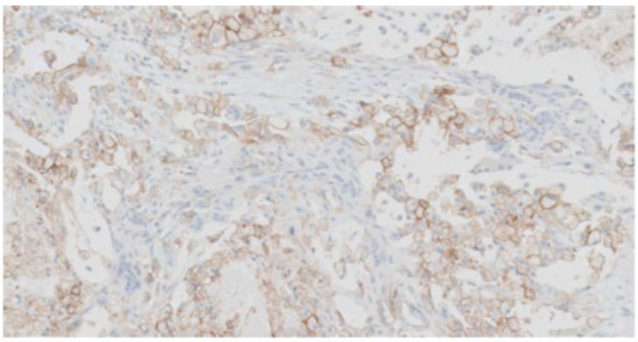


Figure 3: Adenocarcinoma with PD-L1 expression



For pivotal endpoint analysis in KEYNOTE-181 (PD-L1 CPS ≥10) the PD-L1 IHC 22C3 pharmDx assay has been used to detect PD-L1 expression in tumour cells and inflammatory cells.

Analytical performance data for the PD-L1 IHC 22C3 pharmDx assay in clinical studies KEYNOTE-180/181 have been requested because a respective CE marked assay was not available at this time. With the response to the 1st RSI the applicant provided the analytical validation data which cover specificity, sensitivity (for a range of CPS scores from 0 to 100, 34% CPS ≥10 and 66% CPS <10), precision (for a CPS ≥ 10, for combined including inter-instrument/ -operator/ -day/ -lot, and further intra-run, inter/intra-observer, i.e. three pathologists, three days), robustness (for tissue section thickness, microscope slide type, TRS temperature/time/pH/Re-use), external reproducibility (for three sites, inter/intra-site, inter/intra-observer, i.e. three pathologists, three days), and stability (for cut section, stained slide, reagent). The selected validation parameters are adequate and the resulting data indicate that the PD-L1 IHC 22C3 pharmDx assay used in studies KEYNOTE-180/181 has a sufficient performance if using FFPE esophageal cancer specimens and a binary cut-off of CPS ≥10 and that therefore the testing results of the pivotal study KEYNOTE-181 can be considered as reliable for pivotal endpoint analysis.

The Applicant confirmed that the same assay was used in the training set (KEYNOTE-180) and in pivotal KEYNOTE-181.

Sample size

Study enrollment was divided into two periods: global and China extension enrollment. The focus of the analyses provided is only on data from any participant enrolled during the global enrolment period.

For the hypotheses in all subjects, the planned sample size in the Global Cohort was approximately 600. Among all subjects, it was expected that about 400 subjects with squamous cell carcinoma of the esophagus would have been enrolled. For the hypotheses in subjects with PD-L1 CPS≥10, the planned sample size was approximately 280 (based on an observed prevalence rate of ~47% from KN180).

One interim efficacy analysis for OS is planned in this study. The interim analysis is planned to be performed after 1) enrolment is completed, 2) approximately 251 OS events and 385 OS events have been observed among subjects with squamous cell carcinoma of the esophagus and all subjects, respectively, and 3) 8 months after last subject randomized. In addition, if there are fewer than 172 OS events among subjects with PD-L1 CPS≥10 at the time, the interim efficacy analysis may be delayed for up to 2 months or when the target number of OS events in subjects with PD-L1 CPS≥10 is reached, whichever occurs first.

The final analysis is planned to be performed 1) after approximately 310 OS events and 473 OS events have been observed among subjects with squamous cell carcinoma of the esophagus and all subjects, respectively, and 2) 16 months after last subject randomized.

For the primary endpoint, OS in subjects with squamous cell carcinoma of the esophagus, with 310 OS events, the trial has 91.3% power to demonstrate that pembrolizumab is superior to the control at a one-sided 0.8% alpha-level, if the underlying hazard ratio of OS is 0.65.

For the primary endpoint, OS in subjects with PD-L1 CPS≥10, with 213 OS events, the trial has 90.9% power to demonstrate that pembrolizumab is superior to the control at a one-sided 0.9% alpha-level, if the underlying hazard ratio of OS is 0.6.

For the primary endpoint, OS in all subjects, with 473 OS events, the trial has 92.6% power to demonstrate that pembrolizumab is superior to the control at a one-sided 0.8% alpha-level, if the underlying hazard ratio of OS is 0.7.

The sample size and power calculations are based on the following assumptions: 1) Overall survival follows an exponential distribution with a median of 8 months in the control arm; 2) an enrollment period of 17 months and a minimum of 16 months follow-up after enrolment completion; 3) a yearly dropout rate of 2%.

With the given HR and numbers of events the power can be exactly replicated. The provided power takes the interim analysis with Lan-DeMets O'Brien-Fleming alpha spending with IF 0.76 into account. No details were given for the justification of the assumed HRs, however.

Randomisation

Participants were randomized in a 1:1 ratio to receive pembrolizumab or investigator's choice of paclitaxel, docetaxel, or irinotecan, determined prior to randomization. A block randomization schedule was used with a specified block size of 4.

Treatment allocation/randomization were stratified according to the following factors:

1. Tumor histology: Squamous cell carcinoma (ESCC) vs. adenocarcinoma/Siewert type I adenocarcinoma of the EGJ

2. Geographic region: Asia (including but not limited to China, Japan, Korea, Hong Kong, Taiwan, Malaysia, Thailand, Singapore) vs. Rest of World (including but not limited to Europe/Israel/North America, Australia, South America).

While a block size of 4 is considered to be rather small, overall a stratified, block randomization is endorsed.

Blinding (masking)

This was an open-label study.

Imaging data for the primary analysis were centrally reviewed by independent radiologists without knowledge of subject treatment assignment. Central laboratory pathologists were blinded to subject treatment assignment when determining PD-L1 expression levels. Also, the study statistical and statistical programming personnel at the Sponsor were masked to the subject-level allocation schedule in the database. To ensure unbiased use and integrity of the analysis, access to the allocation schedule for summaries or analyses were granted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who had no other responsibilities associated with the study.

The study was an open label study, which is in principle acceptable. However, as discussed in "Statistical methods" and "Conduct of study", the protocol was strongly modified in the conduct of study.

The Applicant was asked to provide a full track record of analyses by treatment group with timing and outcome and to discuss the results in the light of the timing of amendments.

The Applicant provided the requested history of changes in conjunction with conducted interim and final analyses. Of note, the Applicant clarified that the final protocol amendment was completed on 08-MAR-2018, while the data base lock and the corresponding DMC meeting for the efficacy analysis took place later (i.e., on 13-MAR-2018 and 28-MAR-2018). According to the display of the Applicant this was the first and only efficacy analysis before the final analysis. All 3 previous analyses were to be constrained to safety data. Furthermore, it is noted that changes to the protocol were preceded by the same changes in the sSAP on 28-FEB-2018. Yet, all these changes took place after the database cutoff and presumably after the first analyses based on non-locked data. Hence, influence of the data on the sSAP and Protocol is still not completely precluded. The DMC charta and the composition of the eDMC was provided. The Applicant clarified that access to unblinded data prior to the final analysis was restricted to the external unblinded statistician.

Overall, the provided information reduces the risk of choices made in the light of the accruing data.

Statistical methods

The ITT population, which included all participants randomized to an intervention arm regardless of treatment duration, was used for the efficacy analyses of OS, PFS, and ORR. Subjects who showed a confirmed CR or PR were included in analysis of DOR. A total of 628 participants, 314 and 314 participants in the pembrolizumab and SOC arms, respectively, were included in the ITT population.

The China Cohort: after the sample size required for the Global Cohort is reached, the study continued to randomize subjects in China until the sample size for the Chinese subjects meets the target for China. The Chinese subjects randomized after the enrollment of the Global Cohort is closed are not included in

the above primary efficacy analysis population which is based on the Global Cohort. The China Cohort is planned to be analyzed separately per local regulatory requirement.

The FAS population included all randomized participants who have received at least 1 dose of study medication and have completed at least one PRO assessment; it was used for PROs analyses.

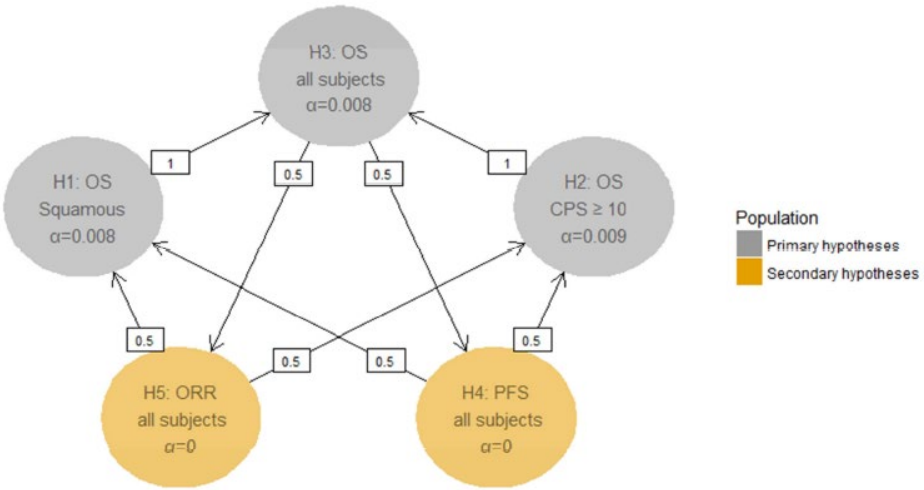
A summary of OS analysis strategy together with the Decision Guidance is shown in the following table (Table 12 of the Protocol/Amendment No.05):

	Criteria for Conduct of Analysis	Endpoint	Value	Efficacy
Interim Efficacy Analysis	~ 25 months after first subject randomized Approximately 251 OS events and 385 OS events have been observed among subjects with squamous cell carcinoma of the esophagus and all subjects, respectively, and 8 months after last subject randomized. If there are fewer than 172 OS events among subjects with PD-L1 CPS≥10 at the time, the interim efficacy analysis may be delayed for up to 2 months or when the target number of OS events in subjects with PD-L1 CPS≥10 is reached, whichever occurs first. OS events among subjects with squamous cell carcinoma of the esophagus: ~251 OS events among subjects with PD-L1 CPS≥10: ~172 OS events among all subjects: 385	OS in subjects with squamous cell carcinoma of the esophagus	p value (1-sided) at boundary ~ HR at boundary	≤0.0023 0.70
		OS in subjects with PD-L1 CPS≥10	p value (1-sided) at boundary ~ HR at boundary	≤0.0027 0.65
		OS in all subjects	p value (1-sided) at boundary ~ HR at boundary	≤0.0023 0.75
Final Analysis	~ 33 months after first subject randomized Approximately 310 OS events and 473 OS events have been observed among subjects with squamous cell carcinoma of the esophagus and all subjects, respectively, and 16 months after last subject randomized. OS events among subjects with squamous cell carcinoma of the esophagus: ~310 OS events among subjects with PD-L1 CPS≥10: ~213 OS events among all subjects: 473	OS in subjects with squamous cell carcinoma of the esophagus	p value (1-sided) at boundary ~ HR at boundary	≤0.0075 0.76
		OS in subjects with PD-L1 CPS≥10	p value (1-sided) at boundary ~ HR at boundary	≤0.0084 0.72
		OS in all subjects	p value (1-sided) at boundary ~ HR at boundary	≤0.0075 0.80

For the OS hypotheses, Lan-DeMets O'Brien-Fleming alpha spending function with specified calendar time fraction (0.76) was used to construct group sequential boundaries to control the Type-I error. The actual boundaries for interim analysis are planned to be determined from the number of OS events

observed at the time of the interim efficacy analysis using the alpha spending function. The boundaries for the final analysis are planned to be adjusted according to the actual alpha spent at IA and the actual number of OS events observed at IA and FA using the alpha spending function.

The alpha reallocation strategy followed the graphical approach of Maurer and Bretz, as reported in the following figure.



The multiplicity strategy was applied to the three primary hypotheses and two secondary hypotheses. The overall Type-I error is strongly controlled at 2.5% (one-sided), with initially 0.8% allocated to OS hypothesis in subjects with squamous cell carcinoma of the esophagus, 0.9% allocated to OS hypothesis in subjects with PD-L1 CPS≥10 and 0.8% allocated to the OS hypotheses in all subjects, and 0% to the PFS and ORR hypotheses. By using the showed graphical approach of Maurer and Bretz, if OS hypothesis in subjects with squamous cell carcinoma of the esophagus is rejected, the corresponding alpha level can be shifted to OS hypothesis in all subjects. If OS hypothesis in subjects with PDL1 CPS≥10 is rejected, the corresponding alpha level can also be shifted to OS hypotheses in all subjects. The key secondary hypotheses of PFS and ORR are tested only if pembrolizumab arm is superior to the control in OS in all subjects. If OS hypothesis in all subjects is rejected, the corresponding alpha level can be shifted by half to PFS in all subjects and by half to ORR in all subjects, respectively.

The non-parametric Kaplan-Meier method was used to estimate the OS and PFS curves in each treatment group. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size were to be reported. Non-responder imputation was to be used.

The hypotheses of treatment difference in OS and PFS in participants with PD-L1 CPS≥10 and in participants with ESCC were tested using a stratified log-rank test.

The hypotheses of treatment difference for OS and PFS curves in all participants were tested using the stratified maximum weighted log-rank (max-combo) test. In addition to a positive test for the treatment difference for OS in all subjects using the stratified max-combo test, the upper bound of the stratified Cox HR is requested to be <1.1.

The stratification factors used for randomisation were to be applied to the stratified log-rank test, stratified max-combo test, and the stratified Cox model if applicable.

A sensitivity analysis, which tests the hypothesis of treatment difference for OS in all subjects using the stratified log-rank test, was also conducted. Sensitivity PFS analyses were performed for comparison of PFS based on investigator's assessment. In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor review, additional sensitivity analyses with a different set of censoring rules (reported in the table below) were performed.

Table 9 Censoring rules for Primary and Sensitivity Analyses of PFS

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

Subjects in the control arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm, and may switch to another anti PD-1 treatment. Exploratory analyses to adjust for the effect of crossover to other PD-1 therapies on OS were to be performed, if deemed appropriate, based on recognized methods, e.g. the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) or a two stage model, based on an examination of the appropriateness of the data to the assumptions required by the methods.

Safety parameters were analysed using descriptive statistics.

Statistical methods for efficacy endpoints are summarized in the following table:

Endpoint/Variable (Description, Time Point)	† Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
OS in subjects with squamous cell carcinoma of the Esophagus.	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in subjects with squamous cell carcinoma of the Esophagus.	Censored at last known alive date
Primary Hypothesis #2			
OS in subjects with PD-L1 CPS≥10.	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in subjects with PD-L1 CPS≥10	Censored at last known alive date
Primary Hypothesis #3			
OS in all subjects	Test: Max-combo test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all subjects	Censored at last known alive date
Key Secondary Endpoints			
PFS per RECIST 1.1 by central imaging vendor review in all subjects	Test: Max-combo test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all subjects	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 9)
ORR per RECIST 1.1 by central imaging vendor review in all subjects	Test: Stratified M & N method‡	ITT in all subjects	Subjects with missing data are considered non-responders

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (See Section 5.4) will be applied to the analysis model if applicable.

‡ Miettinen and Nurminen method [51]

Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the three primary endpoints (OS) was estimated through the stratified Cox model and plotted within each category of the following classification variables:

· Age category (<65 vs. ≥65 years)

- Sex (Female vs. Male)
- Geographic region (Asia vs. Rest of the World)
- ECOG Performance Scale (0 vs. 1)
- Histological subtype (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ)

In addition to the subgroup based on Asia vs. Rest of the World, US vs. ex -US and EU vs. ex-EU were also be assessed.

For OS, the stratified Cox model was used. The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above (for those levels with more than 10% of the ITT population).

Statistical methods for patient-reported outcomes (PRO) endpoints

The PRO analyses are based on the full analysis set (FAS) population. PROs were evaluated using the EORTC QLQ -C30 and QLQ-OES18, eEuroQol-5D (EQ-5D) questionnaires. Since PROs are exploratory objectives in KN181, no formal hypotheses were formulated.

The planned statistical analyses for the PROs are shown in the following table.

Endpoint	Analysis	Primary Statistical Method	Report
Score change from baseline	Treatment effect estimation/comparison	Mixed effect model based on the missing at random (MAR) assumption.	lsmean score (95% CI) by treatment group and visit, lsmean score change (95% CI) from baseline by treatment group and visit, between-group difference in score change from baseline (95% CI, nominal p-value).
Proportion of deterioration/ stable/improvement	Treatment effect estimation/comparison	Summary with multiple imputation based on the MAR assumption	Proportion (95% CI) by treatment group at Week 9
Time to deterioration	Treatment effect estimation/comparison	Stratified log rank test Stratified Cox proportional hazard model Kaplan-Meier plot	Hazard Ratio (95% CI, p-value)

Changes to statistical methods in the conduct of study

The protocol was amended 5 times and via an sSAP. In the conduct of the study many key design elements were changed: primary hypotheses were changed from co-primary endpoints PFS and OS to OS only, the biomarker for key subgroups was changed from GEP to CPS, an additional key analysis population was specified (SCC), the timing of analyses was modified, multiplicity control was changed with Amendment 4, and statistical methods were altered (by using the max-combo test starting from Amendment 5). As it is assumed that Amendment 5 was initiated after the interim analysis this is of special criticality. In the light of these changes, the Applicant is asked for an in-depth discussion of the changes and the timing of the changes. See also conduct of study.

With **Amendment 1** GEP high population was changed to GEP intermediate or high, were GEP cut-offs were now to be based on an external study (KN-180). According to the Applicant, Amendment 1 never came into action and was immediately superseded by Amendment 2. **Amendment 2** kept the definition of GEP intermediate or high and refined how primary, secondary, and exploratory objectives and endpoints were to be met and analysed, respectively, based on these tumour designations. With **Amendment 3**, statistical methods were updated to align the protocol with the updated enrolment status and GEP prevalence, the analysis timing was changed due to faster than expected enrolment, the IA was to driven by events in all subjects instead of GEP intermediate and GEP high and the power and HR boundary were updated. The expected sample size in GEP intermediate and GEP high was updated based on the currently observed prevalence rate. With **Amendment 4** the primary objectives were changed from dual endpoints of OS and PFS to a single endpoint of OS to be tested in patients with squamous cell carcinoma of the oesophagus, followed by patients with CPS ≥ 10% and all subjects. GEP-based analyses populations were no longer considered in the primary endpoints. PFS was moved to a secondary EP. Furthermore, the timing of the interim and final analyses was updated in order to wait for more mature OS data and account for a potential delayed separation in survival curves observed in immuno-oncology studies (based on studies MK3475 and KN180). In **Amendment 5**, the alpha spending function to control the Type-I error based on information fraction was replaced with one based on specified calendar time fraction (0.76). In the all subjects population, for testing the OS and PFS

hypotheses, the stratified log-rank test was replaced with the stratified max-combo test to account for non-proportional hazards. Two major changes were introduced with the **sSAP**: 1) To allow for a robust assessment of the significance of a positive assessment of the treatment effect on OS based only on the stratified max-combo test, the upper bound of the stratified Cox HR was to be <1.1 in addition to a positive test for the treatment difference for OS in all subjects using the stratified max-combo test. 2) Due to the historical precedent for the log-rank test, it was to be evaluated along with the as max combo test in the same fashion. The significance level was to be the same as for the corresponding max-combo test.

As seen above, *the most significant changes were introduced with Amendment 4*, where

- PFS was dropped from the primary endpoints,
- GEP was dropped as biomarker for the primary analysis populations and replaced by CPS,
- and squamous cell carcinoma was included in the primary analysis populations.

Hence, consequently almost all primary endpoints were changed.

Statistical methods

The general methods to assess primary and key secondary endpoints are endorsed.

The Applicant introduced the (stratified) max-combo test with amendment 5 in replacement of the (stratified) log-rank test *in the all-comer population* both for OS and PFS. This was done to account for non-proportional hazards. Within the SAP this was further refined by requiring the confidence interval of the Cox HR to be below 1.1.

Since no profound justification was provided, the Applicant was asked to provide an in-depth discussion of clinical implications of the max-combo test used and provide strong evidence that the max-combo test controls the type 1 error rate (even though no indication for the all-comer population has been sought). The Applicant was asked to discuss misalignment of estimation and testing as well as the boundary of 1.1 on the upper limit of the 95% CI for the HR and its implications.

With the response to the 1st RSI the Applicant provided a rather brief discussion of the raised concerns. Given the ongoing controversial discussions with regulators around the issues raised this is considered to be rather weak. Type 1 error control is currently only shown in simulation studies, while the type 1 error control relies on the known correlation structure between test statistics in the (modified) MaxCombo test (only two out of four test statistics were used). Using simulations as only method to show the type 1 error control is considered a weakness of an approach.

No discussion was provided regarding the misalignment of testing and estimation. The provided reference (Lin et al. [Ref. 5.4: 058S84]) briefly mentions that the weights from the test statistic leading to the smallest p-value could be used in a weighted Cox regression model. Yet, the implications and problems of this approach were also not discussed.

The requirement for the upper boundary of the 95% CI from an (unweighted) Cox model was explained. This is to exclude situations were survival curves cross at a later time point. While the general aim is understood, the choice of the boundary as 1.1 is not. Any other value would also be possible. Given that this additional constraint does not negatively affect the type 1 error (but would reduce the power), this is in principle acceptable.

Overall, the provided response was rather brief and mainly relied on unpublished literature and presentations. The approach to analyse non-proportional hazards has not yet been sufficiently discussed

and understood. It is reiterated that if MaxCombo test was to be used as the primary analysis method in the population of interest, the Applicant would need to provide more information on e.g. the type 1 error control, the estimation and a better rationale for the choices made. However, given that the (modified) MaxCombo test was not applied for the primary analysis in the population of interest in the current procedure, this issue was not further pursued.

Multiplicity

The adjustment for multiple endpoints was changed with protocol Amendment 4. The initial multiplicity approach is depicted in *Figure 4, Protocol Amendment 3* below. In the initial protocol the "GEP-selected group" was restricted to patients with GEP high but multiplicity control was the same otherwise.

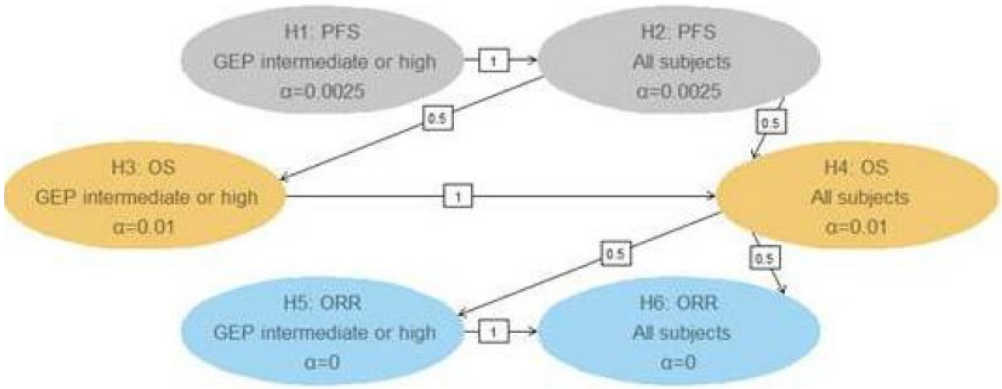


Figure 4, Protocol Amendment 3: Multiplicity control

Interim Analyses

In Protocols Version 1 to 3 (Amendment 2) the *final PFS* analysis was planned at the time of interim OS according to Table 11 in the respective protocols. Hence, PFS was to be tested in a confirmatory manner only once. However, the protocol specified an alpha spending function for PFS, which was not understood. Little or contradictory information was provided regarding the planned interim analysis within the dossier; therefore the Applicant was asked to provide a CSR for the interim analysis detailing the applied methods and results (including but not limited to the timing of the interim analysis, the event that triggered the interim analysis, the number of OS events per primary endpoint and of course analysis results and decisions based on these results). The Applicant provided the results of the efficacy interim analyses as presented to the eDMC. The following results were obtained for OS in the three different populations at interim (not taking the two additional deaths into account):

ITT PD-L1 CPS ≥ 10:
69 + 91= 160 patients had an event
OS events planned at final analysis: 213 →IF = 0.751 (planned: 172/213 = 0.8075)
One sided p-value: 0.003 (logrank)
Significance level at interim: 0.0027
HR = 0.64 (95% CI: 0.46, 0.89)

ITT population (SCC):
138 + 159 = 297 patients had an event
OS events planned at final analysis: 310 → IF = 0.958 (planned: 251/310 = 0.8097)
One sided p-value: 0.021
Significance level at interim: 0.0023

HR = 0.79 (95% CI: 0.63, 0.99)
Late separation and crossing curves after ~23 months

ITT population:

236 + 248 = 484 patients had an event
OS events planned at final analysis:473 →IF = 1.023 (planned: 385/473 = 0.8139)
One sided p-value: 0.177 (logrank) and 0.160 (modified MaxCombo)
Significance level at interim: 0.0023
HR = 0.92 (95% CI: 0.77, 1.10)
Late separation and crossing curves after ~21 months

Initially, the interim analysis was planned after at least 385 events had been observed in the ITT population (de facto observed at IA: 484) and at least 251 events had been observed in the SCC population (de facto: 297). It was furthermore planned that the interim analysis could be delayed by another 2 months of less than 172 events had been observed in the PD-L1 CPS ≥ 10 population (de facto: 160). As can be seen, in the SCC and all patient population severe overrunning (as compared to the planned number of events) was observed while in the PD-L1 CPS ≥ 10 population fewer events were observed than anticipated.

Taking the two additional deaths into account, the following event rates were reported:

H	Analysis	Events
H1	1	299
H1	2	348
H2	1	161
H2	2	191
H3	1	486
H3	2	555

(Source: Appendix 51, Table 4; H1 = OS in SCC, H2 = OS in PD-L1 CPS ≥ 10, H3 = OS in all subjects)

In the final analysis 191 events were observed in PD-L1 CPS ≥ 10 patients, 348 events in SCC patients and 555 events in all patients. Hence, **the true information fraction at interim** was 161/191 = **0.8429** (PD-L1 CPS ≥ 10), 299/348 = 0.8591 (SCC), 486/555 = 0.8757 (all patients).

In line with the interim analysis results provided as Appendix 112 in the response to Q12, the eDMC concluded not to stop the trial for efficacy.

The Applicant was asked to resolve further issues regarding the interim analysis in the LoI and LoOI.

Overall, the answers provided by the Applicant were rather brief and not very illustrative given the central role of the type 1 error control in general and in this procedure in particular. The nominal alpha level of the procedure is computed as 0.00853 and the corresponding p-value just marginally larger as 0.00855. In this light, the type 1 error control of the procedure becomes even more relevant.

The referenced paper of Lan and DeMets (1989) describes an approach for interim analyses based on calendar time in situations where the trial is to be terminated based on the elapsed time span ("maximum duration trial"; the usual approach based on events is called a "maximum information trial"). In that situation, Method 1 describes an approach to control the type 1 error using the timing of interim analyses

to calculate the information fraction but the observed events to calculate the correlation between analyses. It is assumed that this is the approach the Applicant used for planning of the trial.

This has two consequences: 1) the boundary at the first interim analysis is purely chosen based on the observed calendar time in relation to the maximum follow up time; 2) all further boundaries depend on the ratio of the observed calendar times and the ratio of events between the current and the previous analysis.

This is not in line with the presented analyses.

In the Applicants case, the analysis depends on the planned calendar time of the interim analysis in relation to a planned but not fixed calendar time for the final analysis. Of note, the trial was no "maximum duration trial". The end of the trial was to be triggered by the number of events in ESCC and all patients.

Overall, the approach used by the applicant is not in line with the situation in which the approach by Lan and DeMets was presented. No further justification or discussion was provided in response to the LoOI.

Table 16.1: Nominal significance levels at interim (IA) and final analysis (FA) for three scenarios

	IA	FA
Only observed IF (= 0.84)	0.00444	0.00769
Only fixed IF (= 0.76)	0.00273	0.00816
Mixture (Applicant's approach)	0.00273	0.00853

Table 16.1 shows that only the approach chosen by the Applicant (last line) is the best approach for the Applicant as it has a significance level (very) close to the observed p-value. It is the most opportunistic choice of design. If the analysis are only based on the observed numbers of events at interim and final analysis (first row; this would be the usual approach) or only on the fixed calendar time based information fraction (IF; second column), results would be further away from the final significance level.

It is not understood how the last two lines in the table both can control the overall type 1 error. When the combined probability to cross 0.00273 at the interim or 0.00816 at the final analysis is $\leq$ 0.009 (under H0), how can the probability to cross 0.00273 at the very same interim analysis or 0.00853 at the final analysis be the same?

No discussion on this discrepancy and the impact of these late changes (the "mixture" approach was only implemented with Amendment 5) was provided.

The Applicant argued that the chosen approach was conservative if the accrual of events was faster than anticipated. Based on the Applicant's arguments this is indeed true for the interim analysis but not true for the final analysis (compare Table 16.1, first and last line). The Applicant concluded that "the p-value boundary [at interim] is 0.0027 per calendar time and 0.0044 per actual event fraction, which is more conservative." This is however only partly relevant. The more important fact that alpha-allocation at final analysis was less conservative (per calendar time approach 0.00853, per event rate 0.0077) was not commented on.

Overall, uncertainties remain with respect to

1) the applicability of a maximum duration trial (vs. maximum information trial),

2) the theoretical foundation of the chosen approach,

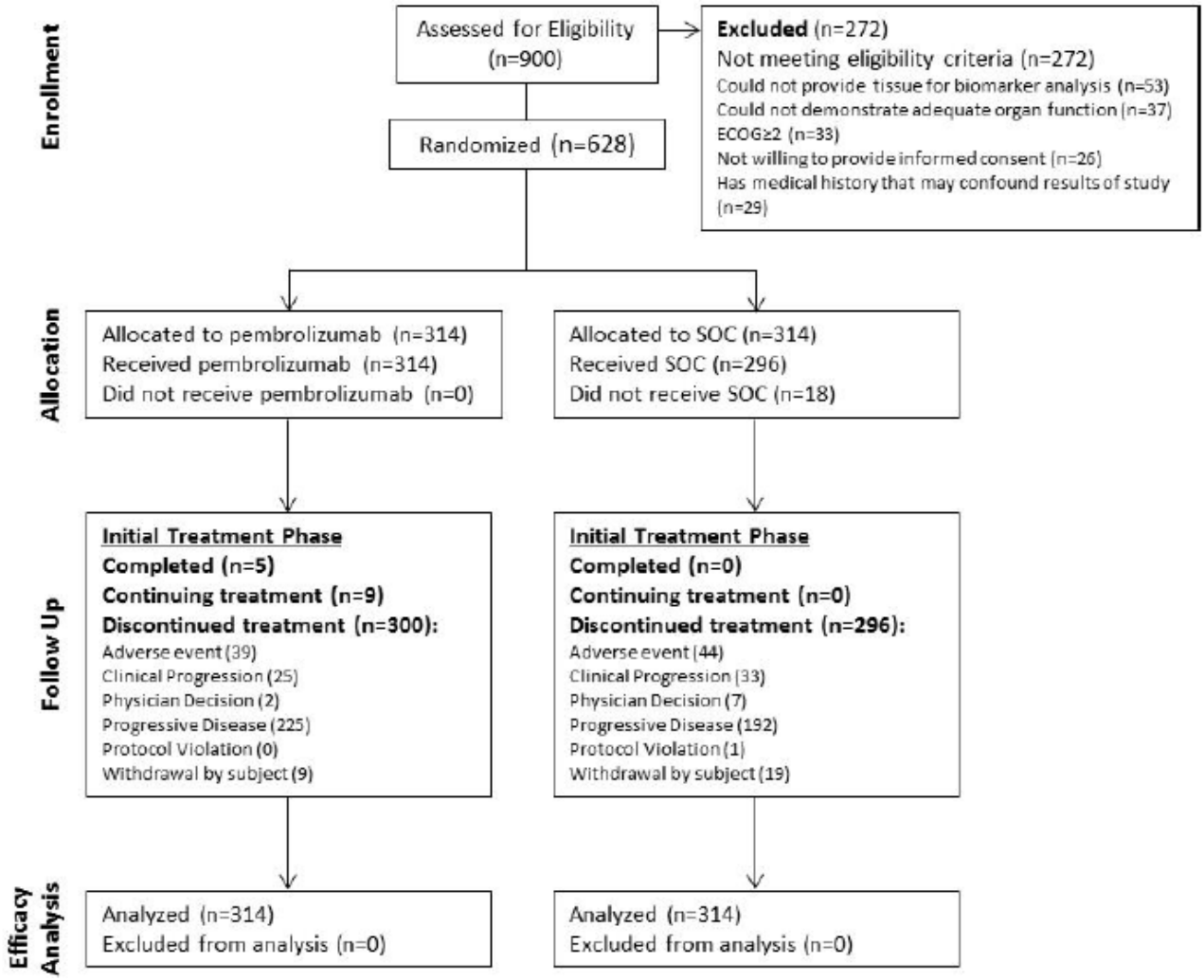
3) the anti-conservative nature of the approach (at final analysis) compared to the event-based approach and an approach with calendar time only (i.e., without correlation matrix based on events) and with respect to the speed of accrual, and

4) the applied software.

Results

Participant flow

Figure: Participant flow figure



Note: Per the study protocol, only participants in the pembrolizumab arm who received 35 cycles of pembrolizumab are categorized as completed; 5 participants in the pembrolizumab arm received 35 cycles of intervention.

Table: Disposition of Subjects (ITT Population)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	314		314		628	
Status For Trial						
Discontinued	272	(86.6)	289	(92.0)	561	(89.3)
Adverse Event	31	(9.9)	29	(9.2)	60	(9.6)
Death	236	(75.2)	242	(77.1)	478	(76.1)
Withdrawal By Subject	5	(1.6)	18	(5.7)	23	(3.7)
Trial Ongoing	42	(13.4)	25	(8.0)	67	(10.7)
Status For Study Medication In Trial Segment Treatment						
Started	314		296		610	
Completed	5	(1.6)	0	(0.0)	5	(0.8)
Discontinued	300	(95.5)	296	(100.0)	596	(97.7)
Adverse Event	39	(12.4)	44	(14.9)	83	(13.6)
Clinical Progression	25	(8.0)	33	(11.1)	58	(9.5)
Physician Decision	2	(0.6)	7	(2.4)	9	(1.5)
Progressive Disease	225	(71.7)	192	(64.9)	417	(68.4)
Protocol Violation	0	(0.0)	1	(0.3)	1	(0.2)
Withdrawal By Subject	9	(2.9)	19	(6.4)	28	(4.6)
Treatment Ongoing	9	(2.9)	0	(0.0)	9	(1.5)
Database Cutoff Date: 15OCT2018.						

In general, the disposition of participants was similar between participants with PD-L1 CPS ≥10 to all participants.

Table: Disposition of Subjects (ITT Population, Subjects with PD-L1 CPS ≥10)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	107		115		222	
Status For Trial						
Discontinued	88	(82.2)	105	(91.3)	193	(86.9)
Adverse Event	10	(9.3)	12	(10.4)	22	(9.9)
Death	77	(72.0)	88	(76.5)	165	(74.3)
Withdrawal By Subject	1	(0.9)	5	(4.3)	6	(2.7)
Trial Ongoing	19	(17.8)	10	(8.7)	29	(13.1)
Status For Study Medication In Trial Segment Treatment						
Started	107		114		221	
Completed	1	(0.9)	0	(0.0)	1	(0.5)
Discontinued	101	(94.4)	114	(100.0)	215	(97.3)
Adverse Event	16	(15.0)	17	(14.9)	33	(14.9)
Clinical Progression	8	(7.5)	15	(13.2)	23	(10.4)
Physician Decision	0	(0.0)	2	(1.8)	2	(0.9)
Progressive Disease	73	(68.2)	72	(63.2)	145	(65.6)
Withdrawal By Subject	4	(3.7)	8	(7.0)	12	(5.4)
Treatment Ongoing	5	(4.7)	0	(0.0)	5	(2.3)
Database Cutoff Date: 15OCT2018.						

A large proportion (30%) of the patients assessed for eligibility was not randomized because of not meeting eligibility criteria.

As to be anticipated the most frequent reason for study intervention discontinuation was disease progression, with a discontinuation rate of 71.7% for pembrolizumab and 64.9% for SOC arm in the overall study population. The percentage of participants who discontinued treatment due to AEs was similar (12.4% and 14.9%).

As already observed in other open-label trials a higher proportion of withdrawals were reported in the SOC arm compared to the pembrolizumab arm, likely driven by the patients' expectations to receive pembrolizumab. 18 patients that were allocated to SOC did not receive treatment compared to none in the pembrolizumab arm. Moreover, more patients discontinued due to physician decision (n=7) or withdrawal by subject (n=19) in the SOC arm compared to the pembrolizumab arm (n=2 discontinued due to physician decision and n=9 were withdrawn by subject decision). The MAH was asked to provide the reasons for not receiving treatment in the SOC treatment and provide sensitivity analyses for OS to account for a potential negative impact on the performance of the SOC arm in the ITT analysis . The Applicant clarified that in about half of the cases of withdrawals before treatment initiation patients withdraw consent after learning about their treatment allocation; among the withdrawals after treatment start in the majority of the participants (18/26) withdrawing was reported "specifically due to SOC and its side effects and impacts on quality of life". By this it is difficult to judge to what extent the knowledge of treatment allocation might have been a driving factor.

While one of the two sensitivity analysis confirmed the OS outcome of the ITT population, the other sensitivity analysis (participants who were untreated or discontinued from study medication due to physician decision or withdrawal by participant were censored at database cutoff date) displayed a OS HR of 1.12 in the ITT population; however it is acknowledged that this latter analysis overestimates survival time in the SOC group.

The analyses were conducted in the overall ITT population and it is considered reassuring that less than half of subjects on SOC who withdrew consent had a PD-L1 CPS ≥10. Thus, although an impact of the higher rate of withdrawals on the performance in the SOC arm cannot be completely excluded, its amount is rather not of important relevance for the evaluation of the B/R in the claimed indication for subjects with CPS≥10.

Recruitment

A total of 628 participants were randomized across 154 global study sites in 32 countries.

The first participant was enrolled (signed informed consent) on 08-DEC-2015, and the last participant was enrolled on 16-JUN-2017. Last participant last visit and data cut-off for the submitted efficacy analysis occurred on 15-OCT-2018, database lock occurred on 06-NOV-2018.

Most randomized participants received at least 1 dose of study. The primary reason for screen failure was the inability to provide a tissue sample for intratumoral biomarker analysis.

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

Follow-up duration (months)	Pembrolizumab 200 mg (N = 314)	SOC (N = 314)
Median (Range)	7.1 (0.5, 31.3)	6.9 (0.2, 32.2)
Mean (SD)	9.2 (7.1)	8.4 (6.4)

Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the subject is still alive.
Database Cutoff Date: 15OCT2018.

Conduct of the study

Changes in the Conduct of the Study or Planned Analyses (excerpts)

Original protocol (dated 25-AUG-2015):

Subjects were required to provide a tumor sample, to be evaluated at a central laboratory, for analysis of immune-related gene expression profile (GEP) for response prediction for pembrolizumab efficacy.

The overall study enrollment was to be driven by the number of subjects with GEP high tumors (n =360). That is, enrollment was to stop when approximately 360 subjects with GEP high tumours had been randomized. If the prevalence of GEP high is 60%, it was estimated that approximately a total of 600 all comers were to be enrolled.

Rationale for using GEP (as provided in the original protocol):

Gene expression signatures measuring mRNA for key immune-related genes have been confirmed to be significantly associated with clinical benefit to pembrolizumab treatment in melanoma, head & neck, and gastric cancers as well as in the esophageal cancer cohort in KN028. The predominant pattern indicates that tumors with relatively low expression of these genes have a low probability of response to pembrolizumab. A GEP combines expression levels for multiple genes into a scalar score and can be used to identify such low-probability of responding patients. In a prospective analysis of a modestly-sized esophageal cancer cohort in KN028, with the population enriched for PD-L1, a prototype version of the GEP showed a clinical response rate of 0% below a receiver operating characteristic (ROC) curve derived cut-off using the Youden Index. The response rate above the cut-off was 58%, with 67% of patients lying above the cut-off. Based on the data described above further evaluation of the GEP response prediction ability in esophageal cancer is warranted.

A GEP cut-off derived using data from KN180 (an all-comers population) will be used in this study to identify "GEP high" vs. "GEP low" patients per the primary objectives, with the aim to identify patients having a very low response rate as "GEP low".

The primary endpoints were to be PFS and OS in GEP high subjects and all subjects (4 hypotheses; no distinction between histology)

To explore the relationship between PD-L1 expression by IHC and response to the treatment was to be one of the exploratory objectives.

Protocol amendments

A total of 13 protocol amendments, including global and country-specific changes, were implemented during the study. The original protocol is dated 25 August 2015.

The key changes introduced by the protocol amendments are summarized below:

Protocol Amendment	Most relevant changes
#01 (20 July 2016)	• Issued, and then soon retracted. At the time of retraction, no new participants had been enrolled at any site. Protocol Amendment #2 replaced this document, with all changes from Amendment #1 reflected in Amendment #2.
#02 (9 Dec 2016)	• Sections were revised to identify GEP low, intermediate, and high tumors; to describe the development of GEP cutoff "GEP intermediate or high" and/or to describe how the primary, secondary, and exploratory objectives and endpoints will be met and analyzed, respectively, based on these tumor designations

	Updated rationale for using GEP (as provided in the amended protocol): Gene expression profiling of tumor specimens from clinical studies KEYNOTE-001 (Melanoma), KEYNOTE-012 (Head and Neck, Bladder, Gastric cancers) and KEYNOTE-028 (Ovarian, Esophageal, and other cancers) led to the identification of an 18-gene immune-related intratumoral GEP that is associated with response to pembrolizumab. Using data from KEYNOTE-012 and KEYNOTE-028, a GEP combining expression levels of 18 genes into a scalar score was developed and two cut-offs on that score which divide tumors into "low", "intermediate", and "high" were determined using data from KEYNOTE-028, KEYNOTE-012, and KEYNOTE-052. The lower cut-off was defined to favour sensitivity in capturing responders by centrally reviewed REC IST and the higher cut-off was selected to enrich for higher response rates at potentially some cost in sensitivity. In this study, the hypothesis is that subjects whose tumors are above the lower cut -off (i.e. are either GEP intermediate or GEP high) may show greater clinical benefit under treatment with pembrolizumab relative to the comparator in a manner that will be more substantial than what is observed in an all comers population that includes subjects whose tumors are GEP low. • Move evaluation of PD-L1 by IHC from exploratory to secondary objective (based on external data indicating PD-L1 as predictive biomarker) • Removed Microsatellite Instability as a biomarker to be evaluated (due to insufficient tissue sample) • Excluded known CNS metastases; excluded the presence of ascites and pleural effusion determined by physical exam; added exclusion criteria for patients with weight loss > 10% over approximately 2 months prior to first dose of study therapy. • Added an additional criterion to specifically exclude subjects who progressed on more than one line of therapy (To ensure that the study population is second line only)
#03 (29 March 2017)	• The China Cohort was introduced. Enrollment period was extended beyond the Global Cohort to achieve the required sample size of the China Cohort and the number of events to investigate efficacy and safety in Chinese 2L EC subjects. The Global Cohort enrollment completion is at 600 subjects irrespective of GEP status (Text updated since GEP assessment is retrospective) • Interim Analysis, Sample Size and Power Calculations: o Analysis timing changed due to faster than expected enrollment o IA driven by events in all subjects instead of GEP intermediate and GEP high o Power and HR boundary revised based on observed prevalence rate of GEP lower/intermediate/high and based on above mentioned changes to IA o The expected sample size in GEP intermediate and GEP high was updated based on the currently observed prevalence rate.
#04 (3 August 2017)	• The primary objectives were changed from dual endpoints of OS and PFS to a single endpoint of OS. Primary objectives were changed to

	○ OS in subjects with squamous cell carcinoma of the Esophagus. ○ OS in subjects with PD-L1 Combined Positive Score (CPS) ≥10% ○ OS in all subjects. • PFS per RECIST 1.1 assessed by central imaging vendor in all subjects was moved to secondary endpoint with multiplicity control. • PFS per RECIST 1.1 assessed by central imaging vendor and OS in subjects whose tumors are GEP intermediate or GEP high were removed. • Primary and secondary endpoints were updated accordingly • Evaluation of efficacy by GEP expression was downgraded as exploratory objective (As outlined by the MAH the revisions were based on recommendations from emerging data in MK3475-KN180). Excerpt from Biomarker Research: Tumor PD-L1 expression PD -L1 expression in tumor cells and inflammatory cells within pre-treatment tumor tissue samples will be characterized by IHC and retrospectively tested for association with response to pembrolizumab. Tumor bank-derived, EC tissues matched for stage and grade with subjects in pembrolizumab studies, as well as EC tissues from KN180, were used to determine the prevalence of PD-L1 positivity greater than or equal to a combined positive score (CPS) of 1% or 10%. CPS is the number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes) over total tumor cells, expressed as a percentage. The prevalence of PD-L1 > 10% CPS in tumor bank or KN180, respectively was 52% or 47.2%. The prevalence of PDL1 > 1% CPS was greater in both the tumor bank (72%) as well as the KN180 study (85.8%). Utility of the PD-L1 CPS measure to enrich for EC patient response to pembrolizumab will be determined in KN180. Further studies of both prevalence as well as utility as a prognostic marker are being evaluated in epidemiology studies. • Interim and final analysis timing were updated: driven by number of OS events and minimum follow up time. Multiplicity updated accordingly. • *Rationale*: The revisions were based on recommendations from emerging data in KN180; the timing of the interim and final analyses was updated in order to wait for more mature OS data and account for a potential delayed separation in survival curves observed in immuno-oncology studies.Changes in exploratory objectives: Removal of Time to progression and removal of PFS per irRECIST in subjects whose tumors are GEP intermediate or GEP high; GEP was replaced by PD-L1 for concordance in archival compared to newly obtained tumor tissue. One exploratory objective was added: To evaluate efficacy by GEP expression.
#05 (8 March 2018)	• The alpha spending function to control the Type-I error based on information fraction was replaced with one based on specified calendar time fraction (0.76). *Rationale*: Information fraction was replaced by calendar time fraction in alpha spending function because:

	1. Accurately estimating number of events in subjects with squamous cell carcinoma of the oesophagus, subjects with PD-L1 CPS≥10 and all subjects is difficult due to potential delayed treatment effects that have been observed with immunotherapy. 2. Since information accrues at varying rates for different hypotheses, this change will control multiplicity across hypotheses. • In the all subjects population, for testing the OS and PFS hypotheses, the "stratified log-rank test" was replaced with the "stratified maximum weighted log rank test" also referred to as the stratified max-combo test. *Rationale*: Due to potential delayed treatment effects that have been observed with immunotherapy, the stratified log-rank test was replaced by a stratified max-combo test for testing the OS and PFS hypotheses in all subjects. Max-combo test statistic is the maximum of test statistics based on the log-rank test and a test that down-weights the early events, and hence, is sensitive to the non-proportional hazards assumption.

The above list of changes was drafted by the Assessors based on the provided protocols. Changes to the statistical analyses are discussed above in the section "Statistical methods".

The Applicant changed the protocol 5 times during the ongoing study and additionally in a supplementary SAP with changes affecting the primary analysis populations and endpoints in almost all cases substantially..

Protocol deviations

The number of important deviations (ie, those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) are listed in the Table below.

Table: Important Protocol Deviation Summary

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		314	
With one or more important protocol deviations	35	(11.1)	35	(11.1)
With no important protocol deviations	279	(88.9)	279	(88.9)
Discontinuation Criteria	**1**	**(0.3)**	**2**	**(0.6)**
Participants who develop trial specific discontinuation criteria but were not discontinued from the trial.	1	(0.3)	2	(0.6)
Inclusion/ Exclusion Criteria	**15**	**(4.8)**	**13**	**(4.1)**
Participants entered into the trial, i.e. progressed beyond screening, who did not meet key inclusion/exclusion criteria.	4	(1.3)	9	(2.9)
Randomization of a patient who did not meet the requirements for prior lines of therapy	11	(3.5)	4	(1.3)
Prohibited Medications	**1**	**(0.3)**	**0**	**(0.0)**
Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment (unless allowed per protocol).	1	(0.3)	0	(0.0)
Safety Reporting	**17**	**(5.4)**	**14**	**(4.5)**
Participants with reportable Safety Events and/or follow up Safety Event information that were not reported per the timelines outlined in the protocol.	17	(5.4)	14	(4.5)
Study Intervention	**2**	**(0.6)**	**5**	**(1.6)**
Participants who received incorrect study treatment and/or were administered improperly stored study treatment.	2	(0.6)	5	(1.6)
Trial Procedures	**3**	**(1.0)**	**1**	**(0.3)**
Participant with 2 consecutive missing imaging assessments	3	(1.0)	1	(0.3)

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

Source: [P181V01MK3475: adam-adsl] [P181V01MK3475: sdtm-dv]

Important protocol deviations were reported for 35 participants in the pembrolizumab arm and 35 in

the SOC arm (11.1%). Important deviations were defined as those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being.

Fifteen participants did not meet the inclusion criteria regarding prior therapy (11 in the pembrolizumab arm and 4 in the SOC arm):

• Two participants previously only treated with neoadjuvant and adjuvant therapy had not experienced disease progression within the 6-month window allowed per study protocol eligibility criteria. For both of these participants, previous courses of treatment were not considered lines of therapy.

• Twelve participants experienced two disease progressions, and therefore it was considered that these participants already had two lines of prior therapy.

• One subject experienced 3 disease progressions on the same chemotherapy, and therefore it was considered that this participant had already had 3 prior lines of therapy.

No participant data were excluded from analyses due to an important protocol deviation.

Important protocol deviations classified as GCP compliance issues occurred at all Australian sites in which Global informed consent form updates released 24-JUL-2017, including updated risk information for pembrolizumab, had not been communicated to the investigators, ethics committees, or participants, impacting participant rights and potentially their safety. The health authority and ethics committees were notified and corrective actions were taken.

The percentage of participants with important deviations was 11.1% in both groups. More participants (n=11) did not meet the inclusion criteria regarding prior therapy compared to the SOC arm (n=4); the main reason was that participants had already received more than one prior line of therapy. Overall the reported protocol deviations do not raise serious concerns regarding the integrity of the study results.

Baseline data

In the ITT population (all participants) the majority were male (86.6%), <65 years of age (56.7%), from outside of Asia (ex-Asia, 61.3%), had an ECOG PS of 1 (61.1%), and metastatic disease (91.7%). A total of 63.9% participants had ESCC histology and 35.4% participants had a PD-L1 CPS ≥10 status.

Fourteen participants were her2/neu positive out of 75 participants with EAC of the EGJ who were tested for her2/neu tumor status; 13 of which were previously treated with trastuzumab per protocol (1 untreated participant was from Brazil, where trastuzumab is not approved as standard treatment in the public system).

Table: Subject Characteristics (ITT Population) (*highlights by Assessor*)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	314		314		628	
Gender						
Male	273	(86.9)	271	(86.3)	544	(86.6)
Female	41	(13.1)	43	(13.7)	84	(13.4)
Age(Years)						

< 65	175	(55.7)	181	(57.6)	356	(56.7)
>= 65	139	(44.3)	133	(42.4)	272	(43.3)
Subjects with data	314		314		628	
Mean	62.6		62.0		62.3	
SD	9.4		9.6		9.5	
Median	63.0		62.0		63.0	
Range	23 to 84		24 to 84		23 to 84	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.3)	1	(0.2)
Asian	126	(40.1)	122	(38.9)	248	(39.5)
Black Or African American	3	(1.0)	3	(1.0)	6	(1.0)
Multiple	2	(0.6)	4	(1.3)	6	(1.0)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.3)	1	(0.2)
White	179	(57.0)	173	(55.1)	352	(56.1)
Missing	4	(1.3)	10	(3.2)	14	(2.2)
Ethnicity						
Hispanic or Latino	19	(6.1)	26	(8.3)	45	(7.2)
Not Hispanic or Latino	288	(91.7)	274	(87.3)	562	(89.5)
Not Reported	4	(1.3)	5	(1.6)	9	(1.4)
Unknown	3	(1.0)	9	(2.9)	12	(1.9)
ECOG Performance Scale						
0	126	(40.1)	116	(36.9)	242	(38.5)
1	187	(59.6)	197	(62.7)	384	(61.1)
2	1	(0.3)	1	(0.3)	2	(0.3)
Geographic Region of Enrolling Site						
Asia	121	(38.5)	122	(38.9)	243	(38.7)
ex-Asia	193	(61.5)	192	(61.1)	385	(61.3)
Current Disease Presentation						
Locally Advanced	24	(7.6)	28	(8.9)	52	(8.3)
Metastatic	290	(92.4)	286	(91.1)	576	(91.7)
Brain Metastasis						
Y	6	(1.9)	4	(1.3)	10	(1.6)
N	308	(98.1)	310	(98.7)	618	(98.4)
Metastatic Staging						
M0	24	(7.6)	28	(8.9)	52	(8.3)
M1	290	(92.4)	286	(91.1)	576	(91.7)
Histological subtype						
Squamous cell carcinoma	198	(63.1)	203	(64.6)	401	(63.9)
Adenocarcinoma of esophagus and EGJ Siewert type I	116	(36.9)	111	(35.4)	227	(36.1)
PD-L1 Status						
PD-L1 CPS >= 10	107	(34.1)	115	(36.6)	222	(35.4)
PD-L1 CPS < 10	201	(64.0)	196	(62.4)	397	(63.2)
Not Evaluable	6	(1.9)	3	(1.0)	9	(1.4)
Prior Adjuvant or Neoadjuvant Therapy						

Yes	32	(10.2)	32	(10.2)	64	(10.2)
No	282	(89.8)	282	(89.8)	564	(89.8)
Number of Prior Therapy						
0	2	(0.6)	0	(0.0)	2	(0.3)
1	303	(96.5)	310	(98.7)	613	(97.6)
2	9	(2.9)	3	(1.0)	12	(1.9)
3	0	(0.0)	1	(0.3)	1	(0.2)
Prior Anthracycline Therapy						
Yes	21	(6.7)	26	(8.3)	47	(7.5)
No	293	(93.3)	288	(91.7)	581	(92.5)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Prior Monoclonal Antibody Therapy						
Yes	21	(6.7)	16	(5.1)	37	(5.9)
No	293	(93.3)	298	(94.9)	591	(94.1)
Prior Irinotecan Therapy						
Yes	8	(2.5)	3	(1.0)	11	(1.8)
No	306	(97.5)	311	(99.0)	617	(98.2)
Prior Platinum Therapy						
Yes	311	(99.0)	310	(98.7)	621	(98.9)
No	3	(1.0)	4	(1.3)	7	(1.1)
Prior Fluoropyrimidine Therapy						
Yes	266	(84.7)	267	(85.0)	533	(84.9)
No	48	(15.3)	47	(15.0)	95	(15.1)
Prior Taxane Therapy						
Yes	105	(33.4)	105	(33.4)	210	(33.4)
No	209	(66.6)	209	(66.6)	418	(66.6)
Database Cutoff Date: 15OCT2018.						

Source: [P181V01MK3475: adam-adsl]

Baseline characteristics were provided separately also for subjects with PD-L1 ≥ 10, the target population of the sought indication.

Table: Subject Characteristics

(ITT Population, Subjects with PD-L1 CPS >=10)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	107		115		222	
Gender						
Male	92	(86.0)	99	(86.1)	191	(86.0)
Female	15	(14.0)	16	(13.9)	31	(14.0)
Age(Years)						
< 65	56	(52.3)	59	(51.3)	115	(51.8)
>= 65	51	(47.7)	56	(48.7)	107	(48.2)
Subjects with data	107		115		222	
Mean	63.3		63.1		63.2	
SD	9.4		9.9		9.6	
Median	64.0		64.0		64.0	
Range	42 to 81		33 to 81		33 to 81	
Race						
Asian	61	(57.0)	55	(47.8)	116	(52.3)

Multiple	0	(0.0)	1	(0.9)	1	(0.5)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.9)	1	(0.5)
White	45	(42.1)	55	(47.8)	100	(45.0)
Missing	1	(0.9)	3	(2.6)	4	(1.8)
Ethnicity						
Hispanic or Latino	3	(2.8)	6	(5.2)	9	(4.1)
Not Hispanic or Latino	103	(96.3)	106	(92.2)	209	(94.1)
Not Reported	1	(0.9)	1	(0.9)	2	(0.9)
Unknown	0	(0.0)	2	(1.7)	2	(0.9)
ECOG Performance Scale						
0	45	(42.1)	36	(31.3)	81	(36.5)
1	62	(57.9)	79	(68.7)	141	(63.5)
Geographic Region of Enrolling Site						
Asia	60	(56.1)	55	(47.8)	115	(51.8)
ex-Asia	47	(43.9)	60	(52.2)	107	(48.2)
Current Disease Presentation						
Locally Advanced	9	(8.4)	10	(8.7)	19	(8.6)
Metastatic	98	(91.6)	105	(91.3)	203	(91.4)
Brain Metastasis						
Y	1	(0.9)	1	(0.9)	2	(0.9)
N	106	(99.1)	114	(99.1)	220	(99.1)
Metastatic Staging						
M0	9	(8.4)	10	(8.7)	19	(8.6)
M1	98	(91.6)	105	(91.3)	203	(91.4)
Histological subtype						
Squamous cell carcinoma	85	(79.4)	82	(71.3)	167	(75.2)
Adenocarcinoma of esophagus and EGJ Siewert type I	22	(20.6)	33	(28.7)	55	(24.8)
PD-L1 Status						
PD-L1 CPS >= 10	107	(100.0)	115	(100.0)	222	(100.0)
Prior Adjuvant or Neoadjuvant Therapy						
Yes	6	(5.6)	16	(13.9)	22	(9.9)
No	101	(94.4)	99	(86.1)	200	(90.1)
Number of Prior Therapy						
1	103	(96.3)	114	(99.1)	217	(97.7)
2	4	(3.7)	1	(0.9)	5	(2.3)
Prior Anthracycline Therapy						
Yes	6	(5.6)	6	(5.2)	12	(5.4)
No	101	(94.4)	109	(94.8)	210	(94.6)
Prior Monoclonal Antibody Therapy						
Yes	3	(2.8)	6	(5.2)	9	(4.1)
No	104	(97.2)	109	(94.8)	213	(95.9)
Prior Irinotecan Therapy						
Yes	1	(0.9)	2	(1.7)	3	(1.4)
No	106	(99.1)	113	(98.3)	219	(98.6)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Prior Platinum Therapy						
Yes	106	(99.1)	113	(98.3)	219	(98.6)
No	1	(0.9)	2	(1.7)	3	(1.4)
Prior Fluoropyrimidine Therapy						
Yes	93	(86.9)	97	(84.3)	190	(85.6)
No	14	(13.1)	18	(15.7)	32	(14.4)
Prior Taxane Therapy						
Yes	27	(25.2)	42	(36.5)	69	(31.1)
No	80	(74.8)	73	(63.5)	153	(68.9)
Database Cutoff Date: 15OCT2018.						

Source: [P181V01MK3475: adam-adsl]

Table: Subject Characteristics (ITT Population, Subjects with Squamous Cell Carcinoma) (*bold highlight by Assessor*)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	198		203		401	
Geographic Region of Enrolling Site						
Asia	115	(58.1)	116	(57.1)	231	(57.6)
ex-Asia	83	(41.9)	87	(42.9)	170	(42.4)
PD-L1 Status						
PD-L1 CPS >= 10	85	(42.9)	82	(40.4)	167	(41.6)
PD-L1 CPS < 10	109	(55.1)	119	(58.6)	228	(56.9)
Not Evaluable	4	(2.0)	2	(1.0)	6	(1.5)

The demographics and baseline characteristics were generally well-balanced in both intervention arms in the overall ITT population. Stratification for region and tumour histology subtypes led to an even distribution of these characteristics in both treatment arms (39% Asian participants, 64% SCC in the ITT). Despite the absence of stratification according to PD-L1 expression the distribution of patients with CPS scores ≥10 was also balanced between the treatment arms (34.1% in the pembrolizumab arm compared to 36.6% in the SOC arm); thus the lack of biomarker stratification did not appear to have exerted a major impact on the equally allocation of patients to treatment arms regarding PD-L1 expression.

However, the stratification for region and tumour histology as applied for the overall study population (not for the PD-L1 CPS ≥ 10 subgroup) obviously did not prevent imbalances in the subgroup of patients with PD-L1 CP≥10, where higher proportions of Asian and SCC patients were observed compared to the overall study population (both subgroups likely associated due to the higher prevalence of SCC in Asia); Furthermore, imbalances in treatment allocation were also observed within the CPS ≥10 population with higher numbers of Asian and SCC patients in the pembrolizumab arm compared to the SOC, possibly due to the lack of stratification for CPS and the sample size.

For subjects with PD-L1 CPS ≥10 51.8% were from Asia compared to 38.7% in the overall study population; the proportion of Asian participants was 56% vs. 48% in the pembrolizumab vs. SOC arms,

respectively. Imbalances are also notable for histology subtypes: SCC 75.2% in the PD-L1 CPS ≥10 population compared to 63.9% in ITT, and the proportion of patients with SCC were 79.4% vs. 71.3% in the pembrolizumab vs. SOC arms, respectively. Numbers for adenocarcinoma were contrariwise.

Further, in the PD-L1 CPS ≥10 population more patients had an ECOG PS of 0 in the pembrolizumab arm (42.1%) compared with the SOC arm (31.3%) and in the pembrolizumab arm fewer patients had prior (neo)adjuvant therapy (5.6% vs. 13.9%) and prior taxane therapy (25.2% vs. 36.5%) compared to the SOC arm.

As requested the MAH provided a sensitivity analysis to account for the imbalances of the prognostic relevant parameters of ECOG PS and SCC between treatment arms in PD-L1 CPS ≥10 participants. The reported OS HR of 0.71 (95% CI 0.53, 0.95) in favor of pembrolizumab alleviated the concern that the imbalances in these prognostic factors might have exerted a large impact on the OS outcome.

Moreover the MAH was asked to discuss whether the higher proportion of SCC (and Asian) participants in the CPS ≥10 subgroup compared to the overall study population was associated with histology (higher proportion of PD-L1 positive expression in SCC and/or Asians compared to adenocarcinoma in general?) or whether these imbalances are a chance finding and thus the CPS≥10 study population might not be considered fully representative for a general PD-L1 positive oesophageal cancer population The MAH outlined that in KN180 and KN181 the prevalence of patients with PD-L1 CPS ≥10 was higher in ESCC relative to EAC. Since ESCC is substantially more prevalent in Asia relative to the rest of the world and PD-L1 expression is higher in ESCC compared to EAC on average, the higher proportion of ESCC and Asian participants in the PD-L1 CPS ≥10 subgroup compared to the overall study population is associated with and reflects global oesophageal cancer epidemiology and differential prevalence of PD-L1 expression by histology.

Nearly all participants (97.6%) had received one line of prior SOC (2L participants). With protocol amendment 2 (9-Dec-2016) an additional criterion was added to specifically exclude subjects who progressed on more than one line of therapy. The restriction to a 2L population is now adequately reflected in the SmPC

Only 2 patients (0.9%) were enrolled with a history of brain metastasis. Although the inclusion of participants with previously treated, stable brain metastases was initially planned to be allowed, patients with known CNS metastasis were excluded with protocol amendment 2. With the same amendment patients with presence of ascites and pleural effusion determined by physical exam and patients with weight loss > 10% over approximately 2 months prior to first dose of study therapy were also excluded. The exclusion of patients with presence of unfavorable prognostic factors are now adequately listed in the description of the baseline characteristics in 5.1 of the SmPC.

The age distribution of the study population (with only 44.3% ≥ 65 years in the ITT) is not considered representative for the general esophageal cancer population. The age distribution for the CPS≥10 subgroup is described in section 5.1 of the SmPC and it is now clarified that there were limited numbers of patients with oesophageal cancer above 75 years of age within section 4.2 (Elderly subsection).

Numbers analysed

Efficacy analyses of OS, PFS, and ORR were based on the ITT population, which included all participants randomized to an intervention arm. Subjects who showed a confirmed CR or PR were included in analysis of DOR (a total of 62 participants with n=41 in the pembrolizumab arm and n=21 in the SOC arm). A

total of 628 participants, 314 and 314 participants in the pembrolizumab and SOC arms, respectively, were included in the ITT population.

The FAS population included all randomized participants (310 in the pembrolizumab arm and 287 in the SOC arm) who have received at least 1 dose of study medication and have completed at least one PRO assessment, was used for PROs analyses.

The safety analyses were conducted in the ASaT population, which included all randomized participants who received at least one dose of study intervention. A total of 610 participants, 314 and 296 participants in pembrolizumab and SOC arms, respectively, were included in the ASaT population and were analysed according to the treatment received.

Table: Study Population

	Pembrolizumab 200 mg	SOC	total
Subjects randomized (planned treatment) (ITT)	314	314	628
Subjects received study treatment (actual treatment) (ASaT)	314	296	610
Subjects who were randomized and did not receive treatment	0	18	18
Database Cutoff Date: 15OCT2018.			

Source: [P181V01MK3475: adam-adsl]

Mismatched histology information

Eight participants had histology information recorded in the histology form for disease details (CDDG) that differed from the IVRS histology information used for stratification. The histology information from IVRS was used for conducting the stratified analysis where applicable.

Listing of Subjects with Mismatched Histology Information
(ITT Population)

Usubjid	Subject ID	Treatment Arm	Histology in CDDG	Histology in IVRS/IWRS
PPD		Pembrolizumab 200 mg	Adenocarcinoma of esophagus and EGJ Siewert type I	SQUAMOUS CELL CARCINOMA
		SOC	Squamous cell carcinoma	ADENOCARCINOMA - SIEWERT TYPE I ADENOCARCINOMA OF THE EGJ
		SOC	Adenocarcinoma of esophagus and EGJ Siewert type I	SQUAMOUS CELL CARCINOMA
		SOC	Adenocarcinoma of esophagus and EGJ Siewert type I	SQUAMOUS CELL CARCINOMA
		SOC	Squamous cell carcinoma	ADENOCARCINOMA - SIEWERT TYPE I ADENOCARCINOMA OF THE EGJ
		Pembrolizumab 200 mg	Adenocarcinoma of esophagus and EGJ Siewert type I	SQUAMOUS CELL CARCINOMA
		Pembrolizumab 200 mg	Adenocarcinoma of esophagus and EGJ Siewert type I	SQUAMOUS CELL CARCINOMA
		SOC	Squamous cell carcinoma	ADENOCARCINOMA - SIEWERT TYPE I ADENOCARCINOMA OF THE EGJ

CDDG: Current Oncologic Diverse Details - Gastrointestinal
IVRS/IWRS: interactive voice response system/integrated web response system.
Database Cutoff Date: 15OCT2018.

We consider that histology was correctly recorded in the CDDG form, i.e., errors occurred at the time of randomization in the IVRS/IWRS database.

In the pembrolizumab 3 patients were wrongly classified; all 3 patients were considered to be SCC at the time of randomization but were AC patients.

In the SOC arm 5 patients were wrongly classified; 2 patients with AC were considered SCC at time of randomization and 3 patients with SCC were considered AC at the time of randomization.

	Histology on CDDG

		SCC	AC
Treatment	Pembrolizumab	0	3
	SOC	3	2

In the CSR mismatched histology information was reported for eight participants (differences between entries in the histology form for disease details [CDDG] and IVRS). The MAH clarified that histology information from IVRS was used for conducting the stratified analysis per ITT principle, whereas the description of subjects' characteristics was based on "correct" histology information from CDDG. Sensitivity analyses using correct histology information based on CDDG were conducted as requested and confirmed that the differences in histology between IVRS and CDDG had no relevant impact on reported efficacy outcomes.

Outcomes and estimation

Efficacy data in this submission are based on the final analysis with a database cut-off date of 15-OCT-2018, about 34 months after study start and about 16 months after the last participant was enrolled. Median follow-up was 7.1 months (range 0.5 to 31.3 months) in the pembrolizumab group and 6.9 months (range: 0.2 to 32.2 months) in the control group.

The three primary hypotheses (superiority of pembrolizumab on OS in participants with tumours expressing PD-L1 CPS ≥10, participants with ESCC, and all participants) were analysed according to the multiplicity strategy presented in Statistical Methods, and the decision guidance as per the table below.

Table: Decision Guidance at Final Analysis of Overall Survival

Population	Alpha-level*
All Participants	0.00772
Participants with PD-L1 CPS ≥10	0.00853
Participants with Squamous Cell Carcinoma	0.00766
*Based on an R program.	

The three primary hypotheses (superiority of pembrolizumab on OS in participants with tumours expressing PD-L1 CPS ≥10, participants with ESCC, and all participants) were analysed according to a multiplicity strategy with separate significance levels for each of the hypothesis (alpha-splitting and alpha-recycling; see statistical methods).

The key secondary hypotheses of PFS and ORR in all participants were to be tested only if pembrolizumab was superior to SOC for OS in all participants (see statistical methods). Nominal p-values, which were not adjusted for multiplicity, were provided for descriptive purposes. For the remaining secondary efficacy endpoints, no formal testing was planned, and nominal p-values were also provided for descriptive purposes.

Results from the final analysis based on a **15-OCT-2018 cutoff date** (primary analysis).

During the procedure, a revised CSR with updated study data was submitted by the MAH, whose results are presented below.

Primary endpoints

Overall Survival in Participants with PD-L1 CPS ≥10

The pre-specified alpha level at final analysis was 0.00853. The obtained p-value was 0.00855.

Table: Analysis of Overall Survival (ITT population, Subjects with PD-L1 CPS ≥10)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	107	88 (82.2)	1149.0	7.7	9.3 (6.6, 12.5)	63.6 (53.7, 71.9)	0.70 (0.52, 0.94)	0.00855
SOC	115	103 (89.6)	913.3	11.3	6.7 (5.1, 8.2)	54.1 (44.5, 62.8)	---	---

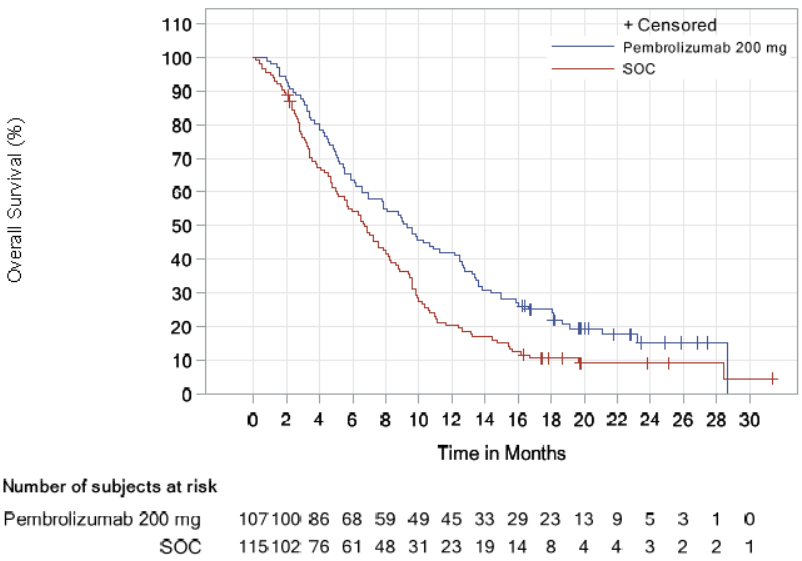
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Table: Summary of Overall Survival Rate over time (ITT population, Subjects with PD-L1 CPS ≥10)

	Pembrolizumab 200 mg (N=107)	SOC (N=115)
Rate at 6 Months in (95% CI)†	63.6 (53.7, 71.9)	54.1 (44.5, 62.8)
Rate at 12 Months in (95% CI)†	42.1 (32.6, 51.2)	20.4 (13.5, 28.3)
Rate at 18 Months in (95% CI)†	25.2 (17.4, 33.7)	10.6 (5.8, 17.1)
Rate at 24 Months in (95% CI)†	15.2 (8.2, 24.1)	9.1 (4.5, 15.6)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 15OCT2018.

Figure: Kaplan-Meier Estimates of Overall Survival (ITT population, Subjects with PD-L1 CPS ≥10)



Database Cutoff Date: 15OCT2018.

The MAH proactively came forward to present updated efficacy data during a TC held on 15 April 2019. The TC was requested by the MAH to inform Rapporteurs about new results with 2 additional events

which occurred before the database lock but were not included in the analysis with the original Application.

In particular:

- Health Authority requested MSD to provide number of participants in OS analysis with at least 12 months of follow up
- Further investigation that was initiated by the MAH showed that 2 participants had died prior to database lock dates (IA and FA) and had disposition listed as death but did not have their death dates entered in the appropriate field in the database
- For these 2 participants, the death dates were not recorded at the right place in the variable used for OS analysis and therefore were censored to alive status at the IA and FA
- Given this discrepancy the team queried the sites to determine correct status (dead or alive and if dead, date of death) and confirmed the date of death was the disposition date
- Subsequently, all of the death events were examined carefully for accuracy and no other errors were found including those from KEYNOTE-180
- Both death events occurred before IA LPLV (15-Feb-2018)

Subject Characteristics:

Subject (number redacted); PDL1 CPS≥10 Esophageal squamous cell carcinoma (ESCC),

Subject (number redacted); PDL1 CPS<10 Esophageal squamous cell carcinoma (ESCC),

The 2 deaths occurred at two distinct sites outside of the EU.

Updated analysis post DBL accounts for these 2 death events and the p-value at the FA boundary is based on the updated event counts at the IA and FA in the appropriate analysis population.

3 analysis Populations	**DBL Primary analysis**		**Post DBL updated analysis**	
	HR (95% CI)	p-value (FA boundary)	HR (95% CI)	p-value (FA boundary)
PD-L1 CPS≥10	0.69 (0.52, 0.93)	0.0074 (0.0085)	0.70 (0.52, 0.94)	0.00855 (0.00853)
ESCC	0.78 (0.63, 0.96)	0.0095 (0.0077)	0.77 (0.63, 0.96)	0.00894 (0.00766)
All Participants	0.89 (0.75, 1.05)	0.0874 (0.0162)	0.89 (0.75, 1.05)	0.08431 (0.00772)

OS Sensitivity Analysis for Subsequent Immunotherapy

There were 31 participants (4.9%) who received subsequent immune checkpoint inhibitors (anti-PD-1 or anti-PD-L1) post-progression: 1 in the pembrolizumab arm (0.3%) and 30 (9.5%) in the SOC arm.

Table: Analysis of Overall Survival Censored At Initiation of Subsequent Immunotherapy (ITT Population, Subjects With PD-L1 CPS≥10)

		Number of	Person-Event Rate/ 100 Person-	Median OS† (Months)	OS Rate at Month 6 in %†	Pembrolizumab 200 mg vs. SOC		
						Hazard Ratio‡		

Treatment	N	Events (%)	Months	Months (%)	(95% CI)	(95% CI)	(95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	107	87 (81.3)	1148.5	7.6	9.3 (6.6, 12.5)	63.6 (53.7, 71.9)	0.68 (0.50, 0.92)	0.0058
SOC	115	92 (80.0)	817.9	11.2	7.1 (5.1, 8.6)	55.4 (45.5, 64.3)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Overall Survival in Participants with Squamous Cell Carcinoma

Superiority of pembrolizumab versus SOC with respect to OS was not demonstrated at the pre-specified alpha level of 0.00766.

Table: Analysis of Overall Survival (ITT population, Subjects with Squamous cell Carcinoma)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	198	166 (83.8)	2054.2	8.1	8.2 (6.7, 10.3)	61.1 (53.9, 67.5)	0.77 (0.63, 0.96)	0.00894
SOC	203	182 (89.7)	1744.6	10.4	7.1 (6.1, 8.2)	58.8 (51.7, 65.2)	---	---

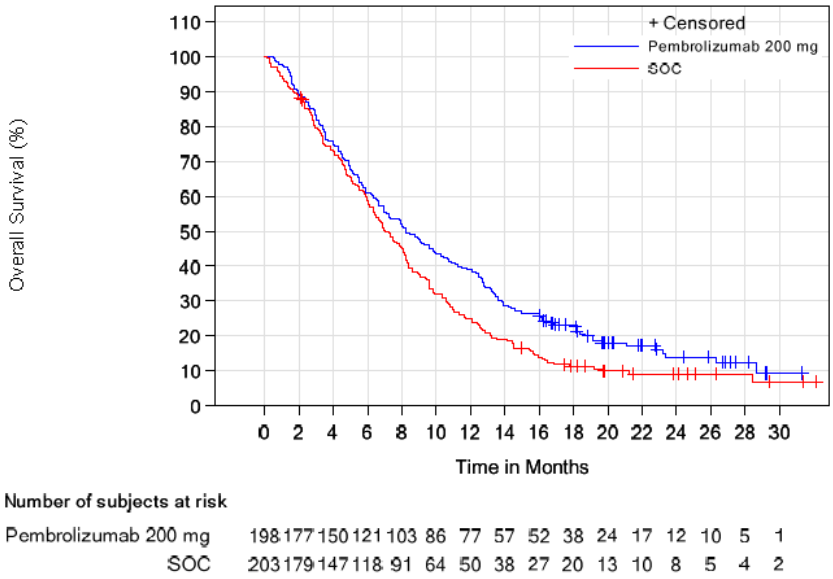
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Table: Summary of Overall Survival Rate over time (ITT population, Subjects with Squamous cell Carcinoma)

	Pembrolizumab 200 mg (N=198)	SOC (N=203)
Rate at 6 Months in (95% CI)†	61.1 (53.9, 67.5)	58.8 (51.7, 65.2)
Rate at 12 Months in (95% CI)†	38.9 (32.1, 45.6)	24.9 (19.2, 31.1)
Rate at 18 Months in (95% CI)†	23.1 (17.5, 29.2)	11.3 (7.4, 16.1)
Rate at 24 Months in (95% CI)†	13.8 (8.8, 19.9)	9.1 (5.5, 13.9)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 15OCT2018.

Figure: Kaplan-Meier Estimates of Overall Survival (ITT population, Subjects with Squamous cell Carcinoma)



Database Cutoff Date: 15OCT2018.

Overall Survival for All Participants

Superiority of pembrolizumab versus SOC with respect to OS was not demonstrated at the pre-specified alpha level of 0.00772.

The HR for OS (pembrolizumab versus SOC) was 0.89 (95% CI: 0.75, 1.05) with a one sided p-value of 0.0531 per the max-combo test (primary analysis) [Table 11-5] and a p-value of 0.08431 per the log rank test (sensitivity analysis).

Table: Analysis of Overall Survival (Primary Analysis) (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	314	271 (86.3)	2895.6	9.4	7.1 (6.2, 8.1)	56.1 (50.4, 61.3)	0.89 (0.75, 1.05)	0.0531
SOC	314	284 (90.4)	2652.9	10.7	7.1 (6.3, 8.0)	58.1 (52.4, 63.3)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified maximum weighted log rank test: the maximum of the log-rank test statistic and a weighted log-rank Fleming-Harrington (0,1) test statistic.
Database Cutoff Date: 15OCT2018.

Table: Analysis of Overall Survival (Sensitivity Analysis) (ITT population)

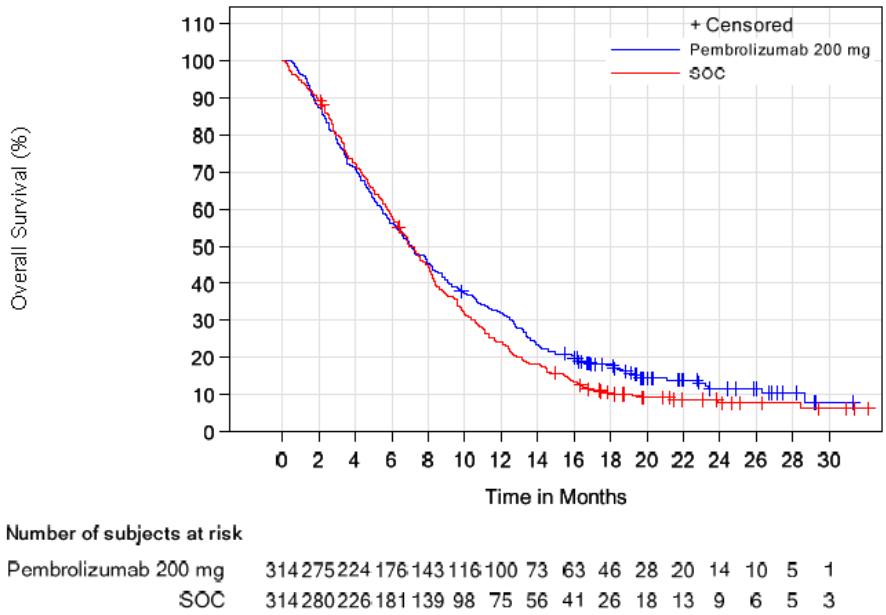
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	314	271 (86.3)	2895.6	9.4	7.1 (6.2, 8.1)	56.1 (50.4, 61.3)	0.89 (0.75, 1.05)	0.08431
SOC	314	284 (90.4)	2652.9	10.7	7.1 (6.3, 8.0)	58.1 (52.4, 63.3)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Table: Summary of Overall Survival Rate over time (ITT population)

	Pembrolizumab 200 mg (N=314)	SOC (N=314)
Rate at 6 Months in (95% CI)[†]	56.1 (50.4, 61.3)	58.1 (52.4, 63.3)
Rate at 12 Months in (95% CI)[†]	32.1 (27.0, 37.3)	24.2 (19.6, 29.1)
Rate at 18 Months in (95% CI)[†]	18.2 (14.1, 22.7)	10.0 (7.0, 13.8)
Rate at 24 Months in (95% CI)[†]	11.5 (7.8, 16.0)	7.7 (4.8, 11.5)
[†] From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 15OCT2018.		

Figure: Kaplan-Meier Estimates of Overall Survival (ITT population)



Database Cutoff Date: 15OCT2018.

Secondary endpoints

The secondary hypotheses of PFS and ORR in all participants were not tested because pembrolizumab was not superior to SOC for OS in all participants. Nominal p-values, which are not adjusted for multiplicity, are provided for descriptive purposes. For the remaining secondary efficacy endpoints, no formal testing was planned, and nominal p values are also provided for descriptive purposes.

Progression-Free Survival in Participants with PD-L1 CPS ≥10

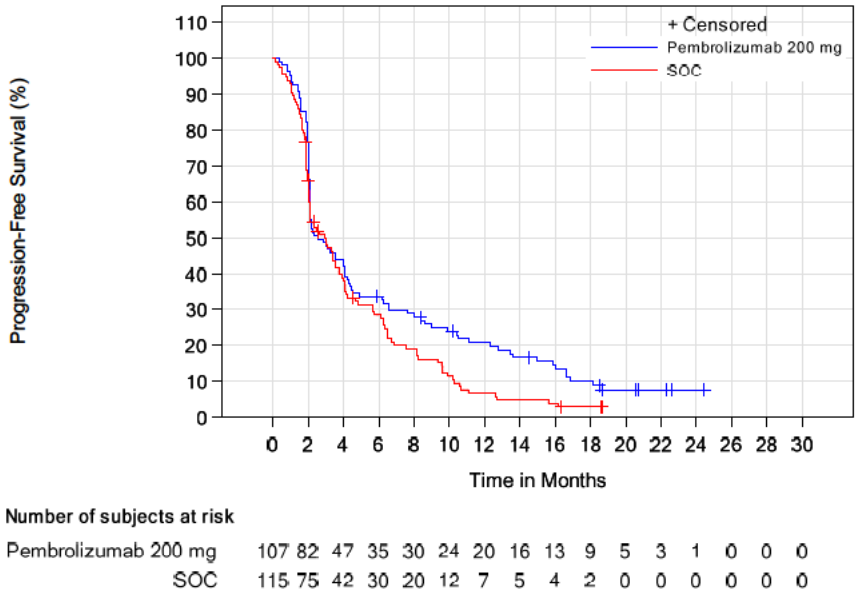
Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population, Subjects with PD-L1 CPS >=10)

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 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	107	96 (89.7)	645.7	14.9	2.6 (2.1, 4.1)	33.6 (24.9, 42.6)	0.73 (0.54, 0.97)	0.015
SOC	115	107 (93.0)	502.0	21.3	3.0 (2.1, 3.7)	28.5 (20.4, 37.1)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

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



Database Cutoff Date: 15OCT2018.

Progression-Free Survival in Participants with Squamous Cell Carcinoma

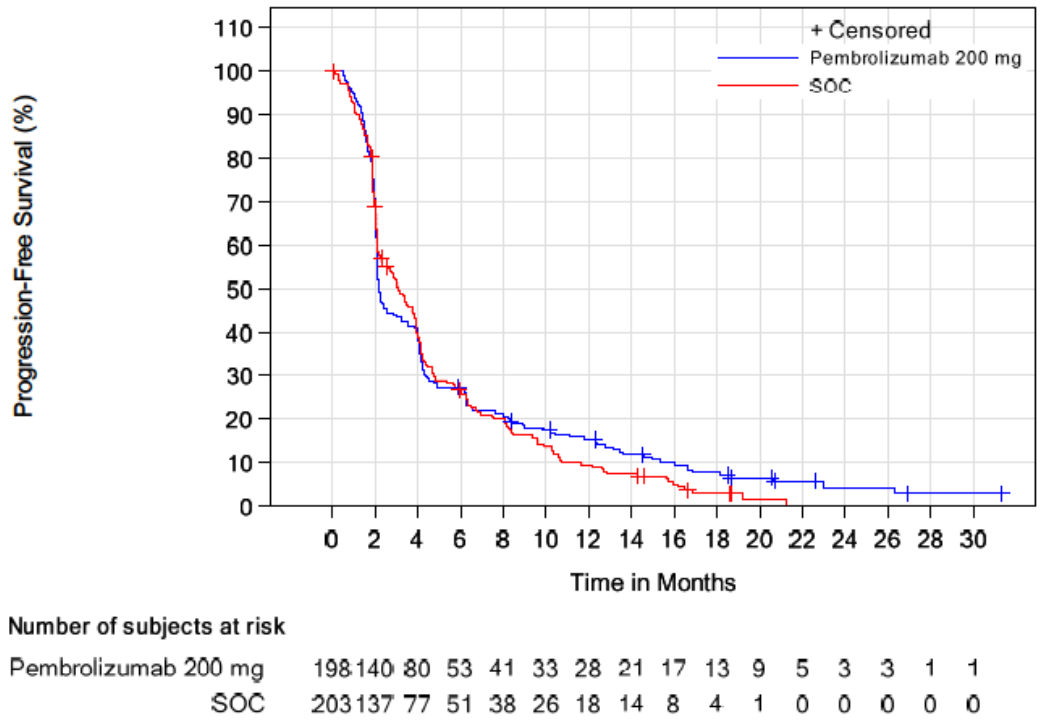
Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population, Subjects with Squamous Cell Carcinoma)

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 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	198	185 (93.4)	1043.6	17.7	2.2 (2.1, 3.2)	27.3 (21.3, 33.6)	0.92 (0.75, 1.13)	0.216
SOC	203	191 (94.1)	941.2	20.3	3.1 (2.2, 3.9)	26.8 (20.8, 33.1)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

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



Database Cutoff Date: 15OCT2018.

Progression-Free Survival for All Participants

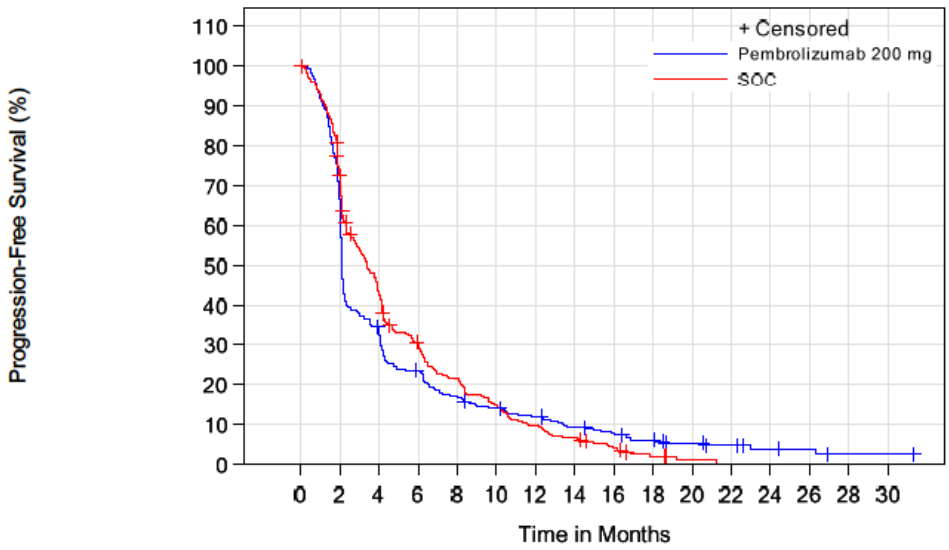
Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population)

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 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	314	295 (93.9)	1453.5	20.3	2.1 (2.1, 2.2)	23.5 (19.0, 28.4)	1.11 (0.94, 1.31)	0.287
SOC	314	297 (94.6)	1507.1	19.7	3.4 (2.8, 3.9)	30.3 (25.2, 35.5)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified maximum weighted log rank test: the maximum of the log-rank test statistic and a weighted log-rank Fleming-Harrington (0,1) test statistic.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

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



Database Cutoff Date: 15OCT2018.

Overall Response Rate in Participants with PD-L1 CPS ≥10

Table: Analysis of Objective Response With Confirmation Based on Central Radiology Assessment per RECIST 1.1
(ITT Population, Subjects with PD-L1 CPS ≥10)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab 200 mg vs. SOC	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab 200 mg	107	23	21.5 (14.1, 30.5)	15.1 (6.2, 24.7)	0.0006
SOC	115	7	6.1 (2.5, 12.1)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type I adenocarcinoma of the EGJ). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Central Radiology Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adrs]

Table: Summary of Best Overall Response Based on Central Radiology Assessment RECIST 1.1 With Confirmation (ITT Population, Subjects with PD-L1 CPS >=10)

	Pembrolizumab 200 mg		SOC	
	n	%	n	%
Number of Subjects in Population	107		115	
Complete Response (CR)	4	3.7	1	0.9
Partial Response (PR)	19	17.8	6	5.2
Best Overall Response (CR+PR)	**23**	**21.5**	**7**	**6.1**
Stable Disease (SD)	30	28.0	47	40.9
Disease Control (CR + PR + SD)	**53**	**49.5**	**54**	**47.0**
Progressive Disease (PD)	46	43.0	39	33.9
Not Evaluable (NE)	0	0.0	4	3.5
No Assessment	8	7.5	18	15.7
Responses are based on Central Radiology Assessment best assessment across timepoints, with confirmation. Database Cutoff Date: 15OCT2018.				

A higher proportion of participants treated with SOC did not have a tumour assessment (18 [15.7%] participants compared to 8 [7.5%] participants in the pembrolizumab arm) or were not evaluable (4 [3.5%] participants compared to 0 participants in the pembrolizumab arm). According to the MAH, this higher proportion of participants with no tumour assessment in the SOC arm was due to a higher proportion that had obvious clinical progression, death, or clinical deterioration when compared to the pembrolizumab arm. The definition of PD does not include participants with obvious clinical progression, death, or clinical deterioration prior to the first tumour assessment time point. No assessment includes participants who had a baseline assessment but no post-baseline assessment at the time of the data cutoff date. This includes participants that have missing data, have discontinued or have died before the first post-baseline scan.

It is noted that despite a complex multiple testing strategy, no adjusted p-values and confidence intervals were provided by the Applicant. The Applicant was asked to amend the CSR and also report adjusted p-values and confidence intervals in the SmPC.

The Applicant did not follow this request. Given the persisting MO on B/R, this issue is **currently not further pursued.**

Overall Response Rate in Participants with Squamous Cell Carcinoma

Table: Analysis of Objective Response With Confirmation Based on Central Radiology Assessment per RECIST 1.1 (ITT Population, Subjects with Squamous Cell Carcinoma)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab 200 mg vs. SOC	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab 200 mg	198	33	16.7 (11.8, 22.6)	9.2 (3.0, 15.8)	0.0022
SOC	203	15	7.4 (4.2, 11.9)		
[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia vs. Rest of the world). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.					
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.					
Responses are based on Central Radiology Assessment per RECIST 1.1 with confirmation.					
Database Cutoff Date: 15OCT2018.					

Source: [P181V01MK3475: adam-adsl; adrs]

Overall Response Rate in All Participants

Table: Analysis of Objective Response With Confirmation Based on Central Radiology

Assessment per RECIST 1.1
(ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab 200 mg vs. SOC	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab 200 mg	314	41	13.1 (9.5, 17.3)	6.4 (1.7, 11.2)	0.0037
SOC	314	21	6.7 (4.2, 10.0)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type I adenocarcinoma of the EGJ). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

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

Responses are based on Central Radiology Assessment per RECIST 1.1 with confirmation.

Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adrs]

Duration of Response in Participants with PD-L1 CPS ≥10

Table: Summary of Time to Response and Duration of Response Based on Central Radiology Assessment per RECIST 1.1 in Subjects with Confirmed Response
(ITT Population, Subjects with PD-L1 CPS >=10)

	Pembrolizumab 200 mg (N=107)	SOC (N=115)
Number of subjects with response[†]	23	7
Time to Response[†] (months)		
Mean (SD)	2.4 (1.0)	3.8 (4.0)
Median (Range)	2.1 (1.4-6.3)	2.0 (1.9-12.6)
Response Duration[‡] (months)		
Median (Range)	9.3 (2.1+ - 22.6+)	7.7 (4.3 - 16.8+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	21 (95.5)	7 (100.0)
≥6 months	16 (76.8)	4 (57.1)
≥9 months	9 (53.5)	2 (38.1)

[†] Includes subjects with confirmed complete response or partial response.

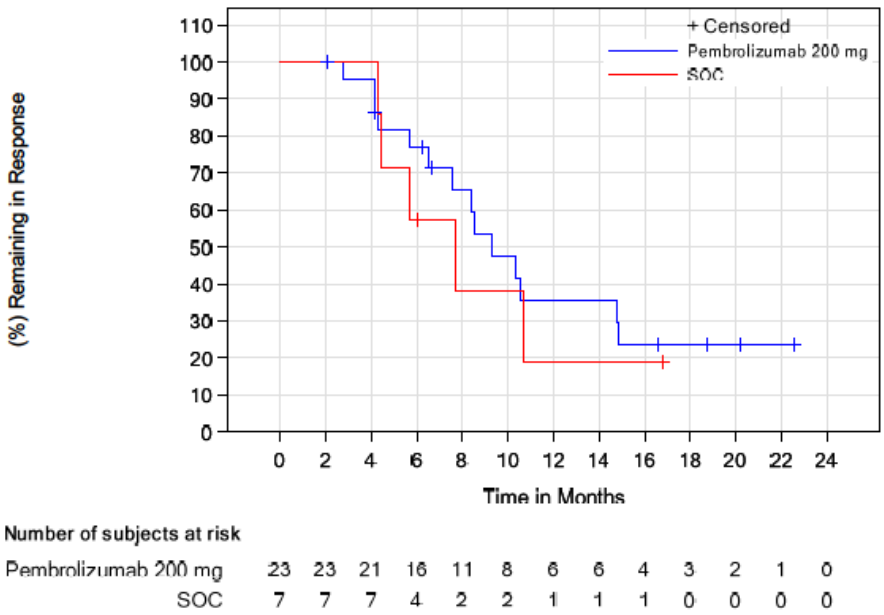
[‡] From product-limit (Kaplan-Meier) method for censored data.

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

Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

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



Database Cutoff Date: 15OCT2018.

Table: Summary of Response Outcome in Subjects with Confirmed Response Based on Central Radiology Assessment per RECIST 1.1(ITT Population, Subjects with PD-L1 CPS ≥10)

	Pembrolizumab 200 mg (N=107)	SOC (N=115)
Number of Subjects with Response[†]	23	7
Subjects Who Progressed or Died[‡] (%)	**14 (60.9)**	**5 (71.4)**
Range of DOR (months)	2.8 to 14.9	4.3 to 10.7
Censored Subjects (%)	**9 (39.1)**	**2 (28.6)**
Subjects who missed 2 or more consecutive disease assessments	3 (13.0)	0 (0.0)
Subjects who started new anti-cancer treatment	2 (8.7)	1 (14.3)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	0 (0.0)	0 (0.0)
Ongoing response[§]	4 (17.4)	1 (14.3)
≥ 3 months	4 (17.4)	1 (14.3)
≥ 6 months	4 (17.4)	1 (14.3)
≥ 9 months	4 (17.4)	0 (0.0)
Range of DOR (months)	16.6+ to 22.6+	6.0+ to 6.0+

[†] Includes subjects with a best overall response as confirmed complete response or partial response.
[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
[§] Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.
'+' indicates there was no progressive disease by the time of last disease assessment.
Database Cutoff Date: 15OCT2018.

Conclusions on DOR results are hampered by small numbers of responders [n=23 out of 107] in the subgroup of participants with PD-L1 CPS ≥10 and the lack of a randomized comparison. Although DOR data tendentially support a benefit of pembrolizumab, it is noted that more than half of the responders (60%) progressed or died during follow-up and only 9 patients (out of 23 responders) demonstrated ongoing responses for ≥ 9 months (compared to 2 out of 7 responders in the SOC arm).

Duration of Response in Participants with Squamous Cell Carcinoma

Table: Summary of Time to Response and Duration of Response Based on Central Radiology Assessment per RECIST 1.1 in Subjects with Confirmed Response (ITT Population, Subjects with Squamous Cell Carcinoma)

	Pembrolizumab 200 mg (N=198)	SOC (N=203)
Number of subjects with response[†]	33	15
Time to Response[†] (months)		
Mean (SD)	4.0 (4.6)	3.6 (3.4)
Median (Range)	2.1 (1.2-22.8)	2.0 (1.4-12.6)
Response Duration[‡] (months)		
Median (Range)	8.5 (2.1+ - 25.8+)	10.7 (2.1+ - 16.8+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	31 (96.9)	14 (100.0)
≥6 months	21 (68.1)	9 (75.0)
≥9 months	11 (49.3)	4 (62.5)

[†] 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: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Duration of Response in All Participants

Table: Summary of Time to Response and Duration of Response Based on Central Radiology Assessment per RECIST 1.1 in Subjects with Confirmed Response (ITT Population)

	Pembrolizumab 200 mg (N=314)	SOC (N=314)
Number of subjects with response[†]	41	21
Time to Response[†] (months)		
Mean (SD)	3.8 (4.2)	3.4 (3.0)
Median (Range)	2.1 (1.2-22.8)	2.0 (1.4-12.6)
Response Duration[‡] (months)		
Median (Range)	8.5 (2.1+ - 25.8+)	10.7 (1.8+ - 16.8+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	39 (97.5)	18 (100.0)
≥6 months	28 (72.0)	9 (61.6)
≥9 months	14 (48.8)	4 (51.3)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Patient Reported Outcomes

PROs assessment was to be performed as specified in the Trial Flow Chart, with some differences in the schedules depending on the treatment received, more frequently in the first 12-18 weeks.

In all cases, PROs collection was to be performed up to a year or End of Treatment, whichever comes first, and at the 30-day post-treatment discontinuation follow-up visit. A visit window of ± 7 days will apply to PRO visit assessment.

Patient Reported Outcomes (PROs) were administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ-5D, followed by EORTC QLQ-C30, and EORTC QLQ-OES18; an exception to this recommendation could occur at the treatment discontinuation visit where patients could have already been notified of their disease status or an AE evaluation was known prior to them arriving to the clinic.

For some sites, the translated OES-18 became available after study startup while for other sites the OES-18 translation was not available for the entire duration of the study.

In the PRO FAS population, there were 310 participants in the pembrolizumab arm and 287 participants in the SOC arm who completed the EORTC QLQ-C30 questionnaire. The compliance rates for the EORTC QLQ-30 were similar and above 90% in both the pembrolizumab and SOC arms at baseline (94.5% versus 95.8%) and remained high at Week 9 (88.9% versus 83.9%). Compliance rates at baseline through Week 9 were similar for the EORTC QLQ-OES18 and EQ-5D. Completion rates decreased at each time point as more participants discontinued from the study due to disease progression. Similar trends were observed in participants with ESCC and participants with PD-L1 CPS ≥10.

For all participants and for participants with ESCC, there were no clinically meaningful differences between intervention arms for the EORTC QLQ-C30, EORTC OES-18, or EQ-5D VAS.

For participants with tumours expressing PD-L1 CPS ≥10, PRO outcomes were similar between intervention arms for all endpoints except the mean change from baseline to Week 9 in EQ-5D VAS score, which improved in the pembrolizumab arm (LS mean=0.73 points; 95% CI: -2.87, 4.33) and deteriorated in the SOC arm (LS mean=-4.84 points; 95% CI: -8.61, -1.08;difference in LS mean 5.57 (95% CI 0.58, 10.56).

No clinically meaningful differences between intervention arms were observed when evaluating health related quality of life items. Only a minor difference in EQ-5D VAS scores (mean change from baseline to Week 9) was noted in the subpopulation of CPS ≥10. Of note, fewer participants completed the EORTC QLQ-C30 questionnaire in the SOC arm (n=287) relative to the pembrolizumab arm (n=310), which might be a related to the open-label study design. Overall, the observed PRO results of this open-label study cannot add any valuable contribution to support a superiority of pembrolizumab over SOC.

MSI status

Determination of MSI status was attempted on those KEYNOTE-181 participants who achieved a confirmed or unconfirmed CR or PR. Of the 102 participants who were selected for testing and had adequate samples for testing, successful MSI testing was achieved for 95 participants. Only one of these participants had a tumour that was determined to be MSI high, and this participant was not a confirmed responder.

MSI status was tested for all participants achieving confirmed CR, or unconfirmed CR or PR as determined by BICR per RECIST 1.1. Of the 102 participants who had adequate samples to enable testing, 95 had successful testing. Only 1 participant was determined to be MSI-H and they were not a confirmed responder. At the final analysis there were 62 confirmed responses, 41 in the pembrolizumab arm and 21 in the SOC arm. MSI status was determined for 33 of the 41 responders in the pembrolizumab arm: 6 responders lacked adequate tissue and/or blood to enable testing, and testing failed for 2 responders. In the SOC arm, MSI status was determined for 16 of the 21 responders: 3 responders lacked adequate tissue and/or blood to enable testing, and testing failed for 2 responders.

Although assessment of MSI status was not conducted in all patients, MSI status was obviously not a confounding factor for ORR.

Ancillary analyses

Sensitivity Analyses

Progression-Free Survival in Participants with PD-L1 CPS ≥10

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

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 200 mg vs. SOC Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab 200 mg	107	88 (82.2)	558.4	15.8	2.3 (2.1, 4.1)	31.9 (23.2, 41.0)	0.75 (0.55, 1.01)	0.027
SOC	115	95 (82.6)	416.3	22.8	2.6 (2.1, 3.5)	23.3 (15.4, 32.2)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
[‡‡] One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (ITT Population, Subjects with PD-L1 CPS ≥10)

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 200 mg vs. SOC Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab 200 mg	107	102 (95.3)	648.9	15.7	2.6 (2.1, 4.1)	33.6 (24.9, 42.6)	0.68 (0.52, 0.91)	0.004
SOC	115	115 (100.0)	494.5	23.3	2.5 (2.1, 3.5)	27.0 (19.2, 35.3)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
[‡‡] One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Progression-Free Survival in Participants with Squamous Cell Carcinoma

Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (ITT Population, Subjects with Squamous Cell Carcinoma)

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 200 mg vs. SOC Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab 200 mg	198	175 (88.4)	945.1	18.5	2.2 (2.1, 3.0)	26.2 (20.2, 32.6)	0.92 (0.74, 1.14)	0.220
SOC	203	172 (84.7)	774.8	22.2	3.1 (2.2, 3.7)	22.8 (16.9, 29.2)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world).
[‡‡] One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (ITT Population, Subjects with Squamous Cell Carcinoma)

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 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	198	194 (98.0)	1025.0	18.9	2.2 (2.1, 3.2)	27.3 (21.3, 33.6)	0.90 (0.73, 1.10)	0.142
SOC	203	203 (100.0)	943.6	21.5	3.0 (2.2, 3.7)	25.6 (19.8, 31.8)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Progression-Free Survival for All Participants

Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	314	280 (89.2)	1316.3	21.3	2.1 (2.1, 2.2)	22.2 (17.7, 27.0)	1.14 (0.96, 1.35)	0.434
SOC	314	269 (85.7)	1278.4	21.0	3.3 (2.7, 3.9)	27.1 (22.0, 32.4)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified maximum weighted log rank test: the maximum of the log-rank test statistic and a weighted log-rank Fleming-Harrington (0,1) test statistic.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Table: Analysis of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	314	307 (97.8)	1436.8	21.4	2.1 (2.1, 2.2)	23.2 (18.7, 28.0)	1.07 (0.91, 1.26)	0.164
SOC	314	314 (100.0)	1502.6	20.9	3.3 (2.6, 3.9)	28.7 (23.8, 33.7)	---	---

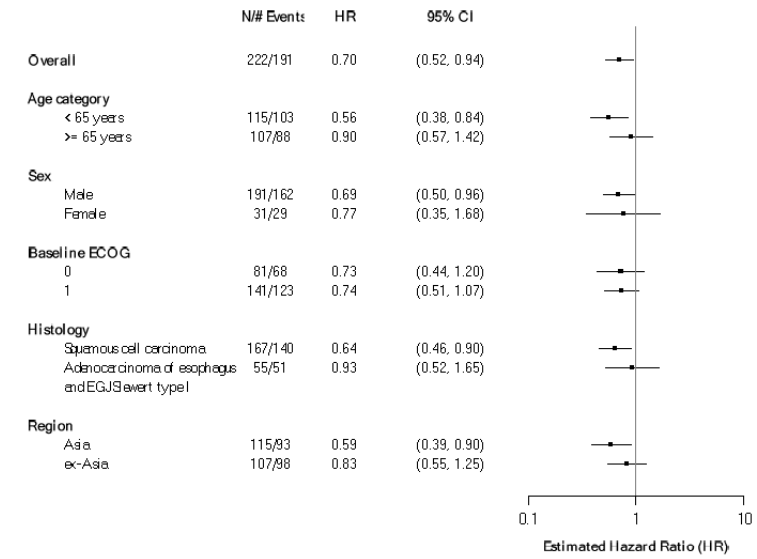
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) and tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified maximum weighted log rank test: the maximum of the log-rank test statistic and a weighted log-rank Fleming-Harrington (0,1) test statistic.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adtte]

Subgroup Analyses

OS subgroups analysis in Participants with PD-L1 CPS ≥10

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

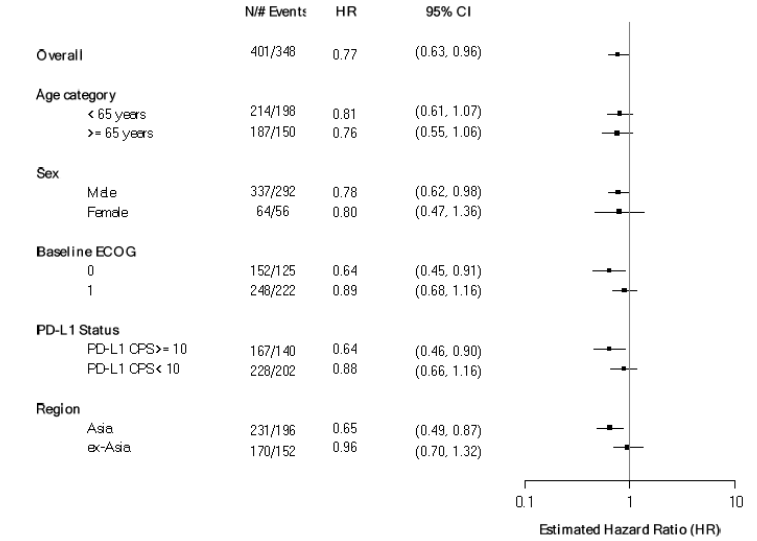


Database Cutoff Date: 15OCT2018.

Graphical presentation of OS subgroup analyses by forest plots indicated less efficacy of pembrolizumab for subjects from Non-Asia, for subjects with adenocarcinoma, and for subjects ≥ 65 years. Results from these subgroups are presented in more detail in the following.

OS subgroups analysis in Participants with Squamous Cell Carcinoma

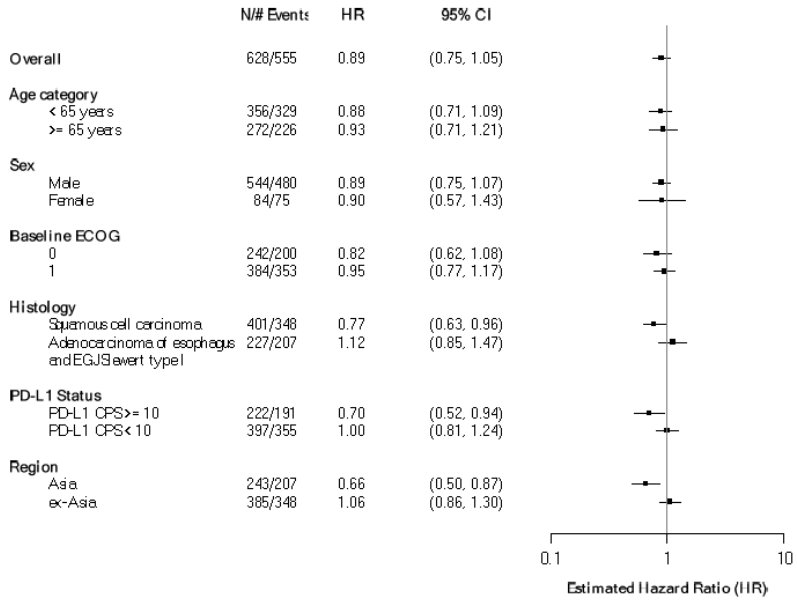
Figure: Forest Plot of OS Hazard Ratio by Subgroup Factor (ITT Population, Subjects with Squamous Cell Carcinoma)



Database Cutoff Date: 15OCT2018.

OS subgroups analysis for All Participants

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



Database Cutoff Date: 15OCT2018.

Post-hoc exploratory analyses

Overall Survival Sensitivity Analysis in Participants with PD-L1 CPS ≥10

Although demographic and baseline characteristics of the PD-L1 CPS ≥10 population were generally well-balanced across intervention arms, some observed differences were noted compared to the overall population. These included a higher proportion of participants in the pembrolizumab arm compared to the SOC arm from Asia, with squamous cell carcinoma, with a baseline ECOG PS of 0, and with no prior adjuvant or neoadjuvant treatment in the pembrolizumab arm compared to the SOC arm. A post-hoc exploratory analysis was performed using these 4 factors as covariates in a Cox model.

Table: updated analysis Of Overall Survival (Sensitivity Analysis with additional Covariates) (ITT Population, Subjects With PD-L1 CPS ≥10)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	107	88 (82.2)	1149.0	7.7	9.3 (6.6, 12.5)	63.6 (53.7, 71.9)	0.73 (0.55, 0.98)	0.0189
SOC	115	103 (89.6)	913.3	11.3	6.7 (5.1, 8.2)	54.1 (44.5, 62.8)	---	---

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

‡ Based on Cox regression model with treatment, tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ), geographic region (Asia vs. Rest of the world), baseline ECOG (0 vs. 1) and prior adjuvant therapy (Yes vs. No) as covariates.

‡‡ One-sided p-value based on type III Wald test.

Database Cutoff Date: 15OCT2018.

Efficacy by region

EU population:

Figure: Updated Forest Plot of **OS** HR by Subgroup Factor (ITT Population, Subjects with PD-L1 **CPS ≥10**)

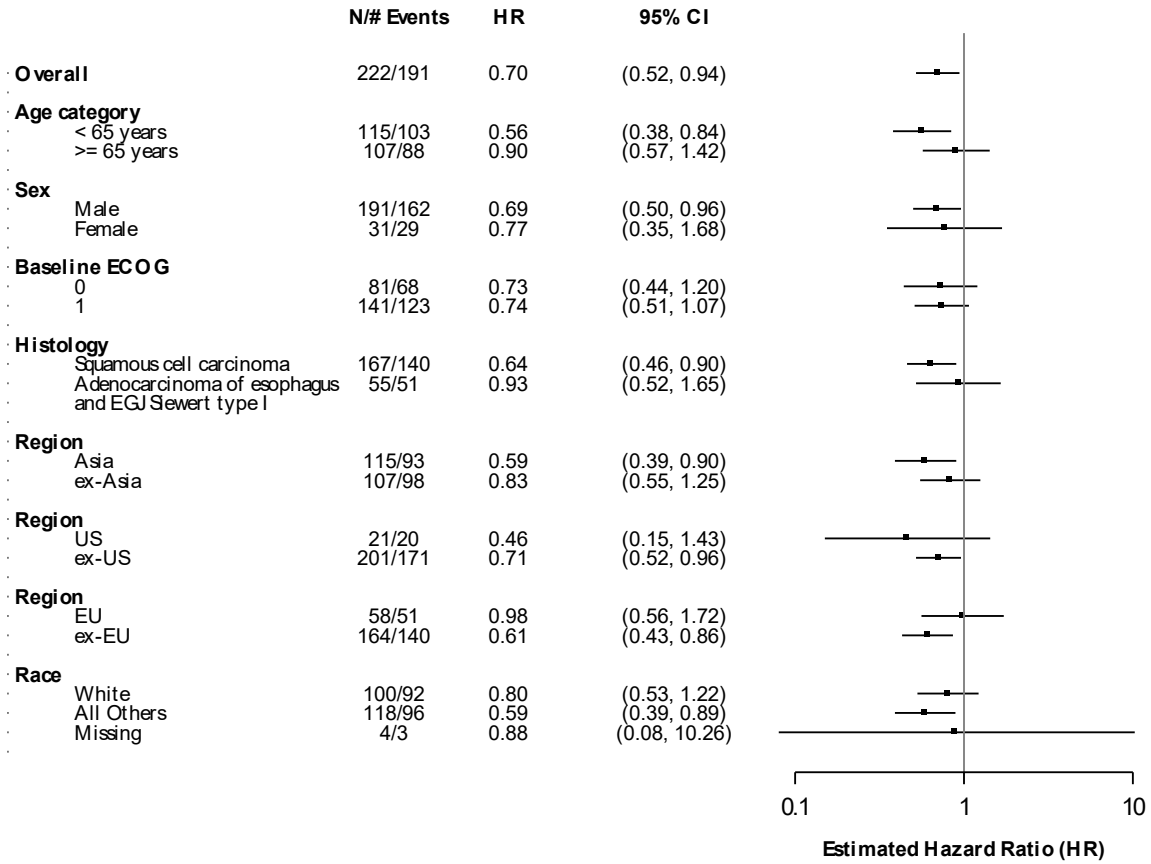


Figure: updated Forest Plot of **OS** HR by Subgroup Factor (ITT Population, Subjects with **SCC**)

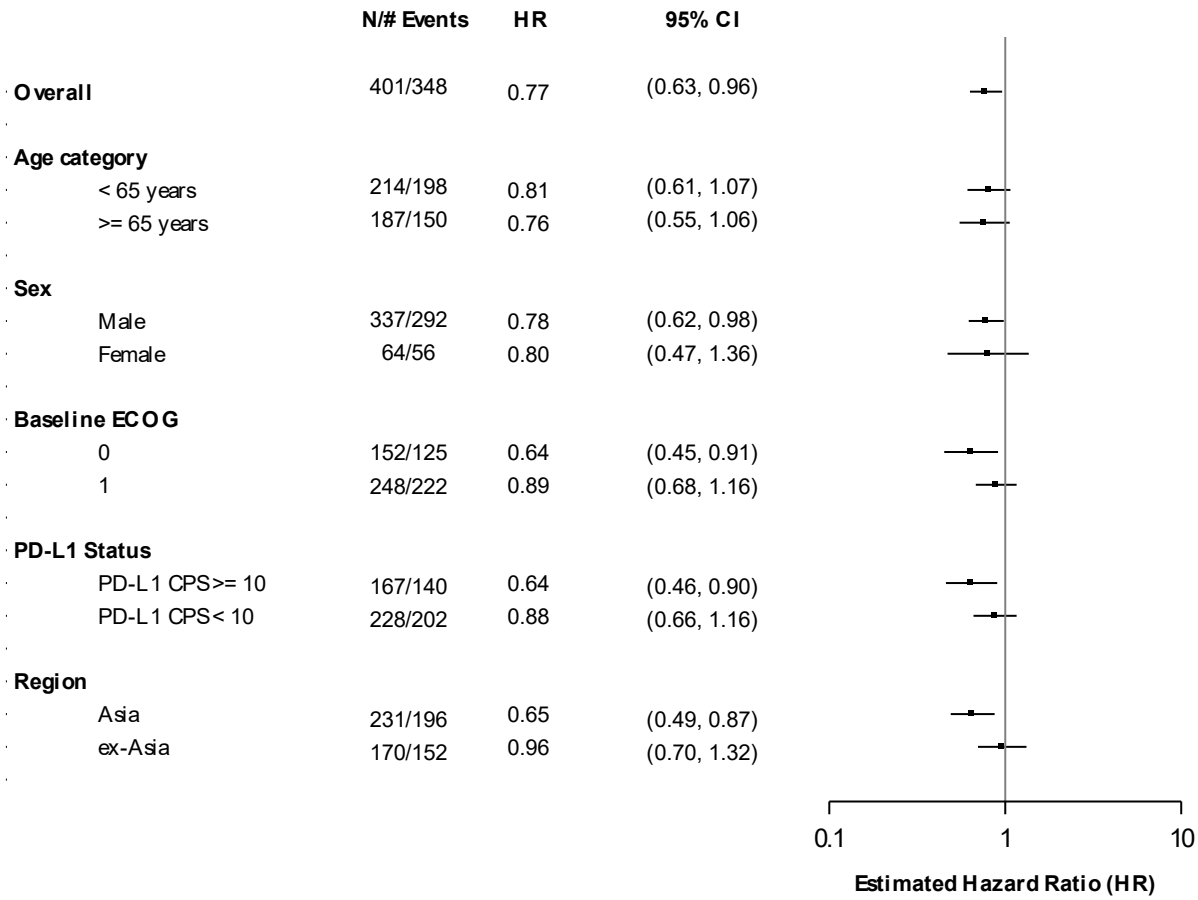
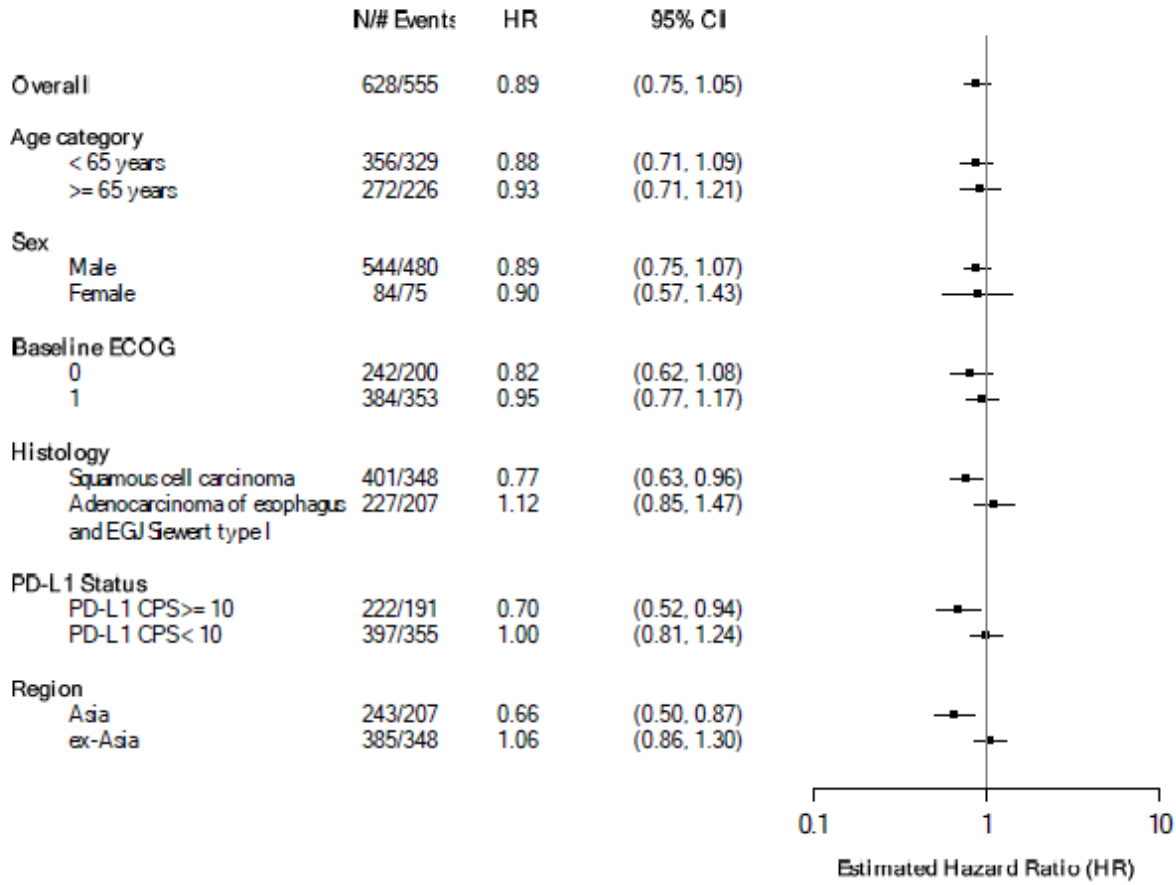


Figure: updated Forest Plot of **OS** HR by Subgroup Factor (ITT Population, **all** participants)



Database Cutoff Date: 15OCT2018.

EU vs. Non-EU

A post-hoc analysis of the treatment effect in EU subpopulation was provided. In this analysis, the OS HR for the participants enrolled in the EU was 0.98 (95% CI: 0.56, 1.72), compared with 0.60 (95% CI: 0.43, 0.85) in non-EU population.

Table: Analysis of Overall Survival
(ITT Population, Subjects with PD-L1 CPS ≥10 in EU)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	27	23 (85.2)	221.0	10.4	5.5 (3.1, 9.6)	48.1 (28.7, 65.2)	0.98 (0.56, 1.72)	0.4687
SOC	31	28 (90.3)	255.3	11.0	8.7 (3.9, 10.0)	67.7 (48.4, 81.2)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

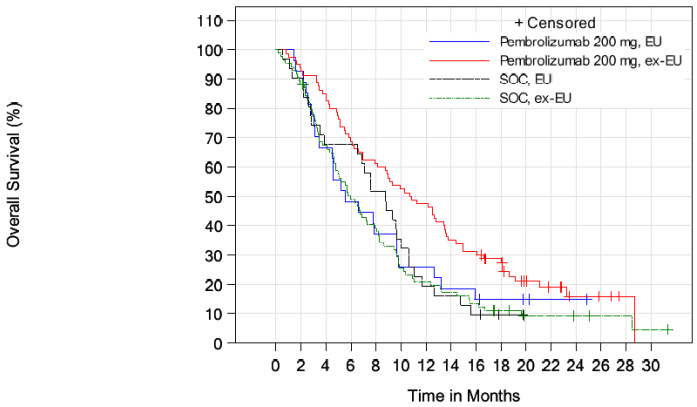
Source: [P181V01MK3475: adam-adsl; adtte]

Table: Analysis of Overall Survival
(ITT Population, Subjects with PD-L1 CPS ≥10 in Ex-EU)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	80	65 (81.3)	928.0	7.0	10.8 (7.9, 13.5)	68.8 (57.4, 77.7)	0.61 (0.43, 0.86)	0.00204
SOC	84	75 (89.3)	658.0	11.4	6.0 (4.7, 7.9)	48.9 (37.8, 59.2)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

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

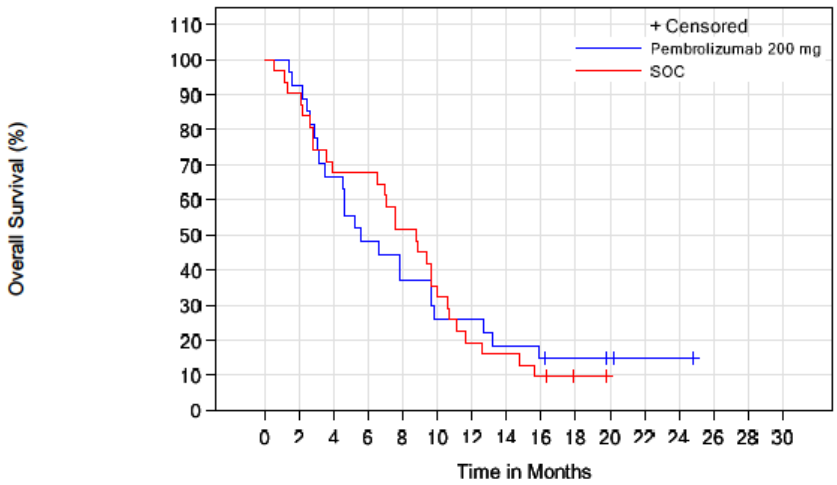


Number of subjects at risk

Pembrolizumab 200 mg, EU	27	25	18	13	10	7	7	5	4	3	2	1	1	0	0	0
Pembrolizumab 200 mg, ex-EU	80	75	68	55	49	42	38	28	25	20	11	8	4	3	1	0
SOC, EU	31	28	21	21	16	10	6	5	3	1	0	0	0	0	0	0
SOC, ex-EU	84	74	55	40	32	21	17	14	11	7	4	4	3	2	2	1

Database Cutoff Date: 15OCT2018.

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

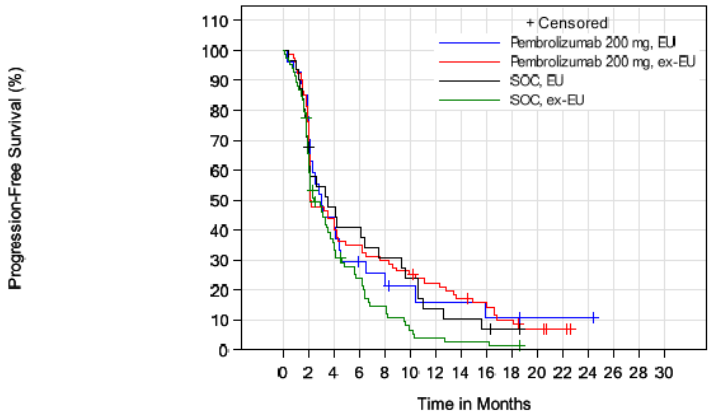


Number of subjects at risk

Pembrolizumab 200 mg	27	25	18	13	10	7	7	5	4	3	2	1	1	0	0	0
SOC	31	28	21	21	16	10	6	5	3	1	0	0	0	0	0	0

Database Cutoff Date: 15OCT2018.

Figure: Kaplan-Meier Estimates of Progression-Free Survival by Region EU Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population, Subjects with PD-L1 CPS >=10)

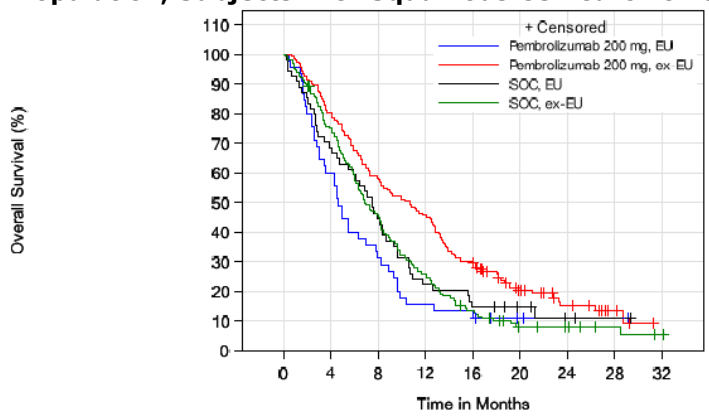


Number of subjects at risk

Pembrolizumab 200 mg, EU	27	21	12	7	6	4	3	3	2	2	1	1	1	0	0	0
Pembrolizumab 200 mg, ex-EU	80	61	35	28	24	20	17	13	11	7	4	2	0	0	0	0
SOC, EU	31	21	14	12	9	7	4	3	2	1	0	0	0	0	0	0
SOC, ex-EU	84	54	28	18	11	5	3	2	2	1	0	0	0	0	0	0

Database Cutoff Date: 15OCT2018.

Figure: Updated Kaplan-Meier Estimates of Overall Survival by Region EU (ITT Population, Subjects with Squamous Cell Carcinoma)

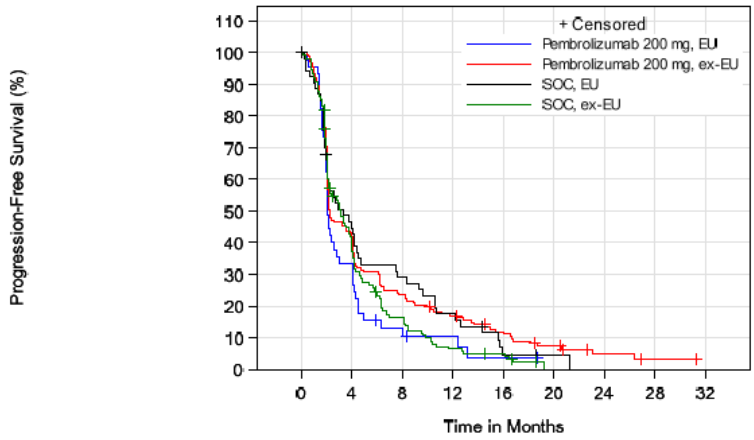


Number of subjects at risk

Pembrolizumab 200 mg, EU	45	27	14	7	6	2	1	1	0
Pembrolizumab 200 mg, ex-EU	153	123	89	70	46	22	11	4	0
SOC, EU	54	37	24	12	8	5	2	1	0
SOC, ex-EU	149	110	67	38	19	8	6	3	1

Database Cutoff Date: 15OCT2018.

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



Number of subjects at risk

Pembrolizumab 200 mg, EU	45	15	5	3	1	0	0	0	0
Pembrolizumab 200 mg, ex-EU	153	65	36	25	16	9	3	1	0
SOC, EU	54	23	15	9	2	1	0	0	0
SOC, ex-EU	149	54	23	9	6	0	0	0	0

Database Cutoff Date: 15OCT2018.

Table: Analysis of Objective Response With Confirmation Based on Central Radiology Assessment per RECIST 1.1 (ITT Population, Subjects with PD-L1 CPS>=10 EU)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab 200 mg vs. SOC	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab 200 mg	27	5	18.5 (6.3, 38.1)	12.2 (-5.6, 32.0)	0.0816
SOC	31	2	6.5 (0.8, 21.4)		

[†] Based on Miettinen & Nurminen method stratified by tumor histology (Squamous cell carcinoma vs. adenocarcinoma/Siewert type I adenocarcinoma of the EGJ). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Central Radiology Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 15OCT2018.

Table: Analysis of Objective Response With Confirmation Based on Central Radiology Assessment per RECIST 1.1 (ITT Population, Subjects with Squamous cell Carcinoma EU)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab 200 mg vs. SOC	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab 200 mg	45	4	8.9 (2.5, 21.2)	3.3 (-7.7, 16.0)	0.2608
SOC	54	3	5.6 (1.2, 15.4)		

[†] Based on Miettinen & Nurminen method.
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Central Radiology Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 15OCT2018.

Baseline characteristics of EU versus non-EU participants in subjects with PD-L1>=10, showing some imbalances, were provided. A higher proportion in the EU had a baseline tumour size larger than the median value, bone metastasis, and liver metastasis. As expected, a higher proportion in the EU had adenocarcinoma relative to the non-EU population.

Table: Subject Characteristics EU vs non-EU
(ITT Population, Subjects With PD-L1 CPS≥10)

	EU		ex-EU		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	58		164		222	
Gender						
Male	50	(86.2)	141	(86.0)	191	(86.0)
Female	8	(13.8)	23	(14.0)	31	(14.0)
Age(Years)						
< 65	35	(60.3)	80	(48.8)	115	(51.8)
>= 65	23	(39.7)	84	(51.2)	107	(48.2)
Subjects with data	58		164		222	
Mean	63.3		63.1		63.2	
SD	9.2		9.8		9.6	
Median	63.5		65.0		64.0	
Range	42 to 81		33 to 81		33 to 81	
Race						
Asian	1	(1.7)	115	(70.1)	116	(52.3)
Multiple	0	(0.0)	1	(0.6)	1	(0.5)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.6)	1	(0.5)
White	53	(91.4)	47	(28.7)	100	(45.0)
Missing	4	(6.9)	0	(0.0)	4	(1.8)
ECOG Performance Scale						
0	19	(32.8)	62	(37.8)	81	(36.5)
1	39	(67.2)	102	(62.2)	141	(63.5)
Geographic Region of Enrolling Site						
Asia	0	(0.0)	115	(70.1)	115	(51.8)
ex-Asia	58	(100.0)	49	(29.9)	107	(48.2)
Current Disease Presentation						
Locally Advanced	5	(8.6)	14	(8.5)	19	(8.6)
Metastatic	53	(91.4)	150	(91.5)	203	(91.4)
Brain Metastasis						
Y	0	(0.0)	2	(1.2)	2	(0.9)
N	58	(100.0)	162	(98.8)	220	(99.1)
Metastatic Staging						
M0	5	(8.6)	14	(8.5)	19	(8.6)
M1	53	(91.4)	150	(91.5)	203	(91.4)
Histological subtype						
Squamous cell carcinoma	34	(58.6)	133	(81.1)	167	(75.2)
Adenocarcinoma of esophagus and EGJ Siewert type I	24	(41.4)	31	(18.9)	55	(24.8)
PD-L1 Status						
PD-L1 CPS >= 10	58	(100.0)	164	(100.0)	222	(100.0)
Prior Adjuvant or Neoadjuvant Therapy						
Yes	3	(5.2)	19	(11.6)	22	(9.9)

No	55	(94.8)	145	(88.4)	200	(90.1)
Number of Prior Therapy						
1	57	(98.3)	160	(97.6)	217	(97.7)
2	1	(1.7)	4	(2.4)	5	(2.3)
Prior Anthracycline Therapy						
Yes	5	(8.6)	7	(4.3)	12	(5.4)
No	53	(91.4)	157	(95.7)	210	(94.6)
Prior Monoclonal Antibody Therapy						
Yes	1	(1.7)	8	(4.9)	9	(4.1)
No	57	(98.3)	156	(95.1)	213	(95.9)
Prior Irinotecan Therapy						
Yes	2	(3.4)	1	(0.6)	3	(1.4)
No	56	(96.6)	163	(99.4)	219	(98.6)
Prior Platinum Therapy						
Yes	56	(96.6)	163	(99.4)	219	(98.6)
No	2	(3.4)	1	(0.6)	3	(1.4)
Prior Fluoropyrimidine Therapy						
Yes	49	(84.5)	141	(86.0)	190	(85.6)
No	9	(15.5)	23	(14.0)	32	(14.4)
Prior Taxane Therapy						
Yes	15	(25.9)	54	(32.9)	69	(31.1)
No	43	(74.1)	110	(67.1)	153	(68.9)
Database Cutoff Date: 15OCT2018.						

Table: Subject Characteristics EU vs non-EU
(ITT Population, Subjects With PD-L1 CPS≥10)

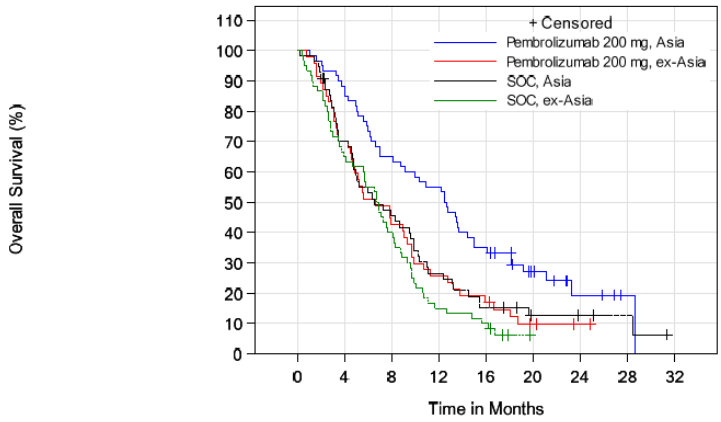
	EU		ex-EU	
	n	(%)	n	(%)
Subjects in population	58		164	
Presence of Ascites				
Yes	0	(0.0)	2	(1.2)
No	58	(100.0)	162	(98.8)
Alkaline phosphatase toxicity grade				
Yes	2	(3.4)	7	(4.3)
No	56	(96.6)	157	(95.7)
Albumin				
Yes	0	(0.0)	1	(0.6)
No	58	(100.0)	163	(99.4)
Hemoglobin decrease				
Yes	4	(6.9)	15	(9.1)
No	54	(93.1)	149	(90.9)
CRP				
No	58	(100.0)	164	(100.0)
Peritoneal metastases				
Yes	0	(0.0)	3	(1.8)

No	58	(100.0)	161	(98.2)
Bone metastases				
Yes	11	(19.0)	20	(12.2)
No	47	(81.0)	144	(87.8)
Number of Metastatic Sites				
0-2	43	(74.1)	110	(67.1)
>=3	15	(25.9)	54	(32.9)
Baseline Tumor Size (mm)-IRC(RECIST 1.1)				
<=median	22	(37.9)	90	(54.9)
>median	29	(50.0)	66	(40.2)
Missing	7	(12.1)	8	(4.9)
Neutrophil to Lymphocyte Ratio Group				
NLR>=5	26	(44.8)	71	(43.3)
NLR<5	32	(55.2)	91	(55.5)
Missing	0	(0.0)	2	(1.2)
Histology Squamous vs.GEJ vs Adeno				
Squamous cell carcinoma	34	(58.6)	133	(81.1)
Adeno GEJ	8	(13.8)	9	(5.5)
Adenocarcinoma	16	(27.6)	22	(13.4)
Liver Mets				
Yes	25	(43.1)	46	(28.0)
No	33	(56.9)	118	(72.0)
Database Cutoff Date: 15OCT2018.				

The MAH compared baseline characteristics of EU versus non-EU participants, and noted that a higher proportion had a baseline tumour size larger than the median value, bone metastasis, and liver metastasis, suggesting that the EU population may have had a higher tumour burden than the non-EU population. In addition, a higher proportion in the EU had adenocarcinoma relative to the non-EU population. The MAH concluded: "While it is plausible that these differences may, in part, contributed to the higher HR in EU population, the magnitude of difference is not considered substantial enough to have meaningful impact on the overall outcome of the study. This represents a consistent trend aligned with the overall population rather than an unlikely case of regional difference."

Asia vs. Ex-Asia

Updated Kaplan-Meier Estimates of Overall Survival by Region Asia
(ITT Population, Subjects with PD-L1 CPS >=10)

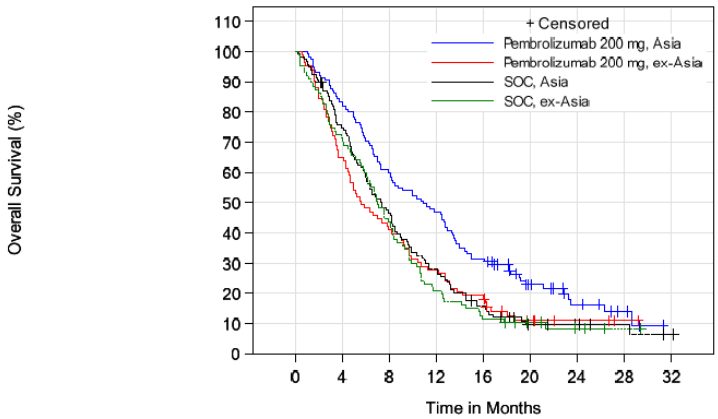


Number of subjects at risk

Pembrolizumab 200 mg, Asia	60	53	39	33	21	10	4	1	0
Pembrolizumab 200 mg, ex-Asia	47	33	20	12	8	3	1	0	0
SOC, Asia	55	37	24	14	8	4	3	2	0
SOC, ex-Asia	60	39	24	9	6	0	0	0	0

Database Cutoff Date: 15OCT2018.

Updated Kaplan-Meier Estimates of Overall Survival by Region Asia
(ITT Population, Subjects with Squamous Cell Carcinoma)



Number of subjects at risk

Pembrolizumab 200 mg, Asia	115	96	69	54	36	18	9	4	0
Pembrolizumab 200 mg, ex-Asia	83	54	34	23	16	6	3	1	0
SOC, Asia	116	85	53	32	17	7	5	3	1
SOC, ex-Asia	87	62	38	18	10	6	3	1	0

Database Cutoff Date: 15OCT2018.

Efficacy by histology

OS in ESCC and CPS ≥10

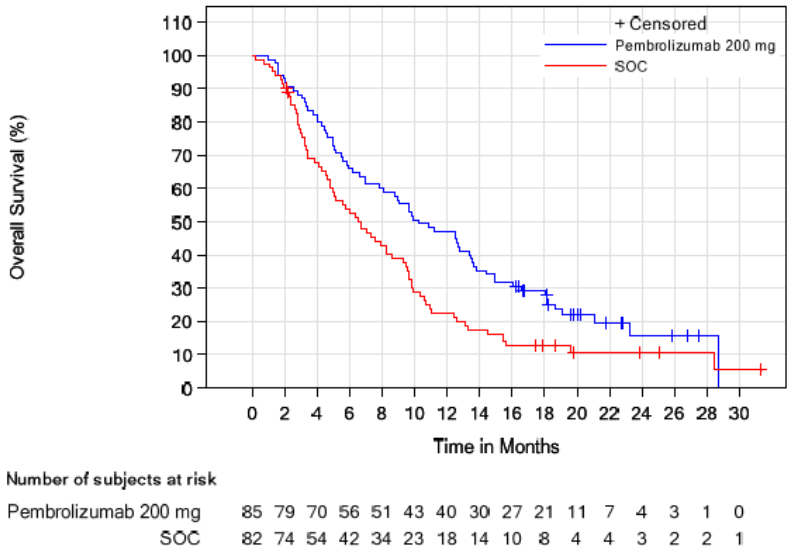
The treatment effect of pembrolizumab in participants with PD-L1≥10 and ESCC resulted in a OS HR of 0.64 (95% CI: 0.46, 0.90).

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

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	85	68 (80.0)	967.4	7.0	10.3 (7.0, 13.5)	65.9 (54.8, 74.9)	0.64 (0.46, 0.90)	0.0042
SOC	82	72 (87.8)	672.3	10.7	6.7 (4.8, 8.6)	52.7 (41.2, 62.9)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world) .
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

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



Database Cutoff Date: 15OCT2018.

OS in AC and CPS ≥10

A post-hoc analysis of the treatment effect in adenocarcinoma subpopulation was provided. In this analysis, the OS HR for the participants with PD-L1 ≥10 and adenocarcinoma histology was 0.93 (95% CI: 0.52, 1.65). A summary of OS rate over time was also provided.

Table: Analysis of Overall Survival
(ITT Population, Subjects With AC and PD-L1 CPS≥10)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab 200 mg vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	22	20 (90.9)	181.7	11.0	6.3 (3.4, 9.3)	54.5 (32.1, 72.4)	0.93 (0.52, 1.65)	0.3988
SOC	33	31 (93.9)	240.9	12.9	6.9 (3.7, 8.7)	57.6 (39.1, 72.3)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 15OCT2018.

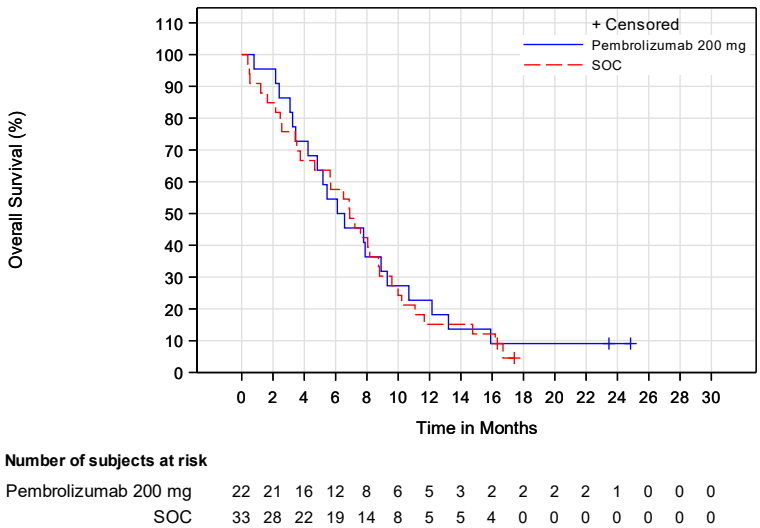
Source: [P181V01MK3475: adam-adsl; adtte]

Table: Summary of updated Overall Survival Rate At 6, 12, 18, 24 Months (ITT Population, Subjects With AC and PD-L1 CPS ≥10)

	Pembrolizumab 200 mg (N=22)	SOC (N=33)
Rate at 6 Months in (95% CI)†	54.5 (32.1, 72.4)	57.6 (39.1, 72.3)
Rate at 12 Months in (95% CI)†	22.7 (8.3, 41.4)	15.2 (5.5, 29.2)
Rate at 18 Months in (95% CI)†	9.1 (1.6, 25.1)	Not reached
Rate at 24 Months in (95% CI)†	9.1 (1.6, 25.1)	Not reached

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 15OCT2018.

Figure: updated KM Estimates of OS (ITT Population, Subjects with AC and PD-L1 CPS ≥10)



PFS in AC and CPS ≥10

Table: Analysis of PFS Based On Central Radiology Assessment Per RECIST 1.1 (Sensitivity Analysis Using Primary Censoring Rule) (ITT Population, Subjects With AC and PD-L1

CPS≥10)

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 200 mg vs. SOC Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	22	20 (90.9)	118.8	16.8	2.1 (1.9, 3.5)	27.3 (11.1, 46.4)	1.00 (0.56, 1.79)	0.509
SOC	33	31 (93.9)	152.3	20.4	3.7 (2.0, 5.7)	33.1 (17.9, 49.1)	---	---

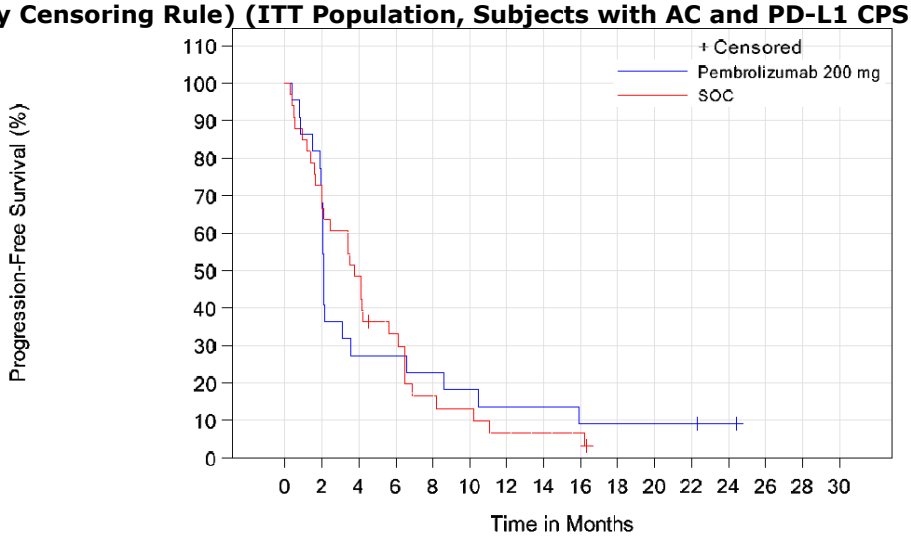
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs. Rest of the world).
‡‡ One-sided p-value based on log-rank test.
Database Cutoff Date: 15OCT2018.

Table: Summary of PFS Rate At 3, 6, 9, 12 Months Based On Central Radiology Assessment Per RECIST 1.1 (ITT Population, Subjects With AC and PD-L1 CPS ≥10)

	Pembrolizumab 200 mg (N=22)	SOC (N=33)
Rate at 3 Months in (95% CI)†	36.4 (17.4, 55.7)	60.6 (42.0, 74.9)
Rate at 6 Months in (95% CI)†	27.3 (11.1, 46.4)	33.1 (17.9, 49.1)
Rate at 9 Months in (95% CI)†	18.2 (5.7, 36.3)	13.2 (4.2, 27.4)
Rate at 12 Months in (95% CI)†	13.6 (3.4, 30.9)	6.6 (1.2, 19.0)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 15OCT2018.

Figure: KM Estimates of PFS Based on Central Radiology Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population, Subjects with AC and PD-L1 CPS>=10)



ORR in AC and CPS ≥10

Table: Analysis of Objective Response with Confirmation Based On Central Radiology Assessment Per RECIST 1.1 (ITT Population, Subjects With AC and PD-L1 CPS≥10)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab 200 mg vs. SOC Estimate (95% CI)†	p-Value††
Pembrolizumab 200 mg	22	4	18.2 (5.2, 40.3)	16.0 (0.2, 37.4)	0.0234
SOC	33	1	3.0 (0.1, 15.8)		

† Based on Miettinen & Nurminen method stratified by geographic region (Asia vs. Rest of the world). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Central Radiology Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 15OCT2018.

Table: summary of best overall response based on central radiology assessment RECIST 1.1 with confirmation (ITT population, subjects with Adenocarcinoma and PD-L1 CPS≥10

	Pembrolizumab 200 mg		SOC	
	n	%	n	%
Number of Subjects in Population	22		33	
Complete Response (CR)	0	0.0	0	0.0
Partial Response (PR)	4	18.2	1	3.0
Best Overall Response (CR+PR)	**4**	**18.2**	**1**	**3.0**
Stable Disease (SD)	3	13.6	17	51.5
Disease Control (CR + PR + SD)	**7**	**31.8**	**18**	**54.5**
Progressive Disease (PD)	13	59.1	7	21.2
Not Evaluable (NE)	0	0.0	3	9.1
No Assessment	2	9.1	5	15.2
Responses are based on Central Radiology Assessment best assessment across timepoints, with confirmation. Database Cutoff Date: 15OCT2018.				

Median **DOR** was 4.4 months in the one responder of the SOC arm. 2 responders on pembrolizumab reported DOR of ≥ 9 months (median not reached).

Subgroup analyses for subjects with adenocarcinoma indicated an inferior efficacy of pembrolizumab for AC compared to SCC. In the PD-L1 CPS ≥10 population OS HR was 0.63 (95% CI 0.45, 0.89) for SCC and 0.93 (95% CI 0.52, 1.65) for subjects with adenocarcinoma. A similar trend was observed in the all participants population with OS HR of 0.78 (95% CI 0.63, 0.96) for SCC and 1.12 (95% CI 0.85, 1.47) for AC.

In the PD-L1 CPS ≥10 population OS KM curves were overlapping in both treatment groups without any relevant differences. Similarly, PFS data did not demonstrate any meaningful differences between pembrolizumab and SOC (HR for PFS was 1.00, 95% CI 0.56, 1.79). ORR was in favour of pembrolizumab (18.2% vs. 3%). The considerably higher rates of PD (59.1% vs 21.2%) and lower rates of both SD (13.6% vs. 51.5%) and disease control (31.8% vs 54.5%) in the pembrolizumab arm versus the SOC treatment arm are a major clinical concern.

Overall, for subjects with adenocarcinoma and PD-L1 CPS ≥10 pembrolizumab appears to have a similar treatment effect as SOC (with neither a superior nor a detrimental effect compared to standard chemotherapy).

Efficacy by Age

Table: Efficacy Results for Overall Survival by Age Categories

Pembrolizumab 200mg 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	0.81 (0.61, 1.08)	0.55 (0.37, 0.82)	0.89 (0.72, 1.11)
HR (95% CI)	65 - 74	0.77 (0.53, 1.12)	0.78 (0.48, 1.27)	0.88 (0.65, 1.19)
HR (95% CI)	75 - 84	0.59 (0.29, 1.18)	0.78 (0.34, 1.81)	0.79 (0.45, 1.38)
†Based on Cox regression model with treatment as a covariate. Database Cutoff Date: 15OCT2018.				

Regarding age the study population is not considered representative for a general oesophagus population; (according to the ESMO guidelines incidence of oesophageal carcinoma increases with age, peaking in the seventh and eighth decade of life); the median age was 64 years in the overall study population (with n=115 for < 65 years and n=107 for ≥ 65 years in the CPS ≥10 population). In this subgroup HR for OS were numerically higher in the older age category 0.89 for subjects ≥65 years compared to 0.55 for < 65 years; (the reported OS HRs for additional age categories did not differ: 0.76 for 65-74 years and 0.78 for 75-84 years).

*Results in the post-hoc population with **squamous cell carcinoma and PD-L1 CPS ≥10***

This subpopulation include 85 patients in pembrolizumab arm and 82 in SOC arm, corresponding to about 30% of the overall study population.

Subject Characteristics
(KN181 ITT Population, Subjects with Squamous Cell Carcinoma and PD-L1 CPS>=10)

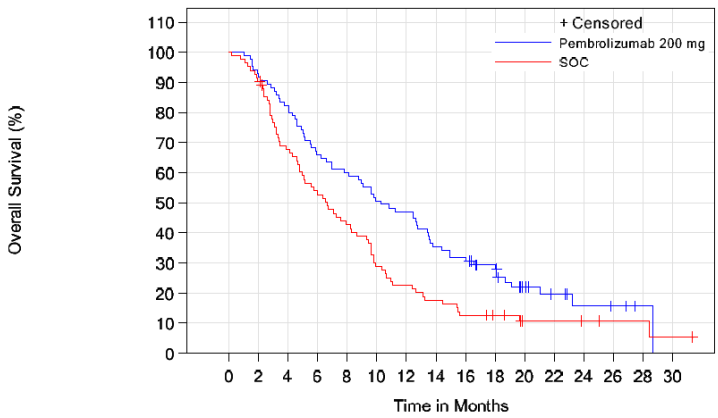
	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	85		82		167	
Gender						
Male	74	(87.1)	67	(81.7)	141	(84.4)
Female	11	(12.9)	15	(18.3)	26	(15.6)
Age(Years)						
< 65	39	(45.9)	43	(52.4)	82	(49.1)
>= 65	46	(54.1)	39	(47.6)	85	(50.9)
Subjects with data	85		82		167	
Mean	64.6		62.7		63.7	
SD	8.6		10.6		9.6	
Median	65.0		64.0		65.0	
Range	45 to 80		33 to 79		33 to 80	
Race						
Asian	59	(69.4)	54	(65.9)	113	(67.7)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(1.2)	1	(0.6)
White	26	(30.6)	27	(32.9)	53	(31.7)
Ethnicity						
Hispanic or Latino	2	(2.4)	4	(4.9)	6	(3.6)
Not Hispanic or Latino	83	(97.6)	78	(95.1)	161	(96.4)
ECOG Performance Scale						
0	36	(42.4)	28	(34.1)	64	(38.3)
1	49	(57.6)	54	(65.9)	103	(61.7)
Geographic Region of Enrolling Site						
Asia	58	(68.2)	54	(65.9)	112	(67.1)
ex-Asia	27	(31.8)	28	(34.1)	55	(32.9)
Current Disease Presentation						
Locally Advanced	9	(10.6)	8	(9.8)	17	(10.2)
Metastatic	76	(89.4)	74	(90.2)	150	(89.8)
Brain Metastasis						

N	85	(100.0)	82	(100.0)	167	(100.0)
Metastatic Staging						
M0	9	(10.6)	8	(9.8)	17	(10.2)
M1	76	(89.4)	74	(90.2)	150	(89.8)
Histological subtype						
Squamous cell carcinoma	85	(100.0)	82	(100.0)	167	(100.0)
PD-L1 Status						
PD-L1 CPS >= 10	85	(100.0)	82	(100.0)	167	(100.0)
Prior Adjuvant or Neoadjuvant Therapy						
Yes	5	(5.9)	10	(12.2)	15	(9.0)
No	80	(94.1)	72	(87.8)	152	(91.0)
Number of Prior Therapy						
1	82	(96.5)	81	(98.8)	163	(97.6)
2	3	(3.5)	1	(1.2)	4	(2.4)
Prior Anthracycline Therapy						
Yes	2	(2.4)	1	(1.2)	3	(1.8)
No	83	(97.6)	81	(98.8)	164	(98.2)
Prior Monoclonal Antibody Therapy						
Yes	0	(0.0)	1	(1.2)	1	(0.6)
No	85	(100.0)	81	(98.8)	166	(99.4)
Prior Irinotecan Therapy						
Yes	0	(0.0)	1	(1.2)	1	(0.6)
No	85	(100.0)	81	(98.8)	166	(99.4)
Prior Platinum Therapy						
Yes	85	(100.0)	81	(98.8)	166	(99.4)
No	0	(0.0)	1	(1.2)	1	(0.6)
Prior Fluoropyrimidine Therapy						
Yes	73	(85.9)	68	(82.9)	141	(84.4)
No	12	(14.1)	14	(17.1)	26	(15.6)
Prior Taxane Therapy						
Yes	23	(27.1)	32	(39.0)	55	(32.9)
No	62	(72.9)	50	(61.0)	112	(67.1)

Database Cutoff Date: 15OCT2018.

Figure 1

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



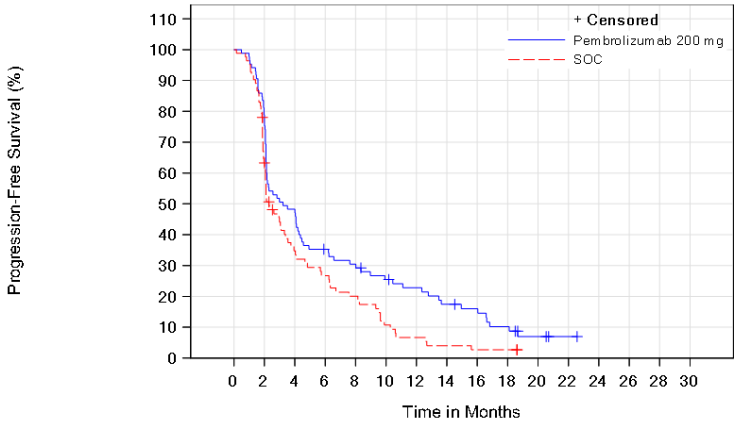
Number of subjects at risk

Pembrolizumab 200 mg	85	79	70	56	51	43	40	30	27	21	11	7	4	3	1	0
SOC	82	74	54	42	34	23	18	14	10	8	4	4	3	2	2	1

Database Cutoff Date: 15OCT2018.
Source: [P181V01MK3475A: adam-adsl; adtte]

Figure 2

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



Number of subjects at risk

Pembrolizumab 200 mg	85	67	41	29	25	20	17	13	11	7	3	1	0	0	0	0
SOC	82	51	26	20	15	8	5	3	2	2	0	0	0	0	0	0

Database Cutoff Date: 15OCT2018.
Source: [P181V01MK3475A: adam-adsl; adtte]

Table 1

KEYNOTE-181 Summary of Efficacy Outcomes
(ITT Population, Participants with PD-L1 CPS ≥10, ESCC, and ESCC PD-L1 CPS ≥10)

	PD-L1 CPS ≥10		ESCC		ESCC PD-L1 CPS ≥10	
	Pembrolizumab (N=107)	**SOC (N=115)**	**Pembrolizumab (N=198)**	**SOC (N=203)**	**Pembrolizumab (N=85)**	**SOC (N=82)**
Primary Outcome: OS						
Number of events (%)	88 (82.2)	103 (89.6)	166 (83.8)	182 (89.7)	68 (80.0)	72 (87.8)
Median OS (95% CI), months†	9.3 (6.6, 12.5)	6.7 (5.1, 8.2)	8.2 (6.7, 10.3)	7.1 (6.1, 8.2)	10.3 (7.0, 13.5)	6.7 (4.8, 8.6)
HR (95% CI)‡	0.70 (0.52, 0.94)		0.77 (0.63, 0.96)		0.64 (0.46, 0.90)	
P-value‡‡	0.00855		0.00894		0.0042	
OS rate, % (95% CI) at 6 Months†	63.6 (53.7, 71.9)	54.1 (44.5, 62.8)	61.1 (53.9, 67.5)	58.8 (51.7, 65.2)	65.9 (54.8, 74.9)	52.7 (41.2, 62.9)
OS rate, % (95% CI) at 12 Months†	42.1 (32.6, 51.2)	20.4 (13.5, 28.3)	38.9 (32.1, 45.6)	24.9 (19.2, 31.1)	47.1 (36.2, 57.2)	22.6 (14.1, 32.2)
OS rate, % (95% CI) at 18 Months†	25.2 (17.4, 33.7)	10.6 (5.8, 17.1)	23.1 (17.5, 29.2)	11.3 (7.4, 16.1)	29.3 (20.0, 39.2)	12.5 (6.4, 20.8)
Secondary Efficacy Outcomes: PFS, ORR, DOR						
PFS (BICR per RECIST 1.1)						
Number of events (%)	96 (89.7)	107 (93.0)	185 (93.4)	191 (94.1)	76 (89.4)	76 (92.7)
Median PFS (95% CI), months†	2.6 (2.1, 4.1)	3.0 (2.1, 3.7)	2.2 (2.1, 3.2)	3.1 (2.2, 3.9)	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
HR (95% CI)‡	0.73 (0.54, 0.97)		0.92 (0.75, 1.13)		0.66 (0.48, 0.92)	
P-value‡‡‡	0.015		0.216		0.007	
PFS rate, % (95% CI) at 6 Months†	33.6 (24.9, 42.6)	28.5 (20.4, 37.1)	27.3 (21.3, 33.6)	26.8 (20.8, 33.1)	35.3 (25.3, 45.4)	26.7 (17.4, 36.9)

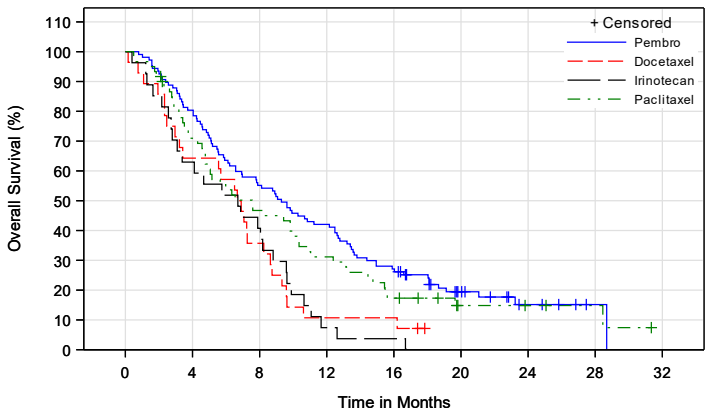
	PD-L1 CPS ≥10		ESCC		ESCC PD-L1 CPS ≥10	
	Pembrolizumab (N=107)	SOC (N=115)	Pembrolizumab (N=198)	SOC (N=203)	Pembrolizumab (N=85)	SOC (N=82)
ORR (BICR per RECIST 1.1)						
ORR (95% CI), %	21.5 (14.1, 30.5)	6.1 (2.5, 12.1)	16.7 (11.8, 22.6)	7.4 (4.2, 11.9)	22.4 (14.0, 32.7)	7.3 (2.7, 15.2)
Difference in % Pembrolizumab vs. SOC:						
Estimate (95% CI)	15.1 (6.2, 24.7)		9.2 (3.0, 15.8)		15.0 (4.4, 26.1)	
P-value‡‡‡	0.0006		0.0022		0.0034	
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Number of responders	23	7	33	15	19	6
Median DOR (range), months††	9.3 (2.1+-22.6+)	7.7 (4.3-16.8+)	8.5 (2.1+-25.8+)	10.7 (2.1+-16.8+)	9.3 (2.1+ - 18.8+)	7.7 (4.3 - 16.8+)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs ex-Asia) and tumor histology (Squamous cell carcinoma vs adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test. Nominal p-values shown for ESCC PD-L1 CPS ≥10 subgroup.
‡‡‡ Nominal one-sided p-value.
†† From product-limit (Kaplan-Meier) method for censored data.
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Response was assessed based on Central Radiology Assessment (BICR = Blinded Independent Central Radiology Review) per RECIST 1.1; only confirmed responses are included. The 95% CIs for response rates were calculated based on the binomial exact method.
"+" indicates there was no progressive disease by the time of last disease assessment.
CI=confidence interval; CR=complete response; DOR=duration of response; ESCC=esophageal squamous cell carcinoma; HR=hazard ratio; ITT=intent to treat; PD-L1 CPS=programmed cell death ligand-1 combined positive score; OS=overall survival; ORR=objective response rate or overall response rate; PFS=progression-free survival; PR=partial response; SD=stable disease; SOC=standard of care.
Database Cutoff Date: 15-OCT-2018
Data derived from KEYNOTE-181 CSR, Table 11-1, Table 11-2, Table 11-3, Table 11-4, Table 11-8, Table 11-9, Table 11-12, Table 11-13, Table 11-15, Table 14.2-26, and Table 14.2-34. Data for ESCC PD-L1 CPS ≥10 subgroup derived from [Appendix 3-3], [Appendix 3-4], [Appendix 3-5], [Appendix 3-6], [Appendix 3-7], [Appendix 3-8].

Efficacy by Standard treatments

OS was analysed by administered standard treatments (docetaxel, irinotecan, or paclitaxel).

Figure: updated Kaplan-Meier Estimates of Overall Survival by SOC (ITT Population, Subjects with PD-L1 CPS ≥10)



Number of subjects at risk

Pembro	107	86	59	45	29	13	5	1	0
Docetaxel	28	18	10	3	3	0	0	0	0
Irinotecan	27	17	11	2	1	0	0	0	0
Paclitaxel	60	41	27	18	10	4	3	2	0

Evaluating efficacy by different standard treatment options, visual inspections of the OS KM curves suggests superior OS for paclitaxel compared to irinotecan or docetaxel; however even in comparison to paclitaxel pembrolizumab appears to maintain a small, though neither clinically meaningful nor statistically significant, OS advantage in the CPS ≥10 subgroup.

The data in PD-L1 CPS<10 provided in the 1st RSI (not shown) support the MAH´s overall conclusion that pembrolizumab did not demonstrate improvement in efficacy in the subgroup of participants with PD-L1 CPS <10. Treatment effects for pembrolizumab were similar (for OS) or tendentially worse (for PFS and response data) compared to SOC. Thus, the clinical data support the chosen PD-L1 CPS cutpoint of CPS ≥10 in esophageal cancer.

Fourteen participants were her2/neu positive out of 75 participants with EAC of the EGJ who were tested for her2/neu tumor status; 13 of which were previously treated with trastuzumab per protocol. The OS HR in patients with EAC of the EGJ who were HER2/neu positive was 1.01; however it is acknowledged that patient numbers are too small to draw firm conclusions.

Likewise, the number of patients with adenocarcinoma of the oesophagus and with EAC of the EGJ are too small to draw final conclusions in the CPS ≥10 subgroup; however no apparent differences can be observed between participants with AC of the oesophagus (OS HR 1.17, n=152) and participants with AC of the EGJ (OS HR 1.01, n=75).).

The MAH seeks an approval for treatment of recurrent locally advanced or metastatic oesophageal cancer. According to the baseline characteristics the vast majority of patients had metastatic disease (91.4%). Thus, again no firm conclusions can be drawn based on the small sample size of patients with recurrent disease. Nonetheless, it appears reassuring that for the PD-L1 CPS≥10 subgroup no large discrepancies are notable between locally advanced and metastatic disease regarding OS and PFS HRs.

Summary of main studies

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 1. Summary of Efficacy for trial KEYNOTE-181

Title: 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 ESOPHAGUS THAT HAVE PROGRESSED AFTER FIRST-LINE STANDARD THERAPY		
Study identifier	KEYNOTE-181 EudraCT NUMBER: 2015-002782-32	
Design	International, randomized, open-label Phase 3 trial of pembrolizumab versus the investigator's choice of paclitaxel, docetaxel, or irinotecan in participants with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus, or advanced/metastatic Siewert type I adenocarcinoma of the oesophagogastric junction	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Enrolment started on 08-DEC-2015; study ongoing not applicable not applicable
Hypothesis	Superiority	

Treatments groups	Pembrolizumab		Pembrolizumab 200 mg every 3 weeks (Q3W) up to 35 doses or until PD/unacceptable adverse event(s)/intercurrent illness that prevents further administration of treatment.
	Standard of Care (SOC)		Docetaxel 75 mg/m^2 every 3 weeks until PD/unacceptable AEs/intercurrent illness that prevents further administration of treatment. OR Paclitaxel 80-100 mg/m^2 day 1, 8, and 15 of 4 weeks cycle until PD/unacceptable AEs/intercurrent illness that prevents further administration of treatment. OR Irinotecan 180 mg/m^2 every 2 weeks cycle until PD/unacceptable AEs/intercurrent illness that prevents further administration of treatment
Endpoints and definitions	Primary endpoint	Overall Survival (OS)	Time from randomization to death due to any cause. Evaluated in subjects with ESCC, in subjects with PD-L1 CPS≥10, and in all subjects.
	Secondary endpoint	Progression -Free Survival (PFS)	Time from randomization to first PD (per RECIST 1.1 based on central imaging vendor review) or death due to any cause, whichever occur first Evaluated in all subjects.
	Secondary endpoint	Objective Response rate (ORR)	Proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR) per RECIST 1.1 based on central imaging vendor review. Evaluated in all subjects
Data cut-off Database lock	Last participant last visit/data cut-off date 15-0ct-2018 database lock date 06-Nov-2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Median follow-up 7.1 months (range 0.5 to 31.3 months) in the pembrolizumab group and 6.9 months (range: 0.2 to 32.2 months) in the control group		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	SOC
	Number of subject	107	115
	OS PD-L1 CPS≥10 N. with events n (%)	88 (82.2)	103 (89.6)
	Median OS PD-L1 CPS⩾10 months (95% CI)	9.3 (6.6,12.5)	6.7 (5.1,8.2)
	PFS PD-L1 CPS≥10 N. with events n (%)	96 (89.7)	107 (93.0)

	Median PFS PD-L1 CPS≥10 months (95% CI)	2.6 (2.1,4.1)	3.0 (2.1,3.7)
	ORR PD-L1 CPS≥10 N. of Objective Responses (%)	23 (21.5%)	7 (6.1%)
	95% CI	(14.1, 30.5)	(2.5, 12.1)
	Number of subject	198	203
	OS ESCC N. with events n (%)	166 (83.8)	182 (89.7)
	Median OS ESCC months (95% CI)	8.2 (6.7,10.3)	7.1 (6.1,8.2)
	PFS ESCC N. with events n (%)	185 (93.4)	191 (94.1)
	Median PFS ESCC months (95% CI)	2.2 (2.1,3.2)	3.1 (2.2,3.9)
	ORR ESCC N. of Objective Responses (%)	33 (16.7%)	15 (7.4%)
	95% CI	(11.8, 22.6)	(4.2, 11.9)
	Number of subject	314	314
	OS All Subjects N. with events n (%)	271 (86.3)	284 (90.4)
	Median OS All Subjects months (95% CI)	7.1 (6.2,8.1)	7.1 (6.3,8.0)
	PFS All Subjects N. with events n (%)	295 (93.9)	297 (94.6)
	Median PFS All Subjects months (95% CI)	2.1 (2.1,2.2)	3.4 (2.8,3.9)
	ORR PD-L1 CPS≥10 All Subjects Responses (%)	41 (13.1%)	21 (6.7%)

	95% CI	(9.5, 17.3)	(4.2, 10.0)
Effect estimate per comparison	OS PD-L1 CPS≥10	Comparison groups	Pembrolizumab vs. SOC
		HR	0.70
		95% CI	(0.52, 0.94)
		P-value	0.00855
	PFS PD-L1 CPS≥10	Comparison groups	Pembrolizumab vs. SOC
		HR	0.73
		95% CI	(0.54, 0.97)
		P-value	0.015
	ORR PD-L1 CPS≥10	Comparison groups	Pembrolizumab vs. SOC
		Difference in ORR	15.1
		95% CI	(6.2, 24.7)
		P-value	0.0006
	OS ESCC	Comparison groups	Pembrolizumab vs. SOC
		HR	0.77
		95% CI	(0.63, 0.96)
		P-value	0.00894
	PFS ESCC	Comparison groups	Pembrolizumab vs. SOC
		HR	0.92
		95% CI	(0.75, 1.13)
		P-value	0.216
	ORR ESCC	Comparison groups	Pembrolizumab vs. SOC
		Difference in ORR	9.2
		95% CI	(3.0, 15.8)
		P-value	0.0022
	OS All Subjects	Comparison groups	Pembrolizumab vs. SOC
		HR	0.89
		95% CI	(0.75, 1.05)
		P-value	0.0531
	PFS All Subjects	Comparison groups	Pembrolizumab vs. SOC
		HR	1.11
		95% CI	(0.94, 1.31)
		P-value	0.287
	ORR All Subjects	Comparison groups	Pembrolizumab vs. SOC
		Difference in ORR	6.4
		95% CI	(1.7, 11.2)
		P-value	0.0037
Notes	Presented p-values are not adjusted for multiplicity. * Significance level for OS in CPS ⩾ 10 at final analysis: 0.00853 ** Significance level for OS in ESCC at final analysis: 0.00766 *** Significance level for OS in all subjects at final analysis: 0.00772		
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**		

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

No pooled efficacy analyses were conducted based on KEYNOTE-181, KEYNOTE-180, and KEYNOTE-028 because KEYNOTE-180 and KEYNOTE-028 were single arm studies with participants with substantially more advanced stages of disease (different lines of therapy).

Clinical studies in special populations

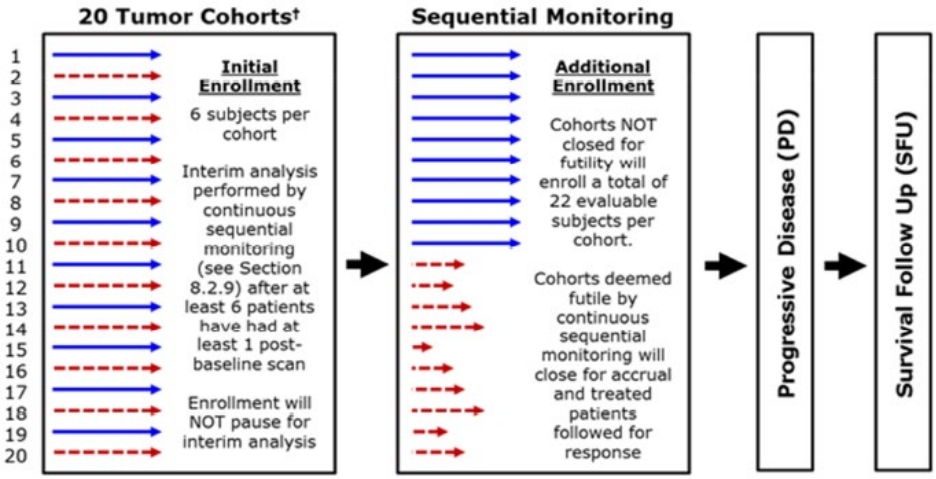
N/A

Supportive studies

Results from other two studies (KEYNOTE-028, Cohort 4A, and KEYNOTE-180) were presented in the submission package, providing additional evidence of efficacy for pembrolizumab monotherapy in oesophageal cancer.

Study KEYNOTE-028

KEYNOTE-028 was a multicenter, non-randomized, single arm, multicohort study of pembrolizumab in participants with PD-L1-positive advanced solid tumors. The trial planned to enroll 440 participants into 1 of 20 solid tumor cohorts, to examine the efficacy, safety and tolerability of a 10 mg/kg pembrolizumab IV dose, administered Q2W.



† List of 20 Advanced Solid Tumor Indication for which No Curative Therapy Exists:

A1 Colon or Rectal Adenocarcinoma
A2 Anal Canal Squamous Cell Carcinoma
A3 Pancreas Adenocarcinoma
A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)
A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers)
A6 Carcinoid Tumors
A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor)

B1 ER Positive HER2 Negative Breast Cancer
B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma
B3 Endometrial Carcinoma
B4 Cervical Squamous Cell Cancer
B5 Vulvar Squamous Cell Carcinoma

C1 Small Cell Lung Cancer
C2 Mesothelioma (Malignant Pleural Mesothelioma)

D1 Thyroid Cancer (Papillary or Follicular Subtype)
D2 Salivary Gland Carcinoma
D3 Nasopharyngeal Carcinoma

E1 Glioblastoma Multiforme
E2 Leiomyosarcoma
E3 Prostate Adenocarcinoma

Participants were required to have measurable disease per RECIST 1.1 and a histologically or cytologically documented, locally-advanced, or metastatic solid malignancy that was incurable and either: (a) failed prior standard therapy, (b) for which no standard therapy exists, or (c) standard therapy was not considered appropriate by the participant and treating physician. There was no limit to the number of prior treatment regimens.

Subjects participating in this trial were allocated by non-random assignment.

Cohort A4 of KEYNOTE-028 included adult participants (≥18 years of age) with PD-L1-positive previously treated metastatic/refractory ESCC/EAC.

The study intervention is outlined in the following table:

Drug	Dose / Potency	Dose Frequency	Route of Administration	Regimen / Treatment Period	Use
Pembrolizumab	10 mg/kg	Q2W	IV infusion	Day 1 of each cycle	Experimental

The pembrolizumab dosing could be withheld due to toxicity.

Objectives and endpoints are reported in the following table:

Primary Objective(s)	**Primary Endpoint(s)**
In each tumor type, evaluate preliminary signals of potential antitumor activity of pembrolizumab in participants with a given histopathologic type of PD-L1-positive advanced solid tumor based on RECIST 1.1, as determined by the investigator.	ORR
Secondary Objective(s)	**Secondary Endpoint(s)**
Across all tumor types, determine the safety and tolerability of pembrolizumab across selected PD-L1-positive advanced solid tumors.	
In each tumor type, evaluate the progression-free survival in participants with a given PD L1 positive advanced solid tumor type receiving pembrolizumab.	PFS
In each tumor type, evaluate the overall survival in participants with a given PD-L1-positive advanced solid tumor type receiving pembrolizumab.	OS
In each tumor type, evaluate the response duration in participants with a given PD-L1-positive advanced solid tumor type receiving pembrolizumab.	DOR

The efficacy endpoints ORR, PFS, and DOR were based on the Full Analysis Set (FAS); OS and safety endpoints were based on the ASaT analysis set. The FAS included all participants who received at least 1 dose of pembrolizumab and had a baseline scan with measureable disease per RECIST 1.1. The ASaT population included all allocated participants who received at least 1 dose of pembrolizumab. At least 1 laboratory or vital sign measurement subsequent to at least 1 dose of pembrolizumab was required for inclusion in the analysis of each safety parameter.

With 22 subjects, this study provided 80% power to demonstrate that the best ORR induced by pembrolizumab exceeds 10% at an overall one-sided 8% alpha-level, if the true best ORR is 35% (that is, the minimum criterion for success was that the lower bound of the repeated CI > 10%).

Multiple interim analyses were performed in this study due to the sequential monitoring approach followed in the trial, with the purpose of stopping for futility or going to future study planning. The false positive rate for testing the primary efficacy endpoint is controlled at 0.08 (1-sided) for each cohort.

For the primary efficacy endpoint investigator assessed RECIST 1.1 best ORR, the point estimate, repeated confidence interval, and adjusted p-value for testing the RECIST 1.1 response rate is greater than 10% were provided using a truncated sequential probability ratio test, which is a specific instance of an exact binomial group sequential design for a single arm trial with a binary outcome. Subjects in the primary analysis population (FAS) without response data were counted as non-responder.

A summary of analysis strategy for key Efficacy Endpoints is presented in the table below:

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1 – Within Indication				
Best ORR using RECIST 1.1 by site radiology assessment (each disease indication evaluated separately)	P	Truncated sequential probability test	FAS	Subjects with missing data are considered non-responders
Best ORR using modified RECIST 1.1 by site radiology assessment (each disease indication evaluated separately)	S	Truncated sequential probability test	FAS	Subjects with missing data are considered non-responders
Secondary Endpoints/Objectives– Within Indication				
PFS using RECIST 1.1 criteria by site assessment	P	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
PFS using modified RECIST 1.1 criteria by site assessment	S	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
OS	P	Kaplan-Meier method	FAS	Censored at last assessment
DOR by site assessment	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Duration of modified RECIST 1.1 response (DOR) by site assessment	S	Summary statistics using Kaplan-Meier method	All modified RECIST 1.1 responders	Non-responders are excluded in analysis

[†] P=Primary approach; S=Secondary approach.

A total of 23 participants with EAC and ESCC were enrolled in Cohort A4 across 9 global study sites.

At the time of study entry, the majority of the participants in Cohort A4 had metastatic disease; of the 23 participants, 5 had EAC and 18 had ESCC. The participants in cohort A4 were primarily male, approximately 2/3 had a baseline ECOG status of 1, and most had no brain metastases. The median age was 65.0 years (range: 26 to 71 years).

Results from this cohort were provided, based on the interim analysis #9 with a data cutoff date of 31 January 2018.

Table: Disposition of subjects

	Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)	
	n	(%)
Subjects in population	23	
Status For Trial		
Discontinued	22	(95.7)
Adverse Event	4	(17.4)
Death	2	(8.7)
Physician Decision	1	(4.3)
Progressive Disease	14	(60.9)
Withdrawal By Subject	1	(4.3)
Ongoing In Trial	1	(4.3)
Status For Study Medication In Trial Segment Of First Course Treatment		
Started	23	
Completed	2	(8.7)
Discontinued	21	(91.3)
Adverse Event	2	(8.7)
Physician Decision	3	(13.0)
Progressive Disease	14	(60.9)
Withdrawal By Subject	2	(8.7)
Status For Study Medication In Trial Segment Of Second Course Treatment		
Started	1	
Discontinued	1	(100.0)
Physician Decision	1	(100.0)

Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record.
Database Cutoff Date: 31JAN2018

Source: [P028V02MK3475: adam-adsl; adpm]

The median duration of follow-up for all participants in the ASaT population in Cohort A4, defined as the time from first dose to the date of death or the database cutoff if the participant was still alive, was 7.1 months.

Table: Summary of Best Overall Response Based on RECIST 1.1 per Site Assessment

(FAS Population by Investigator in the First Course)

Response Evaluation	Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction) (N=23)			
	n	%	95% CI[†]	p-Value[‡]
Complete Response (CR)	0	0.0	(0.0, 14.8)	
Partial Response (PR)	7	30.4	(13.2, 52.9)	
Best Overall Response (CR+PR)	**7**	**30.4**	**(13.2, 52.9)**	**0.0058**
Stable Disease (SD)	2	8.7	(1.1, 28.0)	
Disease Control Rate (CR+PR+SD)	**9**	**39.1**	**(19.7, 61.5)**	
Progressive Disease (PD)	13	56.5	(34.5, 76.8)	
Non-evaluable (NE)	1	4.3	(0.1, 21.9)	

Only confirmed responses are included.
[†] Based on binomial exact confidence interval method.
[‡] One-sided p-value based on exact binomial distribution for testing. H_0: $p \leq 0.10$ versus H_1: $p > 0.10$.
Database Cutoff Date: 31JAN2018

Source: [P028V02MK3475: adam-adsl; adrs; adtte]

Best Overall Response as assessed by central radiology assessment was 18.2% (95% CI 5.2% - 40.3%) (p-value=0.1719).

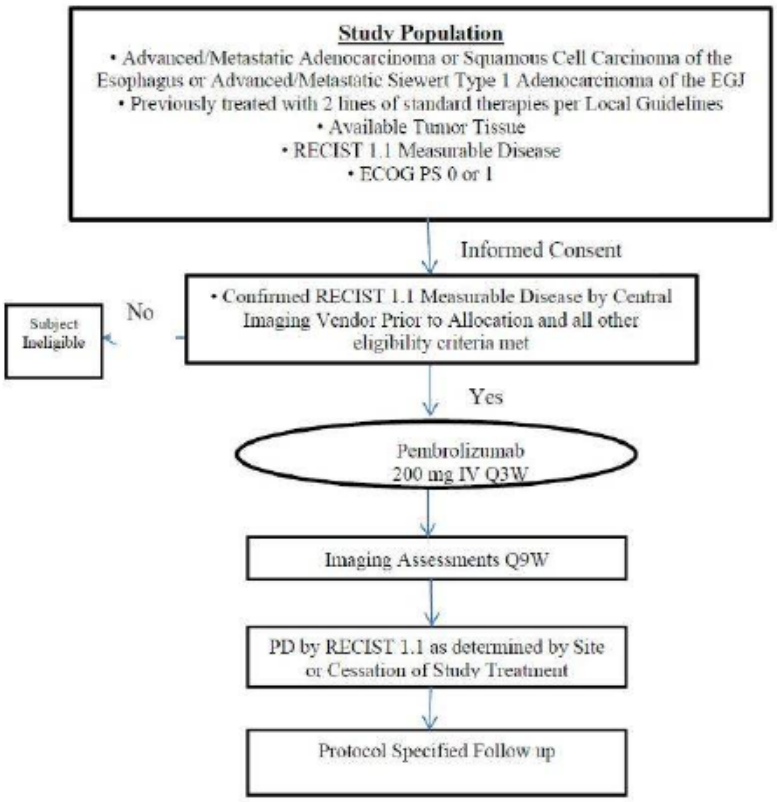
The following results were observed for pre-specified secondary endpoints:

- median DOR in the FAS population of 14.5 (range: 5.6 - 38.4+) by investigator, and of 21.4 months (range: 12.0 - 38.4+) per Central Radiology Assessment;
- a median PFS in the FAS population of 1.8 months by investigator (1.8 months in EAC population and 1.9 months in ESCC population) and of 1.9 months by central radiology assessment (2.5 months in EAC population and 1.8 months in ESCC population);
- a median OS in the ASaT population of 7.0 months (95% CI: 4.3, 17.7); the estimated OS rate was 58.0% at 6 months and 38.6% at 12 months. By histology, the 5 participants with EAC had higher median survival (23.5 months) than the 18 participants with ESCC (7.0 months).

KEYNOTE-028 is an ongoing Phase 1b multi-cohort study to evaluate preliminary signals of potential antitumor activity of pembrolizumab monotherapy in participants with PD-L1-positive advanced solid tumour types. Cohort A4 demonstrated an ORR of 30% or 18% (as assessed by investigator or independent review, respectively) in 23 subjects with ESCC or EAC.

Study KEYNOTE-180

KEYNOTE-180 is a single-arm, open-label, multisite study of pembrolizumab 200 mg IV Q3W in participants with previously treated, advanced/metastatic EAC, including Siewert type I adenocarcinoma of the EGJ, and ESCC.



Participants were required to have at least 1 measureable lesion by RECIST 1.1 for response assessment and to have previously been treated with ≥2 lines of therapy. Participants were enrolled regardless biomarker status but were required to provide either a newly obtained or archival tissue sample for intratumoral immune-related GEP and for PD-L1 by IHC analysis.

Treatment allocation will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS).

The study intervention is outlined in the following table:

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV Infusion	Day 1 of each 21 day cycle	Experimental

Abbreviations: IV = intravenous; Q3W = every 3 weeks

The primary objective was the ORR per RECIST 1.1 assessed by central imaging vendor

- in all participants

- in participants whose tumors are classified as gene expression profile (GEP) intermediate or high

- in participants whose tumors are classified as GEP high.

Secondary objectives included:

- the evaluation of safety and tolerability of pembrolizumab;

- the evaluation of DOR and PFS per RECIST 1.1 assessed by central imaging vendor;

- the evaluation of OS;

- the evaluation of PD-L1 IHC in esophageal cancer for its utility to predict pembrolizumab efficacy.

The All Subjects as Treated (ASaT) population was used for the efficacy and safety analyses and consisted of all allocated participants who received at least 1 dose of study intervention.

No power calculation is provided.

Primary efficacy analysis on ORR was based on binomial exact confidence interval method. Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responder. DOR analyses included responders and used summary statistics using Kaplan-Meier method. PFS and OS analysis used summary statistics using Kaplan-Meier method. PD-L1 expression in tumor cells and inflammatory cells within pre-intervention tumor tissue samples was characterized by IHC using a combined positive score and a cutoff of 10% and retrospectively tested for association with response to pembrolizumab. A CPS ≥1 cut point was initially prespecified to assess PD-L1 status in KEYNOTE-180. Additionally, KEYNOTE-180 served as a training set for evaluating the potential of higher PD-L1 cut points for enrichment of pembrolizumab responders relative to nonresponders in esophageal cancer, and pathologists were instructed to record CPS values precisely across the dynamic range of PD-L1 expression for this purpose.

A total of 185 participants were screened, and 121 were enrolled [Table 14.1-1] across 43 global study sites in 10 countries.

Approximately half of participants were age ≥ 65 years (52.9%), PD-L1 status CPS <10 (52.1%), and tumor histology squamous cell carcinoma (52.1%). Most participants had a baseline ECOG score of 1 (63.6%) [Table 10-2]. Of 121 enrolled subjects, MSI data were available for 98 subjects. Only 1 subject (a nonresponder) was identified as MSI-H; this corresponds to a prevalence of 1%.

Results were provided as of the data cutoff of 30 July 2018; the median duration of follow-up for the overall population was of 5.8 months (range: 0.2 to 27.8 months).

Table: Disposition of subjects

	Pembrolizumab 200 mg	
	n	(%)
Subjects in population	121	
Status for Trial		
Discontinued	107	(88.4)
Death	103	(85.1)
Withdrawal By Subject	4	(3.3)
Ongoing Follow-Up	14	(11.6)
Status for Study Medication in Trial		
Started	121	
Completed	2	(1.7)
Discontinued	117	(96.7)
Adverse Event	13	(10.7)
Clinical Progression	23	(19.0)
Physician Decision	3	(2.5)
Progressive Disease	77	(63.6)
Withdrawal By Subject	1	(0.8)
Ongoing Treatment	2	(1.7)
Database Cutoff Date: 30JUL2018		

Source: [P180V01MK3475: adam-adsl]

Participants were exposed to pembrolizumab for a median of 2 months (range: 0 [1 day] to 24 months), resulting in a median of 4 administrations (range: 1 to 35 administrations).

Table: Summary of Best Objective Response (Confirmed) Based on Central Radiology Assessment per RECIST 1.1

(ASaT Population)

	Pembrolizumab 200 mg (N=121)		
	n	(%)	95% CI†
Complete Response (CR)	2	(1.7)	(0.2, 5.8)
Partial Response (PR)	10	(8.3)	(4.0, 14.7)
Objective Response (CR+PR)	**12**	**(9.9)**	**(5.2, 16.7)**
Stable Disease (SD)	25	(20.7)	(13.8, 29.0)
Disease Control (CR+PR+SD)	**37**	**(30.6)**	**(22.5, 39.6)**
Progressive Disease (PD)	71	(58.7)	(49.4, 67.6)
Non-Evaluable (NE)	0	(0.0)	(0.0, 3.0)
No Assessment (NA)	13	(10.7)	(5.8, 17.7)

† Based on binomial exact confidence interval method.
'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
Database Cutoff Date: 30JUL2018

Source: [P180V01MK3475: adam-adsl; adrs]

The ORR (CR + PR) per BICR was 14.3% (9/63) in participants with ESCC and 5.2% (3/58) in participants with EAC.

13.8% in participants with tumours expressing PD-L1 CPS ≥10

All responding participants had at least 12 months of follow-up after a confirmed response. Median DOR by BICR was not reached (range: 2.1 – 25.1+ months) at the data cutoff, 7 responders (67.0% by Kaplan-Meier estimation) had DORs of ≥6 months, • 5 responders (57.0% by Kaplan-Meier estimation) had DORs ≥12 months, and 4 responders (57.0% by Kaplan-Meier estimation) had DORs ≥15 months.

Median OS for all participants was 5.8 months (95%CI 4.5, 7.2).

Median PFS per BICR in the overall population was 2 months (95%CI 1.8, 2.1).

The PFS rate was 14.9% at 6 months and 9.1% at 9 months by Kaplan-Meier estimation.

Subgroups

- Efficacy by Histology

Table: Summary of Best Objective Response (Confirmed) Based on Central Radiology Assessment per RECIST 1.1 by Histology (ASaT Population)

	Squamous Cell Carcinoma (N=63)			Adenocarcinoma (N=58)		
	n	(%)	95% CI†	n	(%)	95% CI†
Complete Response (CR)	2	(3.2)	(0.4, 11.0)	0	(0.0)	(0.0, 6.2)
Partial Response (PR)	7	(11.1)	(4.6, 21.6)	3	(5.2)	(1.1, 14.4)
Objective Response (CR+PR)	**9**	**(14.3)**	**(6.7, 25.4)**	**3**	**(5.2)**	**(1.1, 14.4)**
Stable Disease (SD)	16	(25.4)	(15.3, 37.9)	9	(15.5)	(7.3, 27.4)
Disease Control (CR+PR+SD)	**25**	**(39.7)**	**(27.6, 52.8)**	**12**	**(20.7)**	**(11.2, 33.4)**
Progressive Disease (PD)	34	(54.0)	(40.9, 66.6)	37	(63.8)	(50.1, 76.0)
Non-Evaluable (NE)	0	(0.0)	(0.0, 5.7)	0	(0.0)	(0.0, 6.2)
No Assessment (NA)	4	(6.3)	(1.8, 15.5)	9	(15.5)	(7.3, 27.4)

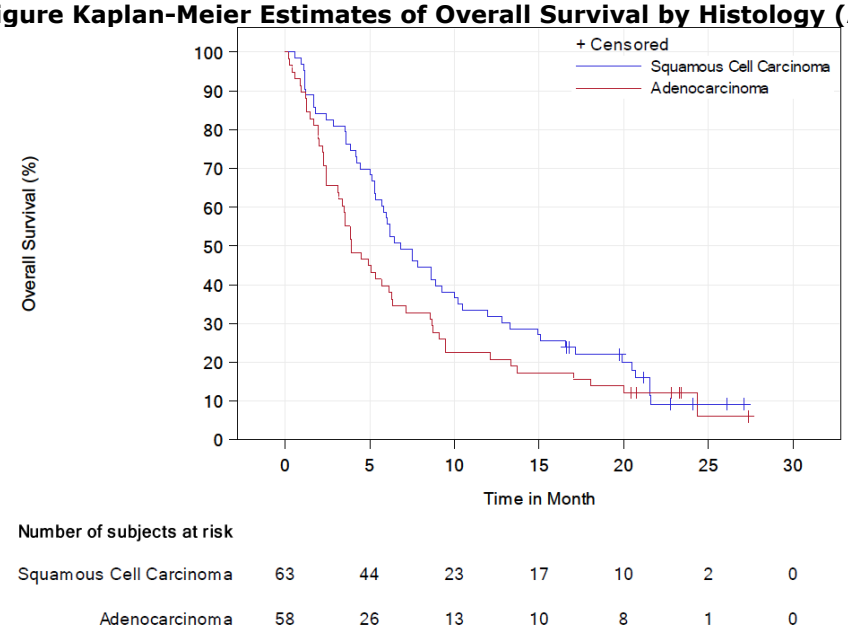
† Based on binomial exact confidence interval method.
'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
Database Cutoff Date: 30JUL2018

Table: Summary of Overall Survival by Histology (ASaT Population)

	Squamous Cell Carcinoma	Adenocarcinoma
Subjects in population	63	58
Number (%) of Deaths	55 (87.3)	52 (89.7)
Median Survival (Month)†	6.8	3.9
95% CI for Median Survival†	(5.4, 9.3)	(3.2, 6.3)
OS Rate (95% CI) at 3 Months in %†	81.0 (68.9, 88.7)	65.5 (51.8, 76.2)
OS Rate (95% CI) at 6 Months in %†	57.1 (44.0, 68.3)	39.7 (27.2, 51.9)
OS Rate (95% CI) at 9 Months in %†	39.7 (27.7, 51.4)	27.6 (16.9, 39.4)
OS Rate (95% CI) at 12 Months in %†	31.7 (20.7, 43.3)	22.4 (12.7, 33.8)

OS: Overall Survival
† From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 30JUL2018

Figure Kaplan-Meier Estimates of Overall Survival by Histology (ASaT Population)



- Efficacy by biomarker analysis

As mentioned above, CPS≥1 cutpoint was pre-specified to assess PD-L1 positive/negative status in KN180. Additionally, since KN180 was a training set for identifying a PD-L1 cutpoint (CPS≥1 or higher

PD-L1 cutpoints) that optimally enriches pembrolizumab responders relative to non-responders in esophageal cancer, pathologists were instructed to record CPS values precisely across the dynamic range of PD-L1 expression.

The evaluation of a general positive association between CPS and objective response rate (ORR) (by central review) in KN180 was investigated via standard logistic regression, rank sum tests, and receiver operating characteristic (ROC) curve analysis.

The potential for an improved alternate to a CPS≥1 cutpoint involved a review of how the positive predictive value (PPV, response rate in those above a cutpoint), negative predictive value (NPV, non-response rate in those below the cutpoint), and fraction of subjects having higher PD-L1 expression change as a function of increasing cutpoints and whether there was evidence for a relative improvement in clinical utility relative to the CPS≥1 cutpoint.

A PD-L1 cutpoint that maintains high NPV, while achieving meaningful enrichment of response was sought. CPS ranges containing potential cutpoints were also gauged in the context of practical implementation and interpretation by pathologists in clinical practice.

An interim analysis of KEYNOTE-180 (cutoff date 17-JUL-2017) was performed to evaluate the association between CPS and response, including evaluation at the CPS≥1 cutpoint as well as evaluating the potential for an improved alternate cutpoint .

The KN180 trial enrolled 121 subjects, all with evaluable PD-L1 data. At the time of the analysis eleven of those subjects were considered confirmed responders (partial or complete responders) via RECIST v1.1 (central review). Some evidence for an association between CPS score and higher probability of response was observed (1-sided p-values: p = 0.022 logistic regression, p = 0.171 rank sum test).

The figure below displays the ROC curve with the location of the CPS 1, 10, and 20 points and their associated (Specificity, Sensitivity) labeled. The area under the ROC curve was 0.59 with 95% confidence interval of (0.35, 0.82).

Figure: ROC curve for CPS in 121 subjects from KN180

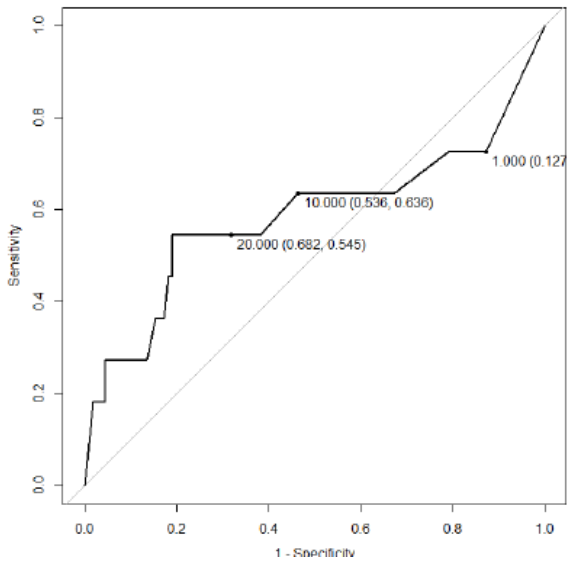


Table: Performance Measures for Several CPS Cutpoints in KN180 (N=121)

	CPS Cutpoint		
Performance Measure:	**≥1**	**≥10**	**≥20**
%PPV/NPV	7.7/82.4	12.1/93.7	14.6/93.8
%Sens./Spec.	72.7/12.7	63.6/53.6	54.5/68.2
%Prevalence	86.0	47.9	33.9
PPV: response rate at or above cutpoint NPV: non-response rate below cutpoint Prevalence: percent of patients with tumors score at or above cutpoint			

The pre-specified cutpoint of CPS≥1 demonstrated no enrichment of response in this population of esophageal cancer patients (7.7%, 8/104) compared with the overall response in the all subjects population of 9.1% (11/121 subjects). At CPS≥10, ORR increased to 12.1% (7/58). As shown in the table above, while the ORR was similar at CPS≥20, there was a drop in sensitivity (1 additional responding subject was not captured using CPS≥20 (n=5 responders not captured) relative to CPS≥10 (n=4 responders not captured) and drop in prevalence compared to CPS≥10. At CPS≥32, the cutpoint which corresponds to the Youden index, while the PPV (22.2%) was higher compared to CPS≥10, the sensitivity and prevalence were lower, 54.5% and 22.3%, respectively.

The table below represents a summary of the best overall response (with confirmation) based on central imaging assessment per RECIST 1.1 using the CPS≥10 cutpoint.

Table: Best response summary data for the CPS>10 cutpoint in KN180

	PD-L1 CPS≥10 (N=58)		PD-L1 CPS<10 (N=63)	
	N (%)	95% CI†	N (%)	95% CI†
Objective Response	7 (12.1)	(5.0, 23.3)	4 (6.3)	(1.8, 15.5)
Stable Disease (SD)	14 (24.1) (13.9, 37.2)		12 (19.0) (10.2, 30.9)	
† Based on binomial exact confidence interval method Database Cutoff Date: 17JUL2017				

Of the 121 subjects enrolled in the trial, 118 subjects were evaluated also for GEP status against objective response. Evidence of a difference in response rates between the GEP groups was observed for both cutpoints ('GEP low' vs. 'GEP intermediate or high' and 'GEP low or intermediate' vs. 'GEP high'). The evaluation of the continuous GEP scores also showed evidence of an association with probability of response (1-sided p-values: p = 0.026 logistic regression, p = 0.040 rank sum test), with an ROC curve with AUC of 0.66 with 95% CI of (0.49, 0.83).

From a clinical standpoint, while GEP enriches for pembrolizumab responders, its enrichment profile at the lower cut-off, in terms of increasing the ORR as compared to all-comers, is comparable to PD-L1. From a technical standpoint, the number of clinical sample slides required to perform the GEP assay proved to be much greater than anticipated. Given that having adequate tissue is often a challenge in clinical development and may also likely be in subsequent clinical practice, the GEP assay may lead to, not infrequently, delay in results and/or no results due to specimen shortage.

In conclusion, the PD-L1 assay (CPS≥10 cutpoint) and GEP status both enrich for responders to pembrolizumab in heavily treated esophageal cancer patients. GEP status while enriching, presents

challenges to implement in clinical trials and practice settings while offering similar performance characteristics as a patient selection biomarker.

Based on the above, the PD-L1 assay (CPS≥10 cutpoint) was selected to serve as an enriching factor for use in the esophageal cancer development program for pembrolizumab.

Table: Summary of Best Objective Response (Confirmed) Based on Central Radiology Assessment per RECIST 1.1 by PD-L1 Status (CPS>=10 vs. CPS<10) (ASaT Population)

	PD-L1 CPS>=10 (N=58)			PD-L1 CPS<10 (N=63)		
	n	(%)	95% CI[†]	n	(%)	95% CI[†]
Complete Response (CR)	1	(1.7)	(0.0, 9.2)	1	(1.6)	(0.0, 8.5)
Partial Response (PR)	7	(12.1)	(5.0, 23.3)	3	(4.8)	(1.0, 13.3)
Objective Response (CR+PR)	**8**	**(13.8)**	**(6.1, 25.4)**	**4**	**(6.3)**	**(1.8, 15.5)**
Stable Disease (SD)	13	(22.4)	(12.5, 35.3)	12	(19.0)	(10.2, 30.9)
Disease Control (CR+PR+SD)	**21**	**(36.2)**	**(24.0, 49.9)**	**16**	**(25.4)**	**(15.3, 37.9)**
Progressive Disease (PD)	33	(56.9)	(43.2, 69.8)	38	(60.3)	(47.2, 72.4)
Non-Evaluable (NE)	0	(0.0)	(0.0, 6.2)	0	(0.0)	(0.0, 5.7)
No Assessment (NA)	4	(6.9)	(1.9, 16.7)	9	(14.3)	(6.7, 25.4)

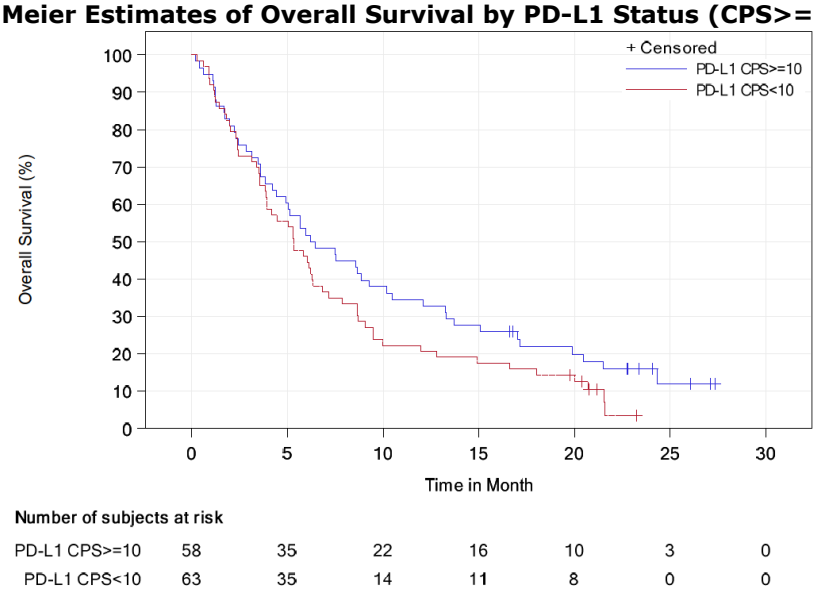
[†] Based on binomial exact confidence interval method.
'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
Database Cutoff Date: 30JUL2018

Table: Summary of Overall Survival by PD-L1 Status (CPS>=10 vs. CPS<10) (ASaT Population)

	PD-L1 CPS>=10	PD-L1 CPS<10
Subjects in population	58	63
Number (%) of Deaths	49 (84.5)	58 (92.1)
Median Survival (Month)[†]	6.3	5.4
95% CI for Median Survival[†]	(4.4, 10.2)	(3.9, 6.3)
OS Rate (95% CI) at 3 Months in %[†]	74.1 (60.8, 83.5)	73.0 (60.2, 82.3)
OS Rate (95% CI) at 6 Months in %[†]	51.7 (38.2, 63.6)	46.0 (33.5, 57.7)
OS Rate (95% CI) at 9 Months in %[†]	39.7 (27.2, 51.9)	28.6 (18.1, 40.0)
OS Rate (95% CI) at 12 Months in %[†]	34.5 (22.6, 46.6)	20.6 (11.7, 31.3)

OS: Overall Survival
[†] From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 30JUL2018

Figure: Kaplan-Meier Estimates of Overall Survival by PD-L1 Status (CPS>=10 vs. CPS<10)



- Efficacy by Histology and PD-L1 Status

Table: Summary of Best Objective Response (Confirmed) Based on Central Radiology Assessment per RECIST 1.1 by Histology and PD-L1 Status (CPS>=10 vs. CPS<10) (ASaT Population)

	Squamous Cell Carcinoma						Adenocarcinoma					
	PD-L1 CPS>=10 (N=35)			PD-L1 CPS<10 (N=28)			PD-L1 CPS>=10 (N=23)			PD-L1 CPS<10 (N=35)		
	n	(%)	95% CI[†]	n	(%)	95% CI[†]	n	(%)	95% CI[†]	n	(%)	95% CI[†]
Complete Response (CR)	1	(2.9)	(0.1, 14.9)	1	(3.6)	(0.1, 18.3)	0	(0.0)	(0.0, 14.8)	0	(0.0)	(0.0, 10.0)
Partial Response (PR)	6	(17.1)	(6.6, 33.6)	1	(3.6)	(0.1, 18.3)	1	(4.3)	(0.1, 21.9)	2	(5.7)	(0.7, 19.2)
Objective Response (CR+PR)	**7**	**(20.0)**	**(8.4, 36.9)**	**2**	**(7.1)**	**(0.9, 23.5)**	**1**	**(4.3)**	**(0.1, 21.9)**	**2**	**(5.7)**	**(0.7, 19.2)**
Stable Disease (SD)	7	(20.0)	(8.4, 36.9)	9	(32.1)	(15.9, 52.4)	6	(26.1)	(10.2, 48.4)	3	(8.6)	(1.8, 23.1)
Disease Control (CR+PR+SD)	**14**	**(40.0)**	**(23.9, 57.9)**	**11**	**(39.3)**	**(21.5, 59.4)**	**7**	**(30.4)**	**(13.2, 52.9)**	**5**	**(14.3)**	**(4.8, 30.3)**
Progressive Disease (PD)	21	(60.0)	(42.1, 76.1)	13	(46.4)	(27.5, 66.1)	12	(52.2)	(30.6, 73.2)	25	(71.4)	(53.7, 85.4)
Non-Evaluable (NE)	0	(0.0)	(0.0, 10.0)	0	(0.0)	(0.0, 12.3)	0	(0.0)	(0.0, 14.8)	0	(0.0)	(0.0, 10.0)
No Assessment (NA)	0	(0.0)	(0.0, 10.0)	4	(14.3)	(4.0, 32.7)	4	(17.4)	(5.0, 38.8)	5	(14.3)	(4.8, 30.3)

[†] Based on binomial exact confidence interval method.

'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

Database Cutoff Date: 30JUL2018

- Efficacy by Baseline **GEP**-Status - **High or Intermediate vs. Low**

Table: Summary of Best Objective Response (Confirmed) Based on Central Radiology Assessment per RECIST 1.1 by Histology and GEP Status (GEP High or Intermediate vs. Low) (ASaT Population)

	Squamous Cell Carcinoma						Adenocarcinoma					
	GEP High or Intermediate (N=26)			GEP Low (N=37)			GEP High or Intermediate (N=25)			GEP Low (N=30)		
	n	(%)	95% CI[†]	n	(%)	95% CI[†]	n	(%)	95% CI[†]	n	(%)	95% CI[†]
Complete Response (CR)	0	(0.0)	(0.0, 13.2)	2	(5.4)	(0.7, 18.2)	0	(0.0)	(0.0, 13.7)	0	(0.0)	(0.0, 11.6)
Partial Response (PR)	4	(15.4)	(4.4, 34.9)	3	(8.1)	(1.7, 21.9)	3	(12.0)	(2.5, 31.2)	0	(0.0)	(0.0, 11.6)
Objective Response (CR+PR)	**4**	**(15.4)**	**(4.4, 34.9)**	**5**	**(13.5)**	**(4.5, 28.8)**	**3**	**(12.0)**	**(2.5, 31.2)**	**0**	**(0.0)**	**(0.0, 11.6)**
Stable Disease (SD)	7	(26.9)	(11.6, 47.8)	9	(24.3)	(11.8, 41.2)	4	(16.0)	(4.5, 36.1)	3	(10.0)	(2.1, 26.5)
Disease Control (CR+PR+SD)	**11**	**(42.3)**	**(23.4, 63.1)**	**14**	**(37.8)**	**(22.5, 55.2)**	**7**	**(28.0)**	**(12.1, 49.4)**	**3**	**(10.0)**	**(2.1, 26.5)**
Progressive Disease (PD)	14	(53.8)	(33.4, 73.4)	20	(54.1)	(36.9, 70.5)	15	(60.0)	(38.7, 78.9)	21	(70.0)	(50.6, 85.3)
Non-Evaluable (NE)	0	(0.0)	(0.0, 13.2)	0	(0.0)	(0.0, 9.5)	0	(0.0)	(0.0, 13.7)	0	(0.0)	(0.0, 11.6)
No Assessment (NA)	1	(3.8)	(0.1, 19.6)	3	(8.1)	(1.7, 21.9)	3	(12.0)	(2.5, 31.2)	6	(20.0)	(7.7, 38.6)

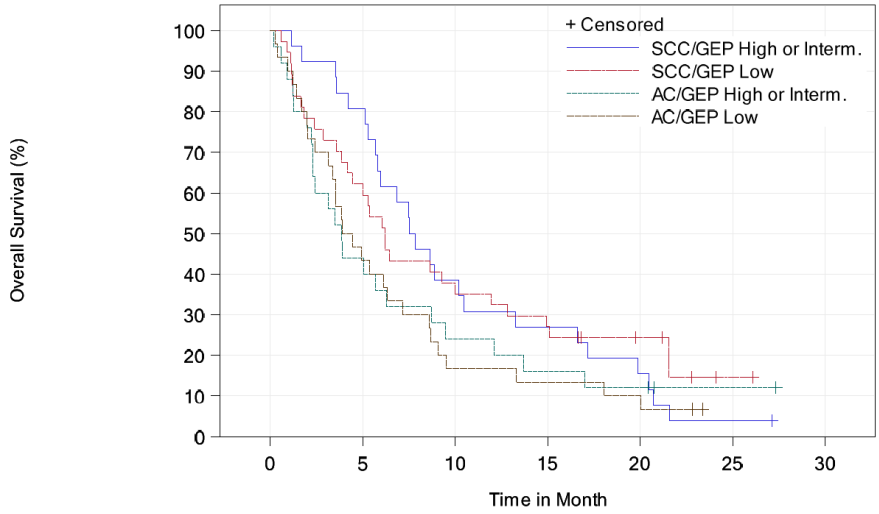
[†] Based on binomial exact confidence interval method.

'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

GEP High or Intermediate: GEP Score ≥-1.540; GEP Low: GEP Score <-1.540

Database Cutoff Date: 30JUL2018

Figure: K-M Estimates of Overall Survival by Histology and GEP Status (High or Intermediate vs. Low)



- Efficacy by Baseline **GEP**-Status - **High vs. Intermediate or Low**

Table: Summary of Best Objective Response (Confirmed) Based on Central Radiology Assessment per RECIST 1.1 by Histology and GEP Status (High vs. Intermediate or Low) (ASaT Population)

	Squamous Cell Carcinoma						Adenocarcinoma					
	GEP High (N=15)			GEP Intermediate or Low (N=48)			GEP High (N=9)			GEP Intermediate or Low (N=46)		
	n	(%)	95% CI†	n	(%)	95% CI†	n	(%)	95% CI†	n	(%)	95% CI†
Complete Response (CR)	0	(0.0)	(0.0, 21.8)	2	(4.2)	(0.5, 14.3)	0	(0.0)	(0.0, 33.6)	0	(0.0)	(0.0, 7.7)
Partial Response (PR)	3	(20.0)	(4.3, 48.1)	4	(8.3)	(2.3, 20.0)	2	(22.2)	(2.8, 60.0)	1	(2.2)	(0.1, 11.5)
Objective Response (CR+PR)	**3**	**(20.0)**	**(4.3, 48.1)**	**6**	**(12.5)**	**(4.7, 25.2)**	**2**	**(22.2)**	**(2.8, 60.0)**	**1**	**(2.2)**	**(0.1, 11.5)**
Stable Disease (SD)	5	(33.3)	(11.8, 61.6)	11	(22.9)	(12.0, 37.3)	1	(11.1)	(0.3, 48.2)	6	(13.0)	(4.9, 26.3)
Disease Control (CR+PR+SD)	**8**	**(53.3)**	**(26.6, 78.7)**	**17**	**(35.4)**	**(22.2, 50.5)**	**3**	**(33.3)**	**(7.5, 70.1)**	**7**	**(15.2)**	**(6.3, 28.9)**
Progressive Disease (PD)	6	(40.0)	(16.3, 67.7)	28	(58.3)	(43.2, 72.4)	5	(55.6)	(21.2, 86.3)	31	(67.4)	(52.0, 80.5)
Non-Evaluable (NE)	0	(0.0)	(0.0, 21.8)	0	(0.0)	(0.0, 7.4)	0	(0.0)	(0.0, 33.6)	0	(0.0)	(0.0, 7.7)
No Assessment (NA)	1	(6.7)	(0.2, 31.9)	3	(6.3)	(1.3, 17.2)	1	(11.1)	(0.3, 48.2)	8	(17.4)	(7.8, 31.4)

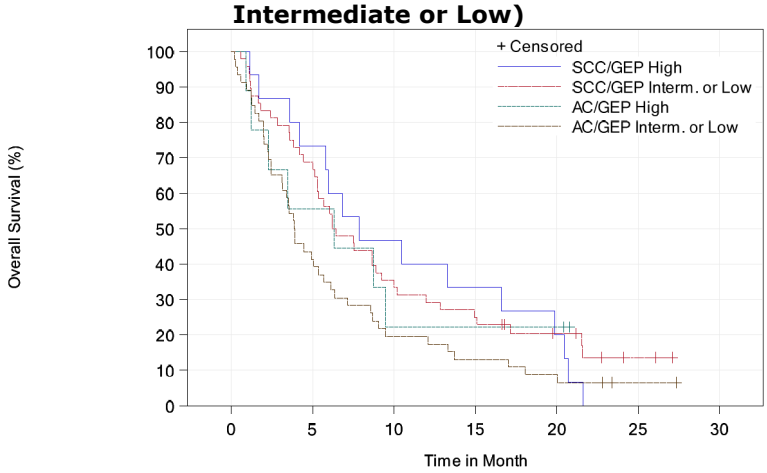
† Based on binomial exact confidence interval method.

'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

GEP High: GEP Score ≥-0.945; GEP Intermediate or Low: GEP Score <-0.945

Database Cutoff Date: 30JUL2018

Figure: K-M Estimates of Overall Survival by Histology and GEP Status (High vs. Intermediate or Low)



Number of subjects at risk

SCC/GEP High	15	11	7	5	3	0	0
SCC/GEP Interm. or Low	48	33	16	12	7	2	0
AC/GEP High	9	5	2	2	2	0	0
AC/GEP Interm. or Low	46	19	9	6	4	1	0

In the single arm trial KEYNOTE-180 a low response rate of only 5.2% and a median OS of 3.9 months were reported for patients with adenocarcinoma (as opposed to 14.3% and 6.8 months in SCC). Based on the low number of responders no association was observed between ORR and PD-L1 expression in adenocarcinoma (ORR 4.3% for CPS ≥10 and 5.7% for CPS <10); but differences were reported for SCC (ORR 20% for CPS≥10 and 7.1% for CPS <10). The GEP status (high or intermediate vs. low) did obviously offer no advantage compared to the PD-L1 IHC assay in predicting treatment benefit of pembrolizumab. On the contrary, the "high vs. intermediate or low" GEP status could serve as an alternative biomarker, but is limited by the only very low prevalence of "high" GEP status.

Based on IA data from KEYNOTE-180 the biomarker selection and the design of KEYNOTE-181 were changed to the evaluation of OS in the 3 subgroups (SCC, CPS ≥10, and all participants).

2.4.3. Discussion on clinical efficacy

A type II Variation for the extension of Keytruda therapeutic indication as monotherapy for the "*treatment of recurrent locally advanced or metastatic oesophageal cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have received prior systemic therapy*" has been submitted by the MAH based on the results of the pivotal trial KEYNOTE-181.

During the procedure, the MAH proposed a restricted indication to: "*KEYTRUDA as monotherapy is indicated for the treatment of recurrent locally advanced or metastatic **squamous cell carcinoma** of the esophagus in adults whose tumors express PD-L1 with a CPS ⩾10 and who have received prior systemic therapy (see section 5.1).*"

Results from two single-arm studies, the phase 1b study KEYNOTE-028 (Cohort 4A, n=22) and the Phase 2 study KEYNOTE-180 (n=121), providing additional evidence of efficacy for pembrolizumab monotherapy in more heavily pre-treated oesophageal cancer patients, were submitted as supportive.

Design and conduct of clinical studies

KEYNOTE-181 is an ongoing, randomised (1:1), multi-site, open-label, Phase 3 study of pembrolizumab versus SOC (investigator's choice of paclitaxel, docetaxel, or irinotecan).

The study enrolled subjects with locally advanced unresectable/metastatic EAC or ESCC, or Siewert type I adenocarcinoma of the EGJ who progressed after first-line standard therapy. Subjects with Siewert type 1 adenocarcinoma of the EGJ should have their HER2/neu status determined, and if HER2/neu positive, they should have documentation of disease progression on a prior line of therapy containing trastuzumab. Neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using standard of care agents or definitive chemoradiation, was counted as a line of therapy if disease progression occurred during treatment or within 6 months of cessation of treatment. This is acceptable, although it is noted that the type of prior treatment was not a stratification factor. Furthermore, in the most recent AJCC staging classification (8th edition 2017) Siewert II adenocarcinomas (centred within 1 cm of the EGJ) are also considered as oesophageal cancer. In the SmPC, it has been clarified that the study population did not include Siewert II EGJ adenocarcinoma and that the population was restricted to a 2L, considering the lower response rates (10%) in the phase 2 study KEYNOTE-180 that enrolled ≥3L patients.

Subjects with direct invasion into adjacent organs such as the aorta or trachea (T4b disease) should be closely evaluated for bleeding risk prior to enrolment, which is endorsed and should be part of a standard assessment in a real-life setting. The study included only patients with ECOG PS 0-1, and from Protocol Amendment #2 (9 Dec 2016), patients with weight loss > 10% over the 2 months prior to first dose of study therapy, and those with clinically apparent ascites or pleural effusion by physical exam were excluded from the trial. Patients with known central nervous system (CNS) metastases were also excluded. Although, these criteria were justified with the aim to ensure "*subject stability when entering the trial*", they somewhat limit the external validity of the trial and the representativeness of the population included in the study compared to the target population of the indication. The median age of 63 years appears to be rather low. In the SmPC it is clarified that there were limited numbers of patients with oesophageal cancer above 75 years.

Patients were enrolled regardless of PD-L1 expression. This is not questioned, taking into account some responses had been observed in both PD-L1 positive and PD-L1 negative patients in prior studies in more heavily pre-treated patients.

The selected comparator, a taxane or irinotecan as single agent based on physician's choice, is accepted in the target population of the trial. The investigator's choice of paclitaxel, docetaxel, or irinotecan, was to be determined prior to randomization, which is endorsed. No criteria were provided for the selection among these three options, which might have been considered. In this regard, it is noted that 33.4% had received prior therapy with taxane. Indeed, there were only 27 participants treated with paclitaxel or docetaxel who received prior taxanes. No detrimental effect in patients with prior history of exposure to taxanes was observed. Conversely, the KM curve for the group with prior taxane exposure appears favorable to the group who did not have prior taxane exposure. The small sample size does not allow any further consideration.

The open-label design is justified on the basis of the different route and schedule of administration of drugs in the two arms, at least for irinotecan and paclitaxel. Due to the expected differences in the tolerability profile the efficacy of blindness might have been anyway questionable. In view of the risk of bias due to the open label-design, the assessment of response has been performed based on blinded independent central review (BICR). The open-label design has nevertheless impacted on the study conduction, which deserves further discussion even though OS is the primary endpoint. Indeed, 18 patients vs. 0 in the control arm and the experimental arm, respectively did not receive SOC, likely due

to the knowledge of the assigned treatment at randomization. It is also noted that discontinuations based on withdrawal by subject (19 vs. 9) and Physicians' Decision (7 vs. 2) were higher in the control arm. Conversely, discontinuations due to Progressive Disease (192 vs. 225) were higher in the experimental arm, although clinical progression was declared slightly more frequently in the control arm (33 vs. 25). A sensitivity OS analyses based on the ASaT population (i.e. all randomized subjects who received at least 1 dose of study treatment) in participants with PD-L1 CPS≥10 was provided. It is understood that only 1 patient out of the 18 patients who were allocated to the SOC arm but were discontinued before receiving treatment had PD-L1 CPS≥10. Since no patients in the experimental arm discontinued before receiving treatment, the result that median OS for pembrolizumab for the ASaT-CPS≥10 population was identical to the ITT-CPS≥10 population was expected. Differently, the median OS for control arm slightly increases, worsening the test significance. Furthermore, the MAH clarified that in about half of the cases of withdrawals before treatment initiation patients withdraw consent after learning about their treatment allocation; among the withdrawals after treatment start in the majority of the participants (18/26) withdrawing was reported "specifically due to SOC and its side effects and impacts on quality of life". By this it is difficult to judge to what extent the knowledge of treatment allocation might have been a driving factor. It is considered reassuring that less than half of subjects on SOC who withdrew consent had a PD-L1 CPS ≥10.

The primary objectives of the study were to compare the OS in all subjects, in participants with squamous cell carcinoma of the esophagus (ESCC), and in subjects with PD-L1 CPS ≥10 when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan. The comparison of PFS and ORR per RECIST 1.1 assessed by central vendor review in all subjects, in subjects with squamous cell carcinoma of the esophagus and subjects with PD-L1 CPS ≥10, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan, were secondary objectives. The choice of OS as primary objective is considered appropriate in this setting.

There are known ethnic differences in incidence, clinical practice, primary tumor location, and prognosis of oesophageal cancer related to geographical region (Asia vs. non-Asia) as also discussed in the EMA SA pertaining to the 1L oesophageal cancer study KN590. Study enrolment of KN181 was divided into two periods: global and China extension enrolment. Participants enrolled during the global enrolment period are the focus of this submission. Participants were stratified according to tumor histology (Squamous cell carcinoma vs. adenocarcinoma - Siewert type I adenocarcinoma of the EGJ) and geographic region: (Asia, including but not limited to China, Japan, Korea, Hong Kong, Taiwan, Malaysia, Thailand, Singapore vs. Rest of World, including but not limited to Europe/Israel/North America, Australia, South America). Stratification factors appear appropriate. Since one of the primary objective of the trial is to compare OS in a biomarker selected population, a stratification based on PD-L1 would have been appropriate.

In this regard, it is noted that the study was originally designed with a dual primary objective to compare PFS and OS, and in all subjects and in subjects with GEP intermediate or GEP high tumours. It's only with Protocol Amendment 04 (03 August 2017), after enrolment completion, that the KEYNOTE-181 protocol was amended to change the original GEP biomarker to PD-L1 and to include OS as a single primary endpoint. While the choice to use the PD-L1 assay, and the CPS≥10 cut-point, instead of GEP is deemed adequately justified based on the analyses conducted in Study KN-180, the fact the KEYNOTE-181 was started before these data were available has the consequence that PD-L1 was not used as a stratification factor in this study, which is a limitation of its design.

The expected median OS time in the control group was 8 months. Based on 473 OS events in All subjects, the trial has 92.6% power to demonstrate that pembrolizumab is superior to the control at a one-sided 0.8% alpha-level, if the underlying hazard ratio of OS is 0.7. In subjects with squamous cell carcinoma of the esophagus, with 310 OS events, the trial has 91.3% power to demonstrate that pembrolizumab

is superior to the control at a one-sided 0.8% alpha-level, if the underlying hazard ratio of OS is 0.65. In subjects with PD-L1 CPS≥10, with 213 OS events, the trial has 90.9% power to demonstrate that pembrolizumab is superior to the control at a one-sided 0.9% alpha-level, if the underlying hazard ratio of OS is 0.6. For the hypotheses in all subjects, the planned sample size in the Global Cohort was approximately 600. Among all subjects, it was expected that about 400 subjects with squamous cell carcinoma of the esophagus would have been enrolled. For the hypotheses in subjects with PD-L1 CPS≥10, the planned sample size was approximately 280 (based on an observed prevalence rate of ~47% from KN180). The sample size calculations result congruent with the assumptions made.

Efficacy analyses were conducted using the intention-to-treat (ITT) population. The statistical methods used for time to events and binary endpoints are considered overall adequate. One interim efficacy analysis for OS was planned in this study.

In Protocol Amendment 04 interim and final analysis timing were updated. Interim and final analyses timing were driven by number of OS events and minimum follow up time, whereas previously the timing of the analyses was based only on a fixed number of events to observe (with follow-up time subjected to change). The criterion was updated to wait for more mature OS data and account for a potential delayed separation in survival curves observed in immune-oncology studies. It is acceptable.

In Protocol Amendment #5 (08 March 2018): 1) The alpha spending function to control the Type-I error based on information fraction was replaced with one based on specified calendar time fraction (0.76) and 2) in the all subjects population, for testing the OS and PFS hypotheses, the "stratified log-rank test" was replaced with the "stratified maximum weighted log rank test" (max-combo test). The Company justified the first change stating that "accurately estimating number of events in ESCC subjects, in subjects with PD-L1 CPS≥10 and in all subjects is difficult due to potential delayed treatment effects that have been observed with immunotherapy". This is understood, also considering that the timing of the analyses were not only event driven but it was also based on a minimum follow up time (that is, the number of OS events observed at the final analysis was subjected to change). Nevertheless, based on the expected number of events reported in the decision guidance (Table 12 of the Protocol/Amendment No.05), the expected information fraction for the three population (ESCC, PD-L1 CPS≥10, and all subjects) would have been of about 81% (greater than 76%, defined with the updated calendar time criterion), likely leading to a less conservative final analysis.

Uncertainties regarding the interim analysis remain with respect to 1) the applicability of a maximum duration trial (vs. maximum information trial), 2) the theoretical foundation of the chosen approach, 3) the anti-conservative nature of the approach (at final analysis) compared to the event-based approach and an approach with calendar time only (i.e., without correlation matrix based on events) and with respect to the speed of accrual, and 4) the applied software.

Reason why different testing approaches are used among the three different primary hypotheses is not reported. The max-combo test is proposed to test OS in all subjects (with the aim to take into account the possible violation of proportionality assumption), whereas the hypotheses of treatment difference for OS curves in subjects with ESCC and OS in subjects with PD-L1 CPS≥10 were tested using the stratified log-rank test. The (un-weighted) stratified log-rank test for testing OS in all subjects was also proposed as sensitivity analysis. The max-combo test is based on Fleming-Harrington (FH) weighted log-rank statistics, enabling to handle a range of non-proportional hazard types with no need to pre-specify the type. The use in the primary analysis of the max-combo test is not a conservative approach and it is not supported: by putting more weights to the part of the survival curves that separate most, this test yields smaller nominal p-value than the un-weighted log-rank test. In this context it seems more appropriate to use the max-combo test as sensitivity analysis. Moreover, the use in the primary analysis of the max-combo test is misleading, considering the Applicant statement (reported in the sSAP, amendment #7) "the log-rank test as an alternative to the max combo test for the overall population

will also be evaluated, including applying the log-rank in the multiplicity scheme in the same fashion as if it were the primary testing method".. Furthermore, if PH does not hold, results from other measures beyond hazard ratio are expected. Stratification factors and p-values for both the maximum weighted log-rank test and the unweighted log-rank test were provided. It is understood that for testing OS in all subjects, the primary analysis was performed using the (un-weighted) stratified log-rank test. Differently, it had been understood that following the last protocol amendment this test was proposed as sensitivity analysis. As no indication for the all-comer population is currently sought, this issue is no further pursued.

A total of 800 participants were screened and 628 were randomly allocated from 08-DEC-2015 to 16-JUN-2017 across 154 global study sites in 32 countries. Screen failure was mostly due to not meeting specific eligibility criteria, the most frequent reason not being able to provide tissue for biomarker analysis.

Important protocol deviations were reported in a similar rate in the 2 groups (11.1% in both arms), and it is considered unlikely that they impacted on the results.

Most patients were enrolled outside EU, and 39.5% of the patients were of Asian race. Overall, there were no meaningful imbalances in patients' baseline characteristics among treatment arms in the overall population. ESCC were more frequently observed than EAC (63.9% vs. 36.1%). As mentioned above, PD-L1 CPS ≥10 was not used as stratification factor at randomization, nor it was applied to the stratified tests and model. The distribution of patients with PD-L1 CPS≥10 was overall balanced between the treatment arms (34.1 in pembro arm vs. 36.6 in SOC arm). However, when considering the PD-L1 CPS≥10 population, some imbalances (>5% difference) in baseline characteristics among the two treatment arms are noted (e.g. more ECOG 0, more ESCC histological subtype, more Asian race subjects in pembro vs. SOC arm; more subjects with prior adjuvant or neoadjuvant therapy, more subjects with prior Taxane therapy in SOC vs. pembro arm). Given the known prognostic relevance of histology and ECOG PS it cannot be excluded that the higher proportion of subjects with good PS and with SCC in the pembrolizumab arm compared to the SOC arm in the CPS ≥10 subpopulation might have exerted an impact on the efficacy results. A sensitivity analysis to account for the imbalances of the prognostic relevant parameters of ECOG PS and SCC between treatment arms in PD-L1 CPS ⩾10 participants reported OS HR of 0.71 (95% CI 0.53, 0.95) in favor of pembrolizumab, which alleviated the concern that the imbalances in these prognostic factors might have exerted a large impact on the OS outcome.

The MAH outlined that in KN180 and KN181 the prevalence of patients with PD-L1 CPS ≥10 was higher in ESCC relative to EAC. Since ESCC is substantially more prevalent in Asia relative to the rest of the world and PD-L1 expression is higher in ESCC compared to EAC on average, the higher proportion of ESCC and Asian participants in the PD-L1 CPS ≥10 subgroup compared to the overall study population is associated with and reflects global oesophageal cancer epidemiology and differential prevalence of PD-L1 expression by histology.

Efficacy data and additional analyses

Efficacy data in this submission are based on the final analysis with a database cut-off date of 15-OCT-2018, about 34 months after study start and about 16 months after the last participant was enrolled. Median follow-up was 7.1 months (range 0.5 to 31.3 months) in the pembrolizumab group and 6.9 months (range: 0.2 to 32.2 months) in the control group.

During the procedure, the MAH came forward and proactively informed the agency that 2 deaths occurred prior to database lock dates (IA and FA). Disposition was listed as death, but death dates were not entered in the appropriate field in the database and therefore, were censored to alive status at the IA

and FA. Subsequently, a revised CSR was submitted including updated analyses with these 2 death events. Thus, the updated revised CSR is considered to be the primary analysis for decision making. All the results reported in this assessment are therefore based on the revised data provided by the MAH. Contrary to the original submission, the revised OS analysis did not reach statistical significance in any of the pre-specified populations. Efficacy for secondary endpoints of PFS, ORR, and DOR were unchanged from the initial analysis.

The ITT population included 628 patients, 314 randomized to pembrolizumab, and 314 to SOC.

Primary endpoints

Superiority of pembrolizumab versus SOC with respect to OS was not demonstrated for ESCC participants, and for the all participants Further, for participants with PD-L1 CPS ≥10, the updated OS analysis including the 2 participants (only 1 with CPS≥10) who had died during the trial but inadvertently censored and not correctly accounted for in the original primary endpoint (OS) analysis, even though the median OS is unchanged (9.3 months [95% CI 6.6, 12.5] for pembrolizumab vs 6.7 months [95% CI 5.1, 8.2] for SOC), the results are no longer statistically significant (p-value 0.00855, boundary 0.00853), with an HR 0.70 [95%CI; 0.52, 0.94]. The fact that with 1 single additional OS event the study results lost the statistical significance in the PD-L1 CPS≥10 population highlights the lack of robustness of the results.

The K-M curves tend to separate early and diverge over time until around month 12, and then converge. OS rate at 12, 18 and 24 months is 42.1% (95% CI 32.6, 51.2) vs. 20.4% (95% CI 13.5, 28.3), 25.2% (95% CI 17.4, 33.7) vs. 10.6% (95% CI 5.8, 17.1), 15.2% (95% CI 8.2, 24.1) vs. 9.1% (95% CI 4.5, 15.6) in the experimental and control arm, respectively. The observed prevalence of PD-L1 CPS≥10 in subjects with esophageal carcinoma (35.4%) was quite lower than that assumed (47%, based on the KN180 study). This had an impact on the OS events occurred in the PD-L1 CPS≥10 population (190, versus the 213 expected) and, ultimately, on the HR minimum detectable that slightly drifts apart the null hypothesis. Anyway, OS test in the PD-L1 CPS≥10 group is performed when a high percentage of events have already been occurred among the PD-L1 CPS≥10 population involved in the trial (88 (82.2%) and 103 (89.6%) OS events occurred in the experimental and the control arm, respectively); that is, the analysis can be considered sufficiently mature.

The Applicant performed a post-hoc exploratory analysis to take into account the imbalances in baseline characteristics between the two arms in PD-L1 CPS≥10 population (indeed, CPS score was not used as stratification factor). A Cox model using 4 factors (ECOG PS, histology, geographic region of enrolling site, and prior adjuvant or neoadjuvant treatment) as covariates was applied and an HR slightly shifted towards the unity was obtained (0.73, 95% CI 0.55, 0.98). The treatment HR estimate slightly increases. Including in the multivariate model the same adjustment factors with Region categorized in EU vs. ex-EU, the treatment HR estimate essentially does not change. In both cases the p-values increase.

Secondary endpoints

The secondary hypotheses of PFS and ORR in all participants were not tested because pembrolizumab was not superior to SOC for OS in all participants. Nominal p-values, which are not adjusted for multiplicity, have been provided for descriptive purposes.

In participants with PD-L1 CPS ≥10, median PFS was slightly shorter for pembrolizumab (2.6 months; 95% CI 2.1, 4.1) compared to SOC (3.0 months; 95% CI 2.1, 3.7), with an HR of 0.73 (95% CI 0.54, 0.97). ORR was higher in subjects with PD-L1 CPS ≥10 treated with pembrolizumab 21.5% (95% CI 14.1, 30.5) compared to SOC 6.1% (95% CI 2.5, 12.1).

For participants with tumours expressing PD-L1 CPS ≥10, PRO outcomes were similar between intervention arms for all endpoints except the mean change from baseline to Week 9 in EQ-5D VAS score, which improved in the pembrolizumab arm (LS mean=0.73 points; 95% CI: -2.87, 4.33) and deteriorated in the SOC arm (LS mean=-4.84 points; 95% CI: -8.61, -1.08).

Subgroups: adenocarcinoma and EU population

Overall, OS subgroup analyses show results consistent with the primary analysis, although the benefit in the subgroup with EAC with 51 events observed out the 55 patients in the PD-L1 CPS ≥10 population is questionable (HR 0.93; 95% CI 0.52, 1.65). Median OS was even shorter in pembrolizumab treated patients (6.3 months, 95% CI 3.4, 9.3) compared to the SOC arm (6.9 months; 95% CI 3.7, 8.7). A similar finding is observed even when looking at the subgroup analysis in the overall population with an HR of 1.12 (95% CI 0.82, 1.25) in the EAC subgroup. Likewise, no solid benefit can be derived from the PFS data, given the PFS HR of 1.00 (95% CI 0.56, 1.79) and the shape of the KM curves, even though the MAH highlights a long-term PFS benefit based on numerically higher 12 months PFS rates for the pembrolizumab arm (13.6% vs 6.6% in the SOC arm). The ORR was higher among participants with EAC and PD-L1 CPS ≥10 in the pembrolizumab arm (18.2%) compared with SOC (3.0%); however the rate of PD was about threefold higher in the pembrolizumab arm (59.1% vs 21.2% in the SOC arm). The higher rate of PD and the lower disease control rate (31.8% vs. 54.5% for pembrolizumab vs SOC, respectively) are of concern considering the clinical relevance of a symptomatic esophageal cancer disease. The main issue with regards to the subgroup of PD-L1 CPS ≥10 EAC patients is the small sample size.

This finding is quite relevant taking into account that EAC represents the majority of esophageal cancer cases in high-income countries, including EU, with excess body weight and gastroesophageal reflux disease among the key risk factors. Furthermore, it is noted that in study KEYNOTE-061 (Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer: a randomised, open-label, controlled, phase 3 trial) pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-oesophageal junction cancer with PD-L1 CPS of 1 or higher (Shitara K, et al. Lancet Oncol 2018).

With regard to the subgroup of PD-L1 CPS ≥10 patients from EU, the small sample size (n=58) and the non-randomized comparison hampers a proper interpretation. As expected, a higher proportion in the EU (41.4%) had adenocarcinoma relative to the non-EU population (18.9%). A post-hoc analysis of the treatment effect in EU subpopulation of participants with PD-L1 CPS ≥10 showed OS HR for the participants enrolled in the EU was 0.98 (95% CI: 0.56, 1.72), compared with 0.60 (95% CI: 0.43, 0.85) in non-EU population. Median OS was even shorter in pembrolizumab treated patients (5.5 months, 95% CI 3.1, 9.6) compared to the SOC arm (8.7 months; 95% CI 3.9, 10.0). The pattern of the OS curves showed an increased risk of early death for subject treated with pembrolizumab compared to those treated with SOC. An exploratory multivariate Cox regression analysis for OS accounting for imbalances in both treatment arms even resulted in a worse OS HR of 1.17 (95% CI 0.59, 2.31). The HR for PFS was 1.03 (95% CI 0.58, 1.81), median PFS and 6 months PFS rate were unfavourable for pembrolizumab compared to SOC (median PFS 3.0 vs 3.5 months and 6 months PFS rate 29.6 vs 40.9%). Objective responses were reported in 5 patients (18.5%) in the pembrolizumab compared to 2 patients (6.5%) in the SOC arm; no data were provided for rates of disease stabilisation or PD. These finding reinforces the concerns on the applicability of the results of the trial to the EU population.

The MAH highlights that the better efficacy outcome in the larger subgroup of "White" (n=100) might be more representative (OS HR 0.80, 95% CI 0.53, 1.22). The subgroup of "White" mirrors the subgroup of "ex-Asia" with n= 107 and OS HR of 0.83 (95% CI 0.55, 1.25)

Pembrolizumab performs clearly superior to SOC in the Asia population. However, the superior treatment effect of pembrolizumab in Asia vs. ex-Asia appears not to be solely driven by the predominant SCC histology; OS data by region indicate superiority in Asian vs. ex-Asia population also within subjects with SCC, suggesting "Asia" being an independent predictive factor.

Subgroup analysis in ESCC subjects whose tumours express PD-L1 CPS ≥10:

In this subgroup, the observed treatment effect is apparently more pronounced than in the overall population of esophageal carcinoma with PD-L1 CPS ≥10: median OS was 10.3 months for the pembrolizumab group (n=85) and 6.7 months for the SOC group (n=82) (HR 0.64; 95% CI: 0.46, 0.90; nominal p=0.0042), the OS rate at 12 months was 47.1 versus 22.6, and at 18 months was 29.3 versus 12.5 in the pembrolizumab and SOC groups, respectively. Median PFS was 3.2 months for the pembrolizumab group and 2.3 months for the SOC group (HR 0.66; 95% CI: 0.48, 0.92; nominal p=0.007). The ORR by BICR was 22.4% (95% CI: 14.0, 32.7) for the pembrolizumab group and 7.3% (95% CI: 2.7, 15.2) for the SOC group (nominal p=0.0034). Baseline characteristics were generally similar between the two arms in the subgroup with a high rate of patients ≥ 65 years in the pembrolizumab arm (54.1 vs 47.6%) and a lower rate of subjects with ECOG PS1 (57.6 vs 65.8%).

Efficacy data for the participants with ESCC and PD-L1 CPS ≥10 reported as "white" (n=53) showed an OS HR of 0.75 (95% CI: 0.42, 1.32). Median OS was 6.7 months for both the pembrolizumab (n=26) and SOC (n=27) groups; 6 months OS rates were numerically slightly inferior for pembrolizumab (50%) compared to SOC (55.6%) suggesting possible initial crossing of OS curves (no KM curves were provided with the responses). Median PFS was 2.7 months for the pembrolizumab group and 3.0 months for the SOC group (HR 0.89; 95% CI: 0.50, 1.59). 6 months PFS rates were inferior for pembrolizumab (30.8% vs 43.7%). A benefit of pembrolizumab was shown in terms of higher OS rate at 12 and 18 months (30.8% vs 14.8% and 18.5% vs 7.4% in the pembrolizumab group and SOC groups, respectively) and in terms of favourable ORR rates (23.2% vs. 7.4% with 6 responders in the pembrolizumab arm compared to 2 responders in the SOC arm).

No firm conclusions can be drawn from these post-hoc exploratory analyses in 53 patients (i.e. from a subgroup of a combination of subgroups); however efficacy data from Ex-Asian ESCC and PD-L1 CPS ≥ 10 patients are less favorable compared to those from the overall ESCC and PD-L1 CPS ≥10 (e.g. median OS 10.3 vs. 6.7 months) suggesting a larger benefit of pembrolizumab for Asian also in the subgroup of ESCC and PD-L1 CPS ≥10.

Additional expert consultation

NA

Assessment of paediatric data on clinical efficacy

NA

2.4.1. Conclusions on the clinical efficacy

Primary analyses of Study KEYNOTE-181 failed to demonstrate statistically significant OS benefit in the predefined ESCC and all subjects populations and after correction of data entry errors also in the initially sought indication for subjects with CPS ⩾10.

With the 2nd response the MAH proposed a revised indication for ESCC subjects whose tumours express

PD-L1 CPS ⩾10. It is acknowledged that a clinically meaningful effect has been apparently observed in this newly defined subgroup (n=167), and that the results are supported by biological plausibility (a relationship between PD-L1 expression and clinical benefit has been generally observed for pembrolizumab across indications) and replication of findings from the Phase II study KEYNOTE-180. The unmet need is also acknowledged.

However, these data are not considered adequate to demonstrate a benefit for a European population. Efficacy results in KEYNOTE 181 are at least partly driven by a higher treatment effect of pembrolizumab in the Asian population independent from histology. 67.1% of the ESCC and PD-L1 CPS ⩾10 subgroup were Asian. Available data in ex-Asia (or "white" or EU) population (n=53) are clearly less favorable compared to those from the overall ESCC and PD-L1 CPS ⩾10. While the MAH argues that there are no biological or pharmacological reasons to believe that the treatment effect would be significantly different in the white population relative to non-white populations, this assumption is not adequately discussed. The MAH is therefore asked to address this issue based on the totality of available data.

It remains that the intrinsic limitation of subgroup analyses from a study that failed to demonstrate statistically significant OS benefit, moreover in a subgroup defined based on multiple factors, raises concerns, and an additional prospective study to establish formal proof of efficacy in this population should be performed, or otherwise the MAH should justify why such a study would be unfeasible.

2.5. Clinical safety

Introduction

The overall safety profile of pembrolizumab, evaluated across clinical studies in patients with different solid tumours, is mainly associated with immune-related adverse reactions, and characterised by general (fatigue, decreased appetite), gastrointestinal (nausea, diarrhoea, constipation), respiratory (cough, dyspnoea), and skin (pruritus and rash) disorders.

The safety evaluation filed to support the use of KEYTRUDA® (pembrolizumab) monotherapy use for the treatment of patients with recurrent locally advanced or metastatic esophageal cancer with disease progression on or after 1 line of prior systemic therapy is primarily based on the final analysis results of the pivotal, randomized, controlled, open-label Phase 3 study, KEYNOTE-181. This study compared safety data from subjects who received pembrolizumab monotherapy to that from participants who received SOC (investigator's choice of paclitaxel, docetaxel, or irinotecan).

As pooled datasets the Esophageal Safety Dataset for Pembrolizumab, representing the most comprehensive safety pooled dataset for pembrolizumab in esophageal cancer (for comparison of KN181 data with pembrolizumab use in the claimed indication), the Reference Safety Dataset for Pembrolizumab, including studies on pembrolizumab monotherapy for EU approved indications (for comparison of KN181 data with established safety profile for pembrolizumab across indications), and the Cumulative Running Safety Dataset for Pembrolizumab, obtained by integrating all pembrolizumab monotherapy studies together with esophageal cancer studies were included.

Descriptions of the datasets provided for safety evaluation are the following:

- KEYNOTE-181 Dataset: Study enrollment was divided into 2 periods: global enrollment followed by China extension enrollment. The focus of this submission is only on data from any participant randomized during the global enrollment period. Data cut-off date was 15-Oct-2018 of ASaT population randomization 1:1 between the following treatments:

- Pembrolizumab arm of participants who received at least 1 dose of pembrolizumab constitute the Indication Safety Dataset. (N=314)
- SOC arm of participants receiving at least one dose of investigator's choice of paclitaxel, docetaxel, or irinotecan (N=296)

- Esophageal Safety Dataset for Pembrolizumab (N=458): All participants with advanced/metastatic esophageal cancer from KEYNOTE-181 (2L), KEYNOTE-180 (2 or more prior lines of therapy), and KEYNOTE-028 Cohort A4 (any line of therapy) who received at least 1 dose of pembrolizumab constitute the Esophageal Safety Dataset. This dataset represents the most comprehensive safety pool for pembrolizumab in esophageal cancer.
  - KEYNOTE-180: ongoing single-arm, open-label, multi-center Phase 2 study of pembrolizumab as monotherapy in participants with advanced/metastatic esophageal cancer who have received 2 or more prior lines o standard systemic therapy (data cut-off date 30-JUL-2018).
  - KEYNOTE-028 Cohort A4: esophageal cancer participants (Cohort A4) of the ongoing Phase 1b, multi-center, single-arm, multicohort study (data cutoff date of 31-JAN-2018).1

- Reference Safety Dataset for Pembrolizumab (N=4439): The 4439 participants from the RSD consist of 1567 participants with advanced melanoma from studies KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, and 1232 participants with NSCLC from studies, KEYNOTE-001 and KEYNOTE-010 who received at least 1 dose of pembrolizumab. In addition, this dataset includes 1640 pembrolizumab-treated participants from KEYNOTE-012 Cohorts B and B2 (head and neck squamous cell cancer [HNSCC]), KEYNOTE-013 Cohort 3 (Hodgkin lymphoma), KEYNOTE-024 (NSCLC), KEYNOTE-040 (HNSCC), KEYNOTE-045 and KEYNOTE-052 (urothelial tract cancer), KEYNOTE-055 (HNSCC), and KEYNOTE-087 (Hodgkin lymphoma).

- Cumulative Running Safety Dataset for Pembrolizumab (N=6784): Participants from KEYNOTE-181 (pembrolizumab arm), the RSD, KEYNOTE-180 and KEYNOTE-028 Cohort A4 (esophageal cancer), and participants treated with pembrolizumab in KEYNOTE-012 Cohort C (urothelial tract cancer) and Cohort D (gastric cancer), KEYNOTE-013 Cohort 4A (PMBCL), KEYNOTE-017 (Merkel cell cancer), KEYNOTE-028 Cohort B4 (cervical cancer), KEYNOTE-042 (NSCLC), KEYNOTE-054 (melanoma), KEYNOTE-059 Cohort 1 (gastric cancer), KEYNOTE-158 Cohort E (cervical cancer), KEYNOTE-164 Cohort A (colorectal cancer), KEYNOTE-170 (PMBCL), and KEYNOTE-224 (hepatocellular cancer) constitute the Cumulative Running Safety Dataset.

Patient exposure

In KEYNOTE-181, participants were enrolled from 08-DEC-2015 to 16-JUN-2017. As of data cut-off date for the final analysis (15-OCT-2018), 314 participants received at least 1 dose of pembrolizumab and 296 at least one dose of SOC.

Table 10-2
Disposition of Subjects
(ITT Population)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	314		314		628	
Status For Trial						
Discontinued	272	(86.6)	289	(92.0)	561	(89.3)
Adverse Event	31	(9.9)	29	(9.2)	60	(9.6)
Death	236	(75.2)	242	(77.1)	478	(76.1)
Withdrawal By Subject	5	(1.6)	18	(5.7)	23	(3.7)
Trial Ongoing	42	(13.4)	25	(8.0)	67	(10.7)
Status For Study Medication In Trial Segment Treatment						
Started	314		296		610	
Completed	5	(1.6)	0	(0.0)	5	(0.8)
Discontinued	300	(95.5)	296	(100.0)	596	(97.7)
Adverse Event	39	(12.4)	44	(14.9)	83	(13.6)
Clinical Progression	25	(8.0)	33	(11.1)	58	(9.5)
Physician Decision	2	(0.6)	7	(2.4)	9	(1.5)
Progressive Disease	225	(71.7)	192	(64.9)	417	(68.4)
Protocol Violation	0	(0.0)	1	(0.3)	1	(0.2)
Withdrawal By Subject	9	(2.9)	19	(6.4)	28	(4.6)
Treatment Ongoing	9	(2.9)	0	(0.0)	9	(1.5)
Database Cutoff Date: 15OCT2018.						

Source: [P181V01MK3475: adam-adsl; adpm]

Table 10-6
Summary of Drug Exposure
(ASaT Population)

	Pembrolizumab 200 mg (N=314)	SOC (N=296)
Study Days on Therapy (days)		
Mean	122.4	94.8
Median	64	63
SD	152.50	90.98
Range	1 to 742	1 to 546
Database Cutoff Date: 15OCT2018.		

Source: [P181V01MK3475: adam-adsl; adexsum]

Table 10-7
Exposure by Duration
(ASaT Population)

	Pembrolizumab 200 mg (N=314)		SOC (N=296)	
	n	(%)	n	(%)
Duration of Exposure				
>0 m	314	(100.0)	296	(100.0)
≥ 1 m	243	(77.4)	230	(77.7)
≥ 3 m	122	(38.9)	118	(39.9)
≥ 6 m	57	(18.2)	41	(13.9)
≥ 12 m	21	(6.7)	7	(2.4)
Each subject is counted once on each applicable duration category row. Duration of exposure is the time from the first dose date to the last dose date. Database Cutoff Date: 15OCT2018.				

Source: [P181V01MK3475: adam-adsl; adexsum]

Table 5.3.5.3.3-esophageal2: 1
Summary of Drug Exposure
(ASaT Population)

	KN181 Data for Pembrolizumab‖ (N=314)	Esophageal Dataset for Pembrolizumab†† (N=458)	Reference Safety Dataset for Pembrolizumab¶ (N=4439)	Cumulative Running Safety Dataset for Pembrolizumab‡‡ (N=6784)
Study Days On-Therapy (Months)				
Mean	4.0	4.1	6.4	6.6
Median	2	2	4	4
SD	5.01	5.27	6.08	6.18
Range	0 to 24	0 to 24	0 to 30	0 to 32
Number of Administrations				
Mean	6.5	6.8	10.7	10.7
Median	4	4	7	7
SD	6.93	7.92	9.56	9.47
Range	1 to 35	1 to 51	1 to 59	1 to 59

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adexsum]

Table 5.3.5.3.3-esophageal2: 2
Drug Exposure by Duration
(ASaT Population)

	KN181 Data for Pembrolizumab‖ (N=314)			Esophageal Dataset for Pembrolizumab†† (N=458)			Reference Safety Dataset for Pembrolizumab¶ (N=4439)			Cumulative Running Safety Dataset for Pembrolizumab‡‡ (N=6784)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Study Days On-Therapy												
>0 m	314	(100.0)	(105.2)	458	(100.0)	(157.9)	4,439	(100.0)	(2,385.6)	6,784	(100.0)	(3,706.8)
>=1 m	243	(77.4)	(102.4)	349	(76.2)	(154.0)	3,747	(84.4)	(2,362.6)	5,712	(84.2)	(3,670.7)
>=3 m	122	(38.9)	(83.9)	182	(39.7)	(128.5)	2,608	(58.8)	(2,173.2)	3,996	(58.9)	(3,388.6)
>=6m	57	(18.2)	(59.9)	83	(18.1)	(92.6)	1,816	(40.9)	(1,885.9)	2,812	(41.5)	(2,959.0)
>=12m	21	(6.7)	(34.9)	39	(8.5)	(62.0)	851	(19.2)	(1,189.9)	1,247	(18.4)	(1,770.9)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adexsum]

Demographic and Other Characteristics

In KN-181 demographics and disease characteristics were well balanced between study arms and 61.3% of participants were enrolled at sites from outside of the Asia region. Overall, participants were male gender in 86.6%, ≥65 years of age in 43.3%, White and Asian race in 56.1% and 29.5%, respectively. With regards to disease characteristics, ECOG PS of 1 was recorded in 61.1% (Pembrolizumab 59.6% vs SOC 62.7%), locally advanced disease was found in 8.3% (Pembrolizumab 7.6% vs SOC 8.9%), M1 was documented in 91.7% of cases. Prior adjuvant therapy or neoadjuvant therapy had been administered to 10.2% of subjects, and 97.6% (Pembrolizumab 96.5% vs SOC 98.7%) had received a first line of treatment (98.9% platinum, 84.9% fluoropyrimidine, 33.4% taxane therapy).

Compared with the RSD, KEYNOTE-181 (pembrolizumab arm) had a higher proportion of male participants (86.9% in KEYNOTE-181 vs 64.6% in the RSD), a higher proportion of participants with ECOG PS 1 (59.6% vs 51.4%), a higher proportion of Asian participants (40.1% vs 9.3%, respectively), and a lower proportion of White/Caucasian participants (57.0% vs 86.3%). These findings are consistent with the known epidemiology of esophageal cancer.

Esophagus: Age standardized rates by sex (2018) Western Europe: 6.8 m 1.7 w (per 100000) Eastern Asia 17.9 m 6.8 w (per 100000).

Table 5.3.5.3.3-esophageal2: 3
Subject Characteristics
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
Gender								
Male	273	(86.9)	392	(85.6)	2,869	(64.6)	4,465	(65.8)
Female	41	(13.1)	66	(14.4)	1,570	(35.4)	2,319	(34.2)
Age (Years)								
<65	175	(55.7)	242	(52.8)	2,453	(55.3)	3,893	(57.4)
>=65	139	(44.3)	216	(47.2)	1,986	(44.7)	2,891	(42.6)
Mean	62.6		62.8		61.1		60.4	
SD	9.4		9.9		13.5		13.4	
Median	63.0		64.0		63.0		62.0	
Range	23 to 84		23 to 87		15 to 94		15 to 94	
Race								
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	14	(0.3)	26	(0.4)
Asian	126	(40.1)	180	(39.3)	411	(9.3)	890	(13.1)
Black Or African American	3	(1.0)	6	(1.3)	94	(2.1)	123	(1.8)
Multiracial	2	(0.6)	2	(0.4)	24	(0.5)	60	(0.9)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	4	(0.1)	6	(0.1)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
White	179	(57.0)	257	(56.1)	3,829	(86.3)	5,066	(74.7)
Missing	4	(1.3)	13	(2.8)	63	(1.4)	609	(9.0)
Ethnicity								
Hispanic Or Latino	19	(6.1)	24	(5.2)	222	(5.0)	398	(5.9)
Not Hispanic Or Latino	288	(91.7)	413	(90.2)	3,952	(89.0)	5,516	(81.3)
Not Reported	4	(1.3)	14	(3.1)	151	(3.4)	209	(3.1)
Unknown	3	(1.0)	4	(0.9)	109	(2.5)	137	(2.0)
Missing	0	(0.0)	3	(0.7)	5	(0.1)	524	(7.7)
Age Class (Years)								
<65	175	(55.7)	242	(52.8)	2,453	(55.3)	3,893	(57.4)
65-74	107	(34.1)	166	(36.2)	1,333	(30.0)	2,023	(29.8)
75-84	32	(10.2)	49	(10.7)	563	(12.7)	762	(11.2)
>=85	0	(0.0)	1	(0.2)	90	(2.0)	106	(1.6)
ECOG Performance Scale								
[0] Normal Activity	126	(40.1)	178	(38.9)	1,987	(44.8)	3,143	(46.3)
[1] Symptoms, but ambulatory	187	(59.6)	279	(60.9)	2,280	(51.4)	3,446	(50.8)
Other/Missing	1	(0.3)	1	(0.2)	172	(3.9)	195	(2.9)
Geographic Region								
US	37	(11.8)	87	(19.0)	1,911	(43.1)	2,294	(33.8)
Ex-US	277	(88.2)	371	(81.0)	2,528	(56.9)	4,490	(66.2)

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)

Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)

Database Cutoff Date for HCC (KN224: 15MAY2018)

Database Cutoff Date for MCC (KN017: 06FEB2018)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl]

Adverse events

In KN-181 MedDRA version 21.0 was used in the generation of the following AE data. The ASaT population, which included all randomized participants who received at least one dose of study intervention, was used for the safety analyses.

Overall and exposure-adjusted Adverse Events

Adverse Events (AEs)

Table 12-1
Adverse Event Summary
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	300	(95.5)	288	(97.3)
with no adverse event	14	(4.5)	8	(2.7)
with drug-related† adverse events	202	(64.3)	255	(86.1)
with toxicity grade 3-5 adverse events	170	(54.1)	183	(61.8)
with toxicity grade 3-5 drug-related adverse events	57	(18.2)	121	(40.9)
with serious adverse events	124	(39.5)	121	(40.9)
with serious drug-related adverse events	40	(12.7)	57	(19.3)
who died	30	(9.6)	32	(10.8)
who died due to a drug-related adverse event	5	(1.6)	5	(1.7)
discontinued drug due to an adverse event	40	(12.7)	42	(14.2)
discontinued drug due to a drug-related adverse event	19	(6.1)	19	(6.4)
discontinued drug due to a serious adverse event	35	(11.1)	30	(10.1)
discontinued drug due to a serious drug-related adverse event	15	(4.8)	10	(3.4)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
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: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 4
Adverse Event Summary
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	300	(95.5)	437	(95.4)	4,313	(97.2)	6,554	(96.6)
with no adverse event	14	(4.5)	21	(4.6)	126	(2.8)	230	(3.4)
with drug-related† adverse events	202	(64.3)	281	(61.4)	3,140	(70.7)	4,704	(69.3)
with toxicity grade 3-5 adverse events	170	(54.1)	245	(53.5)	2,153	(48.5)	3,302	(48.7)
with toxicity grade 3-5 drug-related adverse events	57	(18.2)	80	(17.5)	660	(14.9)	1,068	(15.7)
with serious adverse events	124	(39.5)	180	(39.3)	1,728	(38.9)	2,608	(38.4)
with serious drug-related adverse events	40	(12.7)	56	(12.2)	464	(10.5)	756	(11.1)
who died	30	(9.6)	39	(8.5)	211	(4.8)	365	(5.4)
who died due to a drug-related adverse event	5	(1.6)	6	(1.3)	22	(0.5)	46	(0.7)
discontinued drug due to an adverse event	40	(12.7)	55	(12.0)	538	(12.1)	863	(12.7)
discontinued drug due to a drug-related adverse event	19	(6.1)	27	(5.9)	259	(5.8)	435	(6.4)
discontinued drug due to a serious adverse event	35	(11.1)	44	(9.6)	407	(9.2)	641	(9.4)
discontinued drug due to a serious drug-related adverse event	15	(4.8)	18	(3.9)	172	(3.9)	272	(4.0)

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)

Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)

Database Cutoff Date for HCC (KN224: 15MAY2018)

Database Cutoff Date for MCC (KN017: 06FEB2018)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 5
Exposure-Adjusted Adverse Event Summary
(Including Multiple Occurrences of Events)
(ASaT Population)

	Event Count and Rate (Events/100 person-years)†			
	KN181 Data for Pembrolizumab‖	Esophageal Dataset for Pembrolizumab††	Reference Safety Dataset for Pembrolizumab¶	Cumulative Running Safety Dataset for Pembrolizumab‡‡
Number of subjects exposed	314	458	4439	6784
Total exposure‡ in person-years	130.45	195.04	2696.19	4196.33
Total events (rate)				
adverse events	2317 (1776.11)	3421 (1753.98)	47888 (1776.13)	68286 (1627.28)
drug-related§ adverse events	587 (449.97)	795 (407.61)	14561 (540.06)	21003 (500.51)
toxicity grade 3-5 adverse events	368 (282.09)	571 (292.76)	4785 (177.47)	7296 (173.87)
toxicity grade 3-5 drug-related adverse events	78 (59.79)	116 (59.47)	982 (36.42)	1613 (38.44)
serious adverse events	204 (156.38)	294 (150.74)	3169 (117.54)	4704 (112.10)
serious drug-related adverse events	48 (36.79)	68 (34.86)	627 (23.26)	1048 (24.97)
adverse events leading to death	30 (23.00)	39 (20.00)	218 (8.09)	374 (8.91)
drug-related adverse events leading to death	5 (3.83)	6 (3.08)	22 (0.82)	46 (1.10)
adverse events resulting in drug discontinuation	40 (30.66)	55 (28.20)	584 (21.66)	936 (22.31)
drug-related adverse events resulting in drug discontinuation	19 (14.56)	27 (13.84)	281 (10.42)	473 (11.27)
serious adverse events resulting in drug discontinuation	35 (26.83)	44 (22.56)	432 (16.02)	677 (16.13)
serious drug-related adverse events resulting in drug discontinuation	15 (11.50)	18 (9.23)	181 (6.71)	286 (6.82)

† 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.
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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

All AEs

Subjects with at least one AE were 95.5% in the pembrolizumab arm and 97.3% in the control arm. With regards to SOCs, all categories presented with similar frequencies among the two study arms being differences between treatment groups within 2% of incidence. Only *Psychiatric disorders* slightly less often were found among subjects receiving pembrolizumab monotherapy when compared to SOC (12.7% vs 14.8%, respectively). PTs leading to this difference were *Anxiety* (3.8% vs 4.6%, respectively) and *Depression* PTs (1.0% vs 1.5%, respectively).

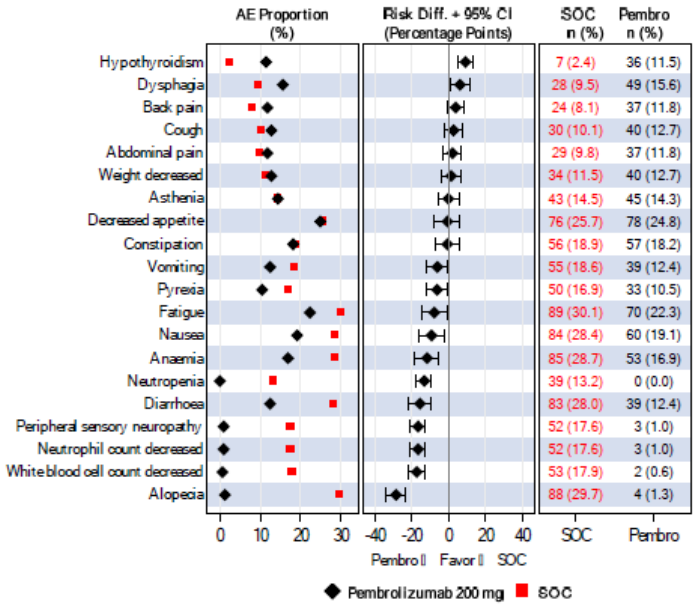
Table 2.7.4-esophageal2: 9
Subjects With Adverse Events By Decreasing Incidence
(Incidence ≥10% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	300	(95.5)	288	(97.3)
with no adverse events	14	(4.5)	8	(2.7)
Decreased appetite	78	(24.8)	76	(25.7)
Fatigue	70	(22.3)	89	(30.1)
Nausea	60	(19.1)	84	(28.4)
Constipation	57	(18.2)	56	(18.9)
Anaemia	53	(16.9)	85	(28.7)
Dysphagia	49	(15.6)	28	(9.5)
Asthenia	45	(14.3)	43	(14.5)
Cough	40	(12.7)	30	(10.1)
Weight decreased	40	(12.7)	34	(11.5)
Diarrhoea	39	(12.4)	83	(28.0)
Vomiting	39	(12.4)	55	(18.6)
Abdominal pain	37	(11.8)	29	(9.8)
Back pain	37	(11.8)	24	(8.1)
Hypothyroidism	36	(11.5)	7	(2.4)
Pyrexia	33	(10.5)	50	(16.9)
Alopecia	4	(1.3)	88	(29.7)
Neutrophil count decreased	3	(1.0)	52	(17.6)
Peripheral sensory neuropathy	3	(1.0)	52	(17.6)
White blood cell count decreased	2	(0.6)	53	(17.9)
Neutropenia	0	(0.0)	39	(13.2)

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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Figure 12-1
Between-treatment Comparison in Adverse Events
Selected Adverse Events (>= 10% Incidence) and Sorted by Risk Difference
(ASaT Population)
Pembrolizumab 200 mg (N=314) vs. SOC (N=296)



Database Cutoff Date: 15OCT2018.
Source: [P181V01MK3475: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 6
Subjects With Adverse Events
(Incidence ≥ 10% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab†		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	300	(95.5)	437	(95.4)	4,313	(97.2)	6,554	(96.6)
with no adverse events	14	(4.5)	21	(4.6)	126	(2.8)	230	(3.4)
Decreased appetite	78	(24.8)	109	(23.8)	927	(20.9)	1,343	(19.8)
Fatigue	70	(22.3)	110	(24.0)	1,518	(34.2)	2,126	(31.3)
Nausea	60	(19.1)	87	(19.0)	987	(22.2)	1,398	(20.6)
Constipation	57	(18.2)	85	(18.6)	814	(18.3)	1,148	(16.9)
Anaemia	53	(16.9)	77	(16.8)	649	(14.6)	987	(14.5)
Dysphagia	49	(15.6)	60	(13.1)	137	(3.1)	254	(3.7)
Asthenia	45	(14.3)	55	(12.0)	518	(11.7)	785	(11.6)
Cough	40	(12.7)	65	(14.2)	908	(20.5)	1,268	(18.7)
Weight decreased	40	(12.7)	49	(10.7)	392	(8.8)	630	(9.3)
Diarrhoea	39	(12.4)	61	(13.3)	925	(20.8)	1,336	(19.7)
Vomiting	39	(12.4)	61	(13.3)	596	(13.4)	860	(12.7)
Abdominal pain	37	(11.8)	48	(10.5)	411	(9.3)	654	(9.6)
Back pain	37	(11.8)	50	(10.9)	530	(11.9)	751	(11.1)
Hypothyroidism	36	(11.5)	49	(10.7)	439	(9.9)	702	(10.3)
Pyrexia	33	(10.5)	45	(9.8)	602	(13.6)	851	(12.5)
Dyspnoea	31	(9.9)	48	(10.5)	785	(17.7)	1,086	(16.0)
Pruritus	23	(7.3)	38	(8.3)	819	(18.5)	1,112	(16.4)
Rash	20	(6.4)	32	(7.0)	712	(16.0)	952	(14.0)
Arthralgia	19	(6.1)	24	(5.2)	692	(15.6)	928	(13.7)

Headache	15	(4.8)	23	(5.0)	527	(11.9)	748	(11.0)

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 following the last dose and serious adverse events up to 90 days following the 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 in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)

Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)

Database Cutoff Date for HCC (KN224: 15MAY2018)

Database Cutoff Date for MCC (KN017: 06FEB2018)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 8
Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	300	(95.5)	437	(95.4)	4,313	(97.2)	6,554	(96.6)
Grade 1	34	(10.8)	58	(12.7)	604	(13.6)	881	(13.0)
Grade 2	96	(30.6)	134	(29.3)	1,556	(35.1)	2,371	(34.9)
Grade 3	117	(37.3)	174	(38.0)	1,677	(37.8)	2,548	(37.6)
Grade 4	23	(7.3)	32	(7.0)	266	(6.0)	390	(5.7)
Grade 5	30	(9.6)	39	(8.5)	210	(4.7)	364	(5.4)
with no adverse events	14	(4.5)	21	(4.6)	126	(2.8)	230	(3.4)

Grade 3-5 AEs

Table 14.3-10
Subjects With Grade 3-5 Adverse Events By Decreasing Incidence
(Incidence ≥5% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	170	(54.1)	183	(61.8)
with no adverse events	144	(45.9)	113	(38.2)
Anaemia	19	(6.1)	31	(10.5)
Pneumonia	14	(4.5)	19	(6.4)
Neutrophil count decreased	2	(0.6)	30	(10.1)
Febrile neutropenia	1	(0.3)	26	(8.8)
White blood cell count decreased	1	(0.3)	31	(10.5)
Neutropenia	0	(0.0)	26	(8.8)

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.
Grades are based on NCI CTCAE v4.0.
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: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 15
Subjects With Grade 3-5 Adverse Events
(Incidence ≥ 1% in One or More Treatment Groups)
By Body System or Organ Class and Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab†		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	170	(54.1)	245	(53.5)	2,153	(48.5)	3,302	(48.7)
with no adverse events	144	(45.9)	213	(46.5)	2,286	(51.5)	3,482	(51.3)
Blood and lymphatic system disorders	**23**	**(7.3)**	**37**	**(8.1)**	**257**	**(5.8)**	**407**	**(6.0)**
Anaemia	19	(6.1)	31	(6.8)	202	(4.6)	315	(4.6)
Cardiac disorders	**5**	**(1.6)**	**8**	**(1.7)**	**124**	**(2.8)**	**189**	**(2.8)**
Endocrine disorders	**3**	**(1.0)**	**7**	**(1.5)**	**48**	**(1.1)**	**73**	**(1.1)**
Eye disorders	**3**	**(1.0)**	**3**	**(0.7)**	**24**	**(0.5)**	**33**	**(0.5)**
Gastrointestinal disorders	**54**	**(17.2)**	**73**	**(15.9)**	**369**	**(8.3)**	**616**	**(9.1)**
Abdominal pain	6	(1.9)	7	(1.5)	41	(0.9)	69	(1.0)
Abdominal pain upper	3	(1.0)	3	(0.7)	6	(0.1)	15	(0.2)
Colitis	3	(1.0)	4	(0.9)	49	(1.1)	69	(1.0)
Constipation	3	(1.0)	4	(0.9)	22	(0.5)	32	(0.5)
Diarrhoea	3	(1.0)	4	(0.9)	65	(1.5)	87	(1.3)
Dysphagia	15	(4.8)	20	(4.4)	23	(0.5)	56	(0.8)
Nausea	3	(1.0)	5	(1.1)	45	(1.0)	62	(0.9)
Oesophageal haemorrhage	5	(1.6)	5	(1.1)	0	(0.0)	5	(0.1)
Oesophageal obstruction	4	(1.3)	5	(1.1)	1	(0.0)	6	(0.1)
Oesophageal stenosis	3	(1.0)	4	(0.9)	2	(0.0)	7	(0.1)
Vomiting	5	(1.6)	6	(1.3)	38	(0.9)	58	(0.9)
General disorders and administration site conditions	**22**	**(7.0)**	**35**	**(7.6)**	**337**	**(7.6)**	**502**	**(7.4)**
Asthenia	8	(2.5)	10	(2.2)	46	(1.0)	81	(1.2)
Death	5	(1.6)	5	(1.1)	30	(0.7)	51	(0.8)
Fatigue	5	(1.6)	9	(2.0)	118	(2.7)	173	(2.6)
Hepatobiliary disorders	**12**	**(3.8)**	**15**	**(3.3)**	**61**	**(1.4)**	**124**	**(1.8)**
Autoimmune hepatitis	6	(1.9)	6	(1.3)	10	(0.2)	22	(0.3)
Infections and infestations	**38**	**(12.1)**	**56**	**(12.2)**	**482**	**(10.9)**	**702**	**(10.3)**
Pneumonia	14	(4.5)	27	(5.9)	146	(3.3)	229	(3.4)
Respiratory tract infection	3	(1.0)	3	(0.7)	13	(0.3)	17	(0.3)
Sepsis	3	(1.0)	5	(1.1)	31	(0.7)	53	(0.8)
Urinary tract infection	3	(1.0)	4	(0.9)	70	(1.6)	86	(1.3)

Injury, poisoning and procedural complications	**8**	**(2.5)**	**9**	**(2.0)**	**84**	**(1.9)**	**109**	**(1.6)**
Investigations	**30**	**(9.6)**	**45**	**(9.8)**	**253**	**(5.7)**	**461**	**(6.8)**
Alanine aminotransferase increased	3	(1.0)	8	(1.7)	41	(0.9)	86	(1.3)
Aspartate aminotransferase increased	5	(1.6)	8	(1.7)	52	(1.2)	109	(1.6)
Blood alkaline phosphatase increased	5	(1.6)	7	(1.5)	38	(0.9)	74	(1.1)
Blood bilirubin increased	2	(0.6)	6	(1.3)	21	(0.5)	41	(0.6)
Lymphocyte count decreased	5	(1.6)	8	(1.7)	27	(0.6)	45	(0.7)
Weight decreased	6	(1.9)	6	(1.3)	17	(0.4)	31	(0.5)
Metabolism and nutrition disorders	**35**	**(11.1)**	**58**	**(12.7)**	**443**	**(10.0)**	**650**	**(9.6)**
Decreased appetite	9	(2.9)	15	(3.3)	57	(1.3)	90	(1.3)
Dehydration	4	(1.3)	7	(1.5)	57	(1.3)	83	(1.2)
Hypercalcaemia	5	(1.6)	6	(1.3)	41	(0.9)	59	(0.9)
Hyperglycaemia	3	(1.0)	5	(1.1)	52	(1.2)	76	(1.1)
Hypoglycaemia	3	(1.0)	3	(0.7)	10	(0.2)	18	(0.3)
Hypokalaemia	1	(0.3)	4	(0.9)	49	(1.1)	65	(1.0)
Hyponatraemia	8	(2.5)	11	(2.4)	117	(2.6)	168	(2.5)
Musculoskeletal and connective tissue disorders	**11**	**(3.5)**	**18**	**(3.9)**	**209**	**(4.7)**	**284**	**(4.2)**
Back pain	5	(1.6)	9	(2.0)	58	(1.3)	81	(1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**(1.3)**	**6**	**(1.3)**	**139**	**(3.1)**	**194**	**(2.9)**
Nervous system disorders	**14**	**(4.5)**	**19**	**(4.1)**	**162**	**(3.6)**	**228**	**(3.4)**
Syncope	3	(1.0)	4	(0.9)	28	(0.6)	40	(0.6)
Product issues	**3**	**(1.0)**	**3**	**(0.7)**	**10**	**(0.2)**	**13**	**(0.2)**
Psychiatric disorders	**4**	**(1.3)**	**8**	**(1.7)**	**43**	**(1.0)**	**63**	**(0.9)**
Renal and urinary disorders	**2**	**(0.6)**	**7**	**(1.5)**	**111**	**(2.5)**	**149**	**(2.2)**
Acute kidney injury	2	(0.6)	6	(1.3)	42	(0.9)	60	(0.9)
Respiratory, thoracic and mediastinal disorders	**32**	**(10.2)**	**47**	**(10.3)**	**401**	**(9.0)**	**604**	**(8.9)**
Dyspnoea	4	(1.3)	5	(1.1)	110	(2.5)	152	(2.2)
Respiratory, thoracic and mediastinal disorders	**32**	**(10.2)**	**47**	**(10.3)**	**401**	**(9.0)**	**604**	**(8.9)**
Pleural effusion	2	(0.6)	3	(0.7)	54	(1.2)	83	(1.2)
Pneumonia aspiration	10	(3.2)	16	(3.5)	25	(0.6)	46	(0.7)
Pneumonitis	3	(1.0)	6	(1.3)	56	(1.3)	90	(1.3)
Pulmonary embolism	7	(2.2)	9	(2.0)	67	(1.5)	109	(1.6)
Skin and subcutaneous tissue disorders	**3**	**(1.0)**	**4**	**(0.9)**	**78**	**(1.8)**	**117**	**(1.7)**
Vascular disorders	**5**	**(1.6)**	**9**	**(2.0)**	**145**	**(3.3)**	**232**	**(3.4)**
Hypertension	3	(1.0)	3	(0.7)	55	(1.2)	105	(1.5)

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

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Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the 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 in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)

Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)

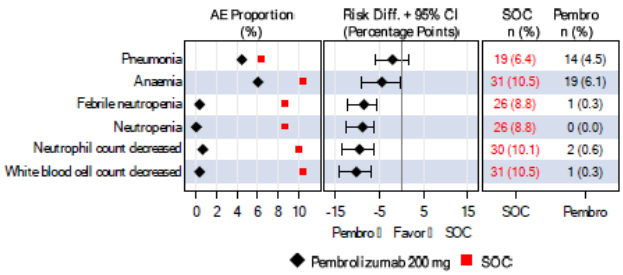
Database Cutoff Date for HCC (KN224: 15MAY2018)

Database Cutoff Date for MCC (KN017: 06FEB2018)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Figure 12-2
Between-treatment Comparison in Grade 3-5 Adverse Events
Selected Adverse Events (>= 5% Incidence) and Sorted by Risk Difference
(ASaT Population)
Pembrolizumab 200 mg (N=314) vs. SOC (N=296)



Database Cutoff Date: 15OCT2018.
Source: [P181V01MK3475: adam-adsl; adae]

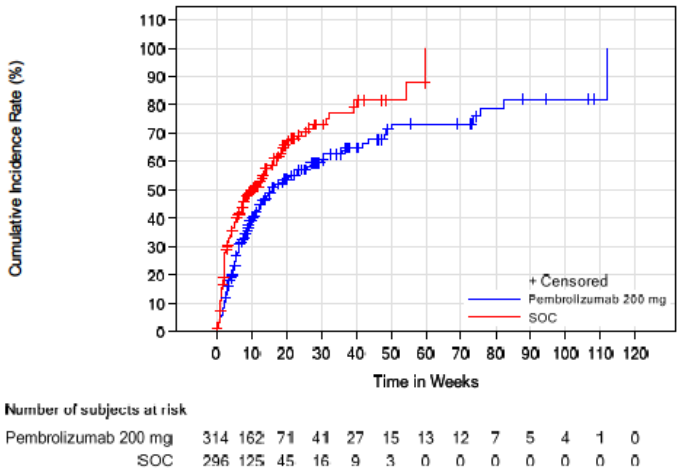
Table 14.3-12
Analysis of Time to First Grade 3, 4 or 5 Adverse Event
(ASaT Population)

Treatment	N	Number of Events (%)	Person-Weeks	Event Rate/ 100 Person-Weeks (%)	Median Time † (Weeks) (95% CI)	Pembrolizumab 200 mg vs. SOC	
						Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab 200 mg	314	170 (54.1)	4970.9	3.4	16.0 (12.1, 22.9)	0.67 (0.54, 0.83)	<0.001
SOC	296	183 (61.8)	3066.3	6.0	10.3 (7.4, 13.9)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate.
‡‡ One-sided p-value based on log-rank test.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adttae]

Figure 14.3-5
Kaplan-Meier Plot of Time to First Grade 3, 4 or 5 Adverse Event
(ASaT Population)



Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first Grade 3-5 adverse event. For subjects without a Grade 3-5 AE, the time to first Grade 3-5 AE is censored at 30 days of last dose.

Source: [P181V01MK3475: adam-adsl; adtte]

Drug-related AEs

Table 14.3-6
Subjects With Drug-related Adverse Events By Decreasing Incidence
(Incidence ≥5% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more drug related adverse events	202	(64.3)	255	(86.1)
with no drug related adverse events	112	(35.7)	41	(13.9)
Fatigue	37	(11.8)	61	(20.6)
Hypothyroidism	33	(10.5)	1	(0.3)
Decreased appetite	27	(8.6)	46	(15.5)
Asthenia	22	(7.0)	34	(11.5)
Nausea	22	(7.0)	64	(21.6)
Diarrhoea	17	(5.4)	60	(20.3)
Pyrexia	14	(4.5)	24	(8.1)
Rash	13	(4.1)	17	(5.7)
Malaise	10	(3.2)	18	(6.1)
Vomiting	10	(3.2)	33	(11.1)
Anaemia	8	(2.5)	66	(22.3)
Stomatitis	4	(1.3)	22	(7.4)
Dysgeusia	3	(1.0)	15	(5.1)
Myalgia	3	(1.0)	21	(7.1)
Alopecia	2	(0.6)	86	(29.1)
Neuropathy peripheral	2	(0.6)	23	(7.8)
Neutrophil count decreased	2	(0.6)	50	(16.9)
Peripheral sensory neuropathy	1	(0.3)	50	(16.9)
White blood cell count decreased	1	(0.3)	49	(16.6)
Febrile neutropenia	0	(0.0)	25	(8.4)
Neutropenia	0	(0.0)	34	(11.5)

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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Among drug-related AEs SOCs, incidence of *General disorders and administration site conditions* was the only category to be found a little more often in the pembrolizumab monotherapy arm when compared to SOC arm (25.8% vs 22.3%, respectively). All other SOC categories were as frequent among the two KN-181 study arms.

Table 14.3-8
Subjects With Drug-related Adverse Events by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more drug-related adverse events	202	(64.3)	255	(86.1)
Grade 1	61	(19.4)	38	(12.8)
Grade 2	84	(26.8)	96	(32.4)
Grade 3	46	(14.6)	82	(27.7)
Grade 4	6	(1.9)	34	(11.5)
Grade 5	5	(1.6)	5	(1.7)
with no drug-related adverse events	112	(35.7)	41	(13.9)

Table 5.3.5.3.3-esophageal2: 9
Subjects With Drug-Related Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	202	(64.3)	281	(61.4)	3,140	(70.7)	4,704	(69.3)
with no adverse events	112	(35.7)	177	(38.6)	1,299	(29.3)	2,080	(30.7)
Fatigue	37	(11.8)	50	(10.9)	929	(20.9)	1,304	(19.2)
Hypothyroidism	33	(10.5)	42	(9.2)	378	(8.5)	614	(9.1)
Decreased appetite	27	(8.6)	32	(7.0)	377	(8.5)	523	(7.7)
Asthenia	22	(7.0)	26	(5.7)	279	(6.3)	414	(6.1)
Nausea	22	(7.0)	25	(5.5)	430	(9.7)	598	(8.8)
Diarrhoea	17	(5.4)	24	(5.2)	480	(10.8)	689	(10.2)
Pruritus	14	(4.5)	23	(5.0)	644	(14.5)	863	(12.7)
Rash	13	(4.1)	24	(5.2)	531	(12.0)	703	(10.4)
Arthralgia	7	(2.2)	10	(2.2)	349	(7.9)	484	(7.1)

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 following the last dose and serious adverse events up to 90 days following the last dose are included.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Source: [ISS: adam-adsl; adae]

The Applicant also provided incidences of drug –related adverse events by SOC with adjustment by exposure as requested. No new safety concerns were identified in these analyses.

Drug-related Grade 3 to 5 Adverse Events

Table 14.3-14
Subjects With Drug-related Grade 3-5 Adverse Events By Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	57	(18.2)	121	(40.9)
with no adverse events	257	(81.8)	175	(59.1)
Autoimmune hepatitis	5	(1.6)	0	(0.0)
Anaemia	4	(1.3)	23	(7.8)
Asthenia	4	(1.3)	3	(1.0)
Colitis	3	(1.0)	0	(0.0)
Pneumonia	3	(1.0)	7	(2.4)
Pneumonitis	3	(1.0)	0	(0.0)
Acute kidney injury	2	(0.6)	0	(0.0)
Decreased appetite	2	(0.6)	3	(1.0)
Diarrhoea	2	(0.6)	9	(3.0)
Dysphagia	2	(0.6)	0	(0.0)
Fatigue	2	(0.6)	1	(0.3)
Hyperglycaemia	2	(0.6)	0	(0.0)
Hyponatraemia	2	(0.6)	6	(2.0)
Alanine aminotransferase increased	1	(0.3)	0	(0.0)
Anastomotic fistula	1	(0.3)	0	(0.0)
Aphthous ulcer	1	(0.3)	0	(0.0)
Arthralgia	1	(0.3)	1	(0.3)
Aspartate aminotransferase increased	1	(0.3)	0	(0.0)
Back pain	1	(0.3)	0	(0.0)
Bacteraemia	1	(0.3)	0	(0.0)
Blood alkaline phosphatase increased	1	(0.3)	0	(0.0)
Blood calcium increased	1	(0.3)	0	(0.0)
Cerebral infarction	1	(0.3)	0	(0.0)
Death	1	(0.3)	0	(0.0)
Demyelination	1	(0.3)	0	(0.0)
Dyspnoea	1	(0.3)	0	(0.0)
Guillain-Barre syndrome	1	(0.3)	0	(0.0)
Haematemesis	1	(0.3)	0	(0.0)
Hepatic function abnormal	1	(0.3)	0	(0.0)
Hepatotoxicity	1	(0.3)	0	(0.0)
Herpes zoster	1	(0.3)	0	(0.0)
Hypertension	1	(0.3)	0	(0.0)
Hypophysitis	1	(0.3)	0	(0.0)
Immune thrombocytopenic purpura	1	(0.3)	0	(0.0)

Infusion related reaction	1	(0.3)	0	(0.0)
Laryngeal oedema	1	(0.3)	0	(0.0)
Liver function test increased	1	(0.3)	0	(0.0)
Lymphocyte count decreased	1	(0.3)	1	(0.3)
Muscular weakness	1	(0.3)	0	(0.0)
Myocarditis	1	(0.3)	0	(0.0)
Myositis	1	(0.3)	0	(0.0)
Neutrophil count decreased	1	(0.3)	29	(9.8)
Oesophageal haemorrhage	1	(0.3)	0	(0.0)
Oesophageal perforation	1	(0.3)	0	(0.0)
Pericardial effusion	1	(0.3)	0	(0.0)
Platelet count decreased	1	(0.3)	1	(0.3)
Pneumonia aspiration	1	(0.3)	1	(0.3)
Polymyositis	1	(0.3)	0	(0.0)
Pulmonary embolism	1	(0.3)	0	(0.0)
Pulmonary necrosis	1	(0.3)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Tracheo-oesophageal fistula	1	(0.3)	1	(0.3)
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)
Varicella zoster virus infection	1	(0.3)	0	(0.0)
Vomiting	1	(0.3)	6	(2.0)
Alopecia	0	(0.0)	1	(0.3)
Bone pain	0	(0.0)	1	(0.3)
Cytopenia	0	(0.0)	1	(0.3)
Febrile neutropenia	0	(0.0)	25	(8.4)
Femoral neck fracture	0	(0.0)	1	(0.3)
Granulocytopenia	0	(0.0)	2	(0.7)
Haemoglobin decreased	0	(0.0)	1	(0.3)
Hypercalcaemia	0	(0.0)	1	(0.3)
Hypokalaemia	0	(0.0)	1	(0.3)
Hypotension	0	(0.0)	1	(0.3)
Ileus	0	(0.0)	1	(0.3)
Impaired gastric emptying	0	(0.0)	1	(0.3)
Infection	0	(0.0)	2	(0.7)
Interstitial lung disease	0	(0.0)	1	(0.3)
Leukopenia	0	(0.0)	6	(2.0)
Lung infection	0	(0.0)	2	(0.7)
Lymphopenia	0	(0.0)	3	(1.0)
Nail toxicity	0	(0.0)	1	(0.3)
Nausea	0	(0.0)	7	(2.4)
Neck pain	0	(0.0)	1	(0.3)
Neuropathy peripheral	0	(0.0)	4	(1.4)
Neutropenia	0	(0.0)	21	(7.1)
Oesophagitis	0	(0.0)	1	(0.3)
Pain	0	(0.0)	1	(0.3)
Paraesthesia	0	(0.0)	1	(0.3)
Peripheral sensory neuropathy	0	(0.0)	1	(0.3)
Pneumonia bacterial	0	(0.0)	2	(0.7)
Sepsis	0	(0.0)	3	(1.0)
Septic shock	0	(0.0)	1	(0.3)
Shock haemorrhagic	0	(0.0)	1	(0.3)
Thrombocytopenia	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.3)
White blood cell count decreased	0	(0.0)	30	(10.1)

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.
Grades are based on NCI CTCAE v4.0.
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: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 17
Subjects With Drug-Related Grade 3-5 Adverse Events
(Incidence ≥ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	57	(18.2)	80	(17.5)	660	(14.9)	1,068	(15.7)
with no adverse events	257	(81.8)	378	(82.5)	3,779	(85.1)	5,716	(84.3)
Autoimmune hepatitis	5	(1.6)	5	(1.1)	10	(0.2)	21	(0.3)
Anaemia	4	(1.3)	4	(0.9)	23	(0.5)	40	(0.6)
Asthenia	4	(1.3)	5	(1.1)	18	(0.4)	29	(0.4)
Colitis	3	(1.0)	4	(0.9)	43	(1.0)	60	(0.9)
Pneumonia	3	(1.0)	4	(0.9)	10	(0.2)	16	(0.2)
Pneumonitis	3	(1.0)	6	(1.3)	51	(1.1)	84	(1.2)
Diarrhoea	2	(0.6)	3	(0.7)	45	(1.0)	61	(0.9)
Fatigue	2	(0.6)	2	(0.4)	52	(1.2)	77	(1.1)

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 following the last dose and serious adverse events up to 90 days following the last dose are included.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

The proportion of subjects with pembrolizumab related Grade 3-5 AEs in the KN181 population was comparable to the reference dataset for pembrolizumab. Among Grade 3-5 drug-related AEs, specific PTs were reported in ≤1.6% of all populations (see table below). Autoimmune hepatitis, Anaemia and Asthenia were more frequent in the esophageal cancer datasets than in the RSD.

Serious adverse event/deaths/other significant events

All SAEs

Table 12-8
Subjects With Serious Adverse Events up to 90 Days of Last Dose By Decreasing Incidence
(Incidence ≥1% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more serious adverse events	124	(39.5)	121	(40.9)
with no serious adverse events	190	(60.5)	175	(59.1)
Pneumonia	14	(4.5)	20	(6.8)
Dysphagia	11	(3.5)	1	(0.3)
Pneumonia aspiration	11	(3.5)	5	(1.7)
Pneumonitis	7	(2.2)	0	(0.0)
Death	5	(1.6)	10	(3.4)
Autoimmune hepatitis	4	(1.3)	0	(0.0)
Oesophageal haemorrhage	4	(1.3)	0	(0.0)
Pyrexia	4	(1.3)	5	(1.7)
Abdominal pain	3	(1.0)	2	(0.7)
Colitis	3	(1.0)	0	(0.0)
Hypercalcaemia	3	(1.0)	0	(0.0)
Oesophageal obstruction	3	(1.0)	1	(0.3)
Pulmonary embolism	3	(1.0)	0	(0.0)
Respiratory tract infection	3	(1.0)	2	(0.7)
Sepsis	3	(1.0)	3	(1.0)
Anaemia	2	(0.6)	5	(1.7)
Dehydration	2	(0.6)	4	(1.4)
Gastrointestinal haemorrhage	2	(0.6)	4	(1.4)
Vomiting	2	(0.6)	5	(1.7)
Diarrhoea	1	(0.3)	5	(1.7)
Febrile neutropenia	1	(0.3)	22	(7.4)
Nausea	1	(0.3)	3	(1.0)
Neutrophil count decreased	1	(0.3)	3	(1.0)
Neutropenia	0	(0.0)	4	(1.4)
Upper gastrointestinal haemorrhage	0	(0.0)	3	(1.0)

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.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Figure 4.5.5.: Between-treatment Comparison in Serious Adverse Events Selected Adverse Events (>= 1% Incidence) and Sorted by Risk Difference (ASaT Population) Pembrolizumab 200 mg (N=314) vs. SOC (N=296)

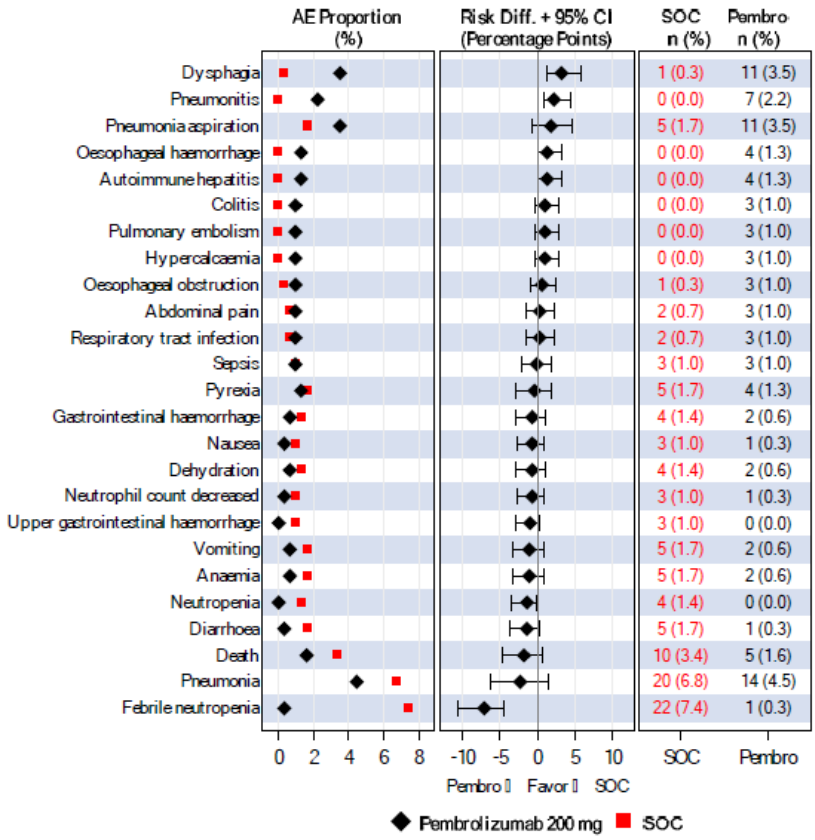


Table 5.3.5.3.3-esophageal2: 22
Subjects With Serious Adverse Events Up to 90 Days of Last Dose
(Incidence ≥ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	124	(39.5)	180	(39.3)	1,728	(38.9)	2,608	(38.4)
with no adverse events	190	(60.5)	278	(60.7)	2,711	(61.1)	4,176	(61.6)
Pneumonia	14	(4.5)	27	(5.9)	153	(3.4)	236	(3.5)
Dysphagia	11	(3.5)	11	(2.4)	12	(0.3)	31	(0.5)
Pneumonia aspiration	11	(3.5)	16	(3.5)	19	(0.4)	39	(0.6)
Pneumonitis	7	(2.2)	10	(2.2)	80	(1.8)	128	(1.9)
Death	5	(1.6)	5	(1.1)	30	(0.7)	51	(0.8)
Autoimmune hepatitis	4	(1.3)	4	(0.9)	10	(0.2)	19	(0.3)
Oesophageal haemorrhage	4	(1.3)	4	(0.9)	0	(0.0)	4	(0.1)
Pyrexia	4	(1.3)	5	(1.1)	56	(1.3)	81	(1.2)
Abdominal pain	3	(1.0)	3	(0.7)	26	(0.6)	40	(0.6)
Colitis	3	(1.0)	3	(0.7)	46	(1.0)	67	(1.0)
Hypercalcaemia	3	(1.0)	4	(0.9)	31	(0.7)	41	(0.6)
Oesophageal obstruction	3	(1.0)	3	(0.7)	1	(0.0)	4	(0.1)
Pulmonary embolism	3	(1.0)	4	(0.9)	54	(1.2)	85	(1.3)
Respiratory tract infection	3	(1.0)	3	(0.7)	12	(0.3)	16	(0.2)
Sepsis	3	(1.0)	4	(0.9)	29	(0.7)	49	(0.7)
Acute kidney injury	2	(0.6)	6	(1.3)	42	(0.9)	62	(0.9)
Anaemia	2	(0.6)	3	(0.7)	55	(1.2)	79	(1.2)
Urinary tract infection	2	(0.6)	2	(0.4)	57	(1.3)	70	(1.0)
Diarrhoea	1	(0.3)	2	(0.4)	46	(1.0)	64	(0.9)
Pleural effusion	1	(0.3)	1	(0.2)	66	(1.5)	98	(1.4)

Dyspnoea	0	(0.0)	1	(0.2)	69	(1.6)	86	(1.3)

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.
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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Drug-related SAEs

Table 14.3-28
Subjects With Serious Drug-related Adverse Events up to 90 Days of Last Dose By Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more serious drug-related adverse events	40	(12.7)	57	(19.3)
with no serious drug-related adverse events	274	(87.3)	239	(80.7)
Pneumonitis	7	(2.2)	0	(0.0)
Autoimmune hepatitis	3	(1.0)	0	(0.0)
Colitis	3	(1.0)	0	(0.0)
Pneumonia	3	(1.0)	8	(2.7)
Acute kidney injury	2	(0.6)	0	(0.0)
Pyrexia	2	(0.6)	4	(1.4)
Anastomotic fistula	1	(0.3)	0	(0.0)
Bacteraemia	1	(0.3)	0	(0.0)
Cerebral infarction	1	(0.3)	0	(0.0)
Death	1	(0.3)	0	(0.0)
Decreased appetite	1	(0.3)	0	(0.0)
Demyelination	1	(0.3)	0	(0.0)
Diarrhoea	1	(0.3)	4	(1.4)
Dysphagia	1	(0.3)	0	(0.0)
Electrolyte imbalance	1	(0.3)	0	(0.0)
Fatigue	1	(0.3)	0	(0.0)
Guillain-Barre syndrome	1	(0.3)	0	(0.0)
Hepatic function abnormal	1	(0.3)	0	(0.0)
Herpes zoster	1	(0.3)	0	(0.0)
Hyperglycaemia	1	(0.3)	0	(0.0)
Hypophysitis	1	(0.3)	0	(0.0)
Immune thrombocytopenic purpura	1	(0.3)	0	(0.0)
Infusion related reaction	1	(0.3)	0	(0.0)
Liver function test increased	1	(0.3)	0	(0.0)
Myocarditis	1	(0.3)	0	(0.0)
Oesophageal haemorrhage	1	(0.3)	0	(0.0)
Oesophageal perforation	1	(0.3)	0	(0.0)
Pneumonia aspiration	1	(0.3)	1	(0.3)
Polymyositis	1	(0.3)	0	(0.0)
Pulmonary necrosis	1	(0.3)	0	(0.0)
Tracheo-oesophageal fistula	1	(0.3)	0	(0.0)
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)
Varicella zoster virus infection	1	(0.3)	0	(0.0)

Vomiting	1	(0.3)	4	(1.4)
Anaemia	0	(0.0)	3	(1.0)
Asthenia	0	(0.0)	1	(0.3)
Dehydration	0	(0.0)	1	(0.3)
Enterocolitis	0	(0.0)	1	(0.3)
Febrile neutropenia	0	(0.0)	21	(7.1)
Femoral neck fracture	0	(0.0)	1	(0.3)
Hyponatraemia	0	(0.0)	1	(0.3)
Impaired gastric emptying	0	(0.0)	1	(0.3)
Infection	0	(0.0)	2	(0.7)
Interstitial lung disease	0	(0.0)	1	(0.3)
Leukopenia	0	(0.0)	1	(0.3)
Lung infection	0	(0.0)	1	(0.3)
Nausea	0	(0.0)	3	(1.0)
Neck pain	0	(0.0)	1	(0.3)
Neuropathy peripheral	0	(0.0)	1	(0.3)
Neutropenia	0	(0.0)	3	(1.0)
Neutrophil count decreased	0	(0.0)	3	(1.0)
Oesophagitis	0	(0.0)	1	(0.3)
Pneumonia bacterial	0	(0.0)	2	(0.7)
Radiation pneumonitis	0	(0.0)	1	(0.3)
Sepsis	0	(0.0)	2	(0.7)
Shock haemorrhagic	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.3)
White blood cell count decreased	0	(0.0)	2	(0.7)

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.
Serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 24
Subjects With Drug-related Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	40	(12.7)	56	(12.2)	464	(10.5)	756	(11.1)
with no adverse events	274	(87.3)	402	(87.8)	3,975	(89.5)	6,028	(88.9)
Pneumonitis	7	(2.2)	10	(2.2)	74	(1.7)	121	(1.8)
Autoimmune hepatitis	3	(1.0)	3	(0.7)	10	(0.2)	18	(0.3)
Colitis	3	(1.0)	3	(0.7)	39	(0.9)	57	(0.8)
Pneumonia	3	(1.0)	4	(0.9)	11	(0.2)	17	(0.3)

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.
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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

The MAH provided an analysis of SAEs and drug-related SAEs by SOC for both treatment arms of Study KN181 as requested. The detailed analysis of SAEs shows that similar proportions of participants experienced SAEs between the 2 treatment arms. SAEs with clearly higher incidences in the immunotherapy arm are pneumonitis, hepatitis and dysphagia, whereas pneumonia and neutropenia are at higher frequency in the SOC arm. These findings were all expected, nevertheless considering the safety profile pembrolizumab monotherapy could be regarded as comparable to SOC, no clear advantage could be detected regarding the rates of serious adverse events.

Deaths Due to AEs

Table 14.3-24
Subjects With Adverse Events Result in Death By Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	30	(9.6)	32	(10.8)
with no adverse events	284	(90.4)	264	(89.2)
Death	5	(1.6)	10	(3.4)
Oesophageal haemorrhage	4	(1.3)	0	(0.0)
Pneumonia aspiration	4	(1.3)	1	(0.3)
Pneumonia	3	(1.0)	5	(1.7)
Completed suicide	2	(0.6)	0	(0.0)
Gastrointestinal haemorrhage	2	(0.6)	1	(0.3)
Pneumonitis	2	(0.6)	0	(0.0)
Acute respiratory failure	1	(0.3)	1	(0.3)
Cardio-respiratory arrest	1	(0.3)	0	(0.0)
Cerebrovascular accident	1	(0.3)	0	(0.0)
Haemoptysis	1	(0.3)	0	(0.0)
Liver injury	1	(0.3)	0	(0.0)
Myocarditis	1	(0.3)	0	(0.0)
Peritonitis	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	1	(0.3)
Cancer pain	0	(0.0)	1	(0.3)
Cerebellar stroke	0	(0.0)	1	(0.3)
Haematemesis	0	(0.0)	1	(0.3)
Haemorrhage	0	(0.0)	1	(0.3)
Haemorrhage intracranial	0	(0.0)	1	(0.3)
Hepatic failure	0	(0.0)	1	(0.3)
Mediastinitis	0	(0.0)	1	(0.3)
Neutrophil count decreased	0	(0.0)	1	(0.3)
Respiratory failure	0	(0.0)	1	(0.3)
Septic shock	0	(0.0)	1	(0.3)
Shock haemorrhagic	0	(0.0)	1	(0.3)
Upper gastrointestinal haemorrhage	0	(0.0)	2	(0.7)
White blood cell count decreased	0	(0.0)	1	(0.3)

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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Drug-related AEs resulting in death were reported in a similar proportion of participants in both treatment arms (5 participants [1.6%] in the pembrolizumab arm and 5 participants [1.7%] in the SOC arm).

In the pembrolizumab arm, 5 deaths were judged to be drug-related by the investigator. In the following table information provided is summarized by the Assessor:

Subject n.	Age	Sex	N. doses	Study day of death	PT for death	SAE	AEOSI	Investigator	Sponsor
PPD			1	23	Myocarditis	Y	Y	Related	Related
			4	73	Death	Y	N	Related	Not evaluated
			2	52	Pneumonitis	Y	Y	Related	Related
			2	32	Pneumonitis	Y	Y	Related	Related
			1	14	Oesophageal haemorrhage	Y	N	Related	Not evaluated

The MAH concludes that information on pembrolizumab's causal relationship with death events in patients with the two subjects () is limited by missing information and confounding factors.

Table 5.3.5.3.3-esophageal2: 20
Subjects With Adverse Events Resulting in Death Up to 90 Days of Last Dose
(Incidence ≥ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	30	(9.6)	39	(8.5)	211	(4.8)	365	(5.4)
with no adverse events	284	(90.4)	419	(91.5)	4,228	(95.2)	6,419	(94.6)
Death	5	(1.6)	5	(1.1)	30	(0.7)	51	(0.8)
Oesophageal haemorrhage	4	(1.3)	4	(0.9)	0	(0.0)	4	(0.1)
Pneumonia aspiration	4	(1.3)	6	(1.3)	7	(0.2)	14	(0.2)
Pneumonia	3	(1.0)	4	(0.9)	24	(0.5)	38	(0.6)

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.
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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Subjects With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
By Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab[†]		Esophageal Dataset for Pembrolizumab[††]		Reference Safety Dataset for Pembrolizumab[¶]		Cumulative Running Safety Dataset for Pembrolizumab[‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	5	(1.6)	9	(2.0)	172	(3.9)	223	(3.3)
with no adverse events	309	(98.4)	449	(98.0)	4,267	(96.1)	6,561	(96.7)
Depression (excl suicide and self injury)	**3**	**(1.0)**	**7**	**(1.5)**	**166**	**(3.7)**	**215**	**(3.2)**
Adjustment disorder with depressed mood	0	(0.0)	0	(0.0)	3	(0.1)	4	(0.1)
Anhedonia	0	(0.0)	0	(0.0)	2	(0.0)	4	(0.1)
Depressed mood	0	(0.0)	0	(0.0)	15	(0.3)	18	(0.3)
Depression	3	(1.0)	7	(1.5)	146	(3.3)	191	(2.8)
Dysphoria	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Suicide/self-injury	**2**	**(0.6)**	**2**	**(0.4)**	**9**	**(0.2)**	**13**	**(0.2)**
Completed suicide	2	(0.6)	2	(0.4)	3	(0.1)	5	(0.1)

Considering the comparable pattern of fatal SAEs in both treatment arms in study KN181, the higher frequency of fatal SAEs as compared to the Reference Safety Dataset seems to generally reflect the course of the underlying disease.

Adverse Events of Special Interest

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or **Severe Skin (continued): If Grade 3 or higher:**	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption; Rash, Rash erythematous, Rash generalised, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus generalised, Pruritus genital	Yes Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis	Yes

Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy, Dermatomyositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes

Table 14.3-33
Adverse Event Summary
Adverse Event of Special Interest (AEOSI)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	73	(23.2)	22	(7.4)
with no adverse event	241	(76.8)	274	(92.6)
with drug-related[†] adverse events	68	(21.7)	9	(3.0)
with toxicity grade 3-5 adverse events	19	(6.1)	1	(0.3)
with toxicity grade 3-5 drug-related adverse events	18	(5.7)	1	(0.3)
with serious adverse events	18	(5.7)	2	(0.7)
with serious drug-related adverse events	17	(5.4)	2	(0.7)
who died	3	(1.0)	0	(0.0)
who died due to a drug-related adverse event	3	(1.0)	0	(0.0)
discontinued drug due to an adverse event	13	(4.1)	1	(0.3)
discontinued drug due to a drug-related adverse event	13	(4.1)	1	(0.3)
discontinued drug due to a serious adverse event	10	(3.2)	1	(0.3)
discontinued drug due to a serious drug-related adverse event	10	(3.2)	1	(0.3)

[†] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Table 14.3-34
Subjects With Adverse Events of Special Interest (AEOSI)
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	73	(23.2)	22	(7.4)
with no adverse events	241	(76.8)	274	(92.6)
Colitis	**3**	**(1.0)**	**2**	**(0.7)**
Colitis	3	(1.0)	1	(0.3)
Enterocolitis	0	(0.0)	1	(0.3)
Guillain-Barre Syndrome	**1**	**(0.3)**	**0**	**(0.0)**
Guillain-Barre syndrome	1	(0.3)	0	(0.0)
Hepatitis	**7**	**(2.2)**	**0**	**(0.0)**
Autoimmune hepatitis	6	(1.9)	0	(0.0)
Immune-mediated hepatitis	1	(0.3)	0	(0.0)
Hyperthyroidism	**13**	**(4.1)**	**2**	**(0.7)**
Hyperthyroidism	13	(4.1)	2	(0.7)
Hypophysitis	**1**	**(0.3)**	**0**	**(0.0)**
Hypophysitis	1	(0.3)	0	(0.0)
Hypothyroidism	**37**	**(11.8)**	**7**	**(2.4)**
Hypothyroidism	36	(11.5)	7	(2.4)
Myxoedema	1	(0.3)	0	(0.0)
Infusion Reactions	**3**	**(1.0)**	**8**	**(2.7)**
Hypersensitivity	0	(0.0)	4	(1.4)
Infusion related reaction	3	(1.0)	4	(1.4)
Myocarditis	**1**	**(0.3)**	**0**	**(0.0)**
Myocarditis	1	(0.3)	0	(0.0)
Myositis	**2**	**(0.6)**	**0**	**(0.0)**

Myositis	**2**	**(0.6)**	**0**	**(0.0)**
Myositis	1	(0.3)	0	(0.0)
Polymyositis	1	(0.3)	0	(0.0)
Nephritis	**2**	**(0.6)**	**0**	**(0.0)**
Nephritis	1	(0.3)	0	(0.0)
Nephrotic syndrome	1	(0.3)	0	(0.0)
Pneumonitis	**15**	**(4.8)**	**2**	**(0.7)**
Interstitial lung disease	2	(0.6)	1	(0.3)
Pneumonitis	13	(4.1)	1	(0.3)
Severe Skin Reactions	**2**	**(0.6)**	**1**	**(0.3)**
Dermatitis bullous	0	(0.0)	1	(0.3)
Erythema multiforme	1	(0.3)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Thyroiditis	**1**	**(0.3)**	**0**	**(0.0)**
Thyroiditis	1	(0.3)	0	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.3)**	**0**	**(0.0)**
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A bolded term 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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Table 14.3-38
Subjects With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more AEOSI	73	(23.2)	22	(7.4)
Grade 1	14	(4.5)	7	(2.4)
Grade 2	40	(12.7)	14	(4.7)
Grade 3	13	(4.1)	0	(0.0)
Grade 4	3	(1.0)	1	(0.3)
Grade 5	3	(1.0)	0	(0.0)
with no AEOSI	241	(76.8)	274	(92.6)

One subject (0.3%) experienced a Grade 4 AEOSI of Type I diabetis mellitus, one subject Grade 4 hepatitis (autoimmune hepatitis) and one subject Grade 4 colitis. Three AEOSI fatal events were registered (1 Grade 5 Myocarditis and 2 Grade 5 Pneumonitis) and recorded as being related to pembrolizumab.

Table 14.3-39
Time to Onset and Duration of AEOSI

	Pembrolizumab 200 mg	SOC
Subjects in population	**314**	**296**
Subjects with AEOSI (%)	73 (23.2)	22 (7.4)
Time to Onset of First AEOSI (days)[†]		
Mean (SD)	83.8 (87.6)	42.6 (48.2)
Median	64.0	22.0
Range	1.0 to 610.0	1.0 to 187.0
Total number of episodes of AEOSI	93	24
Average number of episodes of AEOSI per subject	1.3	1.1
Episode Durations (days)[‡]		
Median	185.0	47.5
Range	1.0 to 629.0+	1.0 to 560.0+

Table 14.3-37
Summary of Outcome for Subjects With AEOSI (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Outcome	Pembrolizumab 200 mg n	Pembrolizumab 200 mg (%)	SOC n	SOC (%)
Subjects in population		314		296	
With one or more AEOSI	**Overall**	**73**	**(23.2)**	**22**	**(7.4)**
	Fatal	3	(4.1)	0	(0.0)
	Not Resolved	41	(56.2)	7	(31.8)
	Resolving	7	(9.6)	4	(18.2)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	22	(30.1)	11	(50.0)

Table 5.3.5.3.3-esophageal2: 31
Subjects With Adverse Events of Special Interest
(Incidence > 0% in One or More Treatment Groups)
By AEOSI Category and Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	73	(23.2)	106	(23.1)	1,007	(22.7)	1,607	(23.7)
with no adverse events	241	(76.8)	352	(76.9)	3,432	(77.3)	5,177	(76.3)
Adrenal Insufficiency	**0**	**(0.0)**	**1**	**(0.2)**	**34**	**(0.8)**	**50**	**(0.7)**
Adrenal insufficiency	0	(0.0)	1	(0.2)	32	(0.7)	47	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Colitis	**3**	**(1.0)**	**7**	**(1.5)**	**79**	**(1.8)**	**127**	**(1.9)**
Autoimmune colitis	0	(0.0)	0	(0.0)	1	(0.0)	7	(0.1)
Colitis	3	(1.0)	5	(1.1)	73	(1.6)	109	(1.6)
Colitis microscopic	0	(0.0)	0	(0.0)	2	(0.0)	4	(0.1)
Enterocolitis	0	(0.0)	2	(0.4)	5	(0.1)	10	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Encephalitis	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Guillain-Barre Syndrome	**1**	**(0.3)**	**1**	**(0.2)**	**4**	**(0.1)**	**6**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	1	(0.3)	1	(0.2)	2	(0.0)	4	(0.1)
Hepatitis	**7**	**(2.2)**	**7**	**(1.5)**	**30**	**(0.7)**	**57**	**(0.8)**
Autoimmune hepatitis	6	(1.9)	6	(1.3)	14	(0.3)	27	(0.4)
Drug-induced liver injury	0	(0.0)	0	(0.0)	4	(0.1)	5	(0.1)
Hepatitis	0	(0.0)	0	(0.0)	13	(0.3)	23	(0.3)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.0)
Hyperthyroidism	**13**	**(4.1)**	**18**	**(3.9)**	**145**	**(3.3)**	**284**	**(4.2)**
Hyperthyroidism	13	(4.1)	18	(3.9)	145	(3.3)	284	(4.2)
Hypophysitis	**1**	**(0.3)**	**3**	**(0.7)**	**21**	**(0.5)**	**38**	**(0.6)**
Hypophysitis	1	(0.3)	1	(0.2)	12	(0.3)	23	(0.3)
Hypopituitarism	0	(0.0)	2	(0.4)	9	(0.2)	15	(0.2)
Hypothyroidism	**37**	**(11.8)**	**50**	**(10.9)**	**440**	**(9.9)**	**704**	**(10.4)**
Hypothyroidism	36	(11.5)	49	(10.7)	439	(9.9)	702	(10.3)
Myxoedema	1	(0.3)	1	(0.2)	1	(0.0)	2	(0.0)

Hypothyroidism	**37**	**(11.8)**	**50**	**(10.9)**	**440**	**(9.9)**	**704**	**(10.4)**
Primary hypothyroidism	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Infusion Reactions	**3**	**(1.0)**	**4**	**(0.9)**	**113**	**(2.5)**	**146**	**(2.2)**
Anaphylactic reaction	0	(0.0)	0	(0.0)	5	(0.1)	9	(0.1)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	8	(0.2)	8	(0.1)
Drug hypersensitivity	0	(0.0)	0	(0.0)	16	(0.4)	20	(0.3)
Hypersensitivity	0	(0.0)	0	(0.0)	37	(0.8)	43	(0.6)
Infusion related reaction	3	(1.0)	4	(0.9)	48	(1.1)	67	(1.0)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**3**	**(0.0)**
Myasthenia gravis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Myocarditis	**1**	**(0.3)**	**1**	**(0.2)**	**3**	**(0.1)**	**7**	**(0.1)**
Myocarditis	1	(0.3)	1	(0.2)	3	(0.1)	7	(0.1)
Myositis	**2**	**(0.6)**	**2**	**(0.4)**	**18**	**(0.4)**	**26**	**(0.4)**
Myopathy	0	(0.0)	0	(0.0)	4	(0.1)	4	(0.1)
Myositis	1	(0.3)	1	(0.2)	13	(0.3)	19	(0.3)
Polymyositis	1	(0.3)	1	(0.2)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Nephritis	**2**	**(0.6)**	**3**	**(0.7)**	**15**	**(0.3)**	**23**	**(0.3)**
Acute kidney injury	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	1	(0.3)	2	(0.4)	1	(0.0)	5	(0.1)
Nephrotic syndrome	1	(0.3)	1	(0.2)	1	(0.0)	2	(0.0)
Renal failure	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	7	(0.2)	8	(0.1)
Pancreatitis	**0**	**(0.0)**	**1**	**(0.2)**	**11**	**(0.2)**	**21**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	1	(0.2)	9	(0.2)	19	(0.3)
Pancreatitis acute	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Pneumonitis	**15**	**(4.8)**	**24**	**(5.2)**	**166**	**(3.7)**	**273**	**(4.0)**
Interstitial lung disease	2	(0.6)	3	(0.7)	13	(0.3)	25	(0.4)

Pneumonitis	**15**	**(4.8)**	**24**	**(5.2)**	**166**	**(3.7)**	**273**	**(4.0)**
Organising pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonitis	13	(4.1)	21	(4.6)	154	(3.5)	249	(3.7)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**10**	**(0.1)**
Sarcoidosis	0	(0.0)	0	(0.0)	3	(0.1)	10	(0.1)
Severe Skin Reactions	**2**	**(0.6)**	**4**	**(0.9)**	**63**	**(1.4)**	**97**	**(1.4)**
Dermatitis bullous	0	(0.0)	0	(0.0)	5	(0.1)	6	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	3	(0.1)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Erythema multiforme	1	(0.3)	1	(0.2)	3	(0.1)	7	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Pemphigoid	0	(0.0)	1	(0.2)	3	(0.1)	5	(0.1)
Pemphigus	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Pruritus	0	(0.0)	0	(0.0)	6	(0.1)	9	(0.1)
Pruritus generalised	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash	1	(0.3)	1	(0.2)	18	(0.4)	27	(0.4)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	1	(0.2)	3	(0.1)	6	(0.1)
Rash maculo-papular	0	(0.0)	0	(0.0)	10	(0.2)	20	(0.3)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Rash pustular	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.0)
Toxic skin eruption	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Thyroiditis	**1**	**(0.3)**	**2**	**(0.4)**	**30**	**(0.7)**	**67**	**(1.0)**
Autoimmune thyroiditis	0	(0.0)	0	(0.0)	7	(0.2)	14	(0.2)
Thyroid disorder	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
Thyroiditis	1	(0.3)	2	(0.4)	22	(0.5)	50	(0.7)
Type 1 Diabetes Mellitus	**1**	**(0.3)**	**3**	**(0.7)**	**15**	**(0.3)**	**24**	**(0.4)**
Diabetic ketoacidosis	0	(0.0)	2	(0.4)	7	(0.2)	11	(0.2)
Type 1 diabetes mellitus	1	(0.3)	2	(0.4)	11	(0.2)	19	(0.3)
Uveitis	**0**	**(0.0)**	**1**	**(0.2)**	**17**	**(0.4)**	**23**	**(0.3)**
Iridocyclitis	0	(0.0)	0	(0.0)	3	(0.1)	4	(0.1)
Iritis	0	(0.0)	1	(0.2)	3	(0.1)	4	(0.1)

Uveitis	**0**	**(0.0)**	**1**	**(0.2)**	**17**	**(0.4)**	**23**	**(0.3)**
Uveitis	0	(0.0)	0	(0.0)	11	(0.2)	15	(0.2)

Every subject is counted a single time for each applicable row and column.
A bolded term 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 following the last dose and serious adverse events up to 90 days following the last dose are included.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 52
Time to Onset and Duration of AEOSI
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4439		6784	
Subjects with AEOSI	73	(23.2)	106	(23.1)	1007	(22.7)	1607	(23.7)
Time to Onset of First AEOSI (days)†								
Mean (Std)	83.8 (87.6)		88.2 (93.2)		109.5 (109.2)		109.3 (109.3)	
Median	64.0		64.0		73.0		71.0	
Range	1 to 610		1 to 610		1 to 682		1 to 739	
Total episodes of AEOSI	93		139		1316		2260	
Average Episodes per patient	1.27		1.31		1.31		1.41	
Episode duration (days)‡								
Median	185.0		233.0		106.0		86.0	
Range	1 to 629+		1 to 657+		1 to 909+		1 to 992+	

(%) = Number of subjects with AEOSI / Number of subjects in population.
† Time to onset statistics are based on number of subjects with AEOSI.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-esophageal2: 73
Subjects With Adverse Events of Special Interest by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
By AEOSI Category and Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‖		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		458		4,439		6,784	
with one or more adverse events	73	(23.2)	106	(23.1)	1,007	(22.7)	1,607	(23.7)
Grade 1	14	(4.5)	20	(4.4)	259	(5.8)	387	(5.7)
Grade 2	40	(12.7)	59	(12.9)	493	(11.1)	813	(12.0)
Grade 3	13	(4.1)	18	(3.9)	217	(4.9)	345	(5.1)
Grade 4	3	(1.0)	5	(1.1)	29	(0.7)	48	(0.7)
Grade 5	3	(1.0)	4	(0.9)	9	(0.2)	14	(0.2)
with no adverse events	241	(76.8)	352	(76.9)	3,432	(77.3)	5,177	(76.3)

Table 5.3.5.3.3-esophageal2: 74
Summary of Outcome for Subjects With AEOSI (Incidence > 0% in One or More Treatment Groups)
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Outcome	KN181 Data for Pembrolizumab‖ n	(%)	Esophageal Dataset for Pembrolizumab†† n	(%)	Reference Safety Dataset for Pembrolizumab¶ n	(%)	Cumulative Running Safety Dataset for Pembrolizumab‡‡ n	(%)
Subjects in population		314		458		4439		6784	
With one or more AEOSI	**Overall**	**73**	**(23.2)**	**106**	**(23.1)**	**1007**	**(22.7)**	**1607**	**(23.7)**
	Fatal	3	(4.1)	4	(3.8)	9	(0.9)	14	(0.9)
	Not Resolved	41	(56.2)	57	(53.8)	469	(46.6)	769	(47.9)
	Resolving	7	(9.6)	10	(9.4)	56	(5.6)	111	(6.9)
	Unknown	0	(0.0)	0	(0.0)	25	(2.5)	28	(1.7)
	Sequelae	0	(0.0)	1	(0.9)	15	(1.5)	27	(1.7)
	Resolved	22	(30.1)	34	(32.1)	433	(43.0)	658	(40.9)

Table 5.3.5.3.3-esophageal2: 96
Summary of Concomitant Corticosteroid Use for AEOSI
(ASaT Population)

	KN181 Data for Pembrolizumab‖	Esophageal Dataset for Pembrolizumab††	Reference Safety Dataset for Pembrolizumab¶	Cumulative Running Safety Dataset for Pembrolizumab‡‡
Total Episodes	93	139	1316	2260
High Starting Dose (%) †	**22 (23.7)**	**34 (24.5)**	**255 (19.4)**	**389 (17.2)**
Starting dose (mg/day)				
Mean (Std)	153 (275)	125 (224)	127 (193)	123 (184)
Median (Range)	50 (40-1250)	55 (40-1250)	75 (40-1250)	75 (40-1250)
Duration (days)§				
Mean (Std)	9 (14)	14 (37)	21 (71)	18 (60)
Median (Range)	6 (1-66)	5 (1-212)	6 (1-876)	6 (1-876)
Low Starting Dose (%) ‡	**8 (8.6)**	**16 (11.5)**	**104 (7.9)**	**160 (7.1)**
Starting dose (mg/day)				
Mean (Std)	21 (8)	18 (9)	18 (11)	18 (10)
Median (Range)	23 (10-30)	20 (1-30)	20 (1-38)	20 (1-38)
Duration (days)§				
Mean (Std)	8 (5)	56 (144)	44 (84)	44 (93)
Median (Range)	8 (2-15)	13 (2-588)	7 (1-370)	7 (1-588)

Not Treated with Systemic Corticosteroid (%)	**63 (67.7)**	**89 (64.0)**	**957 (72.7)**	**1711 (75.7)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.

AEOSI episodes with missing corticosteroid dosage are considered as not treated with systemic corticosteroid.

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)

Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)

Database Cutoff Date for HCC (KN224: 15MAY2018)

Database Cutoff Date for MCC (KN017: 06FEB2018)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae; adcm]

Gastrointestinal toxicity

Adverse events including gastrointestinal perforation, ulceration, hemorrhage, or obstruction in KEYNOTE-181 are provided by treatment group and are displayed with the esophageal dataset for pembrolizumab and the reference safety dataset:

Appendix 5-1

Subjects With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
By Preferred Term
(ASaT Population)

	KN181 Data for Pembrolizumab‡		KN181 Data for SOC‡‡		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	314		296		458		4,439	
with one or more adverse events	37	(11.8)	54	(18.2)	54	(11.8)	740	(16.7)
with no adverse events	277	(88.2)	242	(81.8)	404	(88.2)	3,699	(83.3)
Gastrointestinal haemorrhage	**12**	**(3.8)**	**13**	**(4.4)**	**17**	**(3.7)**	**80**	**(1.8)**
Anal haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Anastomotic haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diverticulitis intestinal haemorrhagic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastric ulcer haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Gastrointestinal haemorrhage	2	(0.6)	4	(1.4)	4	(0.9)	10	(0.2)
Haematemesis	3	(1.0)	1	(0.3)	3	(0.7)	4	(0.1)
Haematochezia	1	(0.3)	1	(0.3)	3	(0.7)	14	(0.3)
Haemorrhoidal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.2)
Lower gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Melaena	1	(0.3)	0	(0.0)	2	(0.4)	6	(0.1)
Occult blood positive	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Oesophageal haemorrhage	6	(1.9)	1	(0.3)	6	(1.3)	0	(0.0)
Rectal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	25	(0.6)
Upper gastrointestinal haemorrhage	1	(0.3)	4	(1.4)	1	(0.2)	6	(0.1)
Gastrointestinal obstruction	**9**	**(2.9)**	**8**	**(2.7)**	**12**	**(2.6)**	**53**	**(1.2)**
Duodenal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ileus	1	(0.3)	2	(0.7)	1	(0.2)	12	(0.3)
Impaired gastric emptying	0	(0.0)	2	(0.7)	0	(0.0)	5	(0.1)
Intestinal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	13	(0.3)
Intussusception	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Large intestinal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Obstruction gastric	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Oesophageal obstruction	5	(1.6)	1	(0.3)	6	(1.3)	1	(0.0)
Oesophageal stenosis	3	(1.0)	2	(0.7)	5	(1.1)	2	(0.0)
Small intestinal obstruction	0	(0.0)	1	(0.3)	1	(0.2)	11	(0.2)
Subileus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastrointestinal perforation	**5**	**(1.6)**	**9**	**(3.0)**	**6**	**(1.3)**	**30**	**(0.7)**
Abdominal abscess	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal wall abscess	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anal abscess	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Anal fistula	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Appendicitis perforated	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Colonic abscess	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)

	KN181 Data for Pembrolizumab‖		KN181 Data for SOC‡‡		Esophageal Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal perforation	**5**	**(1.6)**	**9**	**(3.0)**	**6**	**(1.3)**	**30**	**(0.7)**
Colonic fistula	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Enterocutaneous fistula	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastrointestinal fistula	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastrointestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Intestinal perforation	0	(0.0)	1	(0.3)	0	(0.0)	4	(0.1)
Large intestine perforation	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Oesophageal fistula	3	(1.0)	1	(0.3)	3	(0.7)	0	(0.0)
Oesophageal perforation	1	(0.3)	4	(1.4)	1	(0.2)	1	(0.0)
Oesophagobronchial fistula	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Peritonitis	1	(0.3)	2	(0.7)	2	(0.4)	1	(0.0)
Peritonitis bacterial	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Small intestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.4)**	**5**	**(0.1)**
Gastrointestinal hypomotility	1	(0.3)	1	(0.3)	1	(0.2)	0	(0.0)
Intestinal pseudo-obstruction	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Intra-abdominal haematoma	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Peritoneal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Retroperitoneal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastrointestinal ulceration	**0**	**(0.0)**	**2**	**(0.7)**	**1**	**(0.2)**	**15**	**(0.3)**
Duodenal ulcer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Erosive duodenitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric ulcer	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.1)
Gastric ulcer haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Gastritis erosive	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Gastrointestinal ulcer	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Large intestinal ulcer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Oesophageal ulcer	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Peptic ulcer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stress ulcer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Laboratory findings

Laboratory findings for Pembrolizumab vs Standard Treatment in KN181:

Laboratory values worsening during treatment in >5% of treated subjects were Lymphopenia, Anaemia, Hyponatraemia, and Hypophosphatemia in the pembrolizumab arm. In the standard treatment arm, Lymphopenia, Neutropenia, Hyponatremia, Hypophosphatemia, Leukopenia, and Anaemia were found.

Treatment differences (>10% difference between the 2 treatment arms) for clinically meaningful laboratory findings (defined as Grade 3 to 4 events) included leukocytes decreased and neutrophils decreased reported less frequently in the pembrolizumab arm. The most frequently reported (>10% incidence) clinically meaningful (defined as Grade 3 to 4 events) worsening in CTCAE grades of protocol-specified laboratory tests in the pembrolizumab arm included lymphocytes decreased (20.2%). In the SOC arm, the most frequently reported worsening in CTCAE grades included lymphocytes decreased (28.8%), leukocytes decreased (24.3%), neutrophils decreased (22.2%), and haemoglobin decreased (15.4%)

No participant in either arm had liver function laboratory values that satisfied the predetermined criteria for DILI.

Laboratory findings from the comparison of KN181 with the Pooled Esophageal Dataset, the Reference Safety Dataset, and the Cumulative Running Safety Dataset:

Parameters for which a higher proportion of subjects in the KN181 population than in the Reference Safety Dataset experienced an increase in laboratory test toxicity of Grade 3-4 included: Lymphocytes decreased (20.2% vs 10.4%), Haemoglobin decreased (10.5% vs 4.5%), Alkaline phosphatase

increased (6.8% vs. 2.7%) Aspartate aminotransferase increased (6.5% vs. 2.6%), Bilirubin increased (3.2% vs. 1.8%) and Calcium increased (3.2% vs 1.7%).

Discontinuations from treatment with pembrolizumab due to abnormal laboratory evaluations were infrequent in the KN181 population (2 subjects) and consistent with the Reference Safety Dataset.

There were no new safety concerns identified for pembrolizumab monotherapy based on laboratory abnormalities.

Immunogenicity

The characterization of immunogenicity for pembrolizumab was investigated in KEYNOTE-181. The incidences of the overall ADA rates were consistent with historical monotherapy trials in melanoma, NSCLC, HNSCC and UC. In addition, ADA rates were also investigated by stratifying the data by squamous and non-squamous tumor histology.

The rates in the tumor histologies SCC an AC were comparable in esophageal cancer.

Table 4.5.27: Summary of Subject Immunogenicity Results after Pembrolizumab Monotherapy, 200 mg Pembrolizumab Q3W (KN181)

Stratified by indication			
Immunogenicity status	Total	Squamous cell carcinoma	Adenocarcinoma
Assessable subjects[a]	294	189	105
Inconclusive subjects[b]	11	7	4
Evaluable subjects[c]	**283**	**182**	**101**
Negative[d]	267 (94.3%)	171 (94.0%)	96 (95.0%)
Non-Treatment emergent positive[d]	5 (1.8%)	3 (1.6%)	2 (2.0%)
Neutralizing negative	5 (1.8%)	3 (1.6%)	2 (2.0%)
Neutralizing positive	0	0	0
Treatment emergent positive[d]	11 (3.9%)	8 (4.4%)	3 (3.0%)
Neutralizing negative	11 (3.9%)	8 (4.4%)	3 (3.0%)
Neutralizing positive	0	0	0

a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.

Data source [0544CD: analysis-p181pkada01]

Safety in special populations

Intrinsic Factors

Age

Table 5.3.5.3.3-esophageal2: 119
Adverse Event Summary by Age Category (<65, 65-74, 75-84, ≥85 Years)
(ASaT Population)

	KN181 Data for Pembrolizumab‖								Esophageal Dataset for Pembrolizumab††							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	175		107		32		0		242		166		49		1	
with one or more adverse events	168	(96.0)	100	(93.5)	32	(100.0)	0	(0.0)	233	(96.3)	154	(92.8)	49	(100.0)	1	(100.0)
with no adverse event	7	(4.0)	7	(6.5)	0	(0.0)	0	(0.0)	9	(3.7)	12	(7.2)	0	(0.0)	0	(0.0)
with drug-related† adverse events	109	(62.3)	72	(67.3)	21	(65.6)	0	(0.0)	145	(59.9)	104	(62.7)	32	(65.3)	0	(0.0)
with toxicity grade 3-5 adverse events	95	(54.3)	55	(51.4)	20	(62.5)	0	(0.0)	132	(54.5)	80	(48.2)	32	(65.3)	1	(100.0)
with toxicity grade 3-5 drug-related adverse events	25	(14.3)	22	(20.6)	10	(31.3)	0	(0.0)	37	(15.3)	29	(17.5)	14	(28.6)	0	(0.0)
with serious adverse events	71	(40.6)	36	(33.6)	17	(53.1)	0	(0.0)	94	(38.8)	58	(34.9)	28	(57.1)	0	(0.0)
with serious drug-related adverse events	21	(12.0)	13	(12.1)	6	(18.8)	0	(0.0)	27	(11.2)	20	(12.0)	9	(18.4)	0	(0.0)
who died	14	(8.0)	9	(8.4)	7	(21.9)	0	(0.0)	17	(7.0)	13	(7.8)	9	(18.4)	0	(0.0)
who died due to a drug-related adverse event	1	(0.6)	2	(1.9)	2	(6.3)	0	(0.0)	1	(0.4)	2	(1.2)	3	(6.1)	0	(0.0)
discontinued drug due to an adverse event	22	(12.6)	11	(10.3)	7	(21.9)	0	(0.0)	29	(12.0)	16	(9.6)	10	(20.4)	0	(0.0)
discontinued drug due to a drug-related adverse event	7	(4.0)	7	(6.5)	5	(15.6)	0	(0.0)	12	(5.0)	8	(4.8)	7	(14.3)	0	(0.0)
discontinued drug due to a serious adverse event	21	(12.0)	8	(7.5)	6	(18.8)	0	(0.0)	25	(10.3)	11	(6.6)	8	(16.3)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	7	(4.0)	4	(3.7)	4	(12.5)	0	(0.0)	9	(3.7)	4	(2.4)	5	(10.2)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	79	(3.2)	59	(4.4)	33	(5.9)	1	(1.1)	134	(3.4)	88	(4.3)	46	(6.0)	4	(3.8)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the 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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

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

	Reference Safety Dataset for Pembrolizumab¶								Cumulative Running Safety Dataset for Pembrolizumab‡‡							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2,453		1,333		563		90		3,893		2,023		762		106	
with one or more adverse events	2,381	(97.1)	1,292	(96.9)	551	(97.9)	89	(98.9)	3,755	(96.5)	1,951	(96.4)	743	(97.5)	105	(99.1)
with no adverse event	72	(2.9)	41	(3.1)	12	(2.1)	1	(1.1)	138	(3.5)	72	(3.6)	19	(2.5)	1	(0.9)
with drug-related† adverse events	1,716	(70.0)	951	(71.3)	405	(71.9)	68	(75.6)	2,667	(68.5)	1,425	(70.4)	532	(69.8)	80	(75.5)
with toxicity grade 3-5 adverse events	1,111	(45.3)	681	(51.1)	307	(54.5)	54	(60.0)	1,776	(45.6)	1,028	(50.8)	435	(57.1)	63	(59.4)
with toxicity grade 3-5 drug-related adverse events	318	(13.0)	227	(17.0)	100	(17.8)	15	(16.7)	531	(13.6)	368	(18.2)	150	(19.7)	19	(17.9)
with serious adverse events	865	(35.3)	560	(42.0)	261	(46.4)	42	(46.7)	1,374	(35.3)	825	(40.8)	359	(47.1)	50	(47.2)
with serious drug-related adverse events	228	(9.3)	156	(11.7)	71	(12.6)	9	(10.0)	385	(9.9)	256	(12.7)	101	(13.3)	14	(13.2)
who died	95	(3.9)	70	(5.3)	38	(6.7)	8	(8.9)	165	(4.2)	122	(6.0)	68	(8.9)	10	(9.4)
who died due to a drug-related adverse event	11	(0.4)	7	(0.5)	3	(0.5)	1	(1.1)	21	(0.5)	15	(0.7)	9	(1.2)	1	(0.9)
discontinued drug due to an adverse event	255	(10.4)	176	(13.2)	99	(17.6)	8	(8.9)	435	(11.2)	272	(13.4)	144	(18.9)	12	(11.3)
discontinued drug due to a drug-related adverse event	114	(4.6)	93	(7.0)	49	(8.7)	3	(3.3)	215	(5.5)	144	(7.1)	70	(9.2)	6	(5.7)
discontinued drug due to a serious adverse event	198	(8.1)	127	(9.5)	76	(13.5)	6	(6.7)	324	(8.3)	195	(9.6)	112	(14.7)	10	(9.4)
discontinued drug due to a serious drug-related adverse event	7	(4.0)	4	(3.7)	4	(12.5)	0	(0.0)	9	(3.7)	4	(2.4)	5	(10.2)	0	(0.0)

discontinued drug due to a serious drug-related adverse event	79	(3.2)	59	(4.4)	33	(5.9)	1	(1.1)	134	(3.4)	88	(4.3)	46	(6.0)	4	(3.8)

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

Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the 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 in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)

Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)

Database Cutoff Date for HCC (KN224: 15MAY2018)

Database Cutoff Date for MCC (KN017: 06FEB2018)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: ISS: adam-adsl: adsel

Table 5.3.5.3.3-esophageal2: 120
Adverse Event Summary by Age
(ASaT Population)

	KN181 Data for Pembrolizumab‖								Esophageal Dataset for Pembrolizumab††							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	175	(100.0)	107	(100.0)	32	(100.0)	0	(0.0)	242	(100.0)	166	(100.0)	49	(100.0)	1	(100.0)
with one or more adverse events	168	(96.0)	100	(93.5)	32	(100.0)	0	(0.0)	233	(96.3)	154	(92.8)	49	(100.0)	1	(100.0)
who died	14	(8.0)	9	(8.4)	7	(21.9)	0	(0.0)	17	(7.0)	13	(7.8)	9	(18.4)	0	(0.0)
with serious adverse events	71	(40.6)	36	(33.6)	17	(53.1)	0	(0.0)	94	(38.8)	58	(34.9)	28	(57.1)	0	(0.0)
discontinued‡ due to an adverse event	22	(12.6)	11	(10.3)	7	(21.9)	0	(0.0)	29	(12.0)	16	(9.6)	10	(20.4)	0	(0.0)
CNS (confusion/extrapyramidal)	10	(5.7)	10	(9.3)	4	(12.5)	0	(0.0)	17	(7.0)	14	(8.4)	6	(12.2)	0	(0.0)
AE related to falling	5	(2.9)	4	(3.7)	4	(12.5)	0	(0.0)	11	(4.5)	5	(3.0)	5	(10.2)	0	(0.0)

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 in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018) |Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)|Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017) |Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)|Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017) |Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)|Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018) |Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)|Database Cutoff Date for HCC (KN224: 15MAY2018) |Database Cutoff Date for MCC (KN017: 06FEB2018)|Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Adverse Event Summary by Age
(ASaT Population)

	Reference Safety Dataset for Pembrolizumab¶								Cumulative Running Safety Dataset for Pembrolizumab‡‡							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2453	(100.0)	1333	(100.0)	563	(100.0)	90	(100.0)	3893	(100.0)	2023	(100.0)	762	(100.0)	106	(100.0)
with one or more adverse events	2381	(97.1)	1292	(96.9)	551	(97.9)	89	(98.9)	3755	(96.5)	1951	(96.4)	743	(97.5)	105	(99.1)
who died	95	(3.9)	70	(5.3)	38	(6.7)	8	(8.9)	165	(4.2)	122	(6.0)	68	(8.9)	10	(9.4)
with serious adverse events	865	(35.3)	560	(42.0)	261	(46.4)	42	(46.7)	1374	(35.3)	825	(40.8)	359	(47.1)	50	(47.2)
discontinued‡ due to an adverse event	255	(10.4)	176	(13.2)	99	(17.6)	8	(8.9)	435	(11.2)	272	(13.4)	144	(18.9)	12	(11.3)
CNS (confusion/extrapyramidal)	209	(8.5)	132	(9.9)	41	(7.3)	17	(18.9)	289	(7.4)	184	(9.1)	53	(7.0)	17	(16.0)
AE related to falling	177	(7.2)	132	(9.9)	64	(11.4)	18	(20.0)	241	(6.2)	167	(8.3)	80	(10.5)	20	(18.9)

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 in KN181.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.

¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.

‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.

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: 26FEB2018) |Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)|Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017) |Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)|Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017) |Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)|Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018) |Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)|Database Cutoff Date for HCC (KN224: 15MAY2018) |Database Cutoff Date for MCC (KN017: 06FEB2018)|Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Adverse Event Summary by Age
(ASaT Population)

	KN181 Data for Pembrolizumab‖								Esophageal Dataset for Pembrolizumab††							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
CV events	20	(11.4)	7	(6.5)	5	(15.6)	0	(0.0)	34	(14.0)	12	(7.2)	8	(16.3)	0	(0.0)
Cerebrovascular events	2	(1.1)	1	(0.9)	2	(6.3)	0	(0.0)	3	(1.2)	3	(1.8)	3	(6.1)	0	(0.0)
Infections	58	(33.1)	36	(33.6)	13	(40.6)	0	(0.0)	78	(32.2)	60	(36.1)	19	(38.8)	1	(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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018) |Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)|Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017) |Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)|Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017) |Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)|Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018) |Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)|Database Cutoff Date for HCC (KN224: 15MAY2018) |Database Cutoff Date for MCC (KN017: 06FEB2018)|Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Adverse Event Summary by Age
(ASaT Population)

	Reference Safety Dataset for Pembrolizumab¶								Cumulative Running Safety Dataset for Pembrolizumab‡‡							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
CV events	465	(19.0)	308	(23.1)	130	(23.1)	21	(23.3)	753	(19.3)	433	(21.4)	173	(22.7)	25	(23.6)
Cerebrovascular events	44	(1.8)	33	(2.5)	15	(2.7)	3	(3.3)	65	(1.7)	47	(2.3)	24	(3.1)	3	(2.8)
Infections	1031	(42.0)	596	(44.7)	255	(45.3)	38	(42.2)	1584	(40.7)	860	(42.5)	334	(43.8)	46	(43.4)

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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018) |Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)|Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017) |Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)|Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017) |Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)|Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018) |Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)|Database Cutoff Date for HCC (KN224: 15MAY2018) |Database Cutoff Date for MCC (KN017: 06FEB2018)|Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Table 46

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

	Age (Years)											
	Pembrolizumab 200 mg						SOC					
	<65		>=65 to <75		>=75 to <85		<65		>=65 to <75		>=75 to <85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	175		107		32		168		100		28	
with one or more adverse events	168	(96.0)	100	(93.5)	32	(100.0)	165	(98.2)	96	(96.0)	27	(96.4)
who died	14	(8.0)	9	(8.4)	7	(21.9)	19	(11.3)	10	(10.0)	3	(10.7)
with serious adverse events	71	(40.6)	36	(33.6)	17	(53.1)	67	(39.9)	42	(42.0)	12	(42.9)
discontinued due to an adverse event	22	(12.6)	11	(10.3)	7	(21.9)	27	(16.1)	12	(12.0)	3	(10.7)
CNS (confusion/extrapyramidal)	10	(5.7)	10	(9.3)	4	(12.5)	6	(3.6)	5	(5.0)	2	(7.1)
AE related to falling	5	(2.9)	4	(3.7)	4	(12.5)	8	(4.8)	9	(9.0)	3	(10.7)
CV events	20	(11.4)	7	(6.5)	5	(15.6)	19	(11.3)	14	(14.0)	3	(10.7)
Cerebrovascular events	2	(1.1)	1	(0.9)	2	(6.3)	3	(1.8)	2	(2.0)	1	(3.6)
Infections	58	(33.1)	36	(33.6)	13	(40.6)	62	(36.9)	43	(43.0)	13	(46.4)

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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

A worse safety profile is found in subjects treated with pembrolizumab belonging to the most extreme age group (>=75 to <85) in respect to pembrolizumab-treated subjects of younger age as well as all

age categories of the SOC treatment arm (proportion of subjects who died 21.9% vs 8.0-11.3%, who reported SAEs 53.1% vs 33.6-42.9% or who discontinued drugs due to AEs 21.9% vs 10.3-16.1%). The same picture is found when analysing specific event categories (particularly CNS and cerebrovascular events).

Gender

Table 5.3.5.3.3-esophageal2: 121
Adverse Event Summary by Gender (Male, Female)
(ASaT Population)

	KN181 Data for Pembrolizumab‖				Esophageal Dataset for Pembrolizumab††				Reference Safety Dataset for Pembrolizumab¶				Cumulative Running Safety Dataset for Pembrolizumab‡‡			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	273		41		392		66		2,869		1,570		4,465		2,319	
with one or more adverse events	259	(94.9)	41	(100.0)	372	(94.9)	65	(98.5)	2,788	(97.2)	1,525	(97.1)	4,308	(96.5)	2,246	(96.9)
with no adverse event	14	(5.1)	0	(0.0)	20	(5.1)	1	(1.5)	81	(2.8)	45	(2.9)	157	(3.5)	73	(3.1)
with drug-related† adverse events	174	(63.7)	28	(68.3)	236	(60.2)	45	(68.2)	2,030	(70.8)	1,110	(70.7)	3,069	(68.7)	1,635	(70.5)
with toxicity grade 3-5 adverse events	146	(53.5)	24	(58.5)	211	(53.8)	34	(51.5)	1,414	(49.3)	739	(47.1)	2,209	(49.5)	1,093	(47.1)
with toxicity grade 3-5 drug-related adverse events	49	(17.9)	8	(19.5)	68	(17.3)	12	(18.2)	446	(15.5)	214	(13.6)	739	(16.6)	329	(14.2)
with serious adverse events	109	(39.9)	15	(36.6)	157	(40.1)	23	(34.8)	1,151	(40.1)	577	(36.8)	1,758	(39.4)	850	(36.7)
with serious drug-related adverse events	36	(13.2)	4	(9.8)	47	(12.0)	9	(13.6)	316	(11.0)	148	(9.4)	524	(11.7)	232	(10.0)
who died	29	(10.6)	1	(2.4)	35	(8.9)	4	(6.1)	146	(5.1)	65	(4.1)	267	(6.0)	98	(4.2)
who died due to a drug-related adverse event	5	(1.8)	0	(0.0)	5	(1.3)	1	(1.5)	15	(0.5)	7	(0.4)	32	(0.7)	14	(0.6)
discontinued drug due to an adverse event	35	(12.8)	5	(12.2)	46	(11.7)	9	(13.6)	352	(12.3)	186	(11.8)	579	(13.0)	284	(12.2)
discontinued drug due to a drug-related adverse event	15	(5.5)	4	(9.8)	21	(5.4)	6	(9.1)	176	(6.1)	83	(5.3)	293	(6.6)	142	(6.1)
discontinued drug due to a serious adverse event	31	(11.4)	4	(9.8)	37	(9.4)	7	(10.6)	271	(9.4)	136	(8.7)	437	(9.8)	204	(8.8)
discontinued drug due to a serious drug-related adverse event	12	(4.4)	3	(7.3)	14	(3.6)	4	(6.1)	119	(4.1)	53	(3.4)	189	(4.2)	83	(3.6)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the 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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Source: [ISS: adam-adsl; adae]

The Applicant provided a summary of Adverse Events by Gender in the KN181 trial (pembrolizumab monotherapy vs SOC) as requested. No clear difference could be detected between the genders.

ECOG

Table 5.3.5.3.3-esophageal2: 122
Adverse Event Summary by ECOG Status Category (0, 1)
(ASaT Population)

	KN181 Data for Pembrolizumab‖				Esophageal Dataset for Pembrolizumab††				Reference Safety Dataset for Pembrolizumab¶				Cumulative Running Safety Dataset for Pembrolizumab‡‡			
	[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	126		187		178		279		1,987		2,280		3,143		3,446	
with one or more adverse events	119	(94.4)	180	(96.3)	169	(94.9)	267	(95.7)	1,942	(97.7)	2,206	(96.8)	3,040	(96.7)	3,328	(96.6)
with no adverse event	7	(5.6)	7	(3.7)	9	(5.1)	12	(4.3)	45	(2.3)	74	(3.2)	103	(3.3)	118	(3.4)
with drug-related† adverse events	90	(71.4)	111	(59.4)	124	(69.7)	156	(55.9)	1,519	(76.4)	1,529	(67.1)	2,352	(74.8)	2,245	(65.1)
with toxicity grade 3-5 adverse events	59	(46.8)	110	(58.8)	77	(43.3)	167	(59.9)	810	(40.8)	1,240	(54.4)	1,296	(41.2)	1,897	(55.0)
with toxicity grade 3-5 drug-related adverse events	20	(15.9)	37	(19.8)	27	(15.2)	53	(19.0)	277	(13.9)	353	(15.5)	470	(15.0)	565	(16.4)
with serious adverse events	42	(33.3)	81	(43.3)	58	(32.6)	121	(43.4)	630	(31.7)	1,011	(44.3)	1,002	(31.9)	1,512	(43.9)
with serious drug-related adverse events	19	(15.1)	21	(11.2)	25	(14.0)	31	(11.1)	202	(10.2)	243	(10.7)	347	(11.0)	387	(11.2)
who died	6	(4.8)	24	(12.8)	8	(4.5)	31	(11.1)	55	(2.8)	143	(6.3)	96	(3.1)	256	(7.4)
who died due to a drug-related adverse event	2	(1.6)	3	(1.6)	2	(1.1)	4	(1.4)	8	(0.4)	14	(0.6)	16	(0.5)	30	(0.9)
discontinued drug due to an adverse event	13	(10.3)	27	(14.4)	16	(9.0)	39	(14.0)	195	(9.8)	316	(13.9)	330	(10.5)	501	(14.5)
discontinued drug due to a drug-related adverse event	11	(8.7)	8	(4.3)	13	(7.3)	14	(5.0)	112	(5.6)	134	(5.9)	206	(6.6)	212	(6.2)
discontinued drug due to a serious adverse event	9	(7.1)	26	(13.9)	10	(5.6)	34	(12.2)	137	(6.9)	249	(10.9)	217	(6.9)	400	(11.6)
discontinued drug due to a serious drug-related adverse event	8	(6.3)	7	(3.7)	8	(4.5)	10	(3.6)	70	(3.5)	93	(4.1)	115	(3.7)	146	(4.2)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the 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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Source: [ISS: adam-adsl; adae]

Appendix 6-1

Adverse Event Summary by ECOG Status
(KN181 ASaT Population)

	Pembrolizumab 200 mg						SOC					
	0		1		2		0		1		2	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	126		187		1		109		187		0	
with one or more adverse events	119	(94.4)	180	(96.3)	1	(100.0)	108	(99.1)	180	(96.3)	0	(0.0)
with no adverse event	7	(5.6)	7	(3.7)	0	(0.0)	1	(0.9)	7	(3.7)	0	(0.0)
with drug-related† adverse events	90	(71.4)	111	(59.4)	1	(100.0)	97	(89.0)	158	(84.5)	0	(0.0)
with toxicity grade 3-5 adverse events	59	(46.8)	110	(58.8)	1	(100.0)	60	(55.0)	123	(65.8)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	20	(15.9)	37	(19.8)	0	(0.0)	40	(36.7)	81	(43.3)	0	(0.0)
with non-serious adverse events	118	(93.7)	176	(94.1)	1	(100.0)	107	(98.2)	177	(94.7)	0	(0.0)
with serious adverse events	42	(33.3)	81	(43.3)	1	(100.0)	32	(29.4)	89	(47.6)	0	(0.0)
with serious drug-related adverse events	19	(15.1)	21	(11.2)	0	(0.0)	15	(13.8)	42	(22.5)	0	(0.0)
who died	6	(4.8)	24	(12.8)	0	(0.0)	5	(4.6)	27	(14.4)	0	(0.0)
who died due to a drug-related adverse event	2	(1.6)	3	(1.6)	0	(0.0)	0	(0.0)	5	(2.7)	0	(0.0)
discontinued drug due to an adverse event	13	(10.3)	27	(14.4)	0	(0.0)	12	(11.0)	30	(16.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	11	(8.7)	8	(4.3)	0	(0.0)	7	(6.4)	12	(6.4)	0	(0.0)
discontinued drug due to a serious adverse event	9	(7.1)	26	(13.9)	0	(0.0)	6	(5.5)	24	(12.8)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	8	(6.3)	7	(3.7)	0	(0.0)	2	(1.8)	8	(4.3)	0	(0.0)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
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: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Comparison of safety data by ECOG PS showed numerically higher incidences for subjects with ECOG PS 1 in several categories; however, these differences were observed in the same range also for the RSD.

Region

Table 5.3.5.3.3-esophageal2: 123
Adverse Event Summary by Region (EU, Ex-EU)
(ASaT Population)

	KN181 Data for Pembrolizumab‖				Esophageal Dataset for Pembrolizumab††				Reference Safety Dataset for Pembrolizumab¶				Cumulative Running Safety Dataset for Pembrolizumab‡‡			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	106		208		144		314		1,537		2,902		2,395		4,389	
with one or more adverse events	103	(97.2)	197	(94.7)	140	(97.2)	297	(94.6)	1,480	(96.3)	2,833	(97.6)	2,304	(96.2)	4,250	(96.8)
with no adverse event	3	(2.8)	11	(5.3)	4	(2.8)	17	(5.4)	57	(3.7)	69	(2.4)	91	(3.8)	139	(3.2)
with drug-related† adverse events	55	(51.9)	147	(70.7)	77	(53.5)	204	(65.0)	1,048	(68.2)	2,092	(72.1)	1,618	(67.6)	3,086	(70.3)
with toxicity grade 3-5 adverse events	56	(52.8)	114	(54.8)	75	(52.1)	170	(54.1)	732	(47.6)	1,421	(49.0)	1,127	(47.1)	2,175	(49.6)
with toxicity grade 3-5 drug-related adverse events	16	(15.1)	41	(19.7)	21	(14.6)	59	(18.8)	235	(15.3)	425	(14.6)	368	(15.4)	700	(15.9)
with serious adverse events	45	(42.5)	79	(38.0)	61	(42.4)	119	(37.9)	618	(40.2)	1,110	(38.2)	923	(38.5)	1,685	(38.4)
with serious drug-related adverse events	8	(7.5)	32	(15.4)	11	(7.6)	45	(14.3)	181	(11.8)	283	(9.8)	272	(11.4)	484	(11.0)
who died	10	(9.4)	20	(9.6)	14	(9.7)	25	(8.0)	80	(5.2)	131	(4.5)	128	(5.3)	237	(5.4)
who died due to a drug-related adverse event	1	(0.9)	4	(1.9)	2	(1.4)	4	(1.3)	10	(0.7)	12	(0.4)	16	(0.7)	30	(0.7)
discontinued drug due to an adverse event	12	(11.3)	28	(13.5)	17	(11.8)	38	(12.1)	178	(11.6)	360	(12.4)	295	(12.3)	568	(12.9)
discontinued drug due to a drug-related adverse event	3	(2.8)	16	(7.7)	5	(3.5)	22	(7.0)	94	(6.1)	165	(5.7)	155	(6.5)	280	(6.4)
discontinued drug due to a serious adverse event	11	(10.4)	24	(11.5)	15	(10.4)	29	(9.2)	142	(9.2)	265	(9.1)	220	(9.2)	421	(9.6)
discontinued drug due to a serious drug-related adverse event	2	(1.9)	13	(6.3)	3	(2.1)	15	(4.8)	67	(4.4)	105	(3.6)	95	(4.0)	177	(4.0)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the 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 in KN181.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4.
¶ 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, KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN045, KN052, KN087, KN055, KN040 and KN012 Cohorts B and B2.
‡‡ 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 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort A4 (Esophageal Cancer) and Cohort B4 (Cervical Cancer), KN040, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158 Cohort E (Cervical Cancer), KN164 Cohort A (Colorectal Carcinoma), KN170, KN180, KN181, KN042 and KN224.
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: 26FEB2018)
Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database Cutoff Date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Database Cutoff Date for PMBCL (KN013 Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database Cutoff Date for Cervical (KN028-Cervical: 20FEB2017, KN158- Cervical: 15JAN2018)
Database Cutoff Date for HCC (KN224: 15MAY2018)
Database Cutoff Date for MCC (KN017: 06FEB2018)
Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Source: [ISS: adam-adsl; adae]

With regards to Region of enrollment, subjects enrolled ex-EU tended to have higher proportions of drug-related AEs, grade 3-5 drug-related AEs, SAEs) in both the esophageal cancer datasets, while this was not found for the Pembrolizumab monotherapy RSD. A significant difference in the incidence of AEs reported as drug-related could be observed for the pembrolizumab monotherapy arm KN181, when EU was compares to Ex-EU. Ex-EU participants in the pembrolizumab arm had higher total exposure person-months (1134.29 ex-EU and 431.16 EU). Exposure was almost doubled, reflecting the better efficacy in Asian patients.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

Discontinuation Due to AEs

Table 14.3-29
Subjects With Adverse Events Resulting in Study Medication Discontinuation By Decreasing Incidence
(Incidence >1% in One or More Treatment Groups)
(ASaT Population) (*modified by the Assessor*)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	40	(12.7)	42	(14.2)
with no adverse events	274	(87.3)	254	(85.8)
Autoimmune hepatitis	5	(1.6)	0	(0.0)
Death	4	(1.3)	4	(1.4)
Oesophageal haemorrhage	4	(1.3)	0	(0.0)
Pneumonia	3	(1.0)	5	(1.7)
Pneumonitis	3	(1.0)	0	(0.0)

Table 14.3-30
Subjects With Drug-related Adverse Events Resulting in Study Medication Discontinuation By Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more drug-related adverse events	19	(6.1)	19	(6.4)
with no drug-related adverse events	295	(93.9)	277	(93.6)
Autoimmune hepatitis	5	(1.6)	0	(0.0)
Pneumonitis	3	(1.0)	0	(0.0)
Acute kidney injury	1	(0.3)	0	(0.0)
Alanine aminotransferase increased	1	(0.3)	0	(0.0)
Cerebral infarction	1	(0.3)	0	(0.0)
Colitis	1	(0.3)	0	(0.0)
Death	1	(0.3)	0	(0.0)
Guillain-Barre syndrome	1	(0.3)	0	(0.0)
Liver function test increased	1	(0.3)	0	(0.0)
Myocarditis	1	(0.3)	0	(0.0)
Oesophageal haemorrhage	1	(0.3)	0	(0.0)
Polymyositis	1	(0.3)	0	(0.0)
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)
Dehydration	0	(0.0)	1	(0.3)
Diarrhoea	0	(0.0)	1	(0.3)
Femoral neck fracture	0	(0.0)	1	(0.3)
Interstitial lung disease	0	(0.0)	1	(0.3)
Lung infection	0	(0.0)	1	(0.3)
Malaise	0	(0.0)	2	(0.7)
Nausea	0	(0.0)	1	(0.3)
Neuropathy peripheral	0	(0.0)	3	(1.0)
Neutrophil count decreased	0	(0.0)	1	(0.3)
Paraesthesia	0	(0.0)	1	(0.3)
Peripheral sensory neuropathy	0	(0.0)	1	(0.3)
Pneumonia	0	(0.0)	2	(0.7)
Pneumonia aspiration	0	(0.0)	1	(0.3)
Radiation pneumonitis	0	(0.0)	1	(0.3)
Sepsis	0	(0.0)	1	(0.3)
Vomiting	0	(0.0)	1	(0.3)
White blood cell count decreased	0	(0.0)	1	(0.3)

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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Interruption Due to Adverse Events

Table 14.3-31
Subjects With Adverse Events Resulting in Dose Interruption By Decreasing Incidence
(Incidence >1% in One or More Treatment Groups)
(ASaT Population) (*modified by the Assessor*)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	84	(26.8)	111	(37.5)
with no adverse events	230	(73.2)	185	(62.5)
Aspartate aminotransferase increased	10	(3.2)	2	(0.7)
Pneumonitis	6	(1.9)	0	(0.0)
Alanine aminotransferase increased	5	(1.6)	2	(0.7)
Diarrhoea	4	(1.3)	4	(1.4)
Dysphagia	3	(1.0)	0	(0.0)
Oesophageal fistula	3	(1.0)	0	(0.0)
Pneumonia	3	(1.0)	6	(2.0)
Pneumonia aspiration	3	(1.0)	3	(1.0)
Rash	3	(1.0)	0	(0.0)
Respiratory tract infection	3	(1.0)	0	(0.0)

Table 14.3-32
Subjects With Drug-related Adverse Events Resulting in Dose Interruption By Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more drug-related adverse events	38	(12.1)	75	(25.3)
with no drug-related adverse events	276	(87.9)	221	(74.7)
Aspartate aminotransferase increased	8	(2.5)	1	(0.3)
Pneumonitis	6	(1.9)	0	(0.0)
Diarrhoea	4	(1.3)	4	(1.4)
Alanine aminotransferase increased	3	(1.0)	1	(0.3)
Rash	2	(0.6)	0	(0.0)
Anaemia	1	(0.3)	9	(3.0)
Asthenia	1	(0.3)	0	(0.0)
Demyelination	1	(0.3)	0	(0.0)
Dermatitis	1	(0.3)	0	(0.0)
Facial paralysis	1	(0.3)	0	(0.0)
Hyperglycaemia	1	(0.3)	0	(0.0)
Hypophysitis	1	(0.3)	0	(0.0)
Hypothyroidism	1	(0.3)	0	(0.0)
Immune-mediated hepatitis	1	(0.3)	0	(0.0)
Interstitial lung disease	1	(0.3)	0	(0.0)
Malaise	1	(0.3)	0	(0.0)
Nephritis	1	(0.3)	0	(0.0)
Neutrophil count decreased	1	(0.3)	19	(6.4)
Oesophageal perforation	1	(0.3)	1	(0.3)
Pneumonia	1	(0.3)	3	(1.0)
Pyrexia	1	(0.3)	2	(0.7)
Radiation pneumonitis	1	(0.3)	0	(0.0)
Rash pustular	1	(0.3)	0	(0.0)
Tracheal fistula	1	(0.3)	0	(0.0)
Varicella zoster virus infection	1	(0.3)	0	(0.0)
Bronchitis	0	(0.0)	1	(0.3)
Constipation	0	(0.0)	1	(0.3)
Dehydration	0	(0.0)	1	(0.3)
Depression	0	(0.0)	1	(0.3)
Fatigue	0	(0.0)	4	(1.4)
Febrile neutropenia	0	(0.0)	11	(3.7)
Hypersensitivity	0	(0.0)	3	(1.0)
Hyponatraemia	0	(0.0)	1	(0.3)

Impaired gastric emptying	0	(0.0)	1	(0.3)
Infection	0	(0.0)	1	(0.3)
Irritability	0	(0.0)	1	(0.3)
Leukopenia	0	(0.0)	4	(1.4)
Lung infection	0	(0.0)	1	(0.3)
Lymphopenia	0	(0.0)	2	(0.7)
Mucosal inflammation	0	(0.0)	1	(0.3)
Nail toxicity	0	(0.0)	2	(0.7)
Nausea	0	(0.0)	2	(0.7)
Neutropenia	0	(0.0)	13	(4.4)
Oedema peripheral	0	(0.0)	2	(0.7)
Paraesthesia	0	(0.0)	1	(0.3)
Paronychia	0	(0.0)	1	(0.3)
Peripheral motor neuropathy	0	(0.0)	1	(0.3)
Peripheral sensory neuropathy	0	(0.0)	5	(1.7)
Pneumonia bacterial	0	(0.0)	2	(0.7)
Sepsis	0	(0.0)	1	(0.3)
Soft tissue infection	0	(0.0)	1	(0.3)
Stoma site erythema	0	(0.0)	1	(0.3)
Stomatitis	0	(0.0)	1	(0.3)
Thrombocytopenia	0	(0.0)	1	(0.3)
Tracheo-oesophageal fistula	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.3)
Urticaria	0	(0.0)	1	(0.3)
Vomiting	0	(0.0)	2	(0.7)
White blood cell count decreased	0	(0.0)	14	(4.7)

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.
Database Cutoff Date: 15OCT2018.

Source: [P181V01MK3475: adam-adsl; adae]

Data supporting SmPC section 4.8

Table: Adverse Reactions in patients treated with pembrolizumab monotherapy

		Monotherapy (N=6342)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	pneumonia	6.1% (384)	237
Blood and lymphatic system disorders			
Very common	anaemia	14.1% (895)	264
Common	thrombocytopenia	1.5% (93)	17
Common	lymphopenia	1.1% (68)	17
Uncommon	neutropenia	0.8% (48)	15
Uncommon	leukopenia	0.7% (45)	7
Uncommon	eosinophilia	0.6% (39)	0
Rare	immune thrombocytopenic purpura	0.06% (4)	4
Rare	haemolytic anaemia	0.02% (1)	1
Rare	pure red cell aplasia[#]	(0)	0
Rare	haemophagocytic lymphohistiocytosis[#]	(0)	0
Immune system disorders			
Common	infusion reactions[a]	2.2% (139)	14
Uncommon	sarcoidosis	0.2% (10) Not	0
Not known	solid organ transplant rejection[*]	Calculated	
Endocrine disorders			
Very common	hypothyroidism[b]	11.0% (696)	8
Common	hyperthyroidism	4.1% (263)	7
Uncommon	hypophysitis[c]	0.6% (39)	22
Uncommon	thyroiditis[d]	0.9% (58)	2
Uncommon	adrenal insufficiency	0.7% (42)	18
Metabolism and nutrition disorders			

Very common	decreased appetite	19.3% (1226)	87
Common	hyponatraemia	5.8% (365)	162
Common	hypokalaemia	4.7% (296)	63
Common	hypocalcaemia	1.9% (121)	11
Uncommon	type 1 diabetes mellitus[e]	0.4% (23)	22
Psychiatric disorders			
Common	insomnia	7.2% (455)	7
Nervous system disorders			
Very common	headache	11.4% (726)	20
Common	dizziness	6.9% (437)	11
Common	neuropathy peripheral	2.0% (126)	3
Common	lethargy	1.1% (72)	2
Common	dysgeusia	2.5% (160)	1
Uncommon	epilepsy	0.2% (11)	7
Rare	guillain-barre syndrome[f]	0.08% (5)	3
Rare	myasthenic syndrome[g]	0.05% (3)	1
Rare	meningitis (aseptic)[h]	0.05% (3)	3
Rare	encephalitis	0.03% (2)	2
Eye disorders			
Common	dry eye	1.5% (95)	0
Uncommon	uveitis[i]	0.3% (21)	2
Rare	Vogt-Koyanagi-Harada syndrome[#]	(0)	0
Cardiac disorders			
Uncommon	pericardial effusion	0.8% (52)	26
Uncommon	pericarditis	0.1% (8)	4
Rare	myocarditis	0.09% (6)	6
Vascular disorders			
Common	hypertension	4.7% (297)	102
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	16.1% (1023)	135
Very common	cough	18.6% (1182)	10
Common	pneumonitis[j]	4.4% (278)	97
Gastrointestinal disorders			
Very common	diarrhoea	19.7% (1247)	82
Very common	abdominal pain[k]	12.5% (794)	65
Very common	nausea	20.3% (1286)	54
Very common	vomiting	12.3% (782)	48
Very common	constipation	16.9% (1069)	28
Common	colitis[l]	1.8% (115)	70
Common	dry mouth	4.7% (297)	1
Uncommon	pancreatitis[m]	0.3% (17)	10
Rare	small intestinal perforation	0.03% (2)	1
Hepatobiliary disorders			
Uncommon	hepatitis[n]	0.9% (57)	45
Skin and subcutaneous tissue disorders			

Very common	rash[o]	18.8% (1190)	2
Very common	pruritus[p]	17.6% (1118)	1
Common	severe skin reactions[q]	1.5% (93)	68
Common	erythema	2.7% (169)	2
Common	dry skin	5.0% (314)	1
Common	vitiligo[r]	3.8% (244)	0
Common	eczema	1.5% (95)	0
Common	alopecia	1.4% (88)	0
Common	dermatitis acneiform	1.2% (76)	0
Uncommon	lichenoid keratosis[s]	0.4% (26)	9
Uncommon	psoriasis	0.6% (35)	4
Uncommon	dermatitis	0.9% (59)	1
Uncommon	papule	0.4% (27)	1
Uncommon	hair colour changes	0.3% (20)	0
Rare	stevens-johnson syndrome	0.05% (3)	2
Rare	erythema nodosum	0.05% (3)	0
Rare	toxic epidermal necrolysis[#]	(0)	0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[t]	18.5% (1176)	106
Very common	arthralgia	13.7% (867)	41
Common	myositis[u]	7.3% (464)	19
Common	pain in extremity	6.3% (399)	19
Common	arthritis[v]	2.2% (137)	9
Uncommon	tenosynovitis[w]	0.5% (31)	1
Renal and urinary disorders			
Uncommon	nephritis[x]	0.4% (25)	15

		Monotherapy (N=6342)	
		All AEs % (n)	Gr 3-5 AEs n
General disorders and administration site conditions			
Very common	fatigue	31.2% (1980)	152
Very common	asthenia	11.2% (713)	68
Very common	oedema[y]	11.4% (720)	43
Very common	pyrexia	12.2% (775)	30
Common	influenza like illness	3.5% (224)	1
Common	chills	3.9% (247)	0
Investigations			
Common	aspartate aminotransferase increased	6.6% (419)	72
Common	alanine aminotransferase increased	6.6% (418)	67
Common	hypercalcaemia	3.2% (204)	59
Common	blood alkaline phosphatase increased	4.1% (262)	54
Common	blood bilirubin increased	2.2% (142)	29
Common	blood creatinine increased	4.2% (264)	12
Uncommon	amylase increased	0.3% (18)	8

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

[*] Adverse reaction frequencies presented may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

[#] The "rule of 3" has been applied in calculation.

Includes all subjects who received at least one dose of pembrolizumab in KN181, KN180, KN028 Cohort A4, KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN054, KN055, KN087, KN042 and KN048.

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: 26FEB2018)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016, KN048:13JUN2018)

Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database Cutoff Date for Bladder (KN045: 26OCT2017, KN052: 09MAR2017)

Database Cutoff Date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

a. infusion reactions (anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, infusion related reaction)

b. hypothyroidism (hypothyroidism, myxoedema, primary hypothyroidism)

c. hypophysitis (hypophysitis, hypopituitarism)

d. thyroiditis (autoimmune thyroiditis, thyroid disorder, thyroiditis)

e. type 1 diabetes mellitus (diabetic ketoacidosis, type 1 diabetes mellitus)

f. guillain-barre syndrome (axonal neuropathy, demyelinating polyneuropathy, guillain-barre syndrome)

g. myasthenic syndrome (myasthenia gravis, myasthenic syndrome)

h. meningitis (aseptic) (meningitis, meningitis noninfective)

i. uveitis (iridocyclitis, iritis, uveitis)

j. pneumonitis (interstitial lung disease, organising pneumonia, pneumonitis)

k. abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper)

l. colitis (autoimmune colitis, colitis, colitis microscopic, enterocolitis)

m. pancreatitis (autoimmune pancreatitis, pancreatitis, pancreatitis acute)

n. hepatitis (autoimmune hepatitis, drug-induced liver injury, hepatitis, hepatitis acute, immune-mediated hepatitis)

o. rash (genital rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular)

p. pruritus (pruritus, pruritus generalised, pruritus genital, urticaria, urticaria papular)

q. severe skin reactions (dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, pemphigus, pruritus, pruritus generalised, pruritus genital, rash, rash erythematous, rash generalised, rash maculo-papular, rash pruritic, rash pustular, skin necrosis, stevens-johnson syndrome, toxic skin eruption)

r. vitiligo (hypopigmentation of eyelid, skin depigmentation, skin hypopigmentation, vitiligo)

s. lichenoid keratosis (lichen planus, lichen sclerosus, lichenoid keratosis)

t. musculoskeletal pain (back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, torticollis)

u. myositis (myalgia, myopathy, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis)

v. arthritis (arthritis, joint effusion, joint swelling, polyarthritis)

w. tenosynovitis (synovitis, tendon pain, tendonitis, tenosynovitis)

x. nephritis (acute kidney injury, autoimmune nephritis, glomerulonephritis membranous, nephritis, nephrotic syndrome, renal failure, tubulointerstitial nephritis)

y. oedema (eyelid oedema, face oedema, fluid overload, fluid retention, generalised oedema, lip oedema, localised oedema, oedema, oedema peripheral, periorbital oedema)

Post marketing experience

The safety profile of pembrolizumab was summarized in the PSUR covering the period 04-MAR-2018 through 03-SEP-2018. No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The safety evaluation of pembrolizumab monotherapy for the treatment of patients with recurrent locally advanced or metastatic esophageal cancer with disease progression on or after 1 line of prior systemic therapy is primarily based on the final analysis results of the pivotal, randomized, controlled, open-label Phase 3 study, KEYNOTE-181. As of data cut-off (15-OCT-2018), the KN181 ASaT population included subjects who received pembrolizumab monotherapy (N=314) and those who received SOC based on investigator's choice of paclitaxel, docetaxel, or irinotecan (N=296).

In addition, the Esophageal Safety Dataset for Pembrolizumab (N=458) pooling data of the KEYNOTE-181 (2L), KEYNOTE-180 (2 or more prior lines of therapy), and KEYNOTE-028 Cohort A4 (any line of therapy) who received at least 1 dose of pembrolizumab is also provided, as comprehensive reference dataset for pembrolizumab's safety in esophageal cancer. Further, to compare pembrolizumab's safety profile for esophageal cancer with that across indications, the pooled EU Pembrolizumab Monotherapy RSD (N=4439) and the Cumulative Running Pembrolizumab Monotherapy SD (N=6784) are also submitted.

While a comparable median time on study drug in KN181 study arms (64 and 63 days in pembrolizumab and SOC, respectively) is found, longer mean **exposure** (122 [range 1 to 742] vs 95[range 1 to 546] days on therapy) and higher proportions of subjects reaching either 6 (18.2% vs 13.9%, respectively) or 12 months of observation (6.7% vs 2.4%) were documented for the pembrolizumab arm when compared to SOC. According to what expected for patients with esophageal cancer, these subjects had shorter pembrolizumab exposures in comparison to those treated with the drug for other indications (median months on therapy: 4 (range 0 to 24) in both KN181 and the Esophageal Dataset for Pembrolizumab vs 7 (range 0 to 30) in the Pembrolizumab monotherapy RSD).

With regards to **demographics and disease characteristics**, KN181 study arms were well balanced and overall features were: 87% males, 43% $\geq$65 years, 56% White race, 61% ECOG PS 1, 92% metastases staging M1, 97.6% prior treatment with platinum in 98.9%, fluoropyrimidine in 84.9%, and taxane in 33.4%). When compared to the pooled pembrolizumab monotherapy RSD, esophageal cancer patients were more often male gender, of Asian race or ECOG PS 1, and were more likely to have been enrolled outside the US. Mean age and frequency of subjects with age $\geq$65 years was similar across datasets.

The **Adverse Event Summary** of KN181 showed in pembrolizumab-treated subjects compared to patients treated with SOC, lower proportions of drug-related AEs (64.3% vs 86.1%), grade 3-5 AEs (54.1% vs 61.8%), grade 3-5 drug-related AEs (18.1% vs 40.9%), and drug-related SAEs (12.7% vs 19.3%), whilst having comparable frequencies of overall AEs (95.5% vs 97.3%), SAEs (39.5% vs 40.9%), AEs leading to death (9.6% vs 10.8%), drug-related AEs leading to death (1.6% vs 1.7%), and of drug discontinuations due to AEs (12.7 vs 14.2%), due to drug-related AEs (6.1% vs 6.4%), or due to SAEs (11.1% vs 10.1%).

At comparative evaluation of datasets, consistency between KN181 pembrolizumab arm and the Esophageal dataset for pembrolizumab was found for frequencies of all AE categories. In respect to the Pembrolizumab monotherapy RSD, that included subjects with pembrolizumab use across indications, patients with esophageal cancer participating in the KN181 pembrolizumab arm tended to have higher proportions of grade 3-5 AEs (54.1% vs 48.5%), grade 3-5 drug-related AEs (18.2% vs 14.9%), drug-related SAEs (12.7% vs 10.5%), drug-related AEs leading to death (1.6% vs 0.5%), drug discontinuations due to SAEs (11.1% vs 9.2%). Dataset comparisons after adjusting for pembrolizumab exposure confirmed these findings, showing AE frequencies for the KN181 pembrolizumab arm that were

consistent with those of the Esophageal dataset for pembrolizumab, but increased when compared to those found for Pembrolizumab monotherapy RDS. Taking into account the clinical setting, this is not unexpected.

Among **overall AEs** (95.5% in the pembrolizumab arm and 97.3% in the SOC arm), observed PT patterns found in the two study arms mirrored the known safety profile of the two treatment strategies. The **most common AEs** (incidence ≥20%) in the pembrolizumab arm were *Decreased appetite* (24.8%) and *Fatigue* (22.3%), while in the chemotherapy arm aside from these (*Decrease appetite* 25.7%, *Fatigue* (30.1%), also *Alopecia* (29.7%), *Anemia* (28.7%), *Nausea* (28.4%), *Weight decreased* (28.0%) were found. As expected, pembrolizumab-treated subjects when compared to SOC had lower proportions of several AEs typically associated with cytotoxic agents (*Alopecia* 1.3% vs 29.7%; *WBC count decreased* 0.6% vs 17.9%; *Neutrophil count decreased* 1.0% vs 17.6%; *Neutropenia* 0.0% vs 13.2%; *Anemia* 16.9% vs 28.7%; *Peripheral sensory neuropathy* 1.0% vs 17.6%; *Diarrhea* 12.4% vs 28.0%; *Nausea* 19.1% vs 28.4%; *Fatigue* 22.3% vs 30.1%; *Vomiting* 12.4% vs 18.6%; *Pyrexia* 10.5% vs 16.9%), and higher frequencies of *Hypothyroidism* (11.5% vs 2.4%) and *Dysphagia* (15.6% vs 9.5%). Between-treatment comparisons of AEs with >10% incidence showed increased risks of *Hypothyroidism* and *Dysphagia* in the pembrolizumab arm, and of *Alopecia*, haematologic AEs (*White blood cell count decreased, Neutrophil count decreased, Neutropenia*), *Peripheral sensory neuropathy*, gastrointestinal AEs (*Nausea*, *Vomiting*), *Pyrexia* and *Fatigue* in the chemotherapy arm. **Grade 3-5 AEs** were documented in 54.1% of subjects receiving pembrolizumab and 61.8% of those treated with SOC. *Anaemia* was the most commonly reported PT in both study arms (6.1% in pembrolizumab and 10.5% in SOC). At between-treatment comparisons of PTs with incidence >5%, *White blood cell count decreased* and *Neutrophil Count decreased* both had higher risks in the chemotherapy arm, while no PT resulted more frequent in the pembrolizumab arm. Median time to first grade 3-5 event was significantly longer in pembrolizumab- (16.0 weeks) than in SOC-treated (10.3 weeks) subjects (p-value <0.001). Analysis of exposure-adjusted event rates of Grade 3 to 5 AEs showed that the rate for pembrolizumab group was significantly lower (3.4 vs 6.0 events/100 person-weeks) and the median time to first Grade 3 to 5 AE was longer in the pembrolizumab group than in the chemotherapy group (16.0 weeks vs 10.3 weeks).

In the pembrolizumab arm, **drug-related AEs,** except for *Hypothyroidism* (10.5% vs 0.3%), were less often observed when compared to SOC (64.3% vs 86.1%, respectively), and most commonly drug-related AEs by PT (incidence >5%) in the pembrolizumab arm were more frequently reported in the control arm: *Fatigue* (11.8% vs 20.6%, respectively), *Decreased appetite* (8.6%, 11.5%), *Asthenia* (7.0% vs 11.5%), *Nausea* (7.0% vs 21.6%), and *Diarrhea* (5.4% vs 20.3%). Aside from these PTs, in chemotherapy-treated subjects many other drug-related AEs had incidence >5% with *Alopecia* (29.1% vs 0.6%) and *Anemia* (22.3% vs 2.5%) being the most common. Proportions of subjects with **Grade 3-5 drug-related AEs** were considerably lower in the pembrolizumab arm than in the SOC arm (18.2% vs 40.9%) showing an incidence >1% for *Autoimmune hepatitis* (1.6%), *Anemia* (1.3%), *Asthenia* (1.3%), *Colitis* (1.0%), *Pneumonia* (1.0%), and *Pneumonitis* (1.0%). Notably, all grade 3-5 drug-related AEs reported with ≥5% incidence in chemotherapy-treated subjects, aside from *Anemia* (1.3% vs 7.8%), had negligible proportions in pembrolizumab-treated participants (*White blood cell count decreased* 0.0% vs 10.1%; *Neutrophil count decreased* 0.3% vs 9.8%; *Febrile neutropenia* 0.0% vs 8.4%; *Neutropenia* 0.0% vs 7.1%).

Whilst comparable proportions of subjects had **SAEs** up to 90 days of last dose in the two KN181 study arms (39.5% in pembrolizumab and 40.9% in SOC), **drug-related SAEs** were lower in the pembrolizumab arm (12.7%) than in the SOC arm (19.3%). SAEs most commonly (>2% incidence) reported were *Pneumonia* (4.5%), *Dysphagia* (3.5%), *Pneumonia aspiration* (3.5%), *Pneumonitis* (2.2%) in pembrolizumab-treated and *Febrile neutropenia* (7.4%), *Pneumonia* (6.8%), and *Death* (3.4%) in SOC-treated subjects. Drug-related SAEs most frequently (≥1% incidence) reported for the pembrolizumab arm were almost all immune-mediated events: *Pneumonitis* (7 subjects; 2.2%),

Autoimmune hepatitis (3 subjects; 1.0%), *Colitis* (3 subjects; 1.0%), and *Pneumonia* (3 subjects; 1.0%). SAEs related to drugs used to treat controls were typical chemotherapy-related events, such as *Febrile neutropenia, Pneumonia, Pyrexia, Diarrhea, Vomiting, Anemia, Nausea, Neutropenia,* and *Neutrophil count decreased.*

Subjects with **AEs resulting in deaths** were almost comparable among the two study arms with proportions of 9.6% and 10.8% in the pembrolizumab and the SOC arms, respectively. Reasons for the fatal event with ≥1% incidence were in the pembrolizumab-treated participants: *Death* (5 subjects [1.6%] vs 10 subjects [3.4%] in SOC arm), *Esophageal hemorrhage* (4 subjects [1.3%] vs 0 [0.0%]), *Pneumonia aspiration* (4 subjects [1.3%] vs 1 subject [0.3%]), *Pneumonia* (3 subjects [1.0%] vs 5 subjects [1.7%]). As among reasons for death in pembrolizumab-treated subjects, 2 cases of completed suicide were reported and it is noted that the Keytruda SmPC does not include this type of AE. When looking at pembrolizumab-treated populations, small and consistent proportions of subjects with suicide/self-injury events are found: KN-181 pembrolizumab arm 0.6%, Esophageal Dataset for Pembrolizumab 0.4%, RSD for Pembrolizumab 0.2%. When considering OASE database, which includes pembrolizumab monotherapy safety data from all unblinded randomized trials across indications (31-MAR-2018 database lock, n=9118) as well as comparator safety data on placebo, ipilimumab, cetuximab, and chemotherapy, similar incidences of suicide/self-injury SMQ are found across treatments (0.0-0.2%), while a slightly higher incidence of depressive disorders SMQ is observed in pembrolizumab as compared to the comparator (3.5% vs 1.4-2.7%, respectively). Being also in line with recently published literature (*Minnema L et al. Drug Safety 2019*), it is agreed with the MAH that at present evidence is insufficient to support an association between pembrolizumab and suicidal behavior. When comparing the two KN181 treatment arms, it is noted that a slight increase in Oesophageal/ Gastrointestinal haemorrhages leading to death is reported in subjects receiving pembrolizumab than in those treated with chemotherapy. When looking at each grouped terms "gastrointestinal haemorrhage", "gastrointestinal obstruction", "gastrointestinal perforation" and "gastrointestinal ulceration", the frequencies in pembrolizumab arm and SOC arm appear similar. Nevertheless, when PTs specifically related to the esophageal/upper GI location are analysed, some of them are higher in pembrolizumab arm (eg. Esophageal haemorrhage 1.9% vs 0.3%, esophageal obstruction 1.7% vs 0.3%) while other are increased in SOC arm (e.g. upper gastrointestinal haemorrhage 0.3% vs 1.4%, esophgeal perforation 0.3% vs 1.4%). Submitted additional data do not suggest relevant increase in pembrolizumab-related gastrointestinal AEs compared to SOC in this setting when considered overall. The MAH is however invited to further monitor this type of AEs in the esophageal cancer setting.

Overall, 5 deaths (Myocarditis, Pneumonitis, Esophageal hemorrhage, Death and Pneumonitis, all occurring in one case each, except for pneumonitis that was found in two cases) were judged by the investigator to be related to pembrolizumab. In SOC-treated participants, *Death* (10 subjects; [3.4%]) and *Pneumonia* (5 subjects; [1.7%]) were the only PTs with incidence >1%.

Proportions of **AEOSIs** (23.2% vs 7.4%) and all sub-categories (drug-related AEOSI 21.7% vs 3.0%; grade 3-5 AEOSI 6.1% vs 0.3%, grade 3-5 drug-related AEOSI 5.7% vs 0.3%, serious AEOSI 5.4% vs 0.7%, serious drug-related AEOSI 5.4% vs 0.7%, death due to AEOSI 1.0% vs 0.0%, drug discontinuation due to AEOSI 4.1% vs 0.3%)**,** were considerably higher among subjects receiving pembrolizumab than in those treated with SOC. The following AEOSIs were found more frequently in the pembrolizumab arm than in controls (≥2% difference): *Hepatitis* (2.2% vs 0.0%), *Hyperthyroidism* (4.1% vs 0.7%), *Hypothyroidism* (11.8% vs 2.4%), and *Pneumonitis* (4.8% vs 0.7%). Grade 3-5 AEOSIs were reported in 6.2% of subjects receiving pembrolizumab and only 0.3% of those treated with SOC. Compared to SOC, pembrolizumab-treated subjects had a longer median time to onset (64 vs 22 days, respectively) and less favorable outcome (3 deaths [4.1%] and 56 [56.2%] AEOSI not resolved vs no fatal event [0%] and 7 [31.8%] AEOSI not resolved).

In KN181, **discontinuation of study drug** due to AEs (12.7% of pembrolizumab- and 14.2% of SOC-treated subjects) as well as due to drug-related AES (6.1% and 6.4%, respectively) were comparable among study arms. Among discontinuations due to drug-related AEs accounting for >1% incidence, *Autoimmune hepatitis* (1.6%) and *Pneumonitis* (1.0%) were found in the in the pembrolizumab arm, while none of the PTs exceeded this threshold in the SOC arm.

Comparison of treatment arms with regard to **laboratory findings** showed a >10% difference for clinically meaningful laboratory findings (defined as Grade 3 to 4 events) included leukocytes decreased and neutrophils decreased reported less frequently in the pembrolizumab arm.

At **comparison of KN-181 pembrolizumab arm with the reference datasets**, higher rates of grade 3-5 AEs and drug-related grade 3-5 AEs and deaths were observed in KN-181 pembrolizumab arm when compared with the Reference Safety Dataset (54.1% vs 48.5%; 18.2% vs 14.9% and 9.6% vs 4.8%). Most common AEs patterns show a higher frequency of *Dysphagia* in the esophageal cancer setting (15.6% in KN181; 13.1% in Esophageal Dataset) in respect to the Pembrolizumab monotherapy RSD (3.1%), suggesting an association of this AE with the underlying disease rather than with use of pembrolizumab. In the KN181 pembrolizumab arm lower proportions of *Fatigue* (22.3% vs 34.2 %), *Cough* (12.7% vs 20.5%), *Diarrhea* (20.5% vs 12.4%), *Dyspnoea* (9.9% vs 17.7%), *Pruritus* (7.3% vs 18.5%), *Rash* (6.4% vs 16.0%), and *Arthralgia* (6.1% vs 15.6%) were documented compared to the Pembrolizumab monotherapy RSD. Also, with regards to drug-related AEs proportions and pattern of AEs were comparable between the KN181 pembrolizumab arm and the Esophageal dataset for pembrolizumab. At comparison of these two latter datasets with the Pembrolizumab RDS, pembrolizumab-treated subjects with esophageal cancer had lower frequency of *Fatigue* (11.8% in KN181 and 10.9% in the Esophageal dataset vs 20.9% in the Pembrolizumab RSD), *Pruritus* (4.5% and 4.5% vs 14.5%), *Nausea* (2.0% and 5.5% vs 9.7%), *Diarrhea* (5.4 and 5.2% vs 10.8%), *Rash* (4.1% and 5.2% vs 12%), Arthralgia (2.2% and 2.2% vs 7.9%), and slightly higher proportions of *Hyperthyroidism* (10.5% and 9.2% vs 8.5%). Additionally, numerically higher rates for Grade 3 to 5 auto-immune hepatitis were observed with 6 cases for pembrolizumab in KN181 vs. 10 cases in the whole Reference Safety Dataset. Grade 3-5 drug-related AEs were more commonly reported in subjects with esophageal cancer (KN181 18.2%; esophageal Safety Dataset 17.5%) than in those treated for other indications (Pembrolizumab monotherapy RSD 14.9%). Proportions of PTs, while being comparable between the KN181 pembrolizumab arm and the Esophageal Safety dataset, were slightly higher for *Autoimmune hepatitis* (1.6% and 1.1% vs 0.2%)*, Anemia* (1.3% and 0.9% vs 0.5%)*, Asthenia* (1.3% and 1.1% vs 0.4%) and *Pneumonia* (1.0% and 0.9% vs 0.2%) in esophageal cancer patients than in those receiving pembrolizumab for other indications. Overall SAEs were reported with similar frequencies across datasets (KN181 39.5%, Esophageal dataset 39.3%, Pembrolizumab monotherapy RSD 38.9%). Compared to the Pembrolizumab monotherapy dataset, subjects with esophageal cancer had higher rates of lung disorders (KN181 10.2% and Esophageal Safety dataset 11.6% vs Pembrolizumab monotherapy RSD 5.6%), *Dysphagia* (3.5% and 2.4% vs 0.3%), *Autoimmune hepatitis* (1.3% and 0.9% vs 0.2%), *Esophageal hemorrhage* (1.3% and 0.9% vs 0.2%) and *Pyrexia* (1.3% and 0.9% vs 0.0%). Drug-related SAEs in the pembrolizumab group of KN181 were numerically slightly higher compared to the Reference Safety Dataset (12.7% vs. 10.5%), with the most prominent difference between pembrolizumab datasets for autoimmune hepatitis.

The proportion of subjects with AEs leading to death were rather consistent in esophageal cancer subjects (KN181 9.6% and Esophageal dataset for Pembrolizumab 8.5%), but higher than in the Pembrolizumab Safety RDS (4.8%), suggesting disease-driven higher mortality. Similarity in most commonly reported reasons for death in the two esophageal cancer datasets (*Esophageal hemorrhage, Pneumonia aspiration, Pneumonia*) further supports this hypothesis.

Though overall frequency of **AEOSIs**, average episodes per patient, and event severity were all comparable across pembrolizumab datasets, median time to AEOSI onset was slightly shorter in esophageal cancer patients when compared to the reference dataset (64 days in both datasets vs 73 in the Pembrolizumab monotherapy RSD). Esophageal cancer patients compared to Pembrolizumab monotherapy RSD had marginally increased proportions of *Hepatitis* (2.2% in KN181 pembrolizumab arm and 1.5% in Esophageal Dataset for pembrolizumab vs 0.7% in Pembrolizumab monotherapy RSD) and of *Hypothyroidism* (11.8% and 10.9% vs 9.9%, respectively). Nearly all events of *Hepatitis* were of Grade 3-5; 4 serious events were reported. Furthermore, high-dose corticosteroids were reported in higher proportions (23.7% in KN181 pembrolizumab group, 24.5% in Esophageal dataset for pembrolizumab vs 19.4% in Pembrolizumab monotherapy RSD) as well as events not resolving were more common (56.2% KN181 pembrolizumab arm, 53.8% Esophageal dataset for pembrolizumab vs 46.6% in the Pembrolizumab monotherapy RSD).

AEs summary by **subgroups** shows for age a worse safety profile in subjects of the 75-84 age category when compared to younger age groups among both the esophageal cancer datasets, especially for grade 3-5 AEs (62.5% in 75-84 y vs 54.3% in <65 y and 51.4% in 65-74 y), grade 3-5 drug-related AEs (31.3% in 75-84 y vs 14.3% in <65 y and 20.6% in 65-74 y), SAE (53.1% in 75-84 y vs 40.6% in <65 y and 33.6% in 65-74 y), drug-related SAE (18.8% in 75-84 y vs 12.0% in <65 y and 12.1% in 65-74 y), death (62.5% in 75-84 y vs 54.3% in <65 y and 51.4% in 65-74 y), drug-related deaths (6.3% in 75-84 y vs 0.6% in <65 y and 1.9% in 65-74). CNS disorders, AE related to falling, Cerebrovascular events, and to a lesser extent Infections, were the event categories in which the largest difference between younger and older patient groups was observed. As differences across age categories were less evident in the Pembrolizumab monotherapy RSD and since for evaluation of safety data by age only a comparison between pembrolizumab monotherapy datasets was provided without a comparison to chemotherapy in KN181, it remains unclear to what extent the underlying disease contributed to the worse safety profile of pembrolizumab in elderly subjects with esophageal cancer. The MAH provided an Adverse Event Summary table by age categories comparing KN181 study arms and a worse safety profile is noted in subjects treated with pembrolizumab belonging to the most extreme age group (>=75 to <85) in respect to pembrolizumab-treated subjects of younger age as well as all age categories of the SOC treatment arm (proportion of subjects who died 21.9% vs 8.0-11.3%, who reported SAEs 53.1% vs 33.6-42.9% or who discontinued drugs due to AEs 21.9% vs 10.3-16.1%). The same picture is found when analysing specific event categories (particularly CNS and cerebrovascular events). Recognizing the low patient number, definitive conclusions on pembrolizumab's safety in the more aged patient population cannot be drawn; thus the MAH proposes a modification of section 4.4 of the SmPC, which is agreed. Safety analyses after stratification by gender did not show major differences, but were limited by the relatively low number of female subjects which is expected due to esophageal cancer epidemiology. No major differences were found when stratifying datasets for ECOG state. With regards to Region of enrollment, subjects enrolled exEU tended to have higher proportions of drug-related AEs, grade 3-5 drug-related AEs, SAEs in both the esophageal cancer datasets, while this was not found for the Pembrolizumab monotherapy RSD. The higher rate of AEs was correlated with a considerably higher exposure in the ex-EU compared to the EU participants (the total exposure person-months were 134.29 for ex-EU and 431.16 for EU subjects – in line with lower efficacy observed in EU patients compared to ex-EU subjects). In general, the exposure adjusted AEs occurred at similar frequencies in both regions.

Additional expert consultations

NA

Assessment of paediatric data on clinical safety

NA

2.5.2. Conclusions on clinical safety

In conclusion, pembrolizumab monotherapy compared favorably to investigator's choice chemotherapy for 2L treatment of patients with recurrent locally advanced or metastatic esophageal cancer. While the safety profile in KN181 was consistent with that found in the Esophageal dataset for pembrolizumab and no new safety signals were observed, worse pembrolizumab tolerability is noted in subjects belonging to the highest age group. Notably, at comparison with use of pembrolizumab monotherapy across treatment indications, safety resulted worse in subjects with recurrent locally advanced or metastatic esophageal cancer.

2.5.3. PSUR cycle

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

2.5.4. Direct Healthcare Professional Communication

N/A

2.6. Paediatric studies

The Paediatric Investigation Plan (EMEA-001474-PIP01-13-M01) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) completed PDCO full compliance check with a positive Opinion adopted on 31 January 2019.

3. Risk management plan

The MAH submitted updated RMP version (Version 25.1) with this application. This RMP is being submitted based on the RMP version 23.0 which was approved on 18 October 2018 as part of procedure EMEA/H/C/003820/II/060. The main proposed RMP changes were the following:

Addition of new clinical studies supporting the new indication in Modules SIII and SVII, SVIII; no changes to the risk profile in Modules SIII, SVII SVIII; update to Module SI - epidemiological data concerning relevant adverse events in target populations.

Summary of safety concerns	
Important identified risks	Immune-Related Adverse Reactions • Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis • Immune-related nephritis

Summary of safety concerns	
	• Immune-related endocrinopathies - Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) - Type 1 diabetes mellitus • Severe skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) Other Immune-Related Adverse Reactions • Uveitis • Myositis • Pancreatitis • Myocarditis • Guillain-Barre Syndrome • Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients • Encephalitis • Sarcoidosis Infusion-Related Reactions
Important potential risks	Immune-Related Adverse Events ▪ Gastrointestinal perforation secondary to colitis Other Immune-Related Adverse Events ▪ 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) Immunogenicity
Missing information	Safety in patients with moderate or severe hepatic impairment Safety in patients with severe renal impairment Safety in patients with active systemic autoimmune disease Safety in patients with HIV or Hepatitis B or Hepatitis C Safety in pediatric patients Reproductive and lactation data Long term safety Safety in various ethnic groups Potential pharmacodynamic interaction with systemic immunosuppressants Safety in patients with previous hypersensitivity to another monoclonal antibody Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs

Note that the updates to the list of safety is currently under assessment in a separate variation (II/68).

At this point no amendment to the list of safety specifications is needed in the context of the current extension of indication. The final conclusion is pending the safety assessment of the future rounds.

The pharmacovigilance activities (presented in the table of on-going and planned additional pharmacovigilance activities) are not amended as part of this procedure.

The proposed pharmacovigilance activities could be accepted pending the CHMP discussion on safety.

The risk minimisation measures are not amended as part of this procedure.

Note that the risk minimisation measures are currently under assessment in a separate variation (II/68).

No amendment to the additional risk minimisation measures is needed in the context of the current extension of indication.

4. Changes to the Product Information

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

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The only change in the leaflet is the revision of one paragraph regarding the combination products in section 1 "What KEYTRUDA is and what it is used for". There are no other proposed changes to the content of the package leaflet; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, these proposed revisions do not constitute significant changes that would require the need to conduct a new user consultation.

4.1.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Keytruda (pembrolizumab) is already included in the additional monitoring list.

4.1.3. Quick Response (QR) code

N/A

5. Benefit-Risk Balance

5.1. Therapeutic Context

The MAH is seeking an extension of indication for KEYTRUDA as monotherapy for treatment of adults with recurrent locally advanced or metastatic squamous cell oesophageal cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have received prior systemic therapy based on the final analysis results of the pivotal, randomized, controlled, open-label Phase 3 study KEYNOTE-181.

5.1.1. Disease or condition

According to GLOBOCAN 2018, esophageal cancer ranks seventh in terms of incidence (572,000 new cases) and sixth in mortality overall (509,000 deaths), and is estimated to be responsible for an estimated 1 in every 20 cancer deaths in 2018. Oesophageal cancers are histologically classified as Esophageal Squamous cell Carcinoma (ESCC) or Esophageal Adenocarcinoma (EAC). The distribution of

histology types varies between different geographic regions: ESCC is notably common in south-east and central Asia. EAC is most prevalent in northern and western Europe, North America, and Oceania. EAC represents the majority of esophageal cancer cases in high-income countries, with excess body weight and gastroesophageal reflux disease among the key risk factors.

Metastatic oesophageal cancer is a fatal disease, with an overall 5-year survival rate of 3.4% [Zhang Y, World J Gastroenterol 2013].

5.1.2. Available therapies and unmet medical need

For previously untreated patients (1L), combination chemotherapies are routinely used and guidelines in general recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), which provides moderate benefit but high toxicity. Taxanes or epirubicin are sometimes used in combination with fluoropyrimidine and platinum agents.

The value of palliative chemotherapy is less proved in ESCC. Treatment guidelines for EAC were extrapolated from gastric cancer studies, despite the differences in biology between gastric and oesophageal cancers. For patients with human epidermal growth factor receptor 2 (HER2) positive EAC, based on the results of ToGA trial the guidelines recommend the addition of trastuzumab to first-line chemotherapy.

Several regimens were evaluated as 2L treatments for advanced or metastatic oesophageal cancer. Taxanes are recommended in first-line combinations or as monotherapy in second-line therapy in ESMO guidelines. NCCN treatment guidelines include docetaxel, paclitaxel, and irinotecan among the preferred regimens, which show marginal benefit (median OS ranging from 4.0 months to 8.1 months and ORR ranging from 0% to 28.0%). On July 30, 2019, FDA approved pembrolizumab for patients with recurrent, locally advanced or metastatic, squamous cell carcinoma of the esophagus whose tumors express PD-L1 with CPS≥10, with disease progression after one or more prior lines of systemic therapy.

The poor prognosis for patients with metastatic oesophageal cancer whose disease has progressed on or following 1L therapies highlight the high unmet need for novel therapies.

5.1.3. Main clinical studies

The proposed indication is based on the results of KEYNOTE-181 Study, an ongoing, randomised (1:1), multi-site, open-label, Phase 3 study of pembrolizumab versus SOC (investigator's choice of paclitaxel, docetaxel, or irinotecan) in participants with advanced/metastatic EAC or ESCC, or advanced/metastatic Siewert type I adenocarcinoma of the EGJ who have progressed after first-line standard therapy.
The primary endpoint was OS, in participants with ESCC, in participants with tumours expressing PD-L1 CPS≥10, and in all participants. The key secondary efficacy endpoints were PFS and ORR in all participants. A total of 628 patients were stratified by tumour histology and geographic region (Asia versus ex-Asia) and randomized to the study arms: pembrolizumab (N=314) and SOC (N=314).
Results from other two additional studies, were provided as supportive:

- KEYNOTE-028 (Cohort 4A, n=22), a Phase 1b proof-of-concept study of participants with previously treated esophageal cancer treated with pembrolizumab monotherapy,
- KEYNOTE-180 (n=121) an on-going, single-arm Phase 2 study of pembrolizumab monotherapy in participants with esophageal cancer that have had at least two prior lines of therapy (3L+ advanced/metastatic oesophageal cancer, regardless of histology or biomarker status).

No pooled efficacy analyses were conducted based on KEYNOTE-181, KEYNOTE-180, and KEYNOTE-028 because KEYNOTE-180 and KEYNOTE-028 were single arm studies with participants with substantially more advanced stages of disease (different lines of therapy).

5.2. Favourable effects

- A numerical trend toward improved OS for pembrolizumab over SOC (HR of 0.70, 95% CI 0.52, 0.94; p=0.00855, boundary 0.00853; final analysis, data cut-off 15-OCT-2018) was observed only for participants with PD-L1 CPS ≥10 with 88 (82.2%) and 103 (89.6%) events in the experimental and the control arm, respectively.
- OS rate at 12, 18 and 24 months is 42.1% (95% CI 32.6, 51.2) vs. 20.4% (95% CI 13.5, 28.3), 25.2% (95% CI 17.4, 33.7) vs. 10.6% (95% CI 5.8, 17.1), 15.2% (95% CI 8.2, 24.1) vs. 9.1% (95% CI 4.5, 15.6) in the experimental and control arm, respectively.
- Supportive PFS benefit in favour of pembrolizumab (HR 0.73 [95% CI 0.54, 0.97]; p-value 0.015; assessment by independent review, consistency in sensitivity analysis).
- Higher response rates for pembrolizumab compared to SOC (21.5% vs 6.1%, difference 15.1%, p-value 0.0006).
- The observed treatment effect in a subgroup analysis in ESCC subjects whose tumours express PD-L1 CPS ≥10 is apparently more pronounced than in the overall population of esophageal carcinoma with PD-L1 CPS ≥10.

5.3. Uncertainties and limitations about favourable effects

- KEYNOTE-181 revised OS analysis did not reach statistical significance in any of the pre-specified populations. The fact that with 1 single additional OS event the study results lost the statistical significance in the PD-L1 CPS≥10 population (p-value 0.00855, boundary 0.00853) highlights the lack of robustness of the results.
- PFS and ORR were not formally tested because pembrolizumab was not superior to SOC for OS in all participants.
- Open-label study with multiple and major changes in key design elements.
- The study was not originally designed to test the superiority of pembrolizumab vs. SOC in subjects whose tumour express PD-L1 CPS≥10, and PD-L1 was not a stratification factor with the consequence that some imbalances are observed for baseline characteristics that impact on the interpretation of the results.
- The patient population included in the study is not fully representative of EU population, particularly with regard to the prevalence of EAC. Post-hoc exploratory analyses show a marginal benefit in terms of HR with a median OS even shorter in pembrolizumab treated patients compared to the SOC arm in both EU and EAC patients whose tumour express PD-L1 CPS≥10.
- With regard to EU patients, the small sample size and the non-randomized comparison hampers a proper interpretation, even more if one looks also at histology subtypes.
- Although acknowledging the small sample size, based on the totality of available data, a benefit of pembrolizumab compared to standard treatment has not been demonstrated in the subgroup of patients with EAC and PD-L1 CPS ≥10.

- More pronounced superiority of pembrolizumab compared to standard treatment with irinotecan and docetaxel.
- Exclusion of subjects with unfavourable prognosis, age distribution likely not fully representative.
- Intrinsic limitation of subgroup analyses from a study that failed to demonstrate statistically significant OS benefit, moreover in a subgroup defined based on multiple factors (ESCC and PD-L1 CPS ≥10).
- Efficacy results for ESCC and PD-L1 CPS ≥10 not representative for European population. Inferior treatment effect of pembrolizumab for Ex-Asian SCC subjects compared to Asian SCC subjects and inferior efficacy results for White (Ex-Asian) ESCC and PD-L1 CPS ≥10 subjects compared to the overall ESCC and PD-L1 CPS ≥10 population (including Asian subjects) in the small subset of evaluable patients. While the MAH argues that there are no biological or pharmacological reasons to believe that the treatment effect would be significantly different in the white population relative to non-white populations, this assumption is not adequately discussed. The MAH is therefore asked to address this issue based on the totality of available data.

5.4. Unfavourable effects

- In KN181 study, pembrolizumab-treated subjects compared to patients treated with SOC showed lower proportions of drug-related AEs, grade 3-5 AEs, grade 3-5 drug-related AEs, drug-related SAEs, and drug discontinuations due to AEs, whilst having comparable frequencies of the remaining AE categories.
- All drug-related AEs by PT most commonly reported in the pembrolizumab arm (*Fatigue, Decreased appetite*, *Asthenia*, *Nausea*, and *Diarrhea*), except for *Hypothyroidism*, were less frequent than in the control arm.
- No new safety issues, in particular immune-mediated events, have emerged with pembrolizumab in esophageal cancer.
- Proportions of AEOSIs and all sub-categories were considerably higher among subjects receiving pembrolizumab than in those treated with SOC, but quite consistent across pembrolizumab datasets.
- A higher rate of drug-related hepatitis was seen in the KN181 pembrolizumab arm (1.6%) and in the Pooled esophageal Dataset (1.3%), compared to both the KN181 standard treatment group (0.0%) and to the Reference Safety Dataset (0.3%).
- Not unexpectedly, at comparison with use of pembrolizumab monotherapy across the already approved treatment indications, safety resulted worse in subjects with recurrent locally advanced or metastatic esophageal cancer.

5.5. Uncertainties and limitations about unfavourable effects

- Pembrolizumab appears less tolerated in subjects with esophageal cancer aged >75 years. Data are too limited to draw firm conclusions.

5.6. Effects Table

Table 2. Effects Table for Keytruda in "*treatment of recurrent locally advanced or metastatic*

***oesophageal cancer in adults whose tumours express PD-L1 with a CPS ≥10 and who have received prior systemic therapy*" (study KEYNOTE-181, data cut-off: 15-OCT-2018, Final Analysis)**

Effect	Short description	Unit	Pembrolizumab	SOC	Uncertainties / Strength of evidence
Favourable Effects					
OS (PD-L1 CPS ≥10)	Time from randomization to death due to any cause	Months (95% CI)	9.3 (6.6,12.5)	6.7 (5.1,8.2)	Updated OS analysis post database lock to correct data entry errors narrowly failed statistical significance (p-value 0.00855, boundary 0.00853); Open-label study with multiple and major changes in key design elements; Primary analysis statistically significant Study not originally designed to test the superiority of pembrolizumab vs. SOC in subjects whose tumour express PD-L1 CPS≥10 PD-L1 was not a stratification factor with the consequence that some imbalances are observed for baseline characteristics Patient population not fully representative of EU population, particularly with regard to the prevalence of EAC. Post-hoc exploratory analyses in EU and EAC populations show a marginal benefit in terms of HR with a median OS even shorter in pembrolizumab treated patients compared to the SOC. No benefit in patients with EAC and PD-L1 CPS ⩾10.
		HR (95% CI)	HR of 0.70, (0.52, 094; p=0.00855)		
Unfavourable Effects					
Overall *(selected categories)*	Drug-related AEs	%	64.3	86.1	Drug-related AE categories are less common in pembrolizumab-treated subjects compared to those treated with SOC. No new safety issues with pembrolizumab were identified Pembrolizumab appears less tolerated in subjects with esophageal cancer aged >75 years. Data are too limited to draw firm conclusions.
	Grade 3-5 AEs	%	54.1	61.8	
	Grade 3-5 drug-related AEs	%	18.2	40.9	
	Drug-related SAEs	%	12.7	19.3	
	Drug discontinuations due to AEs	%	12.7	14.2	
Drug-related AEs *(selected PTs)*	Fatigue	%	11.8	20.6	*Hypothyroidism* is the only drug-related AE being more common in pembrolizumab- than in SOC-treated subjects. Frequency was as expected for pembrolizumab monotherapy. More frequent drug-related hepatitis AEs with pembrolizumab
	Hypothyroidism	%	10.5	0.3	
	Decreased appetite	%	8.6	15.5	
	Asthenia	%	7.0	11.5	
	Nausea	%	7.0	21.6	
	Diarrhea	%	5.4	20.3	

Effect	Short description	Unit	Pembrolizumab	SOC	Uncertainties / Strength of evidence
Drug-related grade 3-5 AEs (selected PTs)	Autoimmune hepatitis	%	1.6	0.0	Haematologic AEs were less prevalent in the pembrolizumab arm when compared to SOC.
	Anemia	%	1.3	7.8	
	Asthenia	%	1.3	1.0	
	Colitis	%	1.0	0.0	
	Pneumonia	%	1.0	2.4	
	Pneumonitis	%	1.0	0.0	
	Neutrophil count decreased	%	0.3	9.8	
	Febrile neutropenia	%	0.0	8.4	
	Neutropenia	%	0.0	7.1	
	White blood cell count decreased	%	0.0	10.1	
Serious drug-related AEs (selected PTs)	Pneumonitis	%	2.2	0.0	
	Autoimmune hepatitis	%	1.0	0.0	
	Colitis	%	1.0	0.0	
	Pneumonia	%	1.0	2.7	
AEOSIs	AEOSIs	%	23.2	7.4	Proportions of AEOSIs and all sub-categories were considerably higher among subjects receiving pembrolizumab than in controls
	Grade 3-5 AEOSI	%	6.1	0.3	
	Grade 3-5 drug-related AEOSI	%	5.7	0.3	
	Drug-related serious AEOSI	%	5.4	0.7	
	Drug discontinuation due to AEOSI	%	4.1	0.3	

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

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The revised OS analysis of KEYNOTE-181 did not reach statistical significance in any of the pre-specified populations. The fact that with 1 single additional OS event the study results lost the statistical significance in the PD-L1 CPS≥10 population highlights the lack of robustness of the results.

A trend toward benefit in OS for pembrolizumab over SOC was observed for participants with PD-L1 CPS ≥10. However, the study was not originally designed to test the superiority of pembrolizumab vs. SOC in subjects whose tumour express PD-L1 CPS≥10, and PD-L1 was not a stratification factor with the consequence that some imbalances are observed for baseline characteristics that impact on the interpretation of the results. Concerns are raised by the marginal benefit observed in EAC and EU patients, in whom even shorter median OS has also been observed. In this regard, it is noted that EAC are much more frequently observed in high-income countries, including EU.

Overall, pembrolizumab compares favorably with SOC in terms of tolerability with a lower proportion of drug-related AEs, grade 3-5 AEs, grade 3-5 drug-related AEs, drug-related SAEs, and drug discontinuations due to AEs.

No new safety signals have been identified.

Overall, uncertainties are related to the biomarker selection, the conduct of the open-label study with several changes affecting the primary endpoint analysis, the imbalances in prognostic factors between treatment arms and mainly the lower treatment effect of pembrolizumab in Non-Asian / adenocarcinoma patients. In view of the known ethnic differences in incidence, clinical practice, primary tumor location, histology, and prognosis of oesophageal cancer related to geographical region the observed differences in the efficacy for pembrolizumab might not be a chance finding, but could rather reflect a true regional difference. The limited data in EU patients together with the contrasting results observed in this subgroup compared the overall and complementary population deserve further discussion, especially with regard to potential factors that might affect the benefit from pembrolizumab in EU patients compared to ex-EU patients.

In the subgroup of patients with EAC and PD-L1 CPS ≥10, a benefit of pembrolizumab compared to standard treatment has not been demonstrated.

The updated indication proposed by the MAH (i.e. squamous cell carcinoma with PD-L1 expression CPS≥10) is based on the results from a subgroup analysis where the observed treatment effect is apparently more pronounced than in the overall population of esophageal carcinoma with PD-L1 CPS ≥10.

5.7.2. Balance of benefits and risks

The demonstration of efficacy in the 2L treatment of locally advanced or metastatic oesophageal cancer for patients with ESCC histology and PD-L1 CPS ⩾10 is based on retrospective, exploratory subgroup analyses from a study that failed to demonstrate statistically significant OS benefit. The strength of the data is not considered adequate to conclude on a positive benefit risk. An additional prospective study to establish efficacy is needed (MO).

5.7.3. Additional considerations on the benefit-risk balance

None

5.8. Conclusions

The overall B/R of pembrolizumab is negative.