26 July 2018
EMA/548820/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0043

Note

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

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List of abbreviations

AE	adverse event
AEOSI	adverse events of special interest
ALT	alanine transaminase
ALK	Anaplastic lymphoma kinase
ALP	alkaline phosphatase
APT	All Patients Treated
APaT	All Patients as Treated
BICR	Blinded independent central review
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DDI	Drug-drug interaction
DoR	Duration of response
DS	Dataset
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EU	European Union
FDA	Food and drug Administration
IA1	First interim analysis
IA2	Second interim analysis
ISS	Integrated Summary of Safety
ITT	Intention to treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive Disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand 1
PFS	Progression-free survival
PR	Partial Response
PT	Preferred term
Q3W	Every 3 weeks
RECIST 1.1	Response Evaluation Criteria on Solid Tumors Version 1.1
RSD	Reference Safety Dataset
SAE	Serious Adverse Event
SD	Safety Dataset
SOC	System Organ Class
PS	Performance Status
QoL	Quality of Life
TKI	tyrosine kinase inhibitor
TPS	Tumor Proportion Score
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 13 March 2018 an application for a variation.

The following variation was requested:

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

Extension of Indication to include 1st line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with pemetrexed and platinum chemotherapy based on the efficacy and safety data from pivotal study KEYNOTE-189, supported by data from KEYNOTE-021 cohorts C and G.

KEYNOTE-189 is a phase 3, randomized, placebo-controlled study undertaken to evaluate the efficacy and safety of pembrolizumab +pemetrexed + carboplatin or cisplatin (pembro combo) versus saline placebo + pemetrexed + carboplatin or cisplatin (control) in previously untreated subjects with advanced/metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance.

An updated RMP version 16.2 was provided as part of the 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 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniela Melchiorri Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	13 March 2018
Start of procedure	31 March 2018
CHMP Co-Rapporteur Assessment Report	28 May 2018
CHMP Rapporteur Assessment Report	2 June 2018
PRAC Rapporteur Assessment Report	30 May 2018
PRAC members comments	6 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	19 June 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2018
Request for supplementary information (RSI)	28 June 2018
Re-start of procedure	4 July 2018
PRAC Rapporteur response Assessment Report	11 July 2018
CHMP Rapporteur response Assessment Report	11 July 2018
PRAC members comments	16 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur response Assessment Report	19 July 2018
Updated PRAC Rapporteur response Assessment Report	19 July 2018
Opinion	26 July 2018

2. Scientific discussion

2.1. Introduction

Keytruda (pembrolizumab, MK-3475) is a humanized IgG4 monoclonal antibody targeting the human programmed cell death 1 (PD-1) expressed on the surface of cancer cells and tumour infiltrating lymphocytes. It acts as immune check-point inhibitor by blocking the PD-1/PD-L1 pathway that downregulates the effector function of T cells, with consequent stimulation of the immune-mediated anti-tumour activity (Oncologist. 2017 Jan; 22(1): 81–88).

The pharmacological inhibition of the PD-1/PD-L1 is a consolidated approach in the treatment of different malignancies. In the setting of lung disease, pembrolizumab is recommended as first-line option in metastatic non-small cell lung cancer (NSCLC) highly-expressing PD-L1 (≥50% tumour portion score, TPS) and negative for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements. In the second-line setting, pembrolizumab is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen (patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda). (ESMO Guidelines 2018).For both

these clinical indications, pembrolizumab is used as a monotherapy. Regulatory approval was granted on 29 July 2016 for the treatment of previously treated PD-L1 TPS ≥1% locally advanced or metastatic NSCLC patients on the basis of the KEYNOTE-010 clinical trial, and on 27 January 2017 for the first-line treatment of metastatic PD-L1 TPS ≥50% NSCLC as supported by the KEYNOTE-024 study. With the current type II variation application, the MAH is pursuing an extension of indication of pembrolizumab to be used in combination with platinum-pemetrexed chemotherapy in the treatment of metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

Lung cancer is the main cause of malignancy-related mortality worldwide, accounting for 1.69 million of deaths globally per year as estimated by the World Health Organization (WHO). Around 85%-90% of all lung cancers are Non Small Cell Lung Cancer (NSCLC), that include non-squamous (i.e, adenocarcinoma, large-cell carcinoma, and other cell types) and squamous (epidermoid) cell carcinoma (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011). During the last 25 years, the distribution of NSCLC histological types changed in Europe, with a decrease of squamous cell carcinoma and an increase of adenocarcinoma in men, while in women there was an increase of both histologies. Non-squamous NSCLC is the prevailing histological type diagnosed in never smoker NSCLC patients, with a higher prevalence in females than males. More than half of the patients are diagnosed at an advanced stage of disease, which directly contributes to poor survival, as expressed by an untreated median OS of 4 months and a metastatic 5-year survival rate of <5% (Lindsey A. et al, 2016).

Platinum-pemetrexed chemotherapy has long been considered among the equally effective platinum doublet regimens (cisplatin and carboplatin combinations with gemcitabine, paclitaxel and docetaxel) that current guidelines recommend as 1L approach, in the absence of driver mutations (i.e, EGFR and ALK negative disease), for the treatment of patients who present without major comorbidities and ECOG PS 0-2 (Novello S. et al, 2016). The efficacy of pemetrexed maintenance treatment, either as long-term use of an agent included in the first-line treatment ("continuation maintenance") or as introduction of a new agent after 4 cycles of platinum-based chemotherapy ("switch maintenance") has demonstrated significant improvement in the efficacy outcome of the non-squamous NSCLC histology. With the advent of pembrolizumab and its approval (2016) in the 1L setting as monotherapy in NSCLC with TPS ≥50% based on the positive results of the phase III, randomized, KEYNOTE-024 study (i.e PFS HR: 0.50, p<0.001; OS HR: 0.60, p=0.005 pembrolizumab vs a SOC platinum-based doublet), this is now indicated as first-choice also in non-squamous NSCLC patients highly expressing tumour PD-L1 (TPS ≥50%). (ESMO eUpdate 28 June 2017). However, there remains substantial unmet medical need for patients with previously untreated nonsquamous NSCLC, since a fraction of subjects with highly expressing tumour PD-L1 (TPS ≥50%) does not derive benefit from pembrolizumab as monotherapy, and also considering that only 25% to 30% of patients with NSCLC have tumors with a PD-L1 TPS ≥50%.

Emerging evidence suggest that combining immunotherapy with anticancer agents could provide better clinical outcomes by enhancing the anti-tumour immune response stimulated by chemotherapy (Apetoh L et al, 2015).

The MAH applied for the following change of indication:

"KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations."

The same indication was the subject of a previously submitted Type II variation (EMEA/H/C/003820/II/0027) that the MAH subsequently withdrew.

For the purpose of the current submission, an updated analysis of the KEYNOTE-021 Cohort G is provided as supportive study. Results from the first Interim Analysis (IA1) of the Pivotal/Main study KEYNOTE-189 (*A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without*

Pembrolizumab (MK-3475) in First Line Metastatic Nonsquamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189) are also presented.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

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

2.2.2. Discussion and conclusion on the non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), this is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies in NSCLC

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-3475 P021 [Ref. 5.3.5.1: P021V01MK 3475]	1/2	USA Taiwan	A Phase I/II Study of MK-3475 (SCH900475) in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma Dose finding, safety, and efficacy trial in subjects with Stage IIIb/IV NSCLC	Randomized, open-label, parallel-group, active-controlled	**Cohort G1** Pembrolizumab 200 mg IV Q3W on Day 1 of each cycle for up to 24 months PLUS Carboplatin AUC 5 mg/mL/min IV Q3W on Day 1 for 4 cycles PLUS Pemetrexed 500 mg/m^2 IV Q3W on Day 1 for each cycle for up to 24 months OR Carboplatin AUC 5 mg/mL/min IV Q3W on Day 1 for 4 cycles PLUS Pemetrexed 500 mg/m^2 IV Q3W on Day 1 for each cycle for up to 24 months AFTER PD OPTION TO CROSSOVER TO Pembrolizumab 200 mg IV Q3W **Cohort C** Pembrolizumab 2 mg/kg IV Q3W on Day 1 of each cycle for up to 24 months PLUS Carboplatin AUC 5 mg/mL/min IV Q3W on Day 1 for 4 cycles PLUS Pemetrexed 500 mg/m^2 IV Q3W on Day 1 for each cycle for up to 24 months OR Pembrolizumab 10 mg/kg IV Q3W on Day 1 of each cycle for up to 24 months PLUS Carboplatin AUC 5 mg/mL/min IV Q3W on Day 1 for 4 cycles PLUS Pemetrexed 500 mg/m^2 IV Q3W on Day 1 for each cycle for up to 24 months	Males/females Age: ≥18 years Stage IIIb/IV NSCLC	As of 08-Aug-2016 Pembrolizumab (83 subjects treated in Cohorts G1 and C) **Cohort G1** Pembrolizumab 200 mg/ carboplatin/ pemetrexed (60 subjects; one subject did not receive treatment) Carboplatin/ pemetrexed (63 subjects) **Cohort C** Pembrolizumab 2 mg/kg/ carboplatin/ pemetrexed (12 subjects) Pembrolizumab 10 mg/kg/ carboplatin/ pemetrexed (12 subjects)

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-189 [Ref. 5.3.5.1: P189V01MK 3475]	3	Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherland, Spain, United Kingdom, United States	Phase III Study of Efficacy and Safety of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects	Randomized, active-controlled, parallel-group, double-blind, multi-site, worldwide	Arm 1: Pembrolizumab 200 mg + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 or carboplatin AUC 5, all administered IV Q3W for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2, both IV Q3W until progression Arm 2: Saline placebo + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 or carboplatin AUC 5, all administered IV Q3W for 4 cycles followed by saline placebo + pemetrexed 500 mg/m^2, both IV Q3W until progression	Male and female subjects ≥18 years of age on the day of consent with metastatic nonsquamous non-small cell lung cancer	Arm 1: 405 subjects Arm 2: 202 subjects

2.3.1. Pharmacokinetics

Clinical pharmacology results specific to 1st line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with platinum-pemetrexed chemotherapy indication are available from study KEYNOTE-021 (cohort G1) and are further informed by results obtained in other indications previously approved with pembrolizumab.

The updated clinical pharmacology results in this submission include:

• Pharmacokinetic (PK) data from KEYNOTE-021 (cohort G1)

• A focused analysis to assess the consistency of pembrolizumab pharmacokinetics in patients with NSCLC from study KN021 (Cohort C and G1) who received concomitant pemetrexed and platinum therapy with the established definitive population PK model for pembrolizumab monotherapy.

Pharmacokinetic in target population

Previously, a pooled population PK analysis using data from the KN001, KN002 and KN006 studies was performed to characterize serum pembrolizumab concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications (Report 04DDV3). In support of this specific submission, a focused PK analysis was conducted primarily to show the similarity of observed concentrations in subjects with NSCLC from study KN021 (Cohort C and G1) who received concomitant pemetrexed and platinum therapy with the predictions from the definitive population PK analysis, and is presented in the PK report (Report 04JYRX). See below section on PK/PD Modelling.

2.3.2. Pharmacodynamics

Mechanism of action

Pembrolizumab is an antibody which 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. Pembrolizumab 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

No new primary or secondary pharmacology studies have been submitted.

2.3.3. PK/PD modelling

Previously, a pooled population PK analysis (report 04DDV3) using KN001, KN002 and KN006 studies was performed to characterize serum concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications. This analysis is considered the definitive population PK analysis to characterize pembrolizumab PK and inform the label for pembrolizumab.

The structure of the definitive population PK model for pembrolizumab has a two-compartment model structure with a linear clearance from the central compartment, parameterized in terms of clearance (CL), inter-compartmental clearance (Q), central compartment volume of distribution (Vc), and peripheral compartment volume of distribution (Vp). All PK parameters were allometrically scaled based on body weight with separate exponents estimated for the clearance (CL, Q) and volume (Vc, Vp) parameters, as follows:

$$P^* = \theta_x \cdot \left(\frac{WT}{MedianWT} \right)^{\theta_y}$$

where θx is a typical value of a pharmacokinetic parameter P*, and θy is the fixed-effect parameter to be estimated. WT is the individual body weight, and Median WT is the median body weight across the analysis population.

In addition to body weight, the existing population PK model contained several more covariate relationships, which were established through a stepwise covariate search. The covariate relationships used the following generic form for continuous covariates, similar to the relationships for body weight.

The following function was used to describe the effects of categorical covariates:

$$P^* = \theta_x \cdot (1 + Q \cdot \theta_y)$$

Where θx is a typical value of a pharmacokinetic parameter P*, and θy is the fixed-effect parameter to be estimated, and Cov is the (continuous) covariate value and Q is the indicator variable denoting the category of the (categorical) covariate.

Specifically, the following covariates were included in the model:

Covariate	Type of covariate	Parameter
Gender	Categorical	CL and Vc
Bilirubin	Continuous	CL
eGFR	Continuous	CL
Albumin	Continuous	CL and Vc
Tumor burden	Continuous	CL
ECOG performance status	Categorical	CL
Cancer type	Categorical	CL
Prior IPI treatment	Categorical	CL and Vc

In this model, the impact of these covariates on pembrolizumab exposure was limited (generally less than 20%) and therefore was not considered to be of clinical relevance.

Inter-individual variability (IIV) of the PK parameters (CL, Volume of distributions (Vc and Vp) and inter-compartmental clearance Q) was included using a lognormal random effects model.

Residual variability (RV), a composite measure of assay error, dose/sample time collection errors, model misspecification, and any other unexplained variability within a subject, was modeled using a log-transformed additive error model (for the assessment of the population PK analysis, please refer to the EPAR for variation II/11 of Keytruda).

No additional model development was performed in the current analysis, and the definitive population PK was used as is. For this updated PK evaluation, the data from NSCLC concomitantly treated with pemetrexed and platinum therapy from Cohorts C and G of study KN021 were added to the dataset. The final analysis data set from studies KN001, KN002, KN006 and KN021 used for the population PK based comparisons comprised of a total of 12588 pembrolizumab concentrations from 2259 patients. Of these, 335 observations from KN021 cohort C and G1 are in NSCLC receiving concomitant treatment.

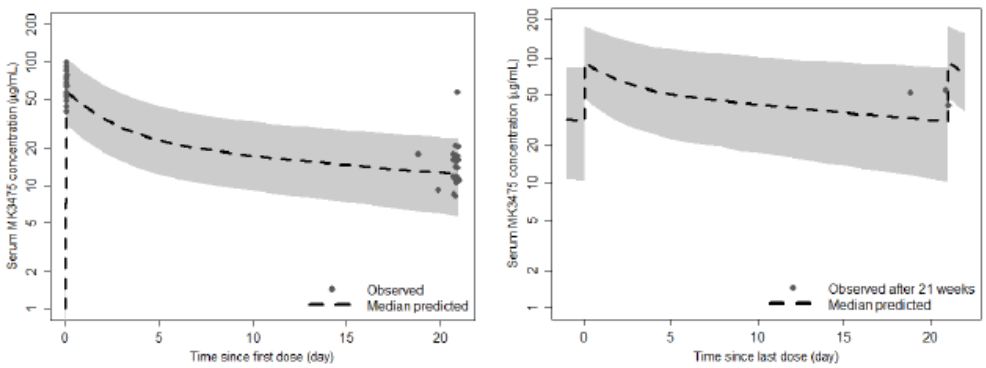
The number of subjects and PK observations by dose in the pooled analysis dataset are provided in the following table:

Table 1: Numbers of subjects and observations by dose and dosing regimen in the pooled analysis dataset (KN001, KN002, KN006, KN021)

Doses	N of subjects	% of subjects	N of PK observations	% of PK observations
1mg/kg Q2W (non-NSCLC)	3	0.133	29	0.23
1mg/kg Q3W (non-NSCLC)	5	0.221	9	0.0715
2mg/kg Q3W (non-NSCLC)	374	16.6	1847	14.7
3mg/kg Q2W (non-NSCLC)	3	0.133	55	0.437
10mg/kg Q2W (non-NSCLC)	456	20.2	2810	22.3
10mg/kg Q3W (non-NSCLC)	793	35.1	4368	34.7
1mg/kg Q2W (NSCLC - KN001)	1	0.0443	14	0.111
1mg/kg Q3W (NSCLC – KN001)	1	0.0443	1	0.00794
2mg/kg Q3W (NSCLC – KN001)	61	2.7	267	2.12
10mg/kg Q2W (NSCLC / – KN001)	204	9.03	1307	10.4
10mg/kg Q3W (NSCLC / – KN001)	287	12.7	1526	12.1
200mg Q3W (NSCLC – KN021 - monotherapy)	13	0.575	55	0.437
2mg/kg Q3W (NSCLC – KN021 - monotherapy)	11	0.487	85	0.675
10mg/kg Q3W (NSCLC – KN021 - combination)	12	0.531	66	0.524
200mg Q3W (NSCLC – KN021 - combination)	35	1.55	149	1.18

Note: some subjects received more than one dose levels under dose escalation cohorts

The figure below shows the pembrolizumab serum concentrations for the NSCLC subjects treated with 200 mg Q3W in combination with pemetrexed and platinum therapy, together with a predicted concentration range (median and 90% prediction interval) from the definitive population PK model, based on the data from patients with melanoma or NSCLC.



Dots are individual data from NSCLC patients from KN021; Solid line is median prediction from the model for a regimen of 200 mg Q3W and the shaded area represents the 90% prediction interval.

Figure 1: Consistency of observed concentrations in NSCLC subjects treated with Pemetrexed and platinum therapy with predictions confirmed based simulations from the population PK model of the reference monotherapy dataset KN001, KN002, KN006: pembrolizumab concentration-time profiles during the first dose (left panel) and at steady state (right panel) at 200 mg Q3W

To further establish the similarity in pembrolizumab exposures across indications, several comparisons have been made of peak and trough concentrations between indications. Observed peak and trough concentrations at 200 mg Q3W in NSCLC patients concomitantly treated with pemetrexed and platinum therapy are compared to predicted peak and trough concentrations in NSCLC patients at this dose regimen (in monotherapy) in the figure and table below.

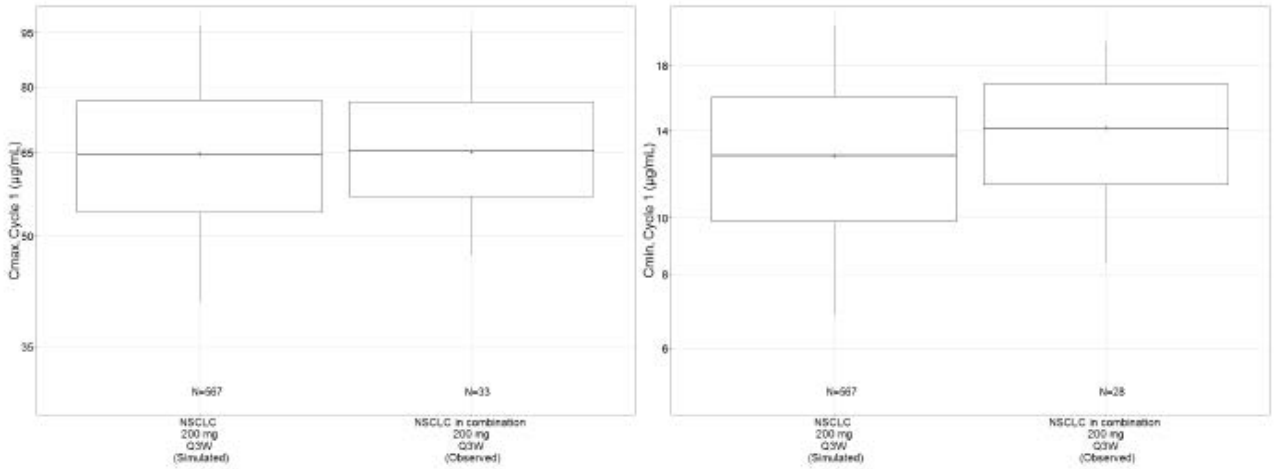


Figure 2: Similar distributions of observed peak and trough concentrations (Cycle 1) in NSCLC at 200 mg Q3W with concomitant Pemetrexed and platinum therapy compared to predicted concentrations in NSCLC at 200 mg Q3W monotherapy

Table 2: Descriptive statistics of observed peak and trough concentrations (cycle 1) in NSCLC at 200 mg Q3W with concomitant Pemetrexed and platinum therapy compared to predicted concentrations in NSCLC 200 mg Q3W monotherapy

Parameter	NSCLC Pembrolizumab 200 mg Q3W + pemetrexed + platinum therapy				NSCLC Pembrolizumab 200 mg Q3W			
	N	Mean	Median	SD	N	Mean	Median	SD
Cmax[a] (µg/mL)	33	68.43	65.2	15.41	567	66.21	64.65	17.65
Cmin[b] (µg/mL)	28	14.07	14.15	3.68	567	13.1	12.7	4.39

[a] Cmax is concentration at time of peak sample in Cycle 1
[b] Cmin is trough concentration following Cycle 1

2.3.4. Discussion and conclusion on clinical pharmacology

The starting point for the population PK analysis submitted in the current variation application was the previous population PK analysis based on dataset including 2188 subjects across the melanoma and NSCLC indications (KN001, KN002 and KN006 studies). This former analysis is considered the definitive population PK model to inform the label for pembrolizumab and no further model development was performed in the current analysis which incorporates data from NSCLC patients concomitantly treated with pemetrexed and carboplatin therapy recruited in study KN021. Thus, the final dataset consist of a total of 12588 determinations of pembrolizumab concentrations from 2259 patients.

The approach taken by the applicant was to utilize the definitive population PK model to predict pembrolizumab levels in NSCLC patients concomitantly treated with pemetrexed and carboplatin therapy after 200 mg Q3W administration. The predictions were compared with observed levels determined in study KN021.

In general, the observed concentrations in this setting (1L NSCLC in combination with pemetrexed and platinum therapy) fall within the range of predicted concentrations, at least during the first cycle, indicating that the definitive population PK model developed on monotherapy data provides an adequate description of the pharmacokinetics of pembrolizumab in combination with pemetrexed and platinum therapy.

It is noted that observed median C_{min} (Cycle 1) of pembrolizumab 200 mg Q3w in NSCLC patients concomitantly treated with pemetrexed and platinum therapy is slightly higher than expected from NSCLC patients treated with pembrolizumab monotherapy at the same dose regimen (14.15 vs. 12.7 µg/mL).

According to the study protocols, PK sampling of study KN021 included several pre- dose trough samples beyond cycle 1. In particular, as reported in the final protocol of the study, "trough (pre-dose) and peak (post-dose) samples will be collected at Cycles 1 and 2. A trough sample will be collected at Cycle 3, 6, 9, 13 and 17. All trough samples should be drawn within 24 hours before infusion of pembrolizumab and the peak samples in cycle 1 and 2 should be drawn within 30 minutes after the end of the infusion".

Regarding immunogenicity, no new data are available for this submission since no more data were collected with respect to the previous dataset.

The existing immunogenicity assessment for pembrolizumab is based on a sufficiently large dataset of 3268 patients, with a very low observed rate of treatment emergent ADA (1.8%) and no demonstrated impact on efficacy or safety. This percentage was consistent across tumour type.

2.4. Clinical efficacy

This submission is based on the first interim analysis (IA1; date cut-off: 08 Nov 2017) of the Phase 3 trial KEYNOTE-189, supported by data from an updated analysis of the Phase 1/2 trial KEYNOTE-021 Cohort G (KEYNOTE-021-G). Both studies evaluated pembrolizumab (MK-3475) in combination with pemetrexed/platinum chemotherapy (pembro combo) compared with pemetrexed/platinum chemotherapy (control) in the first-line treatment of subjects with metastatic nonsquamous NSCLC. Detailed information for both studies are summarised in the following table:

Table 3: Clinical studies supporting the application

Study ID / centres / locations	Study design	Treatment	No of pts planned / random / treated	Demographics	Primary endpoint	Secondary endpoints
KEYNOTE-021		**Cohort G**				
22 enrolling centers in 2 countries: United States (19), Taiwan (3)	Multi-center, randomized, multi-cohort, open-label, Phase 1/2 study in subjects with locally advanced or metastatic NSCLC	**pembrolizumab** 200 mg IV Q3W + **pemetrexed** 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	54/60/59	Sex: 22M/38F Median age (min/max): 62.5 years (40-77)	**ORR** (RECIST 1.1) by BICR	**PFS** (key secondary) **DOR** **OS**
		pemetrexed 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	54/63/62	Sex: 26M/37F Median age (min/max): 66 years (37-80)		
KEYNOTE-189						
143 enrolling centers in 16 countries: Australia (8), Austria (8), Belgium (2), Canada (6), Denmark (3), Finland (2), France (6), Germany (11), Ireland (5), Israel (6), Italy (12), Japan (4), Netherland (3), Spain (12), United Kingdom (7), United States (48)	Multi-center, randomized (2:1), double-blind, placebo-controlled Phase 3 study in subjects with locally advanced or metastatic NSCLC	**pembrolizumab** 200 mg IV Q3W + **pemetrexed** 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W *or* **cisplatin** 75 mg/m^2 IV Q3W	380/410/405	Sex: 254M/156F Median age (min/max): 65 years (34-84)	**PFS** RECIST 1.1 by BICR of imaging **OS**	**ORR** (RECIST 1.1) by BICR **DOR** (RECIST 1.1) by BICR
		saline IV Q3W + **pemetrexed** 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	190/206/202	Sex: 109M/97F Median age (min/max): 63.5 years (34-84)		

		or **cisplatin** 75 mg/m^2 IV Q3W				

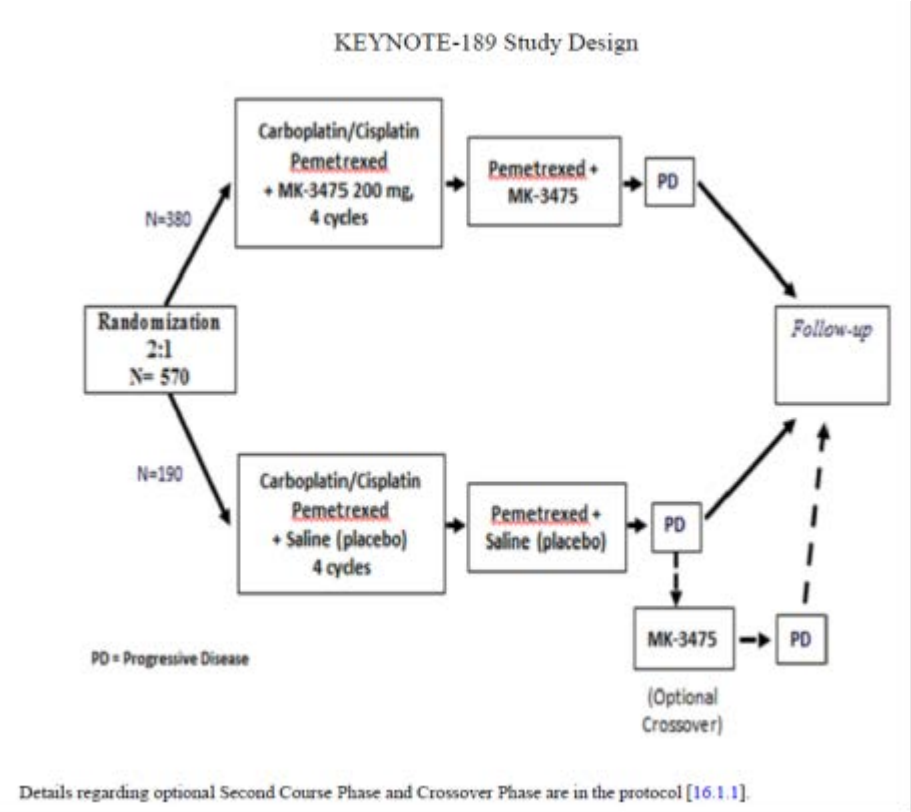
2.4.1. Dose response study(ies)

The recommended dose of 200 mg Q3W of pembrolizumab in combination with pemetrexed/carboplatin, which is also the approved dose of pembrolizumab in monotherapy for previously-untreated PD-L1 strongly positive NSCLC patients, was derived from the KEYNOTE-021 study. The use of the approved 200 mg Q3W monotherapy dose in combination with pemetrexed/carboplatin is supported by consistency in pembrolizumab PK between combination and monotherapy administration. This has been reviewed in the context of a previous application (EMEA/H/C/003820/II/0027) which was withdrawn during the procedure.

2.4.2. Main study

A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Nonsquamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)

KEYNOTE-189 is a worldwide, randomized, active-controlled, parallel-group, multi-site, double-blind study of pembrolizumab combined with pemetrexed/platinum chemotherapy versus saline placebo combined with pemetrexed/platinum chemotherapy in subjects with advanced or metastatic nonsquamous NSCLC who had not previously received systemic therapy for advanced disease and in whom EGFR or ALK-directed therapy was not indicated.



Details regarding optional Second Course Phase and Crossover Phase are in the protocol [16.1.1].

Methods

Study participants

Main inclusion criteria:

- Histologically or cytologically confirmed diagnosis of Stage IV (M1a or M1b-American Joint Committee on Cancer 7th edition) nonsquamous NSCLC.
- Confirmation that EGFR or ALK-directed therapy was not indicated.
- Measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment.
- No prior systemic treatment for their advanced/metastatic NSCLC at screening.
- Tumor tissue from locations not radiated prior to biopsy.
- Age ≥18 years
- Life expectancy of at least 3 months.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Main exclusion criteria:

- Predominantly squamous histology NSCLC.
- Prior systemic cytotoxic chemotherapy for metastatic disease, or other targeted or biological antineoplastic therapy, before the first dose of study treatment; had a major surgery within 3 weeks prior to first dose.
- Radiation therapy to the lung that is >30 Gy within 6 months of the first dose of study treatment.
- Completed palliative radiotherapy within 7 days of the first dose of study treatment.
- Known history of other prior malignancy except if the subject had undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
- Known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Subjects with untreated, asymptomatic brain metastases (i.e., no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) could participate but were required regular imaging of the brain as a site of disease.
- Active autoimmune disease that had required systemic treatment in past 2 years.
- Chronic systemic steroids.
- Subjects unable or unwilling to take folic acid or vitamin B12 supplementation.
- Prior treatment targeting PD-1, PD-L1/PD-L2, or other immune-regulatory receptors or mechanisms.
- Active infection requiring therapy.
- History of (noninfectious) pneumonitis that required steroids or current pneumonitis.

Treatments

Table 4: Trial treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab[1]	200 mg	Q3W	IV infusion	Day 1 of each 21 day cycle	Experimental
Normal saline	N/A	Q3W	IV infusion	Day 1 of each 21 day cycle	Placebo
Cisplatin	75 mg/m^2	Q3W	IV infusion	Day 1 of each 21 day cycle for 4 cycles	Treatment of cancer (comparator)
Carboplatin	AUC 5	Q3W	IV infusion	Day 1 of each 21 day cycle for 4 cycles	Treatment of cancer (comparator)
Pemetrexed	500 mg/m^2	Q3W	IV infusion	Day 1 of each 21 day cycle	Treatment of cancer (comparator)

[1] Pembrolizumab to be administered prior to chemotherapy.

Reduction of one chemotherapy agent and not the other agent was allowed if, in the opinion of the Investigator, the toxicity was clearly related to one of the treatments. If the toxicity was related to the combination of three agents, all three agents were to be reduced, interrupted or discontinued according to scheme below:

Scheme 1: Dose modifications for trial medications

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	AUC 5 Maximum dose 750mg	AUC 3.75 Maximum dose 562.5mg	AUC 2.5 Maximum dose 375mg	Discontinue
Pemetrexed	500mg/m2	375 mg/m2	250 mg/m2	Discontinue
Pembrolizumab/placebo	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

Objectives

Primary Objectives

1. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using PFS per Response Evaluation Criteria on Solid Tumors, Version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR) of imaging.
2. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using OS.

Secondary Objectives

1. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using ORR per RECIST 1.1 as assessed by BICR.
2. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using duration of response (DOR) per RECIST 1.1 as assessed by BICR.
3. To evaluate the safety and tolerability profile of pembrolizumab in combination with pemetrexed/platinum chemotherapy.

Exploratory Objectives

1. To evaluate the effect of PD-L1 expression levels on the efficacy endpoints of PFS, OS, and ORR.

2. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using PFS, ORR, and DOR assessed by the investigator using RECIST 1.1.

3. To evaluate changes in health-related quality-of-life (HRQOL) assessments from baseline in the biomarker-positive strata and in the overall study population using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 items (C30) and EORTC QLQ-Lung Cancer 13 items (LC13).

4. To characterize utilities in subjects treated with pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using the EuroQoL 5 Dimension (EQ-5D).

Outcomes / endpoints

Primary endpoints

- Overall survival (OS) defined as the time from randomization to death due to any cause.

- Progression Free Survival (PFS) defined as the time from randomization to documented PD per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first.

Secondary endpoints

- Overall response rate (ORR) assessed per RECIST 1.1 based on BICR

- Duration of response (DOR)

Sample size

The analyses are event driven. A sample size of 570 subjects was planned to provide an adequate number of events in order to detect an HR of 0.7 at α=0.025 (one-sided) for both PFS and OS with a power of:

- at least 72% for the PFS and 37% for the OS endpoint at the IA1 tests,
- at least 90% for the PFS and 73% for the OS at the IA2 tests (final of PFS), and
- at least 90% at the final analysis for the OS,

assuming a median PFS of ~6.5 months and a median OS of 13 months in the control arm (assumed to follow an exponential distribution), with a randomization ratio of 2:1 between the experimental and control group.

Enrollment of 570 subjects is assumed to occur over 12 months.

One interim analysis of PFS and two interim analyses of OS are planned in addition to the respective final analyses.

Analysis	Endpoint(s)	Timing
IA1	PFS; OS; ORR if both PFS and OS are positive	~370 PFS events (~242 OS events expected at this time)
IA2	PFS; OS	~468 PFS events (~332 OS events expected at this time)
FA	OS	~416 OS events

Randomisation

Treatment allocation/randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects were assigned randomly in a 2:1 ratio to pembrolizumab and chemotherapy or saline placebo and chemotherapy, respectively. The choice of cisplatin or carboplatin treatment was determined prior to randomization and documented in the IVRS/IWRS.

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

1. PD-L1 expression: Tumor Proportion Score ≥1% vs <1%. PD-L1 unevaluable subjects were included in the TPS <1% group.

2. Platinum chemotherapy: cisplatin vs carboplatin

3. Smoking status: never vs former/current

Blinding (masking)

The study was double-blinded, but the clinical supplies were provided open-label. Therefore, an unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab or saline infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits.

Treatment identification information was unmasked only if necessary for the welfare of the subject. Once an emergency unblinding occurred, the principal investigator, site personnel, and Sponsor personnel were unblinded so that appropriate follow-up medical care could be provided to the subject.

Statistical methods

Analysis populations

The Intention-to-Treat (ITT) population served as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized. If an unexpectedly large number of randomized subjects are not treated, analyses may be performed using the Full Analysis Set (FAS), including all randomized subjects who received at least 1 dose of study treatment and did not have a major protocol violation.

Primary Endpoint analyses:

The non-parametric Kaplan-Meier method will be used to estimate the PFS and survival curve in each treatment group. The following table summarizes the primary analysis approach for primary and key secondary efficacy endpoints:

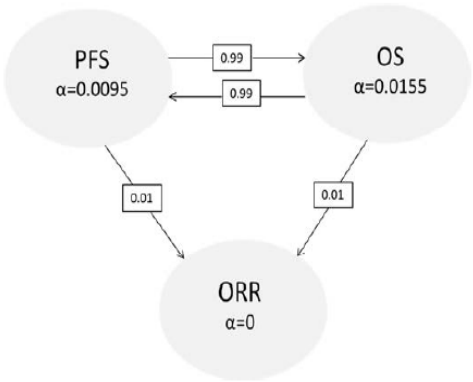
Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by central imaging vendor	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at last known alive date)
Secondary Endpoint			
ORR per RECIST 1.1 by central imaging vendor	Stratified M&N method with sample size weights††	ITT	Subjects without assessments are considered non-responders and conservatively included in denominator

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

†† Miettinen and Nurminen method

Multiplicity

The trial uses the graphical method of Maurer and Bretz to provide multiplicity control for multiple hypotheses as well as interim analyses. The type I error reallocation strategy for endpoints PFS, OS, and ORR is shown in the following figure:



The overall Type I error rate for each endpoint in the group sequential tests is strictly controlled at 2.5% (one-sided); for both PFS and OS, this is based on the Lan-DeMets O'Brien-Fleming spending function. Between the endpoints, the type I error is controlled by the following rollover rule. The total type I error allocated to PFS (0.0095) is subject to rollover to OS if the PFS test is positive. The type I error allocated to OS (0.0155) is subject to rollover to PFS if the OS test is positive. Furthermore, the total type I error (0.025) is subject to rollover to ORR at IA1 if the PFS and OS tests are both positive.

Sensitivity analyses for the primary endpoints

Mainly, sensitivity analyses will be performed for PFS endpoint.

For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, two sensitivity analyses with different sets of censoring rules were performed. The censoring rules for primary and sensitivity analyses are summarized in the following table.

Table 5: Censory rules for primary and sensitivity analyses

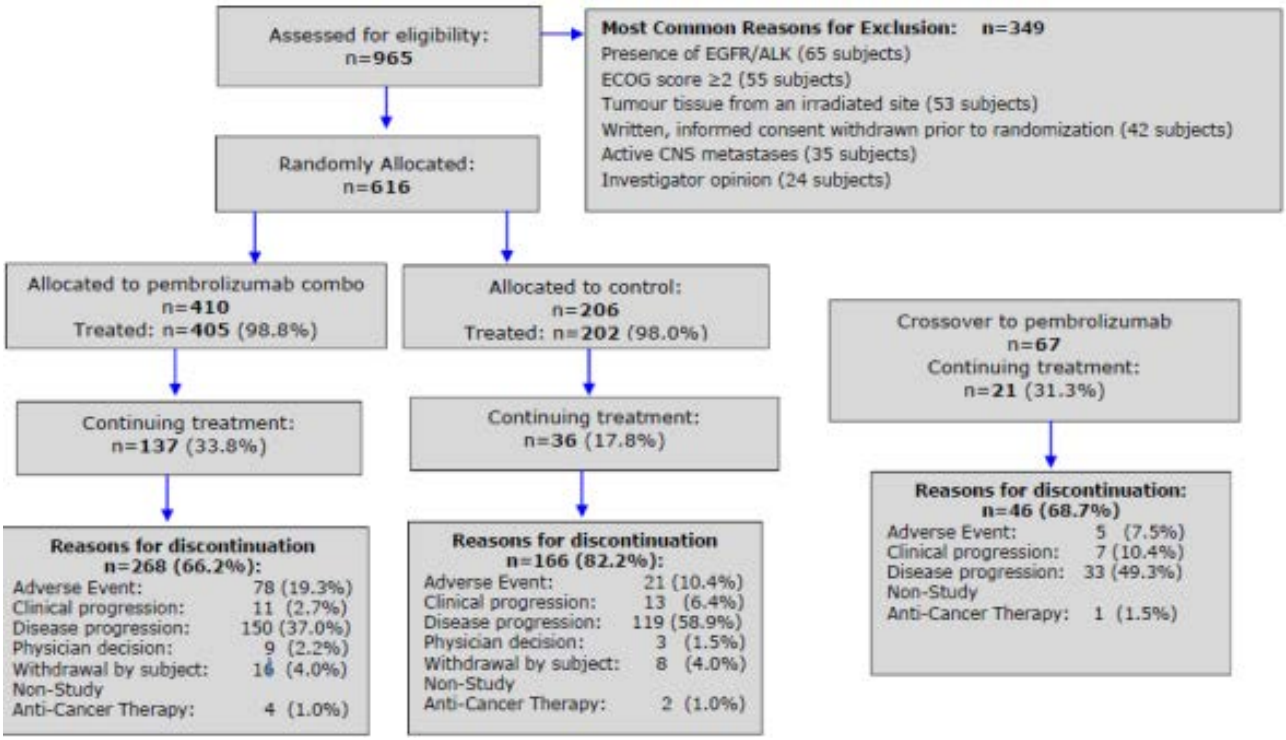
Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation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

Sensitivity analyses will be performed also for comparison of PFS based on investigator's assessment.

In case of potential gross imbalance in baseline prognostic factors in the ITT population with TPS≥50% (due to lack of stratification according to TPS≥50% vs. TPS<50%), sensitivity analyses for OS and PFS may be performed using the multivariate Cox regression to adjust for those imbalanced baseline prognostic factors.

Results

Participant flow



Recruitment

This study was conducted at 143 centers in 16 countries.

Location of Study Centers

Country	Number of Sites
Australia	8
Austria	8
Belgium	2
Canada	6
Denmark	3
Finland	2
France	6
Germany	11
Ireland	5
Israel	6
Italy	12
Japan	4
Netherlands	3
Spain	12
UK	7
USA	48

UK=United Kingdom; USA=United States of America

Conduct of the study

The original protocol was implemented by a total of 8 amendments.

The main changes are summarised below:

Protocol Amendment	Most relevant changes
02 (10 Feb 2016)	Corrected the reporting periods for all AE categories following cessation of study treatment, from 14 to 90 days for SAEs or 30 days in the event of initiation of new anti-cancer therapies; removed inclusion criterion requiring TSH within normal limits; updated the list of concomitant medications allowed and prohibited; updated required assessments for PK analysis, quality of life and safety follow-up
04 (16 Mar 2017)	Revised the SAP and objectives according with FDA input to place more emphasis on OS; addition of exploratory objective n.1 to address the importance of PD-L1 expression on efficacy and objective n.8 to address the importance of outcomes post-Crossover
07 (06 Nov 2017)	Promoted OS to primary endpoint; timing of IA1 was changed to occur at approximately 370 PFS rather than 300 events PFS as previously defined, to provide a more robust analysis of the data, focusing on OS and adjust the alpha spending. In addition, subject accrual was greater than originally expected and estimated timing of interim analyses can now be calculated based on actual enrollment (N=616), rather than the planned enrollment (N=570).

Protocol Deviations

Table 6: Summary of most pertinent protocol deviations

Deviation Category	Number of Subjects
Inclusion criteria	
No. 2 – EGFR/ALK	3
No. 3 – no measurable disease	2
No. 8 – ECOG performance status 2	1
Exclusion criteria	
No. 9 – prior malignancy	1
No. 18 – active infection requiring therapy	1

Baseline data

Table 7: Subject characteristics (ITT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	410		206	
Gender				
Male	254	(62.0)	109	(52.9)
Female	156	(38.0)	97	(47.1)
Age (Years)				
< 65	197	(48.0)	115	(55.8)
>= 65	213	(52.0)	91	(44.2)
Mean	63.2		62.8	
SD	9.4		9.1	
Median	65.0		63.5	
Range	34 to 84		34 to 84	
Race				
Asian	10	(2.4)	8	(3.9)
Black Or African American	11	(2.7)	3	(1.5)
White	387	(94.4)	194	(94.2)
Missing	2	(0.5)	1	(0.5)
Ethnicity				
Hispanic Or Latino	5	(1.2)	7	(3.4)
Not Hispanic Or Latino	384	(93.7)	190	(92.2)
Not Reported	9	(2.2)	4	(1.9)
Unknown	12	(2.9)	5	(2.4)
Region				
US	85	(20.7)	34	(16.5)
Ex US	325	(79.3)	172	(83.5)
Region				
EU	243	(59.3)	131	(63.6)
Ex EU	167	(40.7)	75	(36.4)
Geographic Region				
East-Asian	4	(1.0)	6	(2.9)
Non-East Asian	406	(99.0)	200	(97.1)
Smoking Status				
Never Smoker	48	(11.7)	25	(12.1)
Former/Current Smoker	362	(88.3)	181	(87.9)
ECOG				
0	186	(45.4)	80	(38.8)
1	221	(53.9)	125	(60.7)
2	1	(0.2)	0	(0.0)
Missing	2	(0.5)	1	(0.5)
Histology				
Adenocarcinoma	394	(96.1)	198	(96.1)
NSCLC NOS	10	(2.4)	4	(1.9)
Other	6	(1.5)	4	(1.9)
Brain Metastasis Status at Baseline				
Yes	73	(17.8)	35	(17.0)
No	337	(82.2)	171	(83.0)
Baseline Tumor Size (mm)				
Subjects with data	402		200	
Mean	97.5		105.3	
SD	67.5		66.5	
Median	84.0		87.2	
Range	11.5 to 422.1		19.3 to 466.5	
PD-L1 Status				
< 1%	127	(31.0)	63	(30.6)
>= 1%	260	(63.4)	128	(62.1)
NOT EVALUABLE	23	(5.6)	15	(7.3)
Platinum Chemotherapy				
Cisplatin	113	(27.6)	58	(28.2)
Carboplatin	297	(72.4)	148	(71.8)
Prior Radiation				
Yes	84	(20.5)	46	(22.3)
No	326	(79.5)	160	(77.7)
Prior Thoracic Radiation				
Yes	28	(6.8)	20	(9.7)
No	382	(93.2)	186	(90.3)
Prior Adjuvant Therapy				
Yes	25	(6.1)	14	(6.8)
No	385	(93.9)	192	(93.2)
Prior Neo Adjuvant Therapy				
Yes	5	(1.2)	6	(2.9)
No	405	(98.8)	200	(97.1)
Database Cutoff Date: 08NOV2017				

Source: [P189V01MK3475: adam-adsl]

Numbers analysed

Table 8: Study population

	Pembro Combo	Control	Total
Number of Subjects Screened			965
Number of Subjects Randomized (Planned Treatment)(ITT)	410	206	616
Number of Subjects Received Treatment(Actual Treatment)(ASaT)	405	202	607
Number of Subjects Randomized and Did not Receive Treatment	5	4	9
Number of Subjects Discontinued Study Medication[†](Actual Treatment)	268	99	367
Number of Subjects Crossed Over to Pembrolizumab	0	67	67

[†]Excluded Subjects who crossed over to Pembrolizumab.
Database Cutoff Date: 08NOV2017.

Source: [P189V01MK3475: adam-adsl]

Outcomes and estimation

Primary endpoints:

- Overall survival:

Median duration of follow-up was 10.5 months (0.2-20.4) with 235 (38%) deaths.

Table 9: Analysis of overall survival (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro Combo	410	127 (31.0)	4386.5	2.9	Not Reached (., .)	85.3 (81.5, 88.4)	0.49 (0.38, 0.64)	<0.00001
Control	206	108 (52.4)	1873.0	5.8	11.3 (8.7, 15.1)	72.3 (65.7, 77.9)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
[§] One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

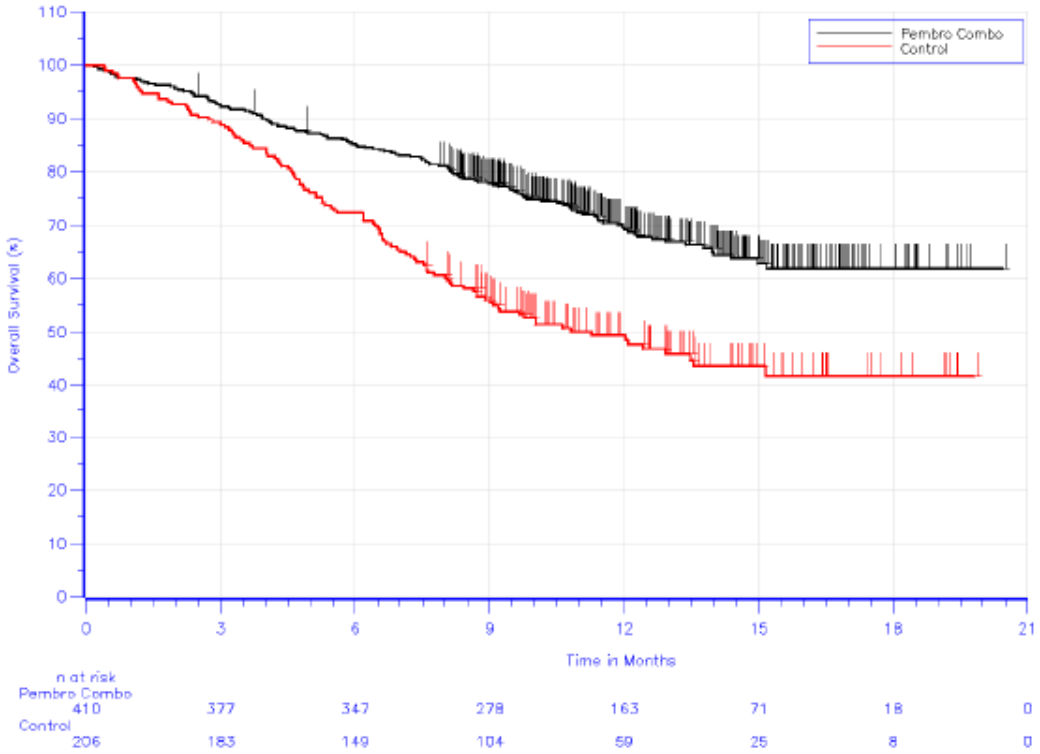
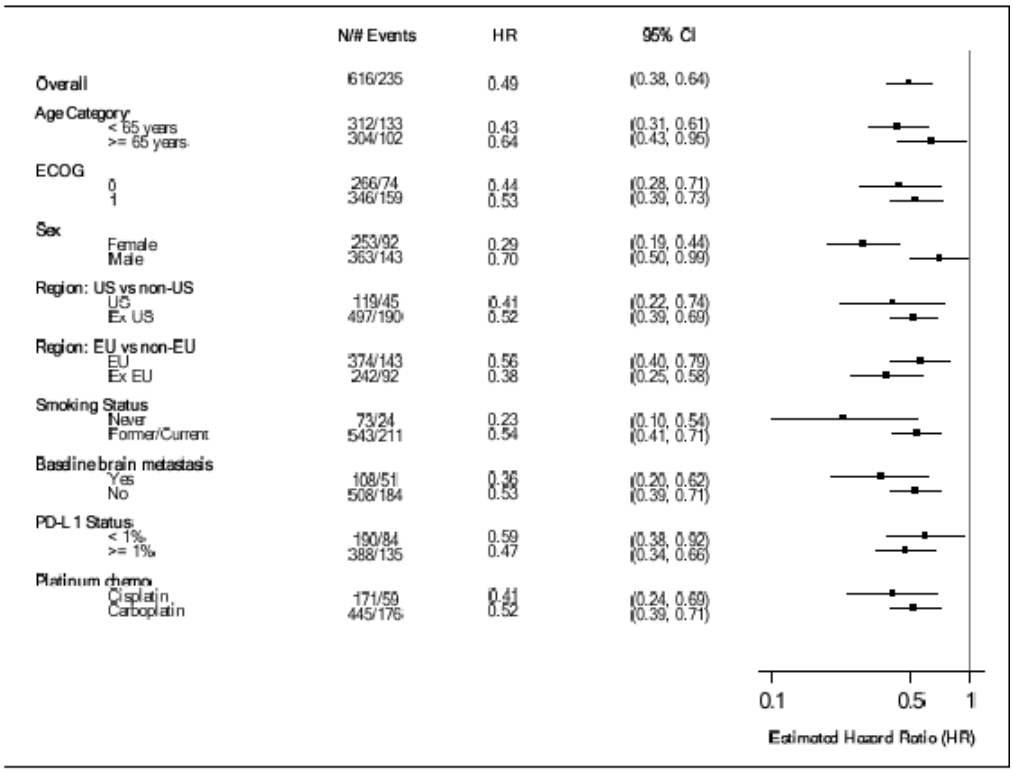


Figure 3: Kaplan-Meier estimates of overall survival (ITT population)



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cutoff Date: 08NOV2017
Source: [P189V01MK3475: adam-adsl; adtte];

Figure 4: Forest plot of OS hazard ratio by subgroup factors (ITT population)

- Progression Free Survival:

Table 10: Analysis of PFS (primary analysis) based on BICR assessment per RECIST 1.1 (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)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro Combo	410	244 (59.5)	3081.8	7.9	8.8 (7.6, 9.2)	66.4 (61.5, 70.8)	0.52 (0.43, 0.64)	<0.00001
Control	206	166 (80.6)	1166.2	14.2	4.9 (4.7, 5.5)	40.1 (33.3, 46.7)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
[§] One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

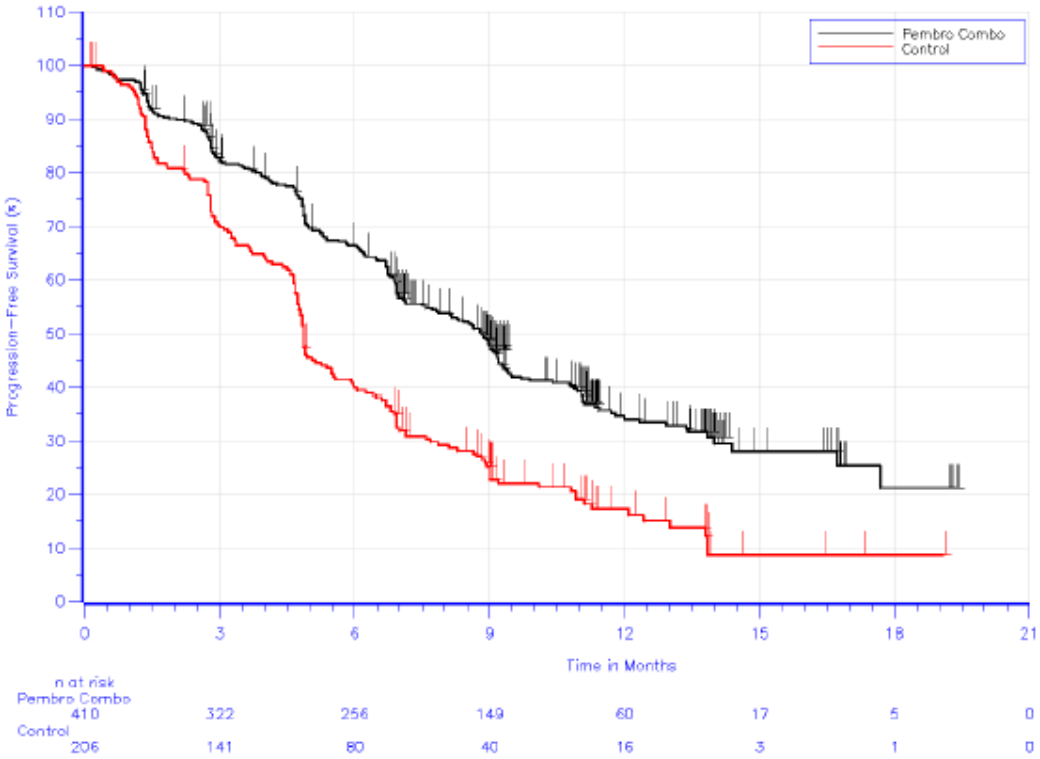
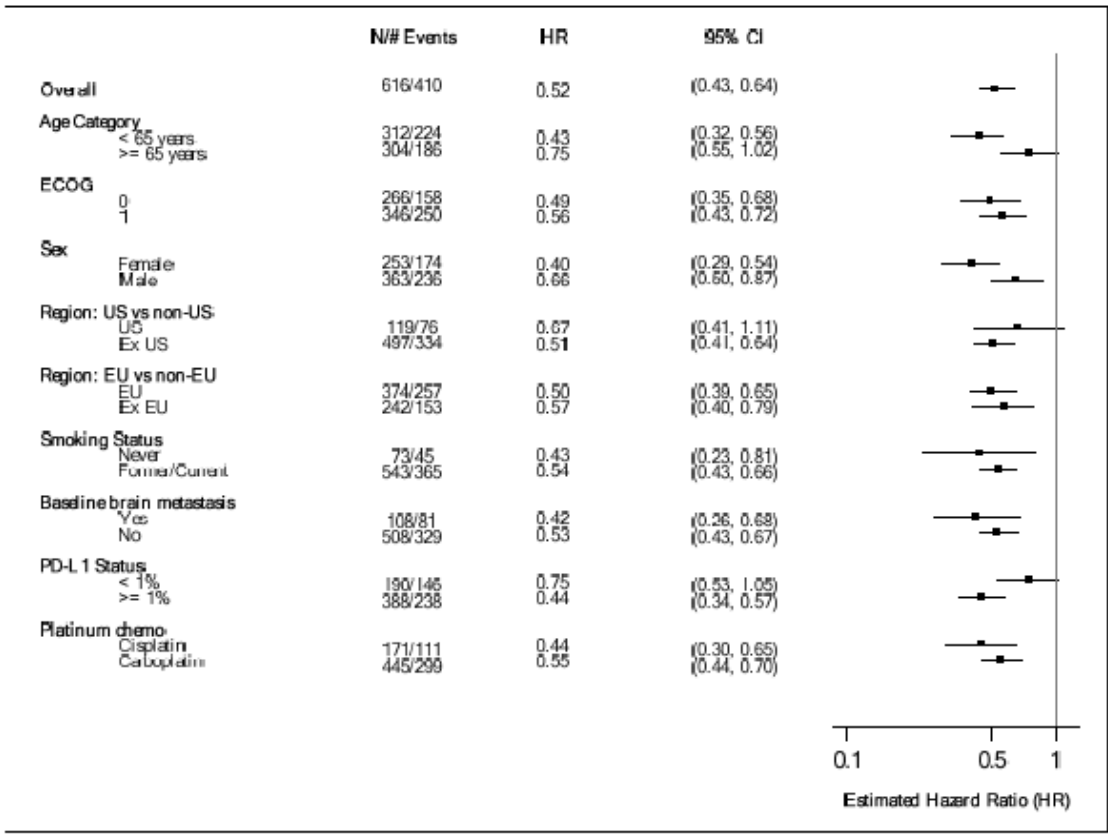


Figure 5: Kaplan-Meier estimates of PFS (primary analysis) based on BICR assessment per RECIST 1.1 (ITT population)



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cutoff Date: 08NOV2017
Source: [P189V01MK3475: adam-adsl; adtte];

Figure 6: Forest plot of PFS hazard ratio by subgroup factors based on BICR assessment per RECIST 1.1 (primary censoring rule) (ITT population)

Secondary endpoints:

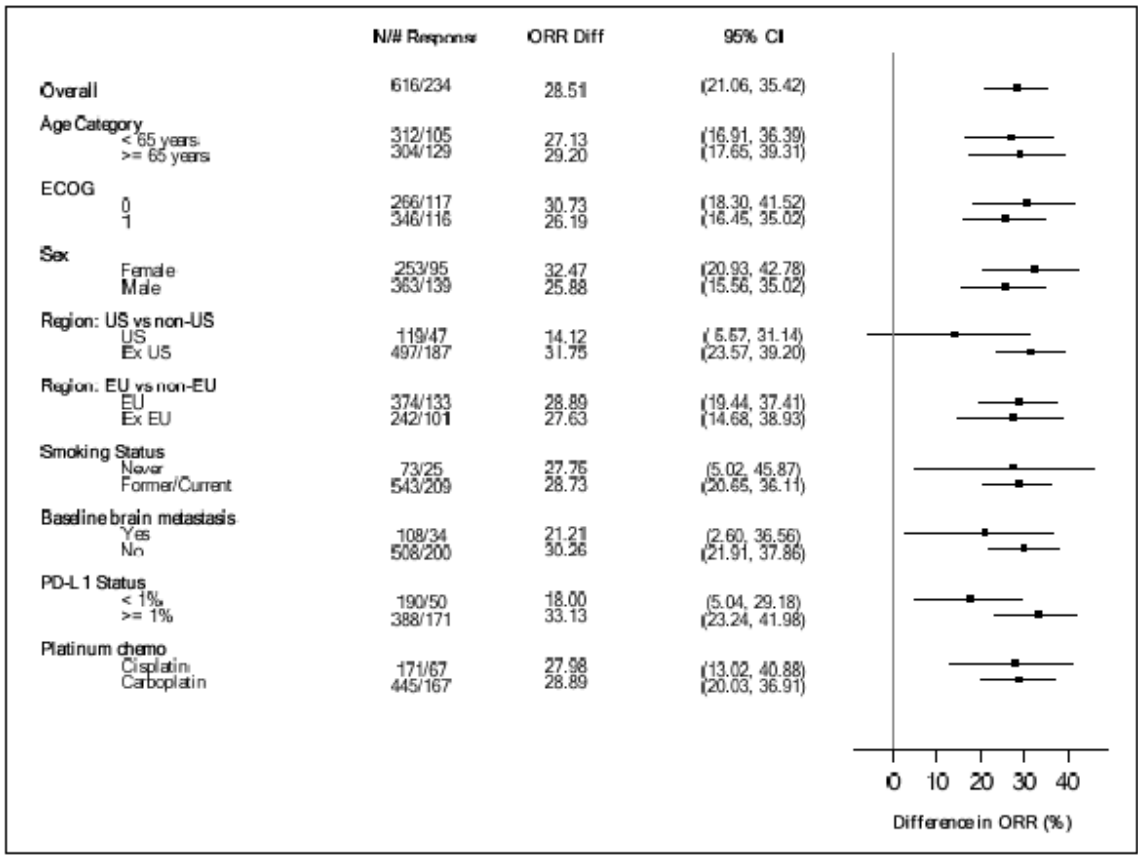
- ORR

Table 11: Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembro Combo	410	195	47.6 (42.6,52.5)	28.5 (21.1,35.4)	<0.0001
Control	206	39	18.9 (13.8,25.0)		

† Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adrs]



Analysis (ORR difference and 95% CI) in the overall population is based on the stratified Miettinen and Nurminen method; analysis in the subgroups is based on the unstratified Miettinen & Nurminen method.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cutoff Date: 08NOV2017
Source: [P189V01MK3475: adam-adsl; adrs];

Figure 7: Forest plot of ORR by subgroup factors based on BICR assessment per RECIST 1.1 (ITT population)

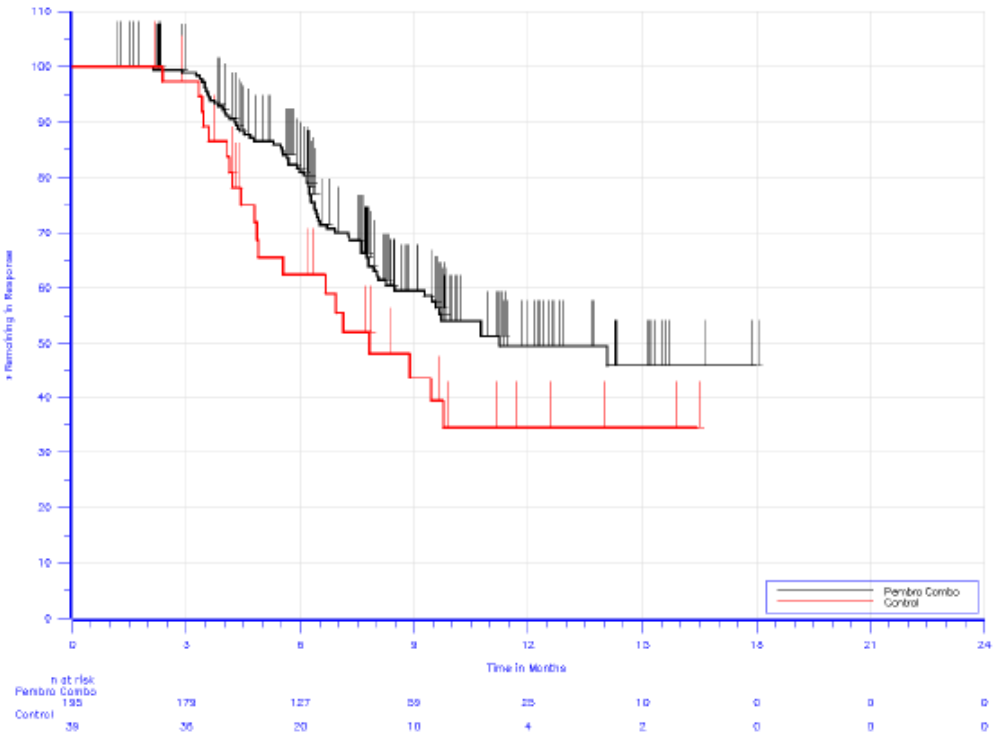
- *DoR*

Table 12: Summary of response outcome in subjects with confirmed response based on BICR assessment per RECIST 1.1 (ITT population)

	Pembro Combo (N=410)	Control (N=206)
Number of Subjects with Response†	195	39
Subjects who progressed or died‡ (%)	**71 (36.4)**	**20 (51.3)**
Range of DoR (months)	2.1 - 14.1	2.4 - 9.8
Censored subjects (%)	**124 (63.6)**	**19 (48.7)**
Subjects who progressed or died after 2 or more missed visits	1 (0.5)	0 (0.0)
Subjects started new anti-cancer treatment	6 (3.1)	0 (0.0)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	5 (2.6)	1 (2.6)
Ongoing response§	112 (57.4)	18 (46.2)
≥3 months	104 (53.3)	16 (41.0)
≥6 months	85 (43.6)	13 (33.3)
≥9 months	48 (24.6)	8 (20.5)
≥12 months	23 (11.8)	4 (10.3)
Range of DoR (months)	2.1+ - 18.0+	2.1+ - 16.4+

† Response: Best overall response as confirmed complete response or partial response.
‡ Include subjects who progressed or died either prior to or without missing 2 or more consecutive disease assessments.
§ Ongoing response: subjects who are alive, have not progressed, have not initiated new anti-cancer treatment,have not been determined to be lost to follow-up and whose last adequate assessment was <5 months prior to the data cutoff date.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]



Database Cutoff Date: 08NOV2017

Figure 8: Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR assessment per RECIST 1.1 (ITT population)

- Patient Reported Outcomes

Table 13: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at week 12 (FAS population)

	Baseline		Week 12		Change from Baseline at Week 12	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembro Combo	359	61.98 (21.270)	319	63.82 (21.495)	402	0.95 (-1.33, 3.24)
Control	180	60.56 (21.425)	150	61.06 (20.786)	200	-2.63 (-5.79, 0.53)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	3.58 (-0.05, 7.22)	0.053

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 12, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Table 14: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at week 21 (FAS population)

	Baseline		Week 21		Change from Baseline at Week 21		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]	
Pembro Combo	359	61.98 (21.270)	248	66.97 (19.429)	402	1.25 (-1.15, 3.64)	
Control	180	60.56 (21.425)	91	62.55 (24.068)	200	-4.02 (-7.70, -0.34)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control						5.27 (1.07, 9.47)	0.014

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 21, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Table 15: Time to true deterioration for cough (LC13-Q1) chest pain (LC13-Q10) or dyspnoea (C30-Q8) (FAS population)

Treatment	N	True Deterioration Events(%)	Median True Deterioration[†] (Months) (95% CI)	Pembrolizumab vs. SOC	
				Hazard Ratio[§](95% CI)[‡]	p-Value[§]
Pembro Combo	402	129 (32.1)	Not Reached (10.2, .)	0.81 (0.60, 1.09)	0.081
Control	200	66 (33.0)	7.0 (4.8, .)	---	---

True deterioration is defined as the time to first onset of 10 or more decrease from baseline with confirmation under right-censoring rule (the last observation).

[†] Based on Cox regression model with treatment as a covariate stratified by PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).

[‡] Two-sided p-value based on stratified log-rank test.

(Database Cutoff Date: 08NOV2017)

Source: [P189V01MK3475: adam-adsl; adttd]

Table 16: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at week 12 (FAS population, TPS≥1%)

	Baseline		Week 12		Change from Baseline at Week 12		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]	
Pembro Combo	228	62.46 (21.726)	211	64.57 (21.375)	253	1.43 (-1.42, 4.27)	
Control	114	60.23 (21.124)	99	60.94 (20.469)	124	-1.57 (-5.48, 2.34)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control						3.00 (-1.47, 7.47)	0.188

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 12, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Table 17: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at week 21 (FAS population, TPS≥1%)

	Baseline		Week 21		Change from Baseline at Week 21		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]	
Pembro Combo	228	62.46 (21.726)	155	67.37 (18.560)	253	1.42 (-1.60, 4.44)	
Control	114	60.23 (21.124)	63	61.24 (24.372)	124	-4.61 (-9.07, -0.16)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control						6.03 (0.90, 11.16)	0.021

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 21, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Ancillary analyses

Overall Survival by PD-L1 Expression Subgroup

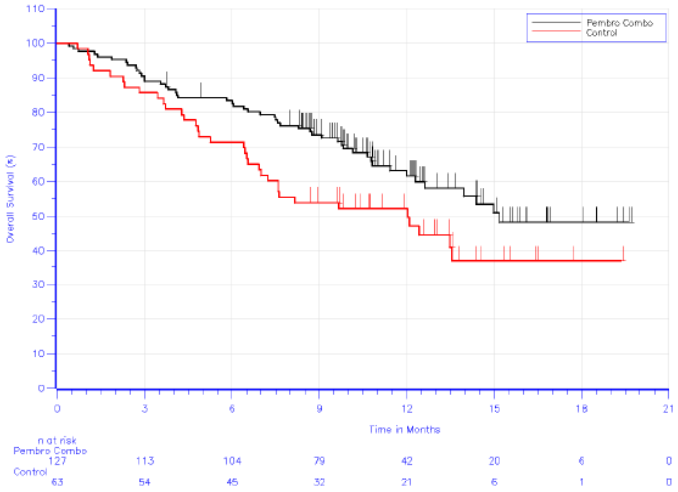


Figure 9: Kaplan-Meier estimates of OS with TPS<1%

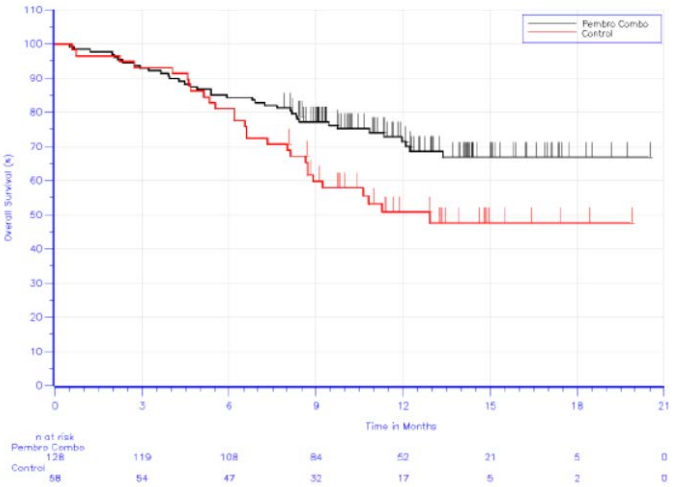


Figure 10: Kaplan-Meier estimates of OS with TPS 1-49%

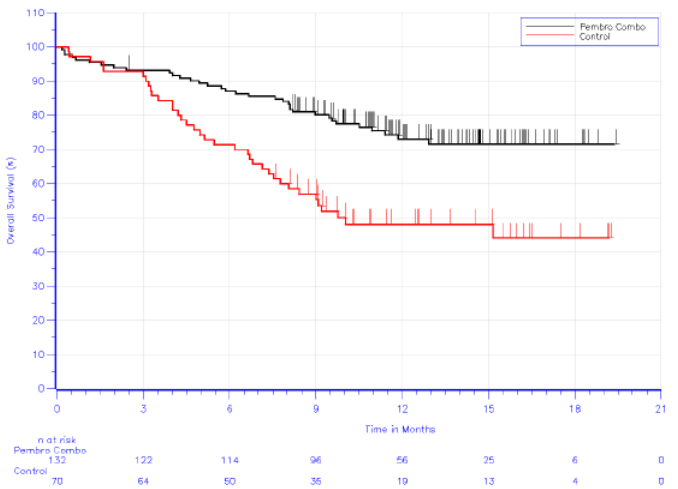


Figure 11: Kaplan-Meier estimates of OS with TPS ≥50%

Table 18: Analysis of overall survival with TPS< 1% (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	127	49 (38.6)	1271.6	3.9	15.2 (12.3, .)	83.4 (75.7, 88.9)	0.59 (0.38, 0.92)	0.00951
Control	63	35 (55.6)	560.4	6.2	12.0 (7.0, .)	71.4 (58.6, 80.9)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Table 19: Analysis of overall survival with TPS 1-49% (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	128	37 (28.9)	1373.2	2.7	Not Reached (., .)	84.4 (76.8, 89.6)	0.55 (0.34, 0.90)	0.00808
Control	58	28 (48.3)	566.7	4.9	12.9 (8.7, .)	81.0 (68.4, 89.0)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Table 20: Analysis of overall survival with TPS≥ 50% (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	132	34 (25.8)	1460.4	2.3	Not Reached (., .)	87.1 (80.0, 91.8)	0.42 (0.26, 0.68)	0.00012
Control	70	36 (51.4)	636.5	5.7	10.0 (7.5, .)	71.4 (59.3, 80.5)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Progression Free Survival by PD-L1 Expression Subgroup

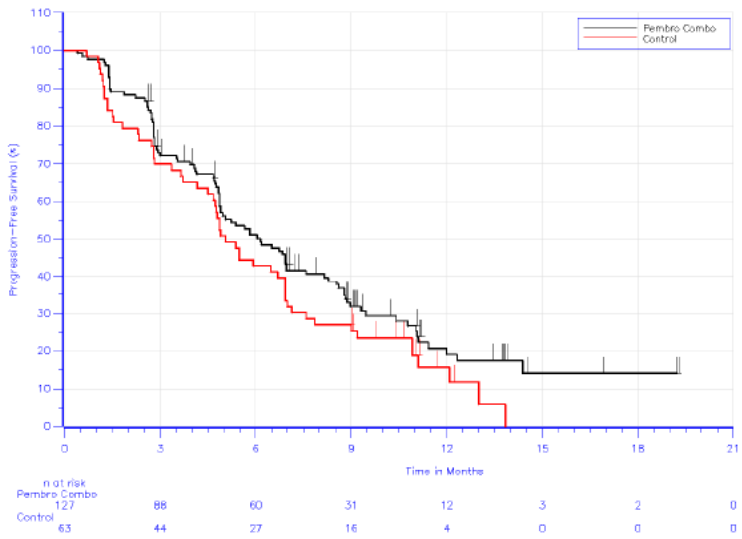


Figure 12: Kaplan-Meier estimates of PFS (primary analysis) based on BICR assessment per RECIST 1.1 with TPS <1% (ITT population)

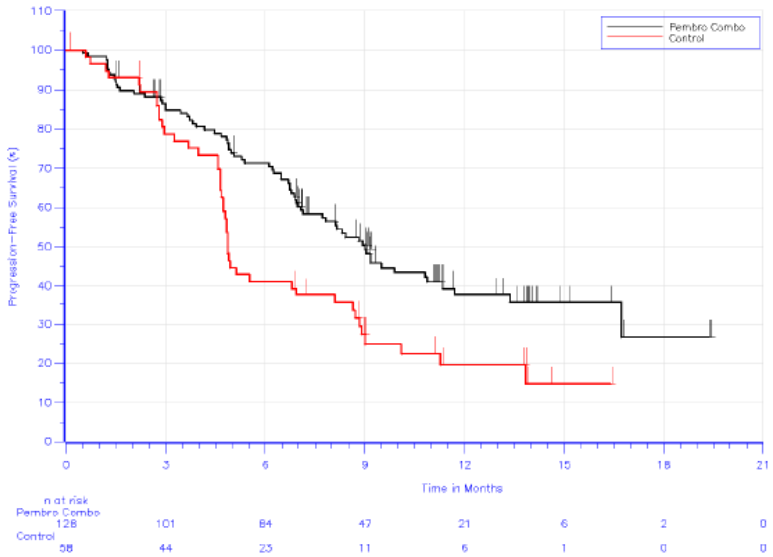


Figure 13: Kaplan-Meier estimates of PFS (primary analysis) based on BICR assessment per RECIST 1.1 with TPS 1-49% (ITT population)

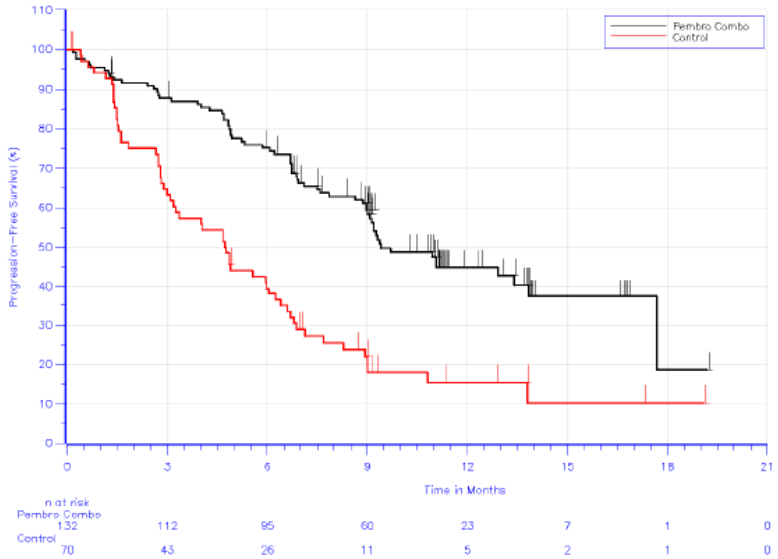


Figure 14: Kaplan-Meier estimates of PFS (primary analysis) based on BICR assessment per RECIST 1.1 with TPS ≥ 50% (ITT population)

Table 21: Analysis of PFS (primary analysis) based on BICR assessment per RECIST 1.1 with TPS< 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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	127	92 (72.4)	808.0	11.4	6.1 (4.9, 7.6)	51.0 (41.8, 59.5)	0.75 (0.53, 1.05)	0.04756
Control	63	54 (85.7)	367.3	14.7	5.1 (4.5, 6.9)	42.9 (30.5, 54.6)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Table 22: Analysis of PFS (primary analysis) based on BICR assessment per RECIST 1.1 with TPS 1-49 % (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	128	70 (54.7)	977.4	7.2	9.0 (7.1, 11.3)	71.3 (62.3, 78.5)	0.55 (0.37, 0.81)	0.00104
Control	58	44 (75.9)	361.1	12.2	4.9 (4.7, 6.9)	41.1 (28.2, 53.6)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Table 23: Analysis of PFS (primary analysis) based on BICR assessment per RECIST 1.1 with TPS ≥ 50% (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	132	68 (51.5)	1094.1	6.2	9.4 (9.0, 13.8)	75.2 (66.7, 81.7)	0.36 (0.25, 0.52)	<0.00001
Control	70	56 (80.0)	364.9	15.3	4.7 (3.1, 6.0)	39.5 (27.9, 50.9)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Objective Response Rate by PD-L1 Expression Subgroup

Table 24: Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1 with TPS< 1% (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembro Combo	127	41	32.3 (24.3,41.2)	17.4 (4.3,28.6)	0.0055
Control	63	9	14.3 (6.7,25.4)		

† Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adrs]

Table 25: Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1 with TPS 1-49% (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembro Combo	128	62	48.4 (39.5,57.4)	28.5 (13.9,41.1)	0.0001
Control	58	12	20.7 (11.2,33.4)		

† Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adrs]

Table 26: Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1 with TPS ≥ 50% (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)[†]	p-Value[††]
Pembro Combo	132	81	61.4 (52.5,69.7)	38.5 (24.6,50.5)	<0.0001
Control	70	16	22.9 (13.7,34.4)		

[†] Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adrs]

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27: Summary of Efficacy for trial KEYNOTE-189

Title: A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)			
Study identifier	KEYNOTE-189		
Design	Multi-center, randomized (2:1), double-blind, placebo-controlled Phase 3 study in subjects with locally advanced or metastatic NSCLC		
Hypothesis	Superiority of pembro combo versus control		
Treatments groups	Pembro combo		Pembrolizumab 200 mg + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5, all on Day 1 every 3 weeks (Q3W) for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2 Q3W until progression 410 patients randomised
	Control		Saline placebo + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5, all on Day 1 Q3W for 4 cycles followed by saline placebo + pemetrexed 500 mg/m^2 Q3W until progression 206 patients randomised
Endpoints and definitions	Dual Primary endpoints	OS	Time from randomization to death due to any cause
		PFS	Time from randomization to PD, based upon RECIST 1.1 by BICR, or death, whichever occurred earlier
	Secondary endpoints	ORR	proportion of subjects who have a CR or a PR by BICR/RECIST 1.1)
		DoR	time from first documented evidence of CR or PR until disease progression or death

	Exploratory endpoints	OS PFS ORR by PD-L1 expression levels	As specified above
Database lock	08 Nov 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembro combo	Control
	Number of subject	410	206
	OS N. with events (%)	127 (31)	108 (52.4)
	Median OS months (95% CI)	Not reached (...)	11.3 (8.7, 15.1)
	Hazard Ratio pembro combo vs control (95% CI)	0.49 (0.38, 0.64)	
	p-value (one sided log-rank test)	<0.00001	
	PFS N. with events (%)	244 (59.5)	166 (80.6)
	Median OS months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
	Hazard Ratio pembro combo vs control (95% CI)	0.52 (0.43, 0.64)	
	p-value (one sided log-rank test)	<0.00001	
	ORR N (%) (95% CI)	195 (47.6) (42.6, 52.5)	39 (18.9) (13.8, 25)
	Difference % vs control (95% CI)	28.5 (21.1, 35.4)	
	p-value (one sided)	<0.0001	
	Duration of response Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

Clinical studies in special populations

Table 28: Efficacy endpoints by age category

Endpoint	Age Category (Years)	Pembro Combo vs Control
OS HR (95% CI)†	<65	0.43 (0.31, 0.61)
	65-74	0.51 (0.32, 0.81)
	75-84	2.09 (0.84, 5.23)
PFS HR (95% CI)†	<65	0.43 (0.32, 0.56)
	65-74	0.64 (0.45, 0.91)
	75-84	1.73 (0.77, 3.90)
ORR Difference in % (95%CI)‡	<65	27.1 (16.9, 36.4)
	65-74	32.2 (19.0, 43.4)
	75-84	14.4 (-11.1, 36.4)

CI=Confidence interval; HR=Hazard ratio; PFS=Progression-free survival; ORR=Objective response rate; OS=Overall survival.
NOTE: Number of subjects per age category: <65 (pembro combo: 197; control: 115); 65-74 (pembro combo: 178; control: 69); 75-84 (pembro combo: 35; control: 22)
†Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs carboplatin), and smoking status (never vs former/current).
‡Based on unstratified Miettinen and Nurminen method.
Database Cutoff Date: 08NOV2017
Source: [P189V01MK3475: adam-adsl; adrs; adtte]

- Overall survival by gender

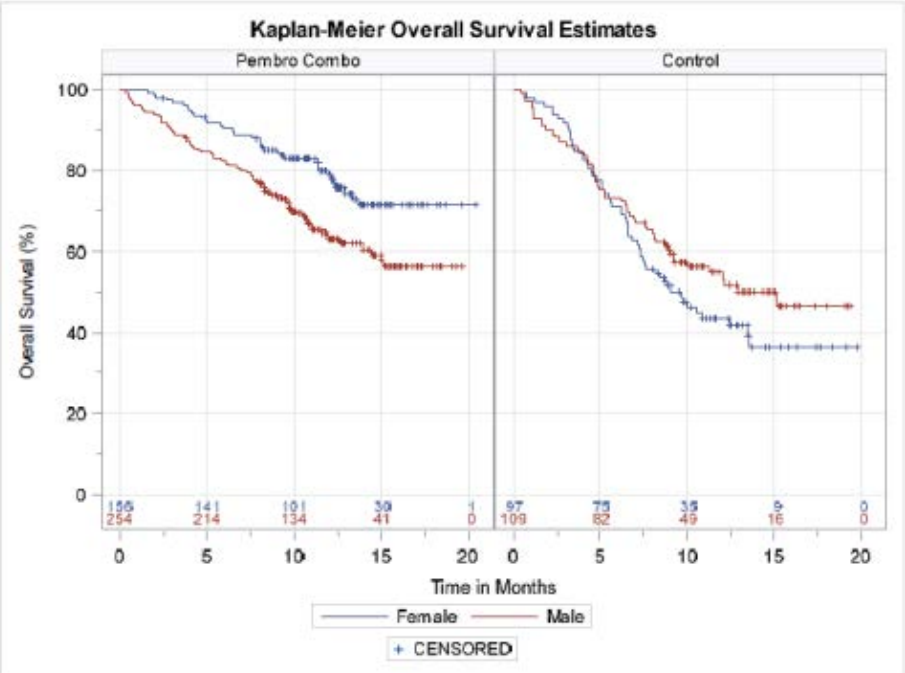


Figure 15: KEYNOTE-189 OS Kaplan-Meier curves for Male and Female by treatment arm

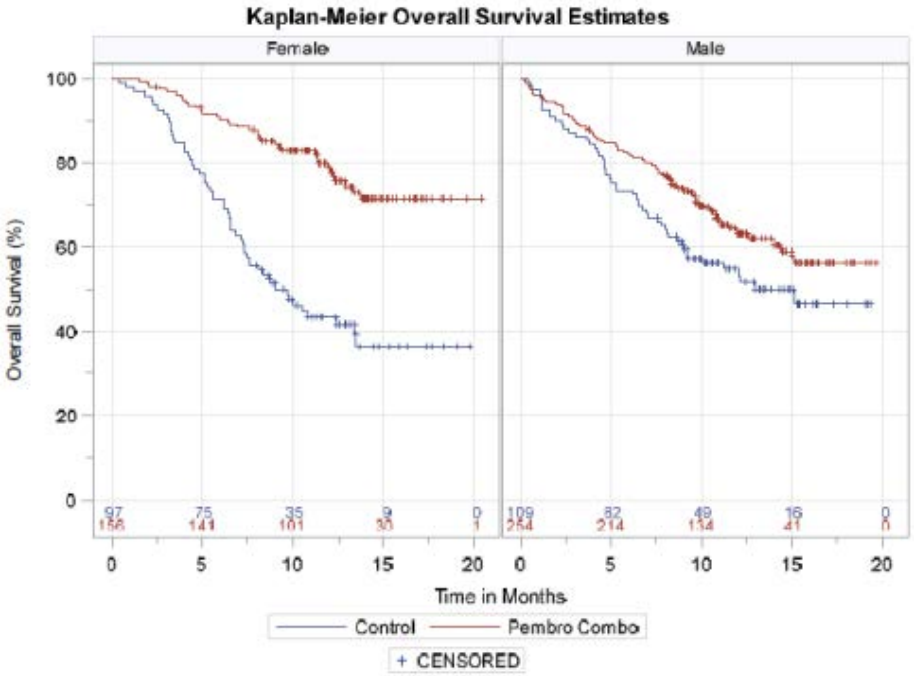


Figure 16: KEYNOTE-189 OS Kaplan-Meier curves for pembrolizumab chemotherapy combination vs. chemotherapy control by gender

Supportive study

A Phase 1/2 Study of MK-3475 (SCH900475) in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-small Cell Lung Carcinoma

An update to the efficacy analysis of KEYNOTE-021-G was performed with a data cutoff date of 31-MAY-2017 to provide long-term OS and PFS results. These updated analyses are post hoc, and the results are provided here without alpha allocation. Nominal p-values for each endpoint were reported where applicable.

As of the data cutoff date of 31-MAY-2017, the median follow-up duration was 18.7 months.

Table 29: Comparison of subject characteristics in KEYNOTE-189 and KEYNOTE-021-G

	KEYNOTE-189		KEYNOTE-021-G	
	Pembro Combo (n=410)	Control (n=206)	Pembro Combo (n=60)	Control (n=63)
Gender- female	38%	47.1%	63.3%	58.7%
Age (Years)- <65 years	48%	55.8%	60%	44.4%
ECOG- 0	45.4%	38.8%	40%	46%
Brain Metastases- yes at baseline†	17.8%	17%	20%	11.1%
Baseline Tumor Size- Mean††	97.5 mm	105.3 mm	70.6 mm	79.1 mm
Smoking- never smoker	11.7%	12.1%	25%	14.3%
PD-L1 TPS <1%	31%	30.6%	35%	36.5%
PD-L1 TPS ≥1%	63.4%	62.1%	65%	63.5%

† Brain metastases: KEYNOTE-21G, stable, treated eligible; KEYNOTE-189, stable, treated or untreated eligible.

†† Calculated from the sum of diameters of target lesions

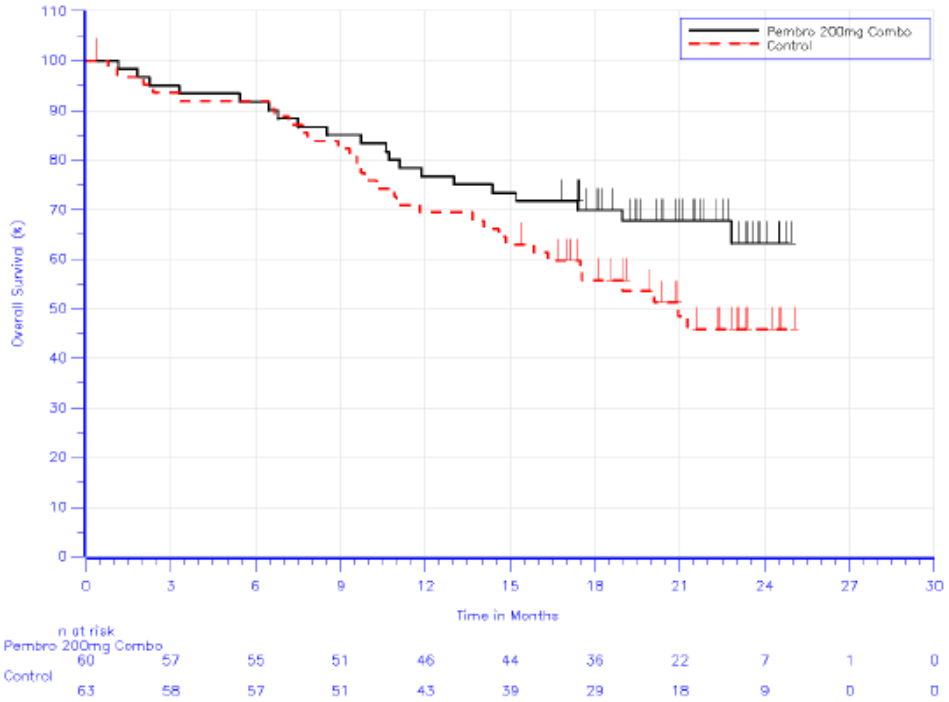


Figure 17: Kaplan-Meier estimates of overall survival cohort G1 subjects (ITT population)

Table 30: Analysis of overall survival cohort G1 subjects (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro 200mg Combo	60	20 (33.3)	1055.6	1.9	Not Reached (22.8, .)	91.7 (81.1, 96.4)	0.59 (0.34, 1.05)	0.03436
Control	63	31 (49.2)	1007.1	3.1	20.9 (14.9, .)	91.9 (81.7, 96.6)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (positive vs. negative).
§ One-sided p-value based on log-rank test.
Database Cutoff Date: 31MAY2017.

Source: [P021V03MK3475: analysis-adsl; adtte]

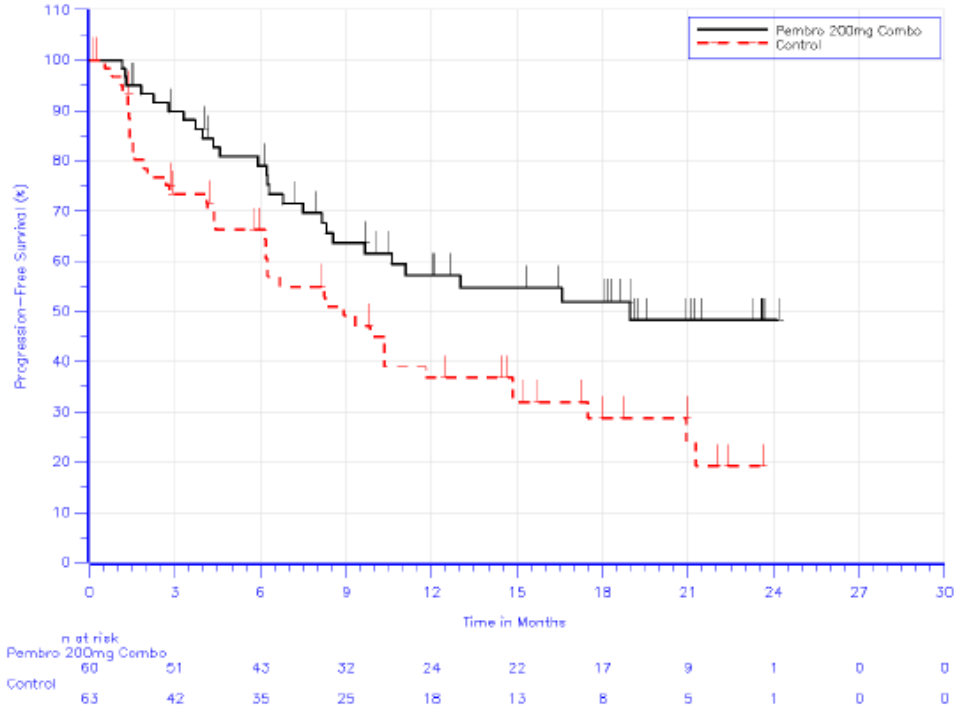


Figure 18: Kaplan-Meier estimates of PFS (primary analysis) based on BICR assessment per RECIST 1.1 cohort G1 subjects (ITT population)

Table 31: Analysis of PFS (primary analysis) based on BICR assessment per RECIST 1.1 cohort G1 subjects (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)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab 200mg Combo	60	26 (43.3)	681.4	3.8	19.0 (8.5, .)	79.0 (65.9, 87.5)	0.54 (0.33, 0.88)	0.00673
Control	63	40 (63.5)	537.0	7.4	8.9 (6.2, 11.8)	66.3 (52.7, 76.8)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (positive vs. negative).
§ One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review
(Database Cutoff Date: 31May2017).

Source: [P021V03MK3475: analysis-adsl; adtte]

Table 32: Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1 cohort G1 subjects (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Standard Treatment	
				Estimate (95% CI)†	p-Value††
Pembro 200mg Combo	60	34	56.7 (43.2,69.4)	24.8 (7.2,40.9)	0.0029
Control	63	20	31.7 (20.6,44.7)		

† Based on Miettinen & Nurminen method stratified by PD-L1 status (positive vs. negative).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 31MAY2017.

Source: [P021V03MK3475: analysis-adsl; adorr]

Table 33: Summary of time to response and duration of response for subjects with confirmed response based on BICR assessment per RECIST 1.1 cohort G1 subjects (ITT population)

	Pembro 200mg Combo (N=60)	Control (N=63)
Number of subjects with response[†]	34	20
Time to Response[†] (months)		
Mean (SD)	2.8 (2.5)	3.1 (2.1)
Median (Range)	1.6 (1.2-12.3)	2.8 (1.1-10.3)
Response Duration[‡] (months)		
Median (Range)	Not reached (1.4+ - 22.7+)	Not reached (2.8 - 23.7+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	31 (96.9)	18 (95.0)
≥6 months	27 (90.3)	12 (77.9)
≥9 months	21 (83.4)	11 (77.9)

[†] Response: Best objective response as confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 31MAY2017.

Source: [P021V03MK3475: analysis-adsl; adtte; adorr]

Table 34: Comparison of efficacy results across studies

Endpoint	KEYNOTE-189	KEYNOTE-021-G*
Overall survival	HR 0.49	HR 0.59
Progression-free survival	HR 0.52	HR 0.54
Objective response rate, difference between treatment groups	28.5%	24.8%
*Nominal data		

Source: [Table 2.7.3-nsclc7: 4] [Table 2.7.3-nsclc7: 5] [Table 2.7.3-nsclc7: 6] [Table 2.7.3-nsclc7: 10] [Table 2.7.3-nsclc7: 11] [Table 2.7.3-nsclc7: 12]

2.4.3. Discussion on clinical efficacy

Pembrolizumab monotherapy is already part of the NSCLC treatment algorithm, having been approved as first-line treatment of metastatic PD-L1 strongly positive (TPS≥50%) NSCLC in the absence of EGFR or ALK gene rearrangements; and in second-line for the treatment of locally advanced or metastatic PD-L1 positive (TPS≥1%) patients who have received at least one prior chemotherapy regimen, including the approved tyrosine kinase inhibitors for EGFR and ALK positive tumours.

The current Type II variation application aims at extending the clinical indication of pembrolizumab as add-on treatment to platinum/pemetrexed chemotherapy in non-squamous metastatic NSCLC patients irrespective of tumour PD-L1 level of expression based on the results of the pivotal phase III trial KEYNOTE-189.

Design and conduct of clinical studies

The efficacy evidence in support of the current regulatory submission are derived from the first interim analysis (IA1 with cut-off date 08 Nov 2017) of the KEYNOTE-189, an ongoing Randomized, Double-Blind, Phase III Study of Platinum + Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Nonsquamous Non-small Cell Lung Cancer Subjects. The data are supported by an updated analysis of cohort G of the Phase I/II study KEYNOTE-021, previously submitted as part of an application (EMEA/H/C/003820/II/0027) subsequently withdrawn, consisting of the group of patients with locally advanced or metastatic (Stage IIIB/IV) NSCLC cancer exposed to the intended dose of pembrolizumab (200

mg Q3W) in combination with carboplatin/pemetrexed. Patients with sensitizing EGFR mutation or ALK translocation were not eligible.

As being a randomised, double blind superiority trial versus chemotherapy alone, the study design of the pivotal KEYNOTE-189 allows for a controlled analysis of the add-on value of pembrolizumab to cytotoxic agents. Overall, patient selection criteria reflect the target population of the pursued clinical indication. The use of platinum/pemetrexed as a study comparator is deemed in line with current clinical practice as it represents a valuable therapeutic option among those recommended as 1L choice in the treatment of non-squamous NCSLC patients with tumours negative for EGFR and ALK mutations. It is acknowledged that KEYNOTE-189 was designed before regulatory approval for pembrolizumab in 1L for NSCLC patients with high PD-L1 expression (TPS≥50%) was granted, and therefore the study design lacks a comparative arm including pembrolizumab monotherapy, that is currently the SoC for the treatment of this patient subgroup. The partial overlapping of the population targeted by the pursued extension of indication with the one for which a licensed indication is already in place, constitutes an element of concern. In the absence of a direct comparison between pembrolizumab as monotherapy and as add-on therapy to platinum-based doublets, a specification was proposed by the MAH to be included in section 4.2 of the SmPC to better reflect the need for treating physicians to consider a B/R ratio evaluation on individual basis, and provide a comprehensive description of currently available clinical trial results that are of clinical value in the process of treatment-decision making (i.e. efficacy outcomes by PD-L1 status and special considerations in the subgroup of patients aged ≥75 years)

The choice of OS and PFS per RECIST 1.1 by BICR as primary endpoints enables a clinical benefit evaluation based on relevant efficacy outcomes in cancer therapy, and it is therefore deemed adequate. The key secondary endpoint was ORR per RECIST 1.1, with additional secondary endpoints to describe DOR and safety and tolerability.

Treatment allocation/randomization was stratified according to PD-L1 expression (TPS ≥1% vs <1%; PD-L1 unevaluable included in the TPS <1% group), Platinum chemotherapy (cisplatin vs carboplatin), smoking status (never vs former/current). This approach is deemed adequate. The sample size calculation of KEYNOTE-189 was appropriate for a comparative analysis between the two treatment arms (pembro combo vs control) in the ITT population (616 patients in total). The IA1 of KEYNOTE-189 that has been presented was event-driven and set-up at around 370 PFS events, as specified by Protocol Amendment n.7 (dated 06 Nov 2017), with an appropriate multiplicity adjustment between the two dual primary endpoints PFS and OS. It is noted that upgrading of OS as primary end-point was introduced with Amendment n.7, in response to FDA suggestions to pose major emphasis on the survival outcome, which is a reasonable approach. However, it should be noted that while PFS reached a maturity level of 88%, the level of maturity of OS analysis was 57% at this stage. Considering that the focus of this application is to extend the clinical indication of pembrolizumab as add-on treatment to chemotherapy irrespective of the PD-L1 level of expression, a robust characterisation of the efficacy profile of the experimental treatment in the different subgroups (TPS<1%, TPS 1-49%, TPS≥50%) would be of value, particularly to contextualize the results taking into account the current treatment landscape. An updated analysis will be submitted post authorisation together with the final CSR by June 2021 (see RMP).

The supportive study KN021, in particular the randomized Cohort G1 of KEYNOTE-021 (ITT population=123 patients), is very similar in terms of eligibility criteria. Differently from study KN-189, cisplatin-based combinations were not allowed in this study, even though based on inclusion criteria, cisplatin-eligible patients could have been enrolled. The primary efficacy endpoint of Study KN021 was ORR per RECIST 1.1 based on BICR, while PFS per RECIST 1.1 based on BICR was considered a key secondary endpoint. These two endpoints were analyzed using a step down procedure, in which the Type I error rate (alpha=2.5%, one-sided) over the multiple endpoints was controlled by a fixed-sequence, closed-testing procedure that tested for a treatment difference for ORR first, followed by a test for a treatment difference for PFS. As additional secondary endpoints, OS and duration of response (DOR) were also evaluated. The primary

efficacy analysis of efficacy was planned to occur with at least 6 months of treatment or follow up for all patients enrolled, which is considered adequate. An updated analysis with 8 additional months of follow-up compared to the prior submission (EMEA/H/C/003820/II/0027) has been submitted (cutoff date 31-MAY-2017 vs 31-DEC-2016 in prior application).

Efficacy data and additional analyses

The study population of both the pivotal study KEYNOTE-189 and supportive study KEYNOTE-021G, can be considered overall representative of the population targeted by the sought indication with regard to disease staging and histology. Baseline characteristics in KEYNOTE-189 appear well balanced between treatment arms, with the exception of age, gender and ECOG PS score. One could get a notion that the baseline characteristics of the pembro/combo group are slightly favourable (eg. ECOG=1 54% vs.61%). On the other hand, a higher percentage of subjects ≥65-year-old were recruited in the pembro combo compared to control (52% vs 44%). In addition, the higher percentage of female patients in the control arm could also favour the chemotherapy vs the pembro-combo arm (47% vs 38%). At the time of inclusion, most patients in the pembrolizumab arm had ECOG 1 status (54%) or 0 (45.4%).

A clinically relevant benefit in OS is reported in KEYNOTE-189, with the Kaplan-Meier curves showing a more favourable outcome of pembro combo versus control, with a compelling HR=0.49 (95% CI: 0.38,0.64; p<0.00001) in the overall study population. The median OS was not reached for the pembro combo but was 11.3 months (95% CI: 8.7, 15.1) for the control. The KM curves for OS demonstrated a separation beginning at Month 1 and these curves never cross, indicating the favourable OS for the pembro-chemo-combo therapy. This will be provided as a post-authorisation measure with the final CSR to be submitted by June 2021.

A benefit is also reported for PFS (with 66% of the total population with a PFS event occurred at the time of IA1) for pembro combo versus the control arm in the overall population, with a reduction in disease progression by 48% and a gain of about 4 months in median PFS (HR=0.52 [0.43, 0.64]; p<0.00001). The data were confirmed by both the Sensitivity analysis 1 (HR=0.51 [0.42, 0.63]; p<0.00001) and Investigator-based assessment (HR=0.53 [0.43, 0.64] P<0.00001), demonstrating robustness of the finding.

The secondary end-point results are in further support of a beneficial effect of pembrolizumab co-administrated with chemotherapy over chemotherapy alone (ORR 47.6% vs 18.9% with a median DoR of 11.2 vs 7.8 months in pembro combo vs control respectively).

Efficacy endpoints by subgroup analysis also demonstrate overall better performance of the combined treatment versus platinum/pemetrexed in all categories for both OS and PFS. However, stratification of results by factors such as age, sex and PD-L1 score demonstrates a variable degree of superiority of pembro combo vs control in OS and PFS, with PFS curves almost superimposable and HR=0.75 (95%CI 0.53-1.05) in the subgroup of patients with PD-L1<1%. The dependency of treatment effect upon PD-L1 status recognises biological plausibility. Despite the 95% CI of PFS HR crossing 1 in the subgroup with PD-L1 score <1%, the significant advantage in terms of OS of the experimental treatment versus chemotherapy only in this subpopulation, makes the results of clinical value.

A total of 57 NSCLC patients aged ≥ 75 years were enrolled in study KEYNOTE-189 (35 in the pembrolizumab combination and 22 in the control). A trend towards reduced performance of pembrolizumab combination according to increasing age was noted with an apparent detrimental effect in subjects aged ≥75 years (HR=2.09 [0.84,5.23] in OS, and HR=1.73 [0.77,3.90] in PFS). Data are limited on the efficacy of pembrolizumab in combination with platinum chemotherapy in this patient population.

Unlike prior clinical studies (KEYNOTE-010; KEYNOTE-024) showing no apparent benefit of pembrolizumab monotherapy in women, the KEYNOTE-189 points toward a higher efficacy of the combined therapy vs

control in female than male subjects. Even in KN021 the ORR difference of male patients compared to female patients was 4%. The results from KN189 seem to be inconsistent. A gender imbalance has been noted between the two arms (38% vs 47.1% of the female population in pembro combo and control arm, respectively) that might constitute a bias in data interpretation, also in view of a historical difference in the clinical outcomes of immunotherapy in prior studies (Conforti F, et al. Lancet Oncol 2018) in favour of males. A sex adjusted analysis was requested and showed no bias due to gender in results analysis. There was underperformance of females in the control arm of KEYNOTE-189 (57.7% deaths compared to 47.7% deaths in males) as well as fewer deaths in females (23.1%) compared to males (35.8%) in the pembrolizumab combination arm. In addition, the therapeutic approach in KEYNOTE-189 is different from all of the studies evaluated by Conforti et al, as none included a treatment arm with an anti-PD-1 inhibitor and chemotherapy. The observed difference between males and females will be monitored in the future submissions.

A benefit for the combination of pembrolizumab and chemotherapy is observed in the overall population. However, the results in the subgroup of patients with PD-L1 score ≥50% should be considered in the context of the already authorised monotherapy indication for Keytruda. In this patient population, the combined therapy led to a substantial benefit with a HR=0.36 (0.25, 0.52; p<0.00001) in PFS and HR=0.42 (0.26, 0.68; p=0.00012) in OS and 4.7 month gain over control in PFS. In the KEYNOTE-024, supporting the use of pembrolizumab as monotherapy in the first line NSCLC indication in patients with PD-L1 score ≥50%, a HR=0.63 (0.47, 0.86) vs SOC (p=0.002) was observed, with a gain of almost 15 months in OS over the control arm (HR=0.66 vs platinum/pemetrexed regimen). Hence, indirect comparison of data from KEYNOTE-024 and KEYNOTE-189 indicates a minimal advantage of the pembrolizumab/chemotherapy combination over pembrolizumab monotherapy. Nevertheless, the outcome in the control arms of both studies differs, suggesting a slightly different (more favourable) patient population in KEYNOTE-189. Thus the effect of chemotherapy could be regarded as borderline and therefore detrimental, because of the superior toxicity. Appropriate evaluations on the B/R ratio should be performed by treating physicians on an individual basis, particularly within the subgroups of patients with TPS≥50% and/or aged ≥75 years, taking into account all the experimental evidence emerged so far.

2.4.4. Conclusions on the clinical efficacy

Efficacy results derived from the IA1 of the pivotal KEYNOTE-189 study provide evidence for a beneficial effect of pembrolizumab as add-on therapy to platinum/pemetrexed in non-squamous NSCLC patients. Data are limited in patients ≥ 75 years of age for whom pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis. No clinically meaningful differences in treatment effect between male and female patients emerged. An updated analysis will be submitted post-authorisation together with the final CSR to better estimate the magnitude of the effect in the overall study population, as well as in the various subgroups taking into account the already authorised indication of pembrolizumab monotherapy as first line treatment in patients with TPS≥50%.

2.5. Clinical safety

Introduction

The evaluation of pembrolizumab's safety in combination with pemetrexed/platinum chemotherapy for first-line treatment of metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumour aberrations is primarily based on results of the pivotal study KEYNOTE-189 trial. Supportive data from Cohorts C and G of the KEYNOTE-021 study are also provided.

Safety data are presented in tabular format including results from the following 5 datasets:

1. KEYNOTE-189 Combo Dataset (Pembro Combo): KEYNOTE-189 participants treated as first-line with pembrolizumab/pemetrexed/carboplatin or cisplatin; n=405;

2. KEYNOTE-189 Combo + KEYNOTE-021-G/C Combo Safety Dataset (Pooled Combo SD): subjects participating in the KEYNOTE-189 (n=405) or in Cohorts C (n=24) and G (n=59) of the KEYNOTE-021, all treated as first-line with pembrolizumab/pemetrexed/carboplatin or cisplatin; n=488;

3. KEYNOTE-189 Chemo + KEYNOTE-021-G Chemo Safety Dataset (Pooled Chemo SD): subjects participating in the KEYNOTE-189 (n=202) or in Cohort G of the KEYNOTE-021 (n=62) and treated with pemetrexed + carboplatin or cisplatin; n=264;

4. Pembrolizumab Monotherapy Reference Safety Dataset (Pembrolizumab Monotherapy RSD): subjects treated with pembrolizumab, including 1567 subjects with advanced melanoma who participated in KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, and 1232 subjects with NSCLC who participated in KEYNOTE-001 and KEYNOTE-010; n=2799;

5. Cumulative Running Safety Dataset for Pembrolizumab Monotherapy (Cumulative Running Pembrolizumab Monotherapy SD): Subjects treated with pembrolizumab from the Pembrolizumab Monotherapy RSD and studies previously submitted for review in the following indications: KEYNOTE-012 Cohort B and B2 (head and neck cancer), Cohort C (bladder cancer), and Cohort D (gastric cancer); KEYNOTE-013 Cohort 3 and KEYNOTE-087 (classical Hodgkin lymphoma); KEYNOTE-024 (NSCLC), KEYNOTE-045 and KEYNOTE-052 (urothelial cancer); KEYNOTE-059 Cohort 1 (gastric cancer); KEYNOTE-164 Cohort A (colorectal cancer); and KEYNOTE-013 Cohort 4a and KEYNOTE-170 (primary mediastinal large B-cell lymphoma); n=4484.

Safety analyses were carried out on the All-Subjects-as-Treated (ASaT) population (randomized subjects receiving at least one study treatment dose at the time of cut-off dates). The 67 subjects who crossed over from chemotherapy (Control arm) to pembrolizumab monotherapy were censored at time of crossover and safety results of these patients are not provided.

No Tier 1 safety parameters were specified in the protocol. Differently from planned in the protocol, between-group comparisons were not performed for all non-prespecified Tier 2 events, occurring in <4 subjects in any treatment group. In the changed safety analyses, between-group comparison was carried out and reported with risk differences and 95% Confidence Interval (CI) only for some selected events within AEs with ≥10% incidence and Grade 3-5 AEs ≥5% incidence. Tier 3 events, occurring in <4 subjects in any treatment group, were evaluated only with point estimates by treatment group.

Table 35: Analysis strategy for safety parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death		
	Specific AEs, SOCs, or PDLCs (incidence ≥4 of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 of subjects in all of the treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

AE=Adverse event; CI=Confidence interval; ECG=Electrocardiogram; Labs=Laboratories; PDLC=Predefined limits of change; SOC=System organ class;

Patient exposure

For KEYNOTE-189, data cut-off was 08 Nov 2017. At that time, out of 616 randomized, a total of 607 participants had received at least one study dose. Treatment was ongoing in 33.8% of 405 subjects treated of the Pembro Combo arm and in 17.8% of 202 patients of the Control arm. Sixty-seven subjects (33.2%) treated with chemotherapy, crossed over to pembrolizumab monotherapy because of disease progression and according to protocol-specified criteria.

Table 36: Exposure by duration (ASaT population)

	Pembro Combo (N=405)		Control (N=202)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	405	250	202	91
>= 1 m	363	248	165	89
>= 3 m	315	240	134	84
>= 6 m	241	212	73	62
>= 12 m	70	87	18	22
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. For subjects who crossed over to pembrolizumab from the control group, doses administered after crossover are excluded. 1 Month = 30.4375 days Database Cutoff Date: 08NOV2017				

Source: [P189V01MK3475: adam-adsl; adexsum]

Table 37: Summary of drug administration by dose regimen (ASaT population – carboplatin / pemetrexed)

Number of Administrations	Pembro Combo (N = 294)			Control (N = 145)		
	Pembrolizumab n (%)	Pemetrexed n (%)	Carboplatin n (%)	Placebo n (%)	Pemetrexed n (%)	Carboplatin n (%)
1	12 (4.1)	14 (4.8)	15 (5.1)	13 (9.0)	15 (10.3)	15 (10.3)
2	22 (7.5)	23 (7.8)	23 (7.8)	16 (11.0)	16 (11.0)	16 (11.0)
3	12 (4.1)	11 (3.7)	12 (4.1)	6 (4.1)	6 (4.1)	9 (6.2)
4	16 (5.4)	23 (7.8)	244 (83.0)	13 (9.0)	14 (9.7)	105 (72.4)
>=5	232 (78.9)	223 (75.9)	0 (0.00)	97 (66.9)	94 (64.8)	0 (0.00)
Mean	10.5	9.5	3.6	7.9	7.4	3.4
SD	6.3	5.8	0.8	5.6	5.4	1.0
Median	10.0	9.0	4.0	6.0	6.0	4.0
Range	1 to 30	1 to 30	1 to 4	1 to 23	1 to 24	1 to 4
For subjects who crossed over to pembrolizumab from the control group, doses administered after crossover are excluded. Database Cutoff Date: 08NOV2017						

Source: [P189V01MK3475: adam-adsl; adexsum]

Table 38: Summary of drug administration by dose regimen (ASaT population – cisplatin / pemetrexed)

Number of Administrations	Pembro Combo (N = 111)			Control (N = 57)		
	Pembrolizumab n (%)	Pemetrexed n (%)	Cisplatin n (%)	Placebo n (%)	Pemetrexed n (%)	Cisplatin n (%)
1	5 (4.5)	6 (5.4)	6 (5.4)	3 (5.3)	3 (5.3)	3 (5.3)
2	8 (7.2)	7 (6.3)	7 (6.3)	7 (12.3)	7 (12.3)	7 (12.3)
3	5 (4.5)	5 (4.5)	8 (7.2)	2 (3.5)	2 (3.5)	2 (3.5)
4	5 (4.5)	6 (5.4)	90 (81.1)	4 (7.0)	4 (7.0)	45 (78.9)
>=5	88 (79.3)	87 (78.4)	0 (0.00)	41 (71.9)	41 (71.9)	0 (0.00)
Mean	11.2	10.4	3.6	8.4	8.0	3.6
SD	6.8	6.6	0.8	5.8	5.1	0.9
Median	11.0	9.0	4.0	7.0	7.0	4.0
Range	1 to 26	1 to 26	1 to 4	1 to 26	1 to 19	1 to 4
For subjects who crossed over to pembrolizumab from the control group, doses administered after crossover are excluded. Database Cutoff Date: 08NOV2017						

Source: [P189V01MK3475: adam-adsl; adexsum]

Table 39: Summary of drug exposure (ASaT population)

	KN189 combo[††] (N=405)	KN189 + KN021-G/C combo[‡‡] (N=488)	KN189 + KN021-G chemo[§§] (N=264)	Reference Safety Dataset for Pembrolizumab monotherapy[†††] (N=2799)	Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡] (N=4484)
Study Days On-Therapy (days)					
Mean	225.58	245.41	177.97	198.05	185.76
Median	218.00	231.00	134.50	127.00	121.00
SD	143.44	168.58	152.85	180.51	178.59
Range	1.00 to 610.00	1.00 to 862.00	1.00 to 760.00	1.00 to 925.00	1.00 to 988.00
Number of Administrations					
Mean	10.85	11.68	8.79	11.10	10.30
Median	10.00	11.00	7.00	7.00	7.00
SD	6.41	7.48	6.89	9.64	9.48

Adverse events

AEs, occurring from the first dose up to 30 days after the last dose of study drug, were coded using MedDRA, Version 20.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. AEs as observed in the KEYNOTE-189 trial are summarized in the table below:

Table 40: Adverse event summary (ASaT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	405		202	
with one or more adverse events	404	(99.8)	200	(99.0)
with no adverse event	1	(0.2)	2	(1.0)
with drug-related[†] adverse events	372	(91.9)	183	(90.6)
with toxicity grade 3-5 adverse events	272	(67.2)	133	(65.8)
with toxicity grade 3-5 drug-related adverse events	196	(48.4)	80	(39.6)
with serious adverse events	202	(49.9)	95	(47.0)
with serious drug-related adverse events	106	(26.2)	42	(20.8)
who died	27	(6.7)	12	(5.9)
who died due to a drug-related adverse event	9	(2.2)	2	(1.0)
discontinued any drug due to an adverse event	112	(27.7)	30	(14.9)
discontinued pembrolizumab or placebo	82	(20.2)	21	(10.4)
discontinued any chemotherapy	96	(23.7)	26	(12.9)
discontinued all drugs	24	(5.9)	9	(4.5)
discontinued any drug due to a drug-related adverse event	85	(21.0)	17	(8.4)
discontinued pembrolizumab or placebo	59	(14.6)	10	(5.0)
discontinued any chemotherapy	73	(18.0)	16	(7.9)
discontinued all drugs	13	(3.2)	5	(2.5)
discontinued any drug due to a serious adverse event	76	(18.8)	19	(9.4)
discontinued pembrolizumab or placebo	63	(15.6)	16	(7.9)
discontinued any chemotherapy	64	(15.8)	16	(7.9)
discontinued all drugs	23	(5.7)	8	(4.0)
discontinued any drug due to a serious drug-related adverse event	54	(13.3)	7	(3.5)
discontinued pembrolizumab or placebo	42	(10.4)	6	(3.0)
discontinued any chemotherapy	45	(11.1)	6	(3.0)
discontinued all drugs	12	(3.0)	4	(2.0)

[†] Determined by the investigator to be related to the drug.
For subjects who crossed over to pembrolizumab from the Control group, adverse events occurred after the first dose of cross phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adae]

Table 41: Subjects with adverse events (incidence ≥ 10 % in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	404	(99.8)	487	(99.8)	261	(98.9)	2,727	(97.4)	4,340	(96.8)
with no adverse events	1	(0.2)	1	(0.2)	3	(1.1)	72	(2.6)	144	(3.2)
Nausea	225	(55.6)	281	(57.6)	141	(53.4)	685	(24.5)	1,016	(22.7)
Anaemia	187	(46.2)	219	(44.9)	130	(49.2)	347	(12.4)	635	(14.2)
Fatigue	165	(40.7)	225	(46.1)	111	(42.0)	1,044	(37.3)	1,532	(34.2)
Constipation	141	(34.8)	188	(38.5)	88	(33.3)	498	(17.8)	807	(18.0)
Diarrhoea	125	(30.9)	159	(32.6)	60	(22.7)	625	(22.3)	926	(20.7)
Decreased appetite	114	(28.1)	144	(29.5)	77	(29.2)	630	(22.5)	964	(21.5)
Neutropenia	110	(27.2)	118	(24.2)	57	(21.6)	17	(0.6)	54	(1.2)
Vomiting	98	(24.2)	127	(26.0)	65	(24.6)	387	(13.8)	616	(13.7)
Cough	87	(21.5)	112	(23.0)	73	(27.7)	615	(22.0)	896	(20.0)
Dyspnoea	86	(21.2)	117	(24.0)	65	(24.6)	534	(19.1)	778	(17.4)
Asthenia	83	(20.5)	85	(17.4)	53	(20.1)	362	(12.9)	519	(11.6)
Rash	82	(20.2)	108	(22.1)	33	(12.5)	500	(17.9)	694	(15.5)
Pyrexia	79	(19.5)	89	(18.2)	33	(12.5)	357	(12.8)	625	(13.9)
Oedema peripheral	78	(19.3)	99	(20.3)	39	(14.8)	286	(10.2)	471	(10.5)
Thrombocytopenia	73	(18.0)	76	(15.6)	33	(12.5)	50	(1.8)	81	(1.8)
Lacrimation increased	69	(17.0)	83	(17.0)	30	(11.4)	22	(0.8)	32	(0.7)
Back pain	52	(12.8)	69	(14.1)	32	(12.1)	349	(12.5)	543	(12.1)
Alanine aminotransferase increased	49	(12.1)	68	(13.9)	29	(11.0)	172	(6.1)	269	(6.0)
Dizziness	49	(12.1)	71	(14.5)	31	(11.7)	244	(8.7)	350	(7.8)
Headache	48	(11.9)	72	(14.8)	33	(12.5)	400	(14.3)	510	(11.4)
Blood creatinine increased	47	(11.6)	67	(13.7)	22	(8.3)	108	(3.9)	216	(4.8)
Dysgeusia	46	(11.4)	60	(12.3)	27	(10.2)	70	(2.5)	112	(2.5)
Hypokalaemia	44	(10.9)	57	(11.7)	22	(8.3)	124	(4.4)	200	(4.5)
Pruritus	43	(10.6)	65	(13.3)	25	(9.5)	562	(20.1)	826	(18.4)
Upper respiratory tract infection	41	(10.1)	61	(12.5)	19	(7.2)	182	(6.5)	257	(5.7)
Aspartate aminotransferase increased	38	(9.4)	57	(11.7)	27	(10.2)	168	(6.0)	287	(6.4)
Arthralgia	36	(8.9)	56	(11.5)	33	(12.5)	504	(18.0)	684	(15.3)
Abdominal pain	30	(7.4)	41	(8.4)	15	(5.7)	274	(9.8)	478	(10.7)

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.

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 treatment in pembro combo arm of KN189.

[‡‡] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.

[§§] Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.

[†††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.

[‡‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)

MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)

Table 42: Exposure-adjusted adverse events (including multiple occurrences of events) (incidence ≥ 10% in one or more treatment groups) (ASaT population)

	Event Count and Rate (Events/100 person-months)[†]	
	Pembro Combo	Control
Number of subjects exposed	405	202
Total exposure[‡] person-months	3317.95	1264.95
Total events (rate)	6437 (194.01)	2672 (211.23)

Table 43: Exposure-adjusted adverse events by observation period (including multiple occurrences of events) (incidence ≥ 10% in one or more treatment groups) (ASaT population)

Observation period of drug exposure	Event Count and Rate (Events/100 person-months)[†]							
	Pembro Combo				Control			
	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of Subjects exposed[‡]	405	348	265	83	202	156	84	23
Total exposure[§] person-months	1142.79	911.04	1030.48	233.63	543.07	361.55	304.63	55.70
Total events (rate)	3497 (306.00)	1493 (163.88)	1225 (118.88)	222 (95.02)	1701 (313.22)	603 (166.78)	322 (105.70)	46 (82.59)
AE Category								
Blood and lymphatic system disorders	**407 (35.6)**	**132 (14.5)**	**82 (8.0)**	**11 (4.7)**	**186 (34.3)**	**69 (19.1)**	**26 (8.5)**	**2 (3.6)**
Anaemia	157 (13.7)	47 (5.2)	31 (3.0)	5 (2.1)	82 (15.1)	32 (8.9)	8 (2.6)	1 (1.8)
Neutropenia	139 (12.2)	43 (4.7)	19 (1.8)	1 (0.4)	58 (10.7)	21 (5.8)	13 (4.3)	0 (0.00)
Thrombocytopenia	67 (5.9)	23 (2.5)	20 (1.9)	4 (1.7)	24 (4.4)	12 (3.3)	4 (1.3)	1 (1.8)
Eye disorders	**93 (8.1)**	**40 (4.4)**	**30 (2.9)**	**7 (3.0)**	**38 (7.0)**	**11 (3.0)**	**8 (2.6)**	**0 (0.00)**
Lacrimation increased	40 (3.5)	21 (2.3)	11 (1.1)	4 (1.7)	14 (2.6)	6 (1.7)	3 (1.0)	0 (0.00)
Gastrointestinal disorders	**794 (69.5)**	**238 (26.1)**	**184 (17.9)**	**36 (15.4)**	**380 (70.0)**	**70 (19.4)**	**54 (17.7)**	**7 (12.6)**
Constipation	141 (12.3)	31 (3.4)	30 (2.9)	0 (0.00)	69 (12.7)	10 (2.8)	4 (1.3)	0 (0.00)
Diarrhoea	94 (8.2)	51 (5.6)	25 (2.4)	3 (1.3)	40 (7.4)	10 (2.8)	9 (3.0)	0 (0.00)
Nausea	285 (24.9)	60 (6.6)	39 (3.8)	12 (5.1)	145 (26.7)	25 (6.9)	13 (4.3)	3 (5.4)
Vomiting	104 (9.1)	30 (3.3)	29 (2.8)	6 (2.6)	55 (10.1)	8 (2.2)	8 (2.6)	0 (0.00)
General disorders and administration site conditions	**434 (38.0)**	**179 (19.7)**	**185 (18.0)**	**34 (14.6)**	**233 (42.9)**	**96 (26.6)**	**45 (14.8)**	**11 (19.8)**
Asthenia	75 (6.6)	30 (3.3)	18 (1.8)	5 (2.1)	49 (9.0)	24 (6.6)	4 (1.3)	3 (5.4)
Fatigue	170 (14.9)	41 (4.5)	45 (4.4)	5 (2.1)	93 (17.1)	18 (5.0)	12 (3.9)	3 (5.4)
Oedema peripheral	25 (2.2)	29 (3.2)	46 (4.5)	8 (3.4)	9 (1.7)	14 (3.9)	10 (3.3)	2 (3.6)
Pyrexia	61 (5.3)	25 (2.7)	16 (1.6)	5 (2.1)	26 (4.8)	9 (2.5)	6 (2.0)	2 (3.6)
Infections and infestations	**191 (16.7)**	**121 (13.3)**	**129 (12.5)**	**25 (10.7)**	**100 (18.4)**	**53 (14.7)**	**31 (10.2)**	**4 (7.2)**
Pneumonia	18 (1.6)	10 (1.1)	14 (1.4)	2 (0.9)	16 (3.0)	7 (1.9)	3 (1.0)	0 (0.00)
Upper respiratory tract infection	16 (1.4)	16 (1.8)	9 (0.9)	6 (2.6)	5 (0.9)	13 (3.6)	2 (0.7)	0 (0.00)
Investigations	**205 (17.9)**	**144 (15.8)**	**109 (10.6)**	**13 (5.6)**	**106 (19.5)**	**53 (14.7)**	**29 (9.5)**	**4 (7.2)**
Alanine aminotransferase increased	25 (2.2)	22 (2.4)	15 (1.5)	0 (0.00)	13 (2.4)	9 (2.5)	1 (0.3)	0 (0.00)
Blood creatinine increased	14 (1.2)	18 (2.0)	33 (3.2)	6 (2.6)	12 (2.2)	5 (1.4)	5 (1.6)	2 (3.6)
Metabolism and nutrition disorders	**283 (24.8)**	**116 (12.7)**	**85 (8.3)**	**13 (5.6)**	**129 (23.8)**	**32 (8.9)**	**19 (6.2)**	**3 (5.4)**
Decreased appetite	91 (8.0)	30 (3.3)	24 (2.3)	4 (1.7)	56 (10.3)	15 (4.2)	7 (2.3)	1 (1.8)
Hypokalaemia	39 (3.4)	18 (2.0)	12 (1.2)	2 (0.9)	13 (2.4)	4 (1.1)	0 (0.00)	1 (1.8)
Musculoskeletal and connective tissue disorders	**138 (12.1)**	**81 (8.9)**	**75 (7.3)**	**20 (8.6)**	**76 (14.0)**	**34 (9.4)**	**16 (5.3)**	**4 (7.2)**
Back pain	33 (2.9)	13 (1.4)	15 (1.5)	1 (0.4)	11 (2.0)	11 (3.0)	3 (1.0)	0 (0.00)
Nervous system disorders	**204 (17.9)**	**81 (8.9)**	**62 (6.0)**	**10 (4.3)**	**93 (17.1)**	**35 (9.7)**	**20 (6.6)**	**0 (0.00)**
Dizziness	31 (2.7)	13 (1.4)	7 (0.7)	1 (0.4)	14 (2.6)	4 (1.1)	2 (0.7)	0 (0.00)
Dysgeusia	36 (3.2)	12 (1.3)	4 (0.4)	0 (0.00)	17 (3.1)	3 (0.8)	0 (0.00)	0 (0.00)
Headache	34 (3.0)	10 (1.1)	10 (1.0)	3 (1.3)	14 (2.6)	6 (1.7)	3 (1.0)	0 (0.00)
Psychiatric disorders	**52 (4.6)**	**28 (3.1)**	**24 (2.3)**	**2 (0.9)**	**32 (5.9)**	**10 (2.8)**	**7 (2.3)**	**2 (3.6)**
Respiratory, thoracic and mediastinal disorders	**247 (21.6)**	**141 (15.5)**	**96 (9.3)**	**20 (8.6)**	**146 (26.9)**	**64 (17.7)**	**27 (8.9)**	**5 (9.0)**
Cough	56 (4.9)	24 (2.6)	25 (2.4)	7 (3.0)	34 (6.3)	22 (6.1)	6 (2.0)	1 (1.8)
Dyspnoea	46 (4.0)	32 (3.5)	20 (1.9)	5 (2.1)	40 (7.4)	15 (4.2)	7 (2.3)	1 (1.8)
Skin and subcutaneous tissue disorders	**219 (19.2)**	**67 (7.4)**	**56 (5.4)**	**10 (4.3)**	**102 (18.8)**	**28 (7.7)**	**12 (3.9)**	**0 (0.00)**
Pruritus	39 (3.4)	7 (0.8)	9 (0.9)	0 (0.00)	16 (3.0)	5 (1.4)	1 (0.3)	0 (0.00)
Rash	74 (6.5)	14 (1.5)	15 (1.5)	6 (2.6)	21 (3.9)	4 (1.1)	3 (1.0)	0 (0.00)
Vascular disorders	**48 (4.2)**	**19 (2.1)**	**18 (1.8)**	**2 (0.9)**	**20 (3.7)**	**6 (1.7)**	**4 (1.3)**	**1 (1.8)**

[†] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[‡] Number of subjects exposed to drug at the start of indicated time interval.
[§] Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of cross phase are excluded.
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 20.1 preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adae]

Table 44: Adverse events summary (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	404	(99.8)	487	(99.8)	261	(98.9)	2,727	(97.4)	4,340	(96.8)
with no adverse event	1	(0.2)	1	(0.2)	3	(1.1)	72	(2.6)	144	(3.2)
with drug-related[†] adverse events	372	(91.9)	451	(92.4)	240	(90.9)	2,062	(73.7)	3,126	(69.7)
with toxicity grade 3-5 adverse events	272	(67.2)	323	(66.2)	167	(63.3)	1,273	(45.5)	2,135	(47.6)
with toxicity grade 3-5 drug-related adverse events	196	(48.4)	231	(47.3)	98	(37.1)	386	(13.8)	657	(14.7)
with non-serious adverse events	401	(99.0)	483	(99.0)	259	(98.1)	2,671	(95.4)	4,253	(94.8)
with serious adverse events	202	(49.9)	244	(50.0)	115	(43.6)	1,041	(37.2)	1,693	(37.8)
with serious drug-related adverse events	106	(26.2)	129	(26.4)	49	(18.6)	281	(10.0)	451	(10.1)
with any dose modification[‡] due to an adverse event	277	(68.4)	329	(67.4)	146	(55.3)	884	(31.6)	1,407	(31.4)
pembrolizumab or placebo dose modification	249	(61.5)	298	(61.1)	109	(41.3)	884	(31.6)	1,407	(31.4)
any chemotherapy dose modification	96	(23.7)	110	(22.5)	35	(13.3)	0	(0.0)	0	(0.0)
all drugs dose modification	24	(5.9)	27	(5.5)	11	(4.2)	884	(31.6)	1,407	(31.4)
who died	27	(6.7)	30	(6.1)	14	(5.3)	110	(3.9)	200	(4.5)
who died due to a drug-related adverse event	9	(2.2)	10	(2.0)	4	(1.5)	10	(0.4)	19	(0.4)
discontinued any drug due to an adverse event	112	(27.7)	129	(26.4)	39	(14.8)	334	(11.9)	489	(10.9)
discontinued pembrolizumab or placebo	82	(20.2)	93	(19.1)	21	(8.0)	334	(11.9)	489	(10.9)
discontinued any chemotherapy	96	(23.7)	110	(22.5)	35	(13.3)	0	(0.0)	0	(0.0)
discontinued all drugs	24	(5.9)	27	(5.5)	11	(4.2)	334	(11.9)	489	(10.9)
discontinued any drug due to a drug-related adverse event	85	(21.0)	100	(20.5)	26	(9.8)	146	(5.2)	229	(5.1)
discontinued pembrolizumab or placebo	59	(14.6)	68	(13.9)	10	(3.8)	146	(5.2)	229	(5.1)
discontinued any chemotherapy	73	(18.0)	85	(17.4)	25	(9.5)	0	(0.0)	0	(0.0)
discontinued all drugs	13	(3.2)	15	(3.1)	7	(2.7)	146	(5.2)	229	(5.1)
discontinued any drug due to a serious adverse event	76	(18.8)	86	(17.6)	22	(8.3)	253	(9.0)	373	(8.3)
discontinued pembrolizumab or placebo	63	(15.6)	72	(14.8)	16	(6.1)	253	(9.0)	373	(8.3)
discontinued any chemotherapy	64	(15.8)	73	(15.0)	19	(7.2)	0	(0.0)	0	(0.0)
discontinued all drugs	23	(5.7)	26	(5.3)	10	(3.8)	253	(9.0)	373	(8.3)
discontinued any drug due to a serious drug-related adverse event	54	(13.3)	62	(12.7)	10	(3.8)	101	(3.6)	158	(3.5)
discontinued pembrolizumab or placebo	42	(10.4)	49	(10.0)	6	(2.3)	101	(3.6)	158	(3.5)
discontinued any chemotherapy	45	(11.1)	52	(10.7)	9	(3.4)	0	(0.0)	0	(0.0)
discontinued all drugs	12	(3.0)	14	(2.9)	6	(2.3)	101	(3.6)	158	(3.5)

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

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

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

[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.

[‡‡] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.

[§§] Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.

[†††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.

[‡‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.

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

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)

MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Drug-related AEs

Table 45: Subjects with drug-related adverse events (incidence ≥ 5% in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	372	(91.9)	451	(92.4)	240	(90.9)	2,062	(73.7)	3,126	(69.7)
with no adverse events	33	(8.1)	37	(7.6)	24	(9.1)	737	(26.3)	1,358	(30.3)
Nausea	187	(46.2)	229	(46.9)	118	(44.7)	304	(10.9)	440	(9.8)
Anaemia	154	(38.0)	182	(37.3)	111	(42.0)	94	(3.4)	152	(3.4)
Fatigue	134	(33.1)	185	(37.9)	89	(33.7)	678	(24.2)	930	(20.7)
Neutropenia	101	(24.9)	107	(21.9)	51	(19.3)	8	(0.3)	35	(0.8)
Decreased appetite	84	(20.7)	101	(20.7)	54	(20.5)	255	(9.1)	373	(8.3)
Diarrhoea	78	(19.3)	98	(20.1)	31	(11.7)	343	(12.3)	472	(10.5)
Vomiting	74	(18.3)	93	(19.1)	50	(18.9)	107	(3.8)	163	(3.6)
Thrombocytopenia	69	(17.0)	72	(14.8)	31	(11.7)	23	(0.8)	33	(0.7)
Constipation	67	(16.5)	82	(16.8)	30	(11.4)	90	(3.2)	128	(2.9)
Asthenia	53	(13.1)	54	(11.1)	33	(12.5)	218	(7.8)	276	(6.2)
Lacrimation increased	51	(12.6)	62	(12.7)	21	(8.0)	9	(0.3)	12	(0.3)
Rash	51	(12.6)	72	(14.8)	26	(9.8)	386	(13.8)	519	(11.6)
Alanine aminotransferase increased	38	(9.4)	55	(11.3)	24	(9.1)	97	(3.5)	149	(3.3)
Dysgeusia	37	(9.1)	49	(10.0)	21	(8.0)	45	(1.6)	65	(1.4)
Pruritus	37	(9.1)	49	(10.0)	15	(5.7)	467	(16.7)	648	(14.5)
Blood creatinine increased	32	(7.9)	45	(9.2)	16	(6.1)	35	(1.3)	55	(1.2)
Mucosal inflammation	30	(7.4)	36	(7.4)	15	(5.7)	23	(0.8)	27	(0.6)
Aspartate aminotransferase increased	28	(6.9)	46	(9.4)	18	(6.8)	94	(3.4)	148	(3.3)
Oedema peripheral	27	(6.7)	38	(7.8)	15	(5.7)	55	(2.0)	88	(2.0)
Stomatitis	26	(6.4)	31	(6.4)	19	(7.2)	33	(1.2)	58	(1.3)
Febrile neutropenia	25	(6.2)	26	(5.3)	4	(1.5)	0	(0.0)	0	(0.0)
Pyrexia	24	(5.9)	30	(6.1)	5	(1.9)	126	(4.5)	226	(5.0)
Hypomagnesaemia	22	(5.4)	28	(5.7)	4	(1.5)	19	(0.7)	22	(0.5)
Hypothyroidism	22	(5.4)	30	(6.1)	3	(1.1)	213	(7.6)	338	(7.5)
Leukopenia	22	(5.4)	23	(4.7)	14	(5.3)	15	(0.5)	21	(0.5)
White blood cell count decreased	22	(5.4)	28	(5.7)	17	(6.4)	14	(0.5)	21	(0.5)
Alopecia	20	(4.9)	30	(6.1)	11	(4.2)	24	(0.9)	32	(0.7)
Arthralgia	15	(3.7)	21	(4.3)	11	(4.2)	281	(10.0)	359	(8.0)
Dry skin	11	(2.7)	16	(3.3)	14	(5.3)	90	(3.2)	140	(3.1)
Myalgia	10	(2.5)	12	(2.5)	4	(1.5)	146	(5.2)	186	(4.1)
Vitiligo	1	(0.2)	1	(0.2)	0	(0.0)	159	(5.7)	160	(3.6)

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.

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

[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.

[‡‡] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.

[§§] Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.

[†††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.

[‡‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)

MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Table 46: Subjects with drug-related adverse events by maximum toxicity grade (incidence ≥ 0% in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	372	(91.9)	451	(92.4)	240	(90.9)	2,062	(73.7)	3,126	(69.7)
Grade 1	55	(13.6)	66	(13.5)	53	(20.1)	839	(30.0)	1,229	(27.4)
Grade 2	121	(29.9)	154	(31.6)	89	(33.7)	837	(29.9)	1,240	(27.7)
Grade 3	137	(33.8)	167	(34.2)	77	(29.2)	336	(12.0)	567	(12.6)
Grade 4	50	(12.3)	54	(11.1)	17	(6.4)	40	(1.4)	71	(1.6)
Grade 5	9	(2.2)	10	(2.0)	4	(1.5)	10	(0.4)	19	(0.4)
with no adverse events	33	(8.1)	37	(7.6)	24	(9.1)	737	(26.3)	1,358	(30.3)

Drug-related Grade 3-5 AEs

Table 47: Subjects with drug-related grade 3-5 adverse events (incidence ≥ 1% in one or more treatment groups) by body system or organ class and preferred term (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	196	(48.4)	231	(47.3)	98	(37.1)	386	(13.8)	657	(14.7)
with no adverse events	209	(51.6)	257	(52.7)	166	(62.9)	2,413	(86.2)	3,827	(85.3)
Blood and lymphatic system disorders	**113**	**(27.9)**	**126**	**(25.8)**	**62**	**(23.5)**	**28**	**(1.0)**	**58**	**(1.3)**
Anaemia	55	(13.6)	64	(13.1)	36	(13.6)	13	(0.5)	26	(0.6)
Febrile neutropenia	24	(5.9)	25	(5.1)	4	(1.5)	0	(0.0)	0	(0.0)
Leukopenia	8	(2.0)	9	(1.8)	1	(0.4)	3	(0.1)	3	(0.1)
Neutropenia	59	(14.6)	61	(12.5)	24	(9.1)	3	(0.1)	15	(0.3)
Pancytopenia	6	(1.5)	7	(1.4)	5	(1.9)	1	(0.0)	1	(0.0)
Thrombocytopenia	31	(7.7)	33	(6.8)	15	(5.7)	3	(0.1)	6	(0.1)
Cardiac disorders	**5**	**(1.2)**	**6**	**(1.2)**	**0**	**(0.0)**	**10**	**(0.4)**	**16**	**(0.4)**
Gastrointestinal disorders	**35**	**(8.6)**	**39**	**(8.0)**	**15**	**(5.7)**	**77**	**(2.8)**	**118**	**(2.6)**
Colitis	2	(0.5)	3	(0.6)	0	(0.0)	27	(1.0)	41	(0.9)
Diarrhoea	15	(3.7)	16	(3.3)	5	(1.9)	25	(0.9)	41	(0.9)
Nausea	12	(3.0)	13	(2.7)	4	(1.5)	10	(0.4)	15	(0.3)
Vomiting	7	(1.7)	8	(1.6)	4	(1.5)	9	(0.3)	10	(0.2)
General disorders and administration site conditions	**46**	**(11.4)**	**49**	**(10.0)**	**9**	**(3.4)**	**50**	**(1.8)**	**99**	**(2.2)**
Asthenia	16	(4.0)	16	(3.3)	3	(1.1)	12	(0.4)	19	(0.4)
Fatigue	20	(4.9)	22	(4.5)	3	(1.1)	30	(1.1)	57	(1.3)
General physical health deterioration	4	(1.0)	4	(0.8)	2	(0.8)	1	(0.0)	1	(0.0)
Hepatobiliary disorders	**6**	**(1.5)**	**6**	**(1.2)**	**0**	**(0.0)**	**16**	**(0.6)**	**27**	**(0.6)**
Infections and infestations	**20**	**(4.9)**	**26**	**(5.3)**	**5**	**(1.9)**	**20**	**(0.7)**	**39**	**(0.9)**
Cellulitis	5	(1.2)	7	(1.4)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	4	(1.0)	5	(1.0)	1	(0.4)	8	(0.3)	10	(0.2)
Investigations	**28**	**(6.9)**	**39**	**(8.0)**	**19**	**(7.2)**	**46**	**(1.6)**	**95**	**(2.1)**
Alanine aminotransferase increased	2	(0.5)	5	(1.0)	4	(1.5)	14	(0.5)	24	(0.5)
Lymphocyte count decreased	1	(0.2)	5	(1.0)	2	(0.8)	4	(0.1)	6	(0.1)

Neutrophil count decreased	7	(1.7)	11	(2.3)	4	(1.5)	2	(0.1)	4	(0.1)
Platelet count decreased	5	(1.2)	6	(1.2)	1	(0.4)	1	(0.0)	2	(0.0)
White blood cell count decreased	7	(1.7)	8	(1.6)	6	(2.3)	0	(0.0)	1	(0.0)
Metabolism and nutrition disorders	**19**	**(4.7)**	**23**	**(4.7)**	**5**	**(1.9)**	**51**	**(1.8)**	**94**	**(2.1)**
Decreased appetite	4	(1.0)	5	(1.0)	1	(0.4)	8	(0.3)	12	(0.3)
Hypomagnesaemia	5	(1.2)	5	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(0.7)**	**3**	**(0.6)**	**3**	**(1.1)**	**21**	**(0.8)**	**42**	**(0.9)**
Nervous system disorders	**6**	**(1.5)**	**6**	**(1.2)**	**1**	**(0.4)**	**15**	**(0.5)**	**23**	**(0.5)**
Renal and urinary disorders	**15**	**(3.7)**	**18**	**(3.7)**	**2**	**(0.8)**	**7**	**(0.3)**	**17**	**(0.4)**
Acute kidney injury	7	(1.7)	10	(2.0)	1	(0.4)	3	(0.1)	6	(0.1)
Respiratory, thoracic and mediastinal disorders	**14**	**(3.5)**	**15**	**(3.1)**	**4**	**(1.5)**	**52**	**(1.9)**	**79**	**(1.8)**
Dyspnoea	4	(1.0)	4	(0.8)	1	(0.4)	12	(0.4)	17	(0.4)
Pneumonitis	10	(2.5)	11	(2.3)	3	(1.1)	32	(1.1)	48	(1.1)
Skin and subcutaneous tissue disorders	**7**	**(1.7)**	**9**	**(1.8)**	**6**	**(2.3)**	**29**	**(1.0)**	**52**	**(1.2)**
Rash	5	(1.2)	7	(1.4)	3	(1.1)	6	(0.2)	13	(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.
[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.
[‡‡] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.
[§§] Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.
[†††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
[‡‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.
Grades are based on NCI CTCAE version 4.03.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Adverse drug reactions (ADRs)

The following approach was used to reflect ADRs in the SmPC section 4.8: events not already included in section 4.8 as associated with pembrolizumab monotherapy and for which clinically meaningful imbalances between treatment arms persisted despite adjustment for exposure and for which there was potential biologic plausibility for an association with exposure to pembrolizumab in combination with chemotherapy were selected for inclusion. The appropriate frequency categories for these events were then determined according to MedDRA definitions. The events, febrile neutropenia and acute kidney injury met these criteria and are proposed for inclusion in section 4.8.

Table 48: Adverse drug reactions from studies KN-189 and KN-021-G/C

	Combination with chemotherapy	**Frequency Treatment Related AEs n=488**
Infections and infestations		
Common	pneumonia	1.6% (8)
Blood and lymphatic system disorders		
Very common	anaemia neutropenia thrombocytopenia	37.3% (182) 21.9% (107) 14.8% (72)
Common	febrile neutropenia leukopenia	5.3% (26) 4.7% (23)

	lymphopenia	1.0% (5)
Immune system disorders		
Common	infusion related reaction[a]	2.5% (12)
Endocrine disorders		
Common	hypothyroidism[b]	8.0% (39)
	hyperthyroidism	4.3% (21)
Uncommon	hypophysitis[c]	0.6% (3)
	thyroiditis	0.2% (1)
	adrenal insufficiency	0.4% (2)
Metabolism and nutrition disorders		
Very common	decreased appetite	20.7% (101)
Common	hypokalaemia	3.5% (17)
	hyponatraemia	1.4% (7)
	hypocalcaemia	1.8% (9)
Uncommon	type 1 diabetes mellitus[d]	0.2% (1)
Psychiatric disorders		
Uncommon	insomnia	0.4% (2)
Nervous system disorders		
Very common	dysgeusia	10.0% (49)
Common	dizziness	3.7% (18)
	headache	2.9% (14)
	lethargy	1.4% (7)
	neuropathy peripheral	2.5% (12)
Eye disorders		
Common	dry eye	3.3% (16)
Cardiac disorders		
Uncommon	pericardial effusion	0.2% (1)
Vascular disorders		
Uncommon	hypertension	0.2% (1)
Respiratory, thoracic and mediastinal disorders		
Common	pneumonitis	4.5% (22)
	dyspnoea	4.1% (20)
	cough	2.9% (14)
Gastrointestinal disorders		
Very common	diarrhoea	20.1% (98)
	nausea	46.9% (229)
	vomiting	19.1% (93)
	constipation	16.8% (82)
Common	Colitis[h]	2.7% (13)
	abdominal pain[k]	4.9% (24)
	dry mouth	2.5% (12)
Uncommon	pancreatitis[l]	0.6% (3)
Hepatobiliary disorders		
Common	Hepatitis[k]	1.0% (5)
Skin and subcutaneous tissue disorders		
Very common	Rash[l]	21.1% (103)
	pruritus[m]	11.1% (54)
Common	severe skin reactions[n]	2.0% (10)
	alopecia	6.1% (30)
	dermatitis acneiform	1.4% (7)
	dry skin	3.3% (16)
	erythema	2.7% (13)
Uncommon	dermatitis	0.6% (3)
	eczema	0.4% (2)
	hair colour changes	0.2% (1)
	lichenoid keratosis[p]	0.2% (1)
	vitiligo[o]	0.8% (4)
Musculoskeletal and connective tissue disorders		
Common	arthralgia	4.3% (21)
	myositis[q]	2.7% (13)
	arthritis[s]	1.2% (6)
	musculoskeletal pain[r]	3.3% (16)
	pain in extremity	2.0% (10)
Renal and urinary disorders		
Common	Nephritis[u]	1.4% (7)
	acute kidney injury	3.7% (18)
General disorders and administration site conditions		
Very common	fatigue	37.9% (185)
	asthenia	11.1% (54)
	oedema[v]	11.3% (55)

Common	pyrexia	6.1% (30)
Uncommon	chills influenza-like illness	0.2% (1) 0.8% (4)
Investigations		
Very common	alanine aminotransferase increased	11.3% (55)
Common	aspartate aminotransferase increased blood creatinine increased blood alkaline phosphatase increased	9.4% (46) 9.2% (45) 1.8% (9)
Uncommon	amylase increased hypercalcaemia	0.2% (1) 0.2% (1)

The following terms represent a group of related events that describe a medical condition rather than a single event.

a. infusion-related reactions (drug hypersensitivity, anaphylactic reaction, hypersensitivity and cytokine release syndrome)
b. hypothyroidism (myxoedema)
c. hypophysitis (hypopituitarism)
d. type 1 diabetes mellitus (diabetic ketoacidosis)
e. myasthenic syndrome (myasthenia gravis)
f. uveitis (iritis and iridocyclitis)
g. pneumonitis (interstitial lung disease)
h. colitis (colitis microscopic and enterocolitis)
i. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
j. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
k. hepatitis (autoimmune hepatitis and drug induced liver injury)
l. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
m. pruritus (urticaria, urticaria papular, pruritus generalized and pruritus genital)
n. severe skin reactions (dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigoid, toxic skin eruption and Grade ≥ 3 of the following: pruritus, rash, rash generalised and rash maculo-papular, dermatitis psoriasiform, pruritus generalised)
o. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
p. lichenoid keratosis (lichen planus and lichen sclerosus)
q. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis)
r. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
s. arthritis (joint swelling, polyarthritis and joint effusion)
t. tenosynovitis (tendonitis, synovitis and tendon pain)
u. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure or renal failure acute with evidence of nephritis, nephrotic syndrome)
v. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localized oedema and periorbital oedema)

Serious adverse event / deaths / other significant events

Drug-related Serious Adverse Events (SAEs)

Table 49: Subjects with drug-related serious adverse events up to 90 days of last dose (Incidence >0% in or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	106	(26.2)	129	(26.4)	49	(18.6)	281	(10.0)	451	(10.1)
with no adverse events	299	(73.8)	359	(73.6)	215	(81.4)	2,518	(90.0)	4,033	(89.9)
Febrile neutropenia	21	(5.2)	22	(4.5)	4	(1.5)	0	(0.0)	0	(0.0)
Thrombocytopenia	13	(3.2)	14	(2.9)	6	(2.3)	2	(0.1)	2	(0.0)
Diarrhoea	12	(3.0)	12	(2.5)	6	(2.3)	17	(0.6)	26	(0.6)
Pneumonitis	11	(2.7)	12	(2.5)	3	(1.1)	44	(1.6)	68	(1.5)
Anaemia	9	(2.2)	10	(2.0)	12	(4.5)	4	(0.1)	5	(0.1)
Acute kidney injury	7	(1.7)	10	(2.0)	0	(0.0)	5	(0.2)	8	(0.2)
Neutropenia	7	(1.7)	7	(1.4)	2	(0.8)	1	(0.0)	3	(0.1)
Vomiting	5	(1.2)	6	(1.2)	4	(1.5)	5	(0.2)	7	(0.2)
Cellulitis	4	(1.0)	6	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pancytopenia	4	(1.0)	5	(1.0)	4	(1.5)	1	(0.0)	1	(0.0)
Pneumonia	4	(1.0)	5	(1.0)	1	(0.4)	8	(0.3)	11	(0.2)
Pyrexia	4	(1.0)	6	(1.2)	1	(0.4)	10	(0.4)	15	(0.3)
Asthenia	3	(0.7)	3	(0.6)	0	(0.0)	4	(0.1)	4	(0.1)
Colitis	3	(0.7)	4	(0.8)	0	(0.0)	25	(0.9)	36	(0.8)
Fatigue	3	(0.7)	5	(1.0)	0	(0.0)	3	(0.1)	6	(0.1)
General physical health deterioration	3	(0.7)	3	(0.6)	1	(0.4)	2	(0.1)	2	(0.0)
Nausea	3	(0.7)	4	(0.8)	4	(1.5)	6	(0.2)	10	(0.2)
Blood creatinine increased	2	(0.5)	2	(0.4)	0	(0.0)	0	(0.0)	2	(0.0)
Dehydration	2	(0.5)	2	(0.4)	1	(0.4)	3	(0.1)	7	(0.2)
Hepatitis	2	(0.5)	2	(0.4)	0	(0.0)	3	(0.1)	5	(0.1)
Hypomagnesaemia	2	(0.5)	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nephritis	2	(0.5)	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.0)
Oedema peripheral	2	(0.5)	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.0)
Tubulointerstitial nephritis	2	(0.5)	2	(0.4)	0	(0.0)	3	(0.1)	5	(0.1)
Upper respiratory tract infection	2	(0.5)	3	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	1	(0.2)	1	(0.2)	0	(0.0)	2	(0.1)	2	(0.0)
Adrenal insufficiency	1	(0.2)	1	(0.2)	0	(0.0)	7	(0.3)	10	(0.2)
Arthralgia	1	(0.2)	1	(0.2)	0	(0.0)	3	(0.1)	4	(0.1)
Autoimmune hepatitis	1	(0.2)	1	(0.2)	0	(0.0)	8	(0.3)	9	(0.2)
Autoimmune nephritis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Cholangitis sclerosing	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Chronic obstructive pulmonary disease	1	(0.2)	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Cytokine release syndrome	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Death	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Encephalopathy	1	(0.2)	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Endocarditis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Folliculitis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Gastroduodenitis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic enzyme increased	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.0)
Hepatotoxicity	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertrophic osteoarthropathy	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	1	(0.2)	1	(0.2)	0	(0.0)	5	(0.2)	6	(0.1)
Infection	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Influenza	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Kidney infection	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	1	(0.2)	1	(0.2)	1	(0.4)	0	(0.0)	0	(0.0)
Mucosal inflammation	1	(0.2)	1	(0.2)	1	(0.4)	0	(0.0)	0	(0.0)
Muscular weakness	1	(0.2)	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Myalgia	1	(0.2)	1	(0.2)	0	(0.0)	1	(0.0)	1	(0.0)
Myocardial infarction	1	(0.2)	2	(0.4)	0	(0.0)	1	(0.0)	1	(0.0)
Neutropenic sepsis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Obstructive airways disorder	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pancreatitis acute	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pericardial effusion	1	(0.2)	1	(0.2)	0	(0.0)	4	(0.1)	4	(0.1)
Peritonitis	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Platelet count decreased	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Prerenal failure	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	1	(0.2)	3	(0.6)	0	(0.0)	2	(0.1)	3	(0.1)
Rash papular	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	1	(0.2)	1	(0.2)	1	(0.4)	4	(0.1)	5	(0.1)
Sepsis	1	(0.2)	2	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Sinus tachycardia	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Small intestinal haemorrhage	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Type 1 diabetes mellitus	1	(0.2)	1	(0.2)	0	(0.0)	4	(0.1)	6	(0.1)
Type 2 diabetes mellitus	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Upper limb fracture	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

Deaths

The proportion of deaths due to AEs was similar between the treatment groups (pembro combo: 27 subjects [6.7%]; control: 12 subjects [5.9%]). Pneumonitis (3 [0.7%]), in the pembro combo, was the most frequently reported AE resulting in death.

Cardiac events (cardiac arrest, cardiac failure, cardiopulmonary failure, and myocardial infarction) resulting in death were more frequently reported in the pembro combo compared with the control (1.2% versus 0.0%, respectively). Cardiac arrest occurred in the setting of Grade 3 dyspnea with Grade 4 neutropenia and thrombocytopenia; cardiac failure occurred in the setting of Grade 2 cerebrovascular accident; and cardiopulmonary failure occurred in the setting of Grade 4 asthenia. Two were acute events: cardiac arrest and myocardial infarction. Autopsies were available for 2 of these events confirming cardiorespiratory decompensation in the setting of NSCLC and myocardial infarction with cardiorespiratory arrest. These all

occurred early in the course of treatment in subjects with multiple comorbidities and were reported as terminal events; none appear associated with immune-related AEs.

Adverse events of Special Interest (AEOSIs)

The following AEOSIs were reported: Pneumonitis (4.5% vs 1.9% in chemo and 3.3% in pembro monotherapy), Hyperthyroidism (4.0% vs 3.3% in pembro monotherapy), Colitis (2.2% vs 1.9% in pembro monotherapy), Severe Skin Reaction (2.0% vs 1.3% in pembro monotherapy), and Hepatitis (1.2% vs 0.6% in pembro monotherapy). Nephritis was observed with increased frequency in the pembro combo than the reference database (1.7% vs 0.2% in pembro monotherapy).

Table 50: Adverse event summary AEOSI including all risk categories (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	92	(22.7)	116	(23.8)	30	(11.4)	594	(21.2)	951	(21.2)
with no adverse event	313	(77.3)	372	(76.2)	234	(88.6)	2,205	(78.8)	3,533	(78.8)
with drug-related[†] adverse events	75	(18.5)	94	(19.3)	20	(7.6)	509	(18.2)	809	(18.0)
with toxicity grade 3-5 adverse events	36	(8.9)	40	(8.2)	9	(3.4)	152	(5.4)	243	(5.4)
with toxicity grade 3-5 drug-related adverse events	32	(7.9)	36	(7.4)	7	(2.7)	127	(4.5)	204	(4.5)
with non-serious adverse events	72	(17.8)	93	(19.1)	25	(9.5)	486	(17.4)	783	(17.5)
with serious adverse events	27	(6.7)	32	(6.6)	5	(1.9)	157	(5.6)	239	(5.3)
with serious drug-related adverse events	25	(6.2)	30	(6.1)	3	(1.1)	135	(4.8)	205	(4.6)
with any dose modification[‡] due to an adverse event	51	(12.6)	61	(12.5)	6	(2.3)	211	(7.5)	321	(7.2)
pembrolizumab or placebo dose modification	49	(12.1)	59	(12.1)	5	(1.9)	211	(7.5)	321	(7.2)
any chemotherapy dose modification	18	(4.4)	19	(3.9)	3	(1.1)	0	(0.0)	0	(0.0)
all drugs dose modification	3	(0.7)	4	(0.8)	1	(0.4)	211	(7.5)	321	(7.2)
who died	3	(0.7)	3	(0.6)	0	(0.0)	4	(0.1)	7	(0.2)
who died due to a drug-related adverse event	3	(0.7)	3	(0.6)	0	(0.0)	4	(0.1)	7	(0.2)
discontinued any drug due to an adverse event	29	(7.2)	32	(6.6)	4	(1.5)	82	(2.9)	125	(2.8)
discontinued pembrolizumab or placebo	26	(6.4)	29	(5.9)	3	(1.1)	82	(2.9)	125	(2.8)
discontinued any chemotherapy	18	(4.4)	19	(3.9)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued all drugs	3	(0.7)	4	(0.8)	1	(0.4)	82	(2.9)	125	(2.8)
discontinued any drug due to a drug-related adverse event	28	(6.9)	31	(6.4)	4	(1.5)	81	(2.9)	124	(2.8)
discontinued pembrolizumab or placebo	25	(6.2)	28	(5.7)	3	(1.1)	81	(2.9)	124	(2.8)
discontinued any chemotherapy	18	(4.4)	19	(3.9)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued all drugs	3	(0.7)	4	(0.8)	1	(0.4)	81	(2.9)	124	(2.8)
discontinued any drug due to a serious adverse event	22	(5.4)	24	(4.9)	3	(1.1)	66	(2.4)	97	(2.2)
discontinued pembrolizumab or placebo	21	(5.2)	23	(4.7)	3	(1.1)	66	(2.4)	97	(2.2)
discontinued any chemotherapy	14	(3.5)	15	(3.1)	2	(0.8)	0	(0.0)	0	(0.0)
discontinued all drugs	3	(0.7)	4	(0.8)	1	(0.4)	66	(2.4)	97	(2.2)
discontinued any drug due to a serious drug-related adverse event	21	(5.2)	23	(4.7)	3	(1.1)	65	(2.3)	96	(2.1)
discontinued pembrolizumab or placebo	20	(4.9)	22	(4.5)	3	(1.1)	65	(2.3)	96	(2.1)
discontinued any chemotherapy	14	(3.5)	15	(3.1)	2	(0.8)	0	(0.0)	0	(0.0)
discontinued all drugs	3	(0.7)	4	(0.8)	1	(0.4)	65	(2.3)	96	(2.1)

[†] Determined by the investigator to be related to the drug.
[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.
[‡‡] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.
[§§] Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.
[†††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
[‡‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Table 51: Summary of outcome for subjects with AEOSI (Incidence >0% in one or more treatment groups) (ASaT population)

		KN189 combo††		KN189 + KN021-G/C combo‡‡		KN189 + KN021-G chemo§§		Reference Safety Dataset for Pembrolizumab monotherapy†††		Cumulative Running Safety Dataset for Pembrolizumab monotherapy‡‡‡	
	Outcome	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population		405		488		264		2799		4484	
With one or more AEOSI	**Overall**	**92**	**(22.7)**	**117**	**(24.0)**	**30**	**(11.4)**	**594**	**(21.2)**	**951**	**(21.2)**
	Fatal	3	(3.3)	3	(2.6)	0	(0.0)	4	(0.7)	7	(0.7)
	Not Resolved	27	(29.3)	38	(32.5)	6	(20.0)	283	(47.6)	436	(45.8)
	Resolving	14	(15.2)	14	(12.0)	0	(0.0)	20	(3.4)	54	(5.7)
	Unknown	2	(2.2)	2	(1.7)	1	(3.3)	12	(2.0)	24	(2.5)
	Sequelae	2	(2.2)	2	(1.7)	0	(0.0)	6	(1.0)	16	(1.7)
	Resolved	44	(47.8)	58	(49.6)	23	(76.7)	269	(45.3)	414	(43.5)

Laboratory findings

The most frequently reported (≥50%) laboratory abnormalities were similar in the Pooled Combo SD and the Pooled Chemo SD, and the majority were CTCAE Grade 1 to 2 toxicity:

• Pooled Combo SD: hemoglobin decreased (84.4%), glucose increased (65.7%), lymphocytes decreased (62.6%), leukocytes decreased (53.2%)

• Pooled Chemo SD: hemoglobin decreased (82.0%), lymphocytes decreased (63.9%), glucose increased (62.0%), leukocytes decreased (52.0%)

The most frequently reported (≥9%) Grade 3 or 4 laboratory abnormalities were similar in the Pooled Combo SD and the Pooled Chemo SD:

• Pooled Combo SD: lymphocytes decreased (22.6%), neutrophils decreased (18.6%), hemoglobin decreased (16.9%), leukocytes decreased (11.7%), platelets decreased (10.9%), phosphate decreased (9.7%)

• Pooled Chemo SD: lymphocytes decreased (24.6%), hemoglobin decreased (19.1%), neutrophils decreased (16.7%), phosphate decreased (13.1%), leukocytes decreased (9.4%), and platelets decreased (9.1%)

Though reported less commonly, the higher frequency of increased creatinine was consistent with the increased frequency of acute kidney injury and nephritis observed in the Pooled Combo SD and Pooled Chemo SD. Increased creatinine was reported more frequently in the Pooled Combo SD compared with the Pooled Chemo SD and the Pembrolizumab Monotherapy RSD, at 36.8%, 23.8%, and 16.0%, respectively. Likewise, the frequency of Grade 3 to 4 increased creatinine was 4.2%, 0.8%, and 0.7%, respectively.

Safety in special populations

Intrinsic factors

Age

Table 52: Adverse event summary by age in KN189 (ASaT population)

	Age (Years)											
	Pembro Combo						Control					
	<65		65 - 74		75 - 84		<65		65 - 74		75 - 84	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	195		176		34		113		68		21	
with one or more adverse events	194	(99.5)	176	(100.0)	34	(100.0)	113	(100.0)	67	(98.5)	20	(95.2)
who died	7	(3.6)	13	(7.4)	7	(20.6)	5	(4.4)	6	(8.8)	1	(4.8)
with serious adverse events	84	(43.1)	96	(54.5)	22	(64.7)	48	(42.5)	34	(50.0)	13	(61.9)
discontinued due to an adverse event	39	(20.0)	61	(34.7)	12	(35.3)	15	(13.3)	12	(17.6)	3	(14.3)
CNS (confusion/extrapyramidal)	16	(8.2)	21	(11.9)	0	(0.0)	7	(6.2)	7	(10.3)	6	(28.6)
AE related to falling	14	(7.2)	19	(10.8)	2	(5.9)	4	(3.5)	8	(11.8)	2	(9.5)
Cardiovascular events	35	(17.9)	45	(25.6)	13	(38.2)	24	(21.2)	12	(17.6)	2	(9.5)
Cerebrovascular events	4	(2.1)	6	(3.4)	5	(14.7)	3	(2.7)	4	(5.9)	0	(0.0)
Infections	104	(53.3)	111	(63.1)	16	(47.1)	52	(46.0)	38	(55.9)	13	(61.9)

MedDRA V20.1 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
For subjects who crossed over to pembrolizumab from the Control group, adverse events occurred after the first dose of cross phase are excluded.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adae]

Table 53: Adverse event summary by age (ASaT population)

	KN189 + KN021-G/C combo‡‡								KN189 + KN021-G chemo§§							
	< 65		>= 65 to < 75		>= 75 to < 85		>= 85		< 65		>= 65 to < 75		>= 75 to < 85		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	245		202		41		0		141		99		24		0	
with one or more adverse events	244	(99.6)	202	(100)	41	(100)	0	(0.0)	141	(100)	98	(99.0)	22	(91.7)	0	(0.0)
Who died	8	(3.3)	15	(7.4)	7	(17.1)	0	(0.0)	5	(3.5)	8	(8.1)	1	(4.2)	0	(0.0)
with serious adverse events	107	(43.7)	112	(55.4)	25	(61.0)	0	(0.0)	56	(39.7)	45	(45.5)	14	(58.3)	0	(0.0)
discontinued due to an adverse event	51	(20.8)	65	(32.2)	13	(31.7)	0	(0.0)	18	(12.8)	18	(18.2)	3	(12.5)	0	(0.0)
CNS (confusion/extrapyramidal)	25	(10.2)	30	(14.9)	4	(9.8)	0	(0.0)	15	(10.6)	13	(13.1)	6	(25.0)	0	(0.0)
AE related to falling	26	(10.6)	24	(11.9)	5	(12.2)	0	(0.0)	7	(5.0)	14	(14.1)	2	(8.3)	0	(0.0)
CV events	53	(21.6)	56	(27.7)	14	(34.1)	0	(0.0)	30	(21.3)	21	(21.2)	2	(8.3)	0	(0.0)
Cerebrovascular events	5	(2.0)	7	(3.5)	5	(12.2)	0	(0.0)	6	(4.3)	4	(4.0)	0	(0.0)	0	(0.0)
Infections	139	(56.7)	130	(64.4)	18	(43.9)	0	(0.0)	63	(44.7)	51	(51.5)	14	(58.3)	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 treatment in pembro combo arm of KN189 and KN021 cohort G/C..
§§ Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G..
MK-3475 Database Cutoff Date for Lung (KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017).

Source: [ISS: adam-adsl; adae]

Table 54: Adverse event summary by age (ASaT population)

	KN189 combo††						KN189 + KN021-G/C combo‡‡						KN189 + KN021-G chemo§§					
	<65		65-74		75-84		<65		65-74		75-84		<65		65-74		75-84	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	195		176		34		245		202		41		141		99		24	
with one or more adverse events	194	(99.5)	176	(100.0)	34	(100.0)	244	(99.6)	202	(100.0)	41	(100.0)	141	(100.0)	98	(99.0)	22	(91.7)
with no adverse event	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	2	(8.3)
with drug-related[1] adverse events	171	(87.7)	169	(96.0)	32	(94.1)	219	(89.4)	194	(96.0)	38	(92.7)	126	(89.4)	92	(92.9)	22	(91.7)
with toxicity grade 3-5 adverse events	127	(65.1)	118	(67.0)	27	(79.4)	156	(63.7)	137	(67.8)	30	(73.2)	86	(61.0)	66	(66.7)	15	(62.5)
with toxicity grade 3-5 drug-related adverse events	88	(45.1)	90	(51.1)	18	(52.9)	108	(44.1)	104	(51.5)	19	(46.3)	49	(34.8)	41	(41.4)	8	(33.3)
with non-serious adverse events	192	(98.5)	175	(99.4)	34	(100.0)	241	(98.4)	201	(99.5)	41	(100.0)	141	(100.0)	96	(97.0)	22	(91.7)
with serious adverse events	84	(43.1)	96	(54.5)	22	(64.7)	107	(43.7)	112	(55.4)	25	(61.0)	56	(39.7)	45	(45.5)	14	(58.3)
with serious drug-related adverse events	40	(20.5)	58	(33.0)	8	(23.5)	53	(21.6)	68	(33.7)	8	(19.5)	23	(16.3)	22	(22.2)	4	(16.7)
with dose modification[2] due to an adverse event	123	(63.1)	128	(72.7)	26	(76.5)	154	(62.9)	145	(71.8)	30	(73.2)	78	(55.3)	53	(53.5)	15	(62.5)
who died	7	(3.6)	13	(7.4)	7	(20.6)	8	(3.3)	15	(7.4)	7	(17.1)	5	(3.5)	8	(8.1)	1	(4.2)
who died due to a drug-related adverse event	2	(1.0)	6	(3.4)	1	(2.9)	3	(1.2)	6	(3.0)	1	(2.4)	1	(0.7)	3	(3.0)	0	(0.0)
discontinued drug due to an adverse event	39	(20.0)	61	(34.7)	12	(35.3)	51	(20.8)	65	(32.2)	13	(31.7)	18	(12.8)	18	(18.2)	3	(12.5)
discontinued drug due to a drug-related adverse event	32	(16.4)	49	(27.8)	4	(11.8)	43	(17.6)	52	(25.7)	5	(12.2)	11	(7.8)	12	(12.1)	3	(12.5)
discontinued drug due to a serious adverse event	28	(14.4)	38	(21.6)	10	(29.4)	36	(14.7)	40	(19.8)	10	(24.4)	10	(7.1)	11	(11.1)	1	(4.2)

Gender

Table 55: Adverse event summary by gender (ASaT population)

	KN189 combo[††]				KN189 + KN021-G/C combo[‡‡]				KN189 + KN021-G chemo[§§]				Reference Safety Dataset for Pembrolizumab monotherapy[†††]				Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]			
	M		F		M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	251		154		284		204		134		130		1,659		1,140		2,839		1,645	
with one or more adverse events	250	(99.6)	154	(100.0)	283	(99.6)	204	(100.0)	132	(98.5)	129	(99.2)	1,616	(97.4)	1,111	(97.5)	2,746	(96.7)	1,594	(96.9)
with no adverse event	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	2	(1.5)	1	(0.8)	43	(2.6)	29	(2.5)	93	(3.3)	51	(3.1)
with drug-related[†] adverse events	228	(90.8)	144	(93.5)	259	(91.2)	192	(94.1)	117	(87.3)	123	(94.6)	1,239	(74.7)	823	(72.2)	1,979	(69.7)	1,147	(69.7)
with toxicity grade 3-5 adverse events	165	(65.7)	107	(69.5)	184	(64.8)	139	(68.1)	83	(61.9)	84	(64.6)	759	(45.8)	514	(45.1)	1,379	(48.6)	756	(46.0)
with toxicity grade 3-5 drug-related adverse events	121	(48.2)	75	(48.7)	134	(47.2)	97	(47.5)	50	(37.3)	48	(36.9)	251	(15.1)	135	(11.8)	443	(15.6)	214	(13.0)
with non-serious adverse events	247	(98.4)	154	(100.0)	280	(98.6)	203	(99.5)	131	(97.8)	128	(98.5)	1,586	(95.6)	1,085	(95.2)	2,695	(94.9)	1,558	(94.7)
with serious adverse events	128	(51.0)	74	(48.1)	144	(50.7)	100	(49.0)	63	(47.0)	52	(40.0)	636	(38.3)	405	(35.5)	1,107	(39.0)	586	(35.6)
with serious drug-related adverse events	69	(27.5)	37	(24.0)	79	(27.8)	50	(24.5)	29	(21.6)	20	(15.4)	184	(11.1)	97	(8.5)	309	(10.9)	142	(8.6)
with dose modification[‡] due to an adverse event	166	(66.1)	111	(72.1)	186	(65.5)	143	(70.1)	78	(58.2)	68	(52.3)	523	(31.5)	361	(31.7)	885	(31.2)	522	(31.7)
who died	21	(8.4)	6	(3.9)	24	(8.5)	6	(2.9)	6	(4.5)	8	(6.2)	69	(4.2)	41	(3.6)	141	(5.0)	59	(3.6)
who died due to a drug-related adverse event	7	(2.8)	2	(1.3)	8	(2.8)	2	(1.0)	1	(0.7)	3	(2.3)	9	(0.5)	1	(0.1)	14	(0.5)	5	(0.3)
discontinued drug due to an adverse event	64	(25.5)	48	(31.2)	70	(24.6)	59	(28.9)	20	(14.9)	19	(14.6)	197	(11.9)	137	(12.0)	317	(11.2)	172	(10.5)
discontinued drug due to a drug-related adverse event	45	(17.9)	40	(26.0)	51	(18.0)	49	(24.0)	13	(9.7)	13	(10.0)	98	(5.9)	48	(4.2)	158	(5.6)	71	(4.3)
discontinued drug due to a serious adverse event	48	(19.1)	28	(18.2)	52	(18.3)	34	(16.7)	12	(9.0)	10	(7.7)	155	(9.3)	98	(8.6)	245	(8.6)	128	(7.8)
discontinued drug due to a serious drug-related adverse event	31	(12.4)	23	(14.9)	35	(12.3)	27	(13.2)	6	(4.5)	4	(3.1)	72	(4.3)	29	(2.5)	111	(3.9)	47	(2.9)

[†] Determined by the investigator to be related to the drug.
[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.
[‡‡] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.
[§§] Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.
[†††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
[‡‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Race

Table 56: Adverse event summary by race (ASaT population)

	Pembro Combo						Control					
	White		Non-White		Null		White		Non-White		Null	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	382		21		2		190		11		1	
with one or more adverse events	381	(99.7)	21	(100.0)	2	(100.0)	188	(98.9)	11	(100.0)	1	(100.0)
with no adverse event	1	(0.3)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	351	(91.9)	19	(90.5)	2	(100.0)	171	(90.0)	11	(100.0)	1	(100.0)
with toxicity grade 3-5 adverse events	258	(67.5)	13	(61.9)	1	(50.0)	124	(65.3)	8	(72.7)	1	(100.0)
with toxicity grade 3-5 drug-related adverse events	187	(49.0)	9	(42.9)	0	(0.0)	74	(38.9)	6	(54.5)	0	(0.0)
with serious adverse events	188	(49.2)	13	(61.9)	1	(50.0)	92	(48.4)	2	(18.2)	1	(100.0)
with serious drug-related adverse events	98	(25.7)	8	(38.1)	0	(0.0)	40	(21.1)	2	(18.2)	0	(0.0)
who died	24	(6.3)	3	(14.3)	0	(0.0)	12	(6.3)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	7	(1.8)	2	(9.5)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	105	(27.5)	7	(33.3)	0	(0.0)	29	(15.3)	1	(9.1)	0	(0.0)
discontinued drug due to a drug-related adverse event	80	(20.9)	5	(23.8)	0	(0.0)	16	(8.4)	1	(9.1)	0	(0.0)
discontinued drug due to a serious adverse event	70	(18.3)	6	(28.6)	0	(0.0)	19	(10.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	50	(13.1)	4	(19.0)	0	(0.0)	7	(3.7)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
For subjects who crossed over to pembrolizumab from the Control group, adverse events occurred after the first dose of cross phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adae]

ECOG PS

Table 57: Adverse event summary by ECOG PS (ASaT population)

	KN189 combo[††]				KN189 + KN021-G/C combo[‡‡]				KN189 + KN021-G chemo[§§]				Reference Safety Dataset for Pembrolizumab monotherapy[†††]				Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	184		220		215		272		107		157		1,446		1,347		2,062		2,251	
with one or more adverse events	184	(100.0)	219	(99.5)	215	(100.0)	271	(99.6)	106	(99.1)	155	(98.7)	1,417	(98.0)	1,305	(96.9)	2,007	(97.3)	2,173	(96.5)
with no adverse event	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)	1	(0.9)	2	(1.3)	29	(2.0)	42	(3.1)	55	(2.7)	78	(3.5)
with drug-related* adverse events	173	(94.0)	198	(90.0)	204	(94.9)	246	(90.4)	98	(91.6)	142	(90.4)	1,149	(79.5)	911	(67.6)	1,550	(75.2)	1,486	(66.0)
with toxicity grade 3-5 adverse events	111	(60.3)	160	(72.7)	132	(61.4)	190	(69.9)	60	(56.1)	107	(68.2)	588	(40.7)	682	(50.6)	842	(40.8)	1,204	(53.5)
with toxicity grade 3-5 drug-related adverse events	86	(46.7)	109	(49.5)	103	(47.9)	127	(46.7)	34	(31.8)	64	(40.8)	201	(13.9)	184	(13.7)	279	(13.5)	354	(15.7)
with non-serious adverse events	184	(100.0)	216	(98.2)	215	(100.0)	267	(98.2)	104	(97.2)	155	(98.7)	1,404	(97.1)	1,263	(93.8)	1,986	(96.3)	2,113	(93.9)
with serious adverse events	73	(39.7)	128	(58.2)	90	(41.9)	153	(56.3)	39	(36.4)	76	(48.4)	466	(32.2)	572	(42.5)	652	(31.6)	970	(43.1)
with serious drug-related adverse events	45	(24.5)	61	(27.7)	57	(26.5)	72	(26.5)	15	(14.0)	34	(21.7)	148	(10.2)	133	(9.9)	193	(9.4)	243	(10.8)
with dose modification‡ due to an adverse event	123	(66.8)	154	(70.0)	142	(66.0)	187	(68.8)	62	(57.9)	84	(53.5)	423	(29.3)	459	(34.1)	577	(28.0)	777	(34.5)
who died	8	(4.3)	19	(8.6)	10	(4.7)	20	(7.4)	10	(9.3)	4	(2.5)	38	(2.6)	71	(5.3)	58	(2.8)	132	(5.9)
who died due to a drug-related adverse event	5	(2.7)	4	(1.8)	6	(2.8)	4	(1.5)	3	(2.8)	1	(0.6)	4	(0.3)	6	(0.4)	7	(0.3)	12	(0.5)
discontinued drug due to an adverse event	48	(26.1)	64	(29.1)	55	(25.6)	74	(27.2)	16	(15.0)	23	(14.6)	148	(10.2)	185	(13.7)	184	(8.9)	286	(12.7)
discontinued drug due to a drug-related adverse event	42	(22.8)	43	(19.5)	49	(22.8)	51	(18.8)	9	(8.4)	17	(10.8)	82	(5.7)	64	(4.8)	104	(5.0)	117	(5.2)
discontinued drug due to a serious adverse event	34	(18.5)	42	(19.1)	39	(18.1)	47	(17.3)	13	(12.1)	9	(5.7)	104	(7.2)	148	(11.0)	130	(6.3)	228	(10.1)
discontinued drug due to a serious drug-related adverse event	29	(15.8)	25	(11.4)	34	(15.8)	28	(10.3)	6	(5.6)	4	(2.5)	52	(3.6)	49	(3.6)	66	(3.2)	86	(3.8)

* Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
†† Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.
‡‡ Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.
§§ Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.
††† Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
‡‡‡ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)
Source: [ISS: adam-adsl; adae]

Extrinsic factors

Region

Table 58: Adverse event summary by region (ASaT population)

	KN189 combo[††]				KN189 + KN021-G/C combo[‡‡]				KN189 + KN021-G chemo[§§]				Reference Safety Dataset for Pembrolizumab monotherapy[†††]				Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	240		165		240		248		130		134		961		1,838		1,497		2,987	
with one or more adverse events	239	(99.6)	165	(100.0)	239	(99.6)	248	(100.0)	128	(98.5)	133	(99.3)	927	(96.5)	1,800	(97.9)	1,433	(95.7)	2,907	(97.3)
with no adverse event	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	2	(1.5)	1	(0.7)	34	(3.5)	38	(2.1)	64	(4.3)	80	(2.7)
with drug-related* adverse events	215	(89.6)	157	(95.2)	215	(89.6)	236	(95.2)	115	(88.5)	125	(93.3)	689	(71.7)	1,373	(74.7)	1,011	(67.5)	2,115	(70.8)
with toxicity grade 3-5 adverse events	153	(63.8)	119	(72.1)	153	(63.8)	170	(68.5)	87	(66.9)	80	(59.7)	440	(45.8)	833	(45.3)	697	(46.6)	1,438	(48.1)
with toxicity grade 3-5 drug-related adverse events	109	(45.4)	87	(52.7)	109	(45.4)	122	(49.2)	53	(40.8)	45	(33.6)	149	(15.5)	237	(12.9)	224	(15.0)	433	(14.5)
with non-serious adverse events	236	(98.3)	165	(100.0)	236	(98.3)	247	(99.6)	127	(97.7)	132	(98.5)	898	(93.4)	1,773	(96.5)	1,393	(93.1)	2,860	(95.7)
with serious adverse events	112	(46.7)	90	(54.5)	112	(46.7)	132	(53.2)	65	(50.0)	50	(37.3)	384	(40.0)	657	(35.7)	586	(39.1)	1,107	(37.1)
with serious drug-related adverse events	60	(25.0)	46	(27.9)	60	(25.0)	69	(27.8)	30	(23.1)	19	(14.2)	119	(12.4)	162	(8.8)	169	(11.3)	282	(9.4)
with dose modification‡ due to an adverse event	173	(72.1)	104	(63.0)	173	(72.1)	156	(62.9)	80	(61.5)	66	(49.3)	307	(31.9)	577	(31.4)	470	(31.4)	937	(31.4)
who died	17	(7.1)	10	(6.1)	17	(7.1)	13	(5.2)	10	(7.7)	4	(3.0)	47	(4.9)	63	(3.4)	73	(4.9)	127	(4.3)
who died due to a drug-related adverse event	4	(1.7)	5	(3.0)	4	(1.7)	6	(2.4)	1	(0.8)	3	(2.2)	5	(0.5)	5	(0.3)	7	(0.5)	12	(0.4)
discontinued drug due to an adverse event	68	(28.3)	44	(26.7)	68	(28.3)	61	(24.6)	24	(18.5)	15	(11.2)	114	(11.9)	220	(12.0)	155	(10.4)	334	(11.2)
discontinued drug due to a drug-related adverse event	50	(20.8)	35	(21.2)	50	(20.8)	50	(20.2)	14	(10.8)	12	(9.0)	56	(5.8)	90	(4.9)	80	(5.3)	149	(5.0)
discontinued drug due to a serious adverse event	46	(19.2)	30	(18.2)	46	(19.2)	40	(16.1)	15	(11.5)	7	(5.2)	95	(9.9)	158	(8.6)	124	(8.3)	249	(8.3)

discontinued drug due to a serious drug-related adverse event	31	(12.9)	23	(13.9)	31	(12.9)	31	(12.5)	6	(4.6)	4	(3.0)	45	(4.7)	56	(3.0)	58	(3.9)	100	(3.3)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
†† Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189.
‡‡ Includes all subjects who received at least one dose of treatment in pembro combo arm of KN189 and KN021 cohort G/C.
§§ Includes all subjects who received at least one dose of treatment in chemo arm of KN189 and KN021 cohort G.
¶¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
‡‡‡ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), and Cohort 4A (PMBCL), KN024, KN045, KN052, KN059 Cohort 1, KN087, KN164 Cohort A (Colorectal Carcinoma), and KN170.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
MK-3475 Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 Cohort G/C: 31MAY2017, KN024: 10JUL2017, KN189: 8NOV2017)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 03APR2017, KN170: 14APR2017)
Source: [TSS: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

No formal DDI studies have been conducted as part of this application.

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. Drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of cytochrome P450 enzymes, other enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed. In addition, in vitro experiments and studies conducted in preclinical species have been shown to have limited value in predicting DDI potential in humans. Therefore, no preclinical pharmacokinetic studies were conducted to assess the propensity of pembrolizumab to be a victim or perpetrator of pharmacokinetic DDIs.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, given the study design, exclusion criteria, and immunomodulatory mechanism of action, the use of systemic corticosteroids (at doses greater than physiologic replacement), or other immunosuppressants before the start of pembrolizumab treatment, is not recommended. However, systemic corticosteroids, or other immunosuppressants, can be used during pembrolizumab treatment to treat immune-related adverse reactions.

Discontinuation due to adverse events

Discontinuation

Table 59: Subjects with drug-related adverse events resulting in treatment discontinuation of pembrolizumab / placebo (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	59	(14.6)	68	(13.9)	10	(3.8)	146	(5.2)	229	(5.1)
with no adverse events	346	(85.4)	420	(86.1)	254	(96.2)	2,653	(94.8)	4,255	(94.9)
Pneumonitis	11	(2.7)	12	(2.5)	3	(1.1)	34	(1.2)	56	(1.2)
Acute kidney injury	7	(1.7)	10	(2.0)	0	(0.0)	2	(0.1)	2	(0.0)

Table 60: Subjects with drug-related adverse events resulting in treatment discontinuation of chemotherapy (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264	
with one or more adverse events	73	(18.0)	85	(17.4)	25	(9.5)
with no adverse events	332	(82.0)	403	(82.6)	239	(90.5)
Acute kidney injury	10	(2.5)	13	(2.7)	1	(0.4)
Pneumonitis	7	(1.7)	7	(1.4)	2	(0.8)
Diarrhoea	4	(1.0)	4	(0.8)	0	(0.0)
Fatigue	4	(1.0)	4	(0.8)	6	(2.3)
Renal failure	4	(1.0)	4	(0.8)	1	(0.4)

Interruption

Table 61: Subjects with drug-related adverse events resulting in treatment interruption of pembrolizumab / placebo (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]		Reference Safety Dataset for Pembrolizumab monotherapy[†††]		Cumulative Running Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264		2,799		4,484	
with one or more adverse events	148	(36.5)	181	(37.1)	61	(23.1)	351	(12.5)	550	(12.3)
with no adverse events	257	(63.5)	307	(62.9)	203	(76.9)	2,448	(87.5)	3,934	(87.7)
Neutropenia	47	(11.6)	49	(10.0)	22	(8.3)	2	(0.1)	3	(0.1)
Anaemia	26	(6.4)	29	(5.9)	14	(5.3)	6	(0.2)	10	(0.2)
Thrombocytopenia	17	(4.2)	18	(3.7)	2	(0.8)	1	(0.0)	2	(0.0)
Diarrhoea	12	(3.0)	14	(2.9)	1	(0.4)	35	(1.3)	55	(1.2)
Blood creatinine increased	10	(2.5)	14	(2.9)	6	(2.3)	5	(0.2)	6	(0.1)
Fatigue	10	(2.5)	15	(3.1)	3	(1.1)	21	(0.8)	28	(0.6)
Febrile neutropenia	9	(2.2)	9	(1.8)	0	(0.0)	0	(0.0)	0	(0.0)
Asthenia	8	(2.0)	8	(1.6)	2	(0.8)	6	(0.2)	7	(0.2)
Alanine aminotransferase increased	7	(1.7)	9	(1.8)	8	(3.0)	19	(0.7)	34	(0.8)
Pneumonitis	6	(1.5)	9	(1.8)	0	(0.0)	21	(0.8)	35	(0.8)
Acute kidney injury	5	(1.2)	5	(1.0)	0	(0.0)	0	(0.0)	1	(0.0)
Leukopenia	4	(1.0)	4	(0.8)	2	(0.8)	1	(0.0)	1	(0.0)
Oedema peripheral	4	(1.0)	5	(1.0)	1	(0.4)	1	(0.0)	2	(0.0)
White blood cell count decreased	4	(1.0)	4	(0.8)	1	(0.4)	0	(0.0)	0	(0.0)

Table 62: Subjects with drug-related adverse events resulting in treatment interruption of chemotherapy (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term in KN189 combo (ASaT population)

	KN189 combo[††]		KN189 + KN021-G/C combo[‡‡]		KN189 + KN021-G chemo[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	405		488		264	
with one or more adverse events	132	(32.6)	163	(33.4)	78	(29.5)
with no adverse events	273	(67.4)	325	(66.6)	186	(70.5)
Neutropenia	46	(11.4)	48	(9.8)	23	(8.7)
Anaemia	25	(6.2)	30	(6.1)	22	(8.3)
Thrombocytopenia	15	(3.7)	16	(3.3)	5	(1.9)
Blood creatinine increased	10	(2.5)	16	(3.3)	6	(2.3)
Fatigue	9	(2.2)	16	(3.3)	2	(0.8)
Diarrhoea	7	(1.7)	8	(1.6)	2	(0.8)
Asthenia	6	(1.5)	6	(1.2)	2	(0.8)
Febrile neutropenia	6	(1.5)	6	(1.2)	0	(0.0)
Acute kidney injury	4	(1.0)	4	(0.8)	0	(0.0)
Alanine aminotransferase increased	4	(1.0)	6	(1.2)	9	(3.4)
Leukopenia	4	(1.0)	4	(0.8)	2	(0.8)
Pneumonitis	4	(1.0)	7	(1.4)	1	(0.4)
White blood cell count decreased	4	(1.0)	4	(0.8)	1	(0.4)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-Mar-2017 through 03-Sep-2017 (EMEA/H/C/PSUSA/00010403/201709).

As a result of the review of the PSUR, the SmPC section 4.8 was updated to add pericarditis and pericardial effusion as new adverse drug reactions (ADR) with a frequency uncommon and to add a footnote to the existing ADR 'myasthenic syndrome' to indicate that the event 'myasthenia gravis' is included.

2.5.1. Discussion on clinical safety

The evaluation of pembrolizumab's safety in combination with pemetrexed/platinum chemotherapy for first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations is primarily based on the results of the first interim analysis of the ongoing pivotal KEYNOTE-189 trial supported by data from Cohorts C and G of the KEYNOTE-021 study. The two study populations were grouped in a Pooled Combo (n=488) and Pooled Chemo (n=264) dataset for a comparative analysis, which is acceptable in light of the consistency in clinical and disease characteristics between the two study populations, and only minor dissimilarities in patient demographics. Furthermore, the safety database include a reference dataset for the Pembrolizumab Monotherapy RSD (NSCLC and melanoma, n=2799) and the Cumulative Running Pembrolizumab Monotherapy SD, regardless of indication (n=4484).

Overall, the submitted dataset is considered numerically appropriate for safety evaluation, also in consideration of the fact that long-term exposure data derived from the KEYNOTE-189 study were available in 51.7% and 14.5% of the study population for ≥6 months and ≥12 months, respectively.

The duration of exposure was considerably longer for the pembro combo compared with the control (and the Pembrolizumab Monotherapy RSD). This included a higher exposure to pemetrexed with more patients entering the maintenance phase and a higher exposure to carboplatin in the induction phase in the pembro combo arm compared with the control. It is acknowledged that these differences in exposure have to be taken into consideration when evaluating the safety profile of the different treatment options.

While overall adverse events (AEs, Grade 3-5 AEs, SAEs) compared similarly among treatment strategies, the frequency of drug-related Grade 3-5 AEs (47.3% vs 37.1%), SAEs (50% vs 43.6%), and drug-related SAEs (26.4% vs 18.6%), as well as the rate of subjects who discontinued any drug due to either AEs (26.4% vs 14.8%), drug-related AEs (20.5% *vs* 9.8%), or SAEs (17.6% vs 8.3%) were all increased in patients treated with pembrolizumab+chemotherapy compared to those who received chemotherapy only. In both treatment groups, evaluation over time of exposure-adjusted incidences (0-3, 3-6, 6-12, >12 months) in Study KEYNOTE-189 shows that overall and SOC-specific AE frequencies were higher during the first two periods, with declining rates thereafter, likely due to the more toxic platinum-based induction phase than the pemetrexed maintenance period.

Exposure-adjusted event rate was slightly lower in the Pembro Combo compared to the Control arm (194.01 vs 211.23 person-years of follow-up). Exposure adjusted incidences of drug-related Grade 3-5 AEs, SAEs, drug-related SAEs, that were more frequently reported with combo compared to chemotherapy were not reported, and have been requested.

Most common AEs (incidence ≥40%) were nausea, anaemia and fatigue in both treatment arms. Diarrhoea and rash were reported with higher incidences in the pembro combo arm compared to control (95% CI of risk difference exceeding 0). But most of the point estimates of other common AEs also favoured the control group. The risks of dyspnoea and cough occurred more commonly in the control group which possibly suggests improved disease control in the pembro combo in line with the more favourable efficacy results.

Drug-related Grade 3-5 AEs were mainly associated with the known toxicity profile of chemotherapeutic agents, as being dominated by Blood and lymphatic system disorders (25.8% vs 23.5% in Pooled Pembro vs Pooled Chemo) that are uncommon in pembrolizumab monotherapy. However, within this SOC category, an additive effect of pembrolizumab could be recognised on the incidence of febrile neutropenia and Neutropenia. As regards the other categories, pembrolizumab as add-on therapy has worsen the safety profile of chemotherapy in all the different SOCs, with a particularly marked effect on Diarrhoea,

Thrombocytopenia, Lacrimation increased, Constipation, Rash, Alanine Aminotransferase increase, Blood creatinine increased; in addition, 6 cases of both cardiac disorders and hepatobiliary disorders were reported in the population exposed to combined therapy compared to none in the control arm.

Myelotoxicity, gastrointestinal disorders, pneumonitis and renal toxicity were among the most frequent drug-related SAEs for both the combined therapy group and control arm, although with higher frequency in the former than the latter.

Pneumonitis and acute kidney injury were also among the major reasons for drug-related AEs leading to pembrolizumab discontinuation. On the contrarily, myelotoxicity represented the major cause of drug-related interruption for both pembrolizumab and chemotherapy.

Overall, type and frequency of specific AEOSIs was consistent with the established pembrolizumab safety profile with the exception of Pneumonitis, Hyperthyroidism, Colitis, Severe Skin Reaction, Nephritis, and Hepatitis. No new indication-specific, immune-mediated AE causally associated with pembrolizumab was found. These findings likely reflect overlapping toxicities associated with pembrolizumab monotherapy and pemetrexed/platinum chemotherapy alone. Prior exposure to thoracic radiation was identified as risk factor associated with a higher incidence of pneumonitis.

In conclusion, it appears that the addition of pembrolizumab increases the risk of some expected toxicities with chemotherapy regimens. Based on the submitted data it is not possible to understand if such an increase is observed regardless of the platinum-based regimen used, or whether the added toxicity is more pronounced with one treatment or the other.

For the purpose of better understanding the relation between the toxicities observed with the combination compared to chemotherapy alone, the MAH has been requested to present safety data from both arms of KEYNOTE-189 by the type of chemotherapy regimen (i.e. cisplatin- or carboplatin-based), and summarize the pattern of AEs observed when pembrolizumab is combined with either cisplatin-based chemotherapy or carboplatin-based chemotherapy (data not shown). The combination of pembrolizumab to either cisplatin or carboplatin-based doublets showed a similar safety profile. No differences emerged in terms of AE pattern across the different SOC categories between the groups of patients treated with pembrolizumab in combination to either cisplatin or carboplatin-based chemotherapy.

Death rate in Study KEYNOTE-189 was slightly higher in the Pembro Combo arm when compared to Controls (27 subjects [6.7%] vs 12 subjects [5.9%], respectively). All narratives of these events were reviewed, drug-related deaths were reported in 9 subjects [2.2%] in the Pembro Combo versus 2 subjects [1%] in the Control. In the pembro combo arm 3 patients suffered deaths due to pneumonitis. 5 subjects died due to cardiac events (versus 0 in the control). Apart from two acute cardiac events concomitant AEs in the 3 further subjects were myelotoxicity (Grade 4 neutropenia and thrombocytopenia), cerebrovascular accident and Grade 4 asthenia (with pneumonia and PE in the autopsy). Neutropenia appeared to be a relevant underlying factor also for other deaths with and without infections (e.g. grade 5 neutropenic sepsis; grade 5 peritonitis with Grade 4 febrile neutropenia; Grade 5 Pneumocystis jirovecii pneumonia with Grade 4 neutropenia; Grade 5 acute kidney injury with neutropenic sepsis in two cases; Grade 5 intestinal ischaemia with grade 4 decreased neutrophil count; Grade 5 Chronic obstructive pulmonary disease with grade 4 neutropenia and 4 decreased platelet count).

Fatal infections without (relevant) neutropenia were reported in three further patients (pneumonia in the context of malignant neoplasm progression, septic shock and lung infection).

Further notable is a higher proportion of fatal ischaemic vascular events (2 cases of ischaemic stroke/cerebral infarction) and 3 cases of intestinal ischaemia/mesenteric artery embolism compared to none in the control arm).

The 27 fatal events in the KEYNOTE-189 Pembro Combo arm occurred predominantly in males and all cases were >60 years. Specifically, within the group of patients aged ≥75 years (34 patients in the experimental arm and 21 in the control group), fatalities were considerably higher in pembrolizumab+chemotherapy (20.6%) compared to chemotherapy only (4.8%). In agreement with this, the comparison between Pooled Combo vs Pooled Chemo in subjects aged ≥65 years revealed reduced tolerability of the combined therapy in more elderly patients as demonstrated by an increased incidence of drug-related grade 3-5 AEs (50.6% vs 39.8%), drug-related SAE (31.3% vs 21.1%), discontinuation due to drug-related AEs (23.5% vs 12.2%) and discontinuation due to drug related SAEs (13.6% vs 4.9%) . Particulalry marked it is the difference in drug-related Grade 3-5 AEs within the subgroup aged ≥75 years (46.3% vs 33.3%) and discontinuations due to drug-related SAEs (24.4% vs 4.2%). Because of the relatively low number of subjects, and the potential for baseline comorbities as a confounding factor, the B/R profile for patients ≥75 years has not been established. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis (see section 4.4 of the SmPC). As regards other subgroup analysis, the safety profile of pembro combo versus control arm looks overall comparable between gender and, as expected, the proportion of subjects in the Pooled Combo SD with an ECOG status of 0 who experienced AEs was generally lower than that of subjects with an ECOG status of 1.

2.5.2. Conclusions on clinical safety

The pembrolizumab/chemotherapy regimen was overall more toxic than chemotherapy alone or pembrolizumab monotherapy, especially in older patients. An additive effect of the immune check-point inhibitor on toxicities due to cytotoxic agents was observed, as well as an increased incidence of AEOSI such as pneumonitis and renal disorders that occurred at uncommon frequency in pembrolizumab monotherapy. Some adverse events (or the combination of AEs) are of concern and highlight the need for special awareness for treating physicians (such as severe and serious febrile neutropenia associated with fatal events, acute kidney injury and nephritis. Toxicities observed with the combination compared to chemotherapy alone were similar between cisplatin and carboplatin-based regimens. Due to the partial overlapping of the target population of the sought indication with non-squamous NSCLC patients expressing high levels of PD-L1 (TPS ≥50%) for whom pembrolizumab monotherapy is recommended as SOC, evaluation of the B/R ratio on an individual basis should be considered by treating physicians in treatment decision-making, as supported by the experimental evidence reported in the SmPC.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 17 is acceptable.

The CHMP endorsed the Risk Management Plan version 17 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-Related Adverse Reactions • Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis • Immune-related nephritis • 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

No changes to the list of safety concerns were made as a result of this extension of indication.

Pharmacovigilance plan *(changes in blue italic)*

Study Status	Study / activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities					
Started	Clinical trial A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (KN010)	To examine the overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and long term efficacy and safety of MK-3475 in previously treated subjects with NSCLC whose tumors express PD-L1.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety	Final Study Report	Aug 2019
Started	Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (KN024)	To evaluate the overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) and the safety and tolerability profile of pembrolizumab in subjects with 1L metastatic NSCLC, whose tumors express PD-L1, treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT; Immunogenicity) -Long term safety	Final Study Report	Sep 2018
Started	Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer	To evaluate the overall survival (OS) and progression free survival (PFS) and to examine the safety and tolerability profile of pembrolizumab in subjects with PD-L1 positive 1L advanced/metastatic NSCLC, treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Dec 2019

Study Status	Study / activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	(KN042)		-Long term safety		
Started	Clinical Trial A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies (KN013)	To examine the safety and tolerability of pembrolizumab in subjects with hematologic malignancies including, Hodgkin lymphoma, mediastinal large B cell lymphoma (MLBCL), relapsed/refractory non-Hodgkin lymphoma (NHL), myelodysplastic syndrome (MDS) and multiple myeloma .	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Mar 2019

Study Status	Study / activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical Trial A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (KN087)	To determine the safety and tolerability of pembrolizumab in subjects with relapsed or refractory classical Hodgkin Lymphoma (cHL) and to evaluate overall response rate (ORR), progression free survival (PFS), duration of response (DOR) and overall survival (OS) of pembrolizumab in study subjects.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Aug 2021
Started	Clinical Trial A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204)	To compare overall survival (OS), progression free survival (PFS) and overall response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Apr 2021

Study Status	Study / activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical trial A Phase I/II Study of Pembrolizumab (MK-3475) in Children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma (KN051)	To define the toxicities and maximum tolerated, maximum administered dose of pembrolizumab when administered as monotherapy to children between 6 months to 18 years of age with advanced melanoma, advanced, relapsed or refractory solid tumors or lymphoma. Study is designed to determine the safety and tolerability of pembrolizumab in all children between 6 months to 18 years of age.	Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis); GVHD after pembrolizumab administration in patients with a history of allogeneic SCT; -Safety in pediatric patients	Final Study Report	July 2019
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risks of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT.	Important identified risks of encephalitis, sarcoidosis; potiental risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	PSUR	2019
Started	*Clinical trial A Phase I/II Study of MK-3475 in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma (KN021)*	*To determine the recommended Phase II dose for MK-3475 in combination with chemotherapy or immunotherapy in subjects with unresectable or metastatic NSCLC.*	*Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety*	*Final Study Report*	*Apr 2020*

Study Status	Study / activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	*Clinical Trial A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KN189)*	*To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy and to evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using OS.*	*Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety*	*Final Study Report*	*Jun 2021*

Two ongoing studies which are supporting the new indication (KN021 and KN189) have been added to the Pharmacovigilance plan in order to investigate existing safety concerns but in the new target population.

Risk minimisation measures

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related Pneumonitis	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reaction of pneumonitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).~~ • Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immune-related Colitis	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reaction of colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: ▪ Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).~~ • Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Hepatitis	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reaction of hepatitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: ▪ ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).~~ • Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immune-related Nephritis	Routine risk Minimisation measures: ▪ The risk of the immune-related adverse reaction of nephritis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: • ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).~~Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Endocrinopathies -Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis) - Type 1 Diabetes Mellitus	Routine risk Minimisation measures: ▪ The risk of the immune-related endocrinopathies [Hypophysitis (including hypopituitarism and secondary adrenal insufficiency); Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis); Type 1 Diabetes Mellitus] associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4 and 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: ▪ Safety monitoring in the ~~ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).~~ • Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Severe Skin Reactions including SJS and TEN	Routine risk Minimisation measures: ▪ The risk of severe skin reactions including SJS and TEN associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: ▪ Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions
	Additional risk minimisation measures: ▪ Educational materials	Additional pharmacovigilance including: • ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361~~). • Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
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	Routine risk Minimisation measures: ▪ The risk of 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) associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 (Guillain-Barre Syndrome, Myocarditis, Encephalitis are also described in Section 4.2) and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: ▪ Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Educational materials	Additional pharmacovigilance including: • ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UCtrials (KN045, KN052, KN361).~~Safety monitoring in all~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types • Cumulative review of literature, clinical trial and post-marketing cases of encephalitis and sarcoidosis to be included with PSUR submission in 2019.
Important Identified Risks: Infusion-Related Reactions		
Infusion-Related Reactions	Routine risk Minimisation measures: ▪ The risk of infusion-related reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk Additional risk minimisation measures: Educational materials.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: ▪ Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: ▪ ~~Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).~~ • Safety monitoring in all ~~other~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Important Potential Risks: Immune-Related Adverse Events		
Gastrointestinal perforation secondary to colitis	Routine risk Minimisation measures: ▪ The risk of the immune-related adverse event of gastrointestinal perforation secondary to colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: ▪ Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: ▪ ~~*Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).*~~ • Safety monitoring in all ~~*other*~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Other Immune-related adverse events- For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk Minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: Educational materials	Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trials (KN013, KN087, KN204).
Other Immune-related adverse events- GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk Minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities

	Additional risk minimisation measures: ▪ Educational materials	Additional pharmacovigilance including: ▪ ~~*Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), and UC trials (KN045, KN052, KN361).*~~ • Safety monitoring in all ~~*other*~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types • Cumulative review of literature, clinical trial and post-marketing cases of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT with PSUR submission in 2019.
Important Potential Risks: Immunogenicity		
Immunogenicity	Routine risk Minimisation measures: ▪ The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 4.8.	Routine pharmacovigilance activities Additional pharmacovigilance including: • Conducting anti-drug antibody (ADA) assessments in multiple MAH- sponsored clinical trials in different tumor types in the pembrolizumab program.
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	Routine risk Minimisation measures: ▪ The missing information of safety in these patients is described in the SmPC, Section 4.2, 4.4.	Routine pharmacovigilance activities
Safety in patients with active systemic autoimmune disease	Routine risk Minimisation measures: ▪ The missing information of safety in patients with active systemic autoimmune disease is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities
Safety in patients with HIV or Hepatitis B or Hepatitis C	Routine risk Minimisation measures: ▪ The missing information of safety in patients with patients with HIV or Hepatitis B or Hepatitis C is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities

Safety in Pediatric patients	Routine risk Minimisation measures: ▪ The missing information of safety in pediatric patients is described in the SmPC, Section 4.2.	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the paediatric investigation plan (PIP): A Phase I/II Study of Pembrolizumab (MK-3475) in Children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma (KN051)
Reproductive and lactation data	Routine risk Minimisation measures: ▪ Use during pregnancy and use in nursing mothers is described in the SmPC, Section 4.6, 5.3.	Routine pharmacovigilance activities
Long term safety	No risk Minimisation warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in ~~*the ongoing NSCLC trials (KN001, KN010, KN024, KN042)*~~ ▪ ~~*Safety monitoring in other*~~ ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Safety in various ethnic groups	No risk Minimisation warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in ongoing global MAH-sponsored clinical trials for pembrolizumab
Potential pharmacodynamic interaction with systemic immunosuppressants	Routine risk Minimisation measures: ▪ The missing information of potential pharmacodynamic interaction with systemic immunosuppressants is described in the SmPC, Section 4.4, 4.5.	Routine pharmacovigilance activities
Safety in patients with previous hypersensitivity to another monoclonal antibody	Routine risk Minimisation measures: ▪ The missing information of safety in patients with previous hypersensitivity to another monoclonal antibody is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities

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	Routine risk Minimisation measures: ▪ The missing information of 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 is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: ▪ Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions

No changes to the risk minimisation measures have been introduced as a result of the new indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptablefor the following reasons:

- A CHMP request was received during variation EMEA/H/C/003820/II/0023/G (new indications in urothelial carcinoma approved on 24-Aug-2017) to perform new user testing considering that all sections of the package leaflet were affected since marketing authorization. The proposed revisions included in this variation for 1L NSCLC do not constitute significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH proposes an extension of indication for KEYTRUDA as add-on therapy to platinum-pemetrexed chemotherapy in the first-line setting of non-squamous NSCLC negative for EGFR and ALK gene aberrations.

3.1.1. Disease or condition

Lung cancer is the main cause of malignancy-related mortality worldwide, accounting for 1.69 million of deaths globally per year as estimated by the World Health Organization (WHO). Around 85%-90% of all lung cancers are Non Small Cell Lung Cancer (NSCLC), that include non-squamous (i.e, adenocarcinoma, large-cell carcinoma, and other cell types) and squamous (epidermoid) cell carcinoma (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011). During the last 25 years, the distribution of NSCLC histological types changed in Europe, with a decrease of squamous cell carcinoma and an increase of adenocarcinoma in men, while in women there was an increase of both histologies.

Non-squamous NSCLC is the prevailing histological type diagnosed in never smoker NSCLC patients, with a higher prevalence in females than males. More than half of the patients are diagnosed at an advanced stage

of disease, which directly contributes to poor survival, as expressed by an untreated median OS of 4 months and a metastatic 5-year survival rate of <5% (Lindsey A. et al, 2016).

3.1.2. Available therapies and unmet medical need

In the first-line setting in non-squamous NSCLC not harbouring driver mutations (i.e, EGFR, ALK and ROS1 negative disease), chemotherapy represents the recommended choice for patients presenting with a tumour PD-L1 score <50%. Platinum-based doublets (four to a maximum of six cycles) are considered the standard of care in patients with PS 0-1, as well as selected PS 2 and adequate organ function, with no major differences in terms of efficacy across combinations. Among these, platinum/pemetrexed represents a valid alternative and consists of a first induction phase with the two cytotoxic agents, followed by a continuation maintenance treatment with pemetrexed only, in the absence of progression after the first cycles of combined chemotherapy (ESMO guidelines). Introduction into clinical practice of this therapeutic scheme was based upon the positive results of the Phase III PARAMOUNT trial, providing evidence for an OS advantage of cisplatin induction (4 cycles) followed by pemetrexed over cisplatin induction plus placebo (median 13.9 months versus 11.0 months, hazard ratio = 0.78, 95%CI=0.64-0.96, p=0.0195) that was consistent across patient subgroups (including disease stage, induction response, ECOG PS, smoking status, gender, histology and age).

With the advent of pembrolizumab and its approval (2016) in the 1L setting as monotherapy in NSCLC with TPS ≥50% based on the positive results of the phase III, randomized, KEYNOTE-024 study (i.e PFS HR: 0.50, p<0.001; OS HR: 0.60, p=0.005 pembrolizumab vs a SOC platinum-based doublet), this is now indicated as first-choice also in non-squamous NSCLC patients highly expressing tumour PD-L1 (TPS ≥50%). (ESMO eUpdate 28 June 2017). However, there remains substantial unmet medical need for patients with previously untreated nonsquamous NSCLC. Available systemic therapies, except that for tumors not harbouring EGFR sensitizing mutations or ALK rearrangements, can only determine a limited improvement in survival up to 8–12 months, with an enhanced symptom control and a better quality of life in 60%–70% despite treatment toxicity (Leighl NB. et al, 2012). In addition, a fraction of subjects with highly expressing tumour PD-L1 (TPS ≥50%) does not derive benefit from pembrolizumab as monotherapy, and only 25% to 30% of patients with NSCLC have tumours with a PD-L1 TPS ≥50%.

KEYTRUDA as monotherapy is already part of the treatment algorithm of NSCLC, with a licensed indication in the following therapeutic settings:

- Second-line in locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen, and targeted therapy for patients with EGFR and ALK positive tumour mutations
- First-line in metastatic NSCLC (including both squamous and non-squamous hystology) in adults whose tumours express PD-L1 with a ≥50% TPS and no EGFR or ALK positive tumour mutations.

3.1.3. Main clinical studies

The current application is based upon results of the Phase III KEYNOTE-189 trial, a Randomized, Double-Blind, Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Nonsquamous Non-small Cell Lung Cancer Subjects. This is an ongoing study currently at its first interim analysis (IA1; date cut-off: 08 Nov 2017).

3.2. Favourable effects

- A more favourable outcome of pembrolizumab combination versus control in terms of OS was demonstrated in the overall study population (HR=0.49 [95% CI: 0.38,0.64]; p<0.00001)

- A gain of about 4.7 months in median PFS (HR=0.52 [0.43, 0.64]; p<0.00001) was reported for the pembrolizumab combination vs control in the overall population.
- ORR was 47.6% vs 18.9% in the pembrolizumab combination vs control respectively, resulting in 28.5% difference in response rates in the overall population. Additionally the median DOR was 11.2 months for the pembrolizumab combination and 7.8 months for the control.

3.3. Uncertainties and limitations about favourable effects

- Immaturity in OS (57% of events at the planned IA1); however the MAH committed to provide updated data as post-authorisation measure with the CSR to be expected by June 2021
- Decreased survival (HR=2.09 [0.84, 5.23] in OS), reduction in PFS (HR=1.73 [0.77,3.90] and an increase in ORR (14.4% difference [-11.1,36.4]) induced by pembrolizumab combination in patients aged ≥ 75 years; the limited sample size of this subgroup does not allow definitive conclusions to be made and the limitations have been reflected in sections 4.2 and 4.4 of the SmPC.
- Lack of comparison with a control arm consisting of pembrolizumab in monotherapy for NSCLC patients with TPS≥50% (reflecting currently licensed indication); in the absence of direct comparative analysis, the B/R should be considered on an individual basis by treating physicians on the basis of experimental data as detailed in sections 4.2 and 4.4 of the SmPC.

3.4. Unfavourable effects

- In KEYNOTE-189, frequency of drug-related Grade 3-5 AEs (48.4% vs 39.6%), and of subjects who discontinued any drug due to either AEs (27.7% vs 14.9%), or drug-related AEs (21.0% vs 8.4%), or SAEs (18.8% vs 9.4) or drug-related SAEs (13.3 vs 3.5) were all increased in patients treated with pembrolizumab+chemotherapy compared to those who received chemotherapy only.
- Patients treated with pembrolizumab+chemotherapy displayed a higher occurrence of drug-related *Diarrhoea* (20.1% *vs* 11.7%), *Thrombocytopenia* (14.8% *vs* 11.7%), *Lacrimation increased* (12.7% *vs 8*%), %), *Constipation* (16.8% vs 11.4%), *Rash* (14.8% *vs* 9.8%), *Alanine Aminotransferase increase* (11.3% vs 9.1%), *Blood creatinine increased* (9.2% vs 6.1%), *Febrile neutropenia* (5.3% vs 1.5%)*, Acute kidney injury* (3.7% vs 0.4%), *Pyrexia* (6.1% vs 1.9%), *Dysgeusia* (10% vs 8%), *Peripheral Oedema* (7.8% vs 5.7%). Moreover, an increased rate of drug-related AEOSI for pembrolizumab were generally reported in the combined regimen than in pembrolizumab monotherapy, with particular reference to pneumonitis (4.1% vs 3.1% in the Pooled Combo and Cumulative Reference SD; 1.1% in the Pooled Chemo) and nephritis (1.4% vs 0.2% in the Pooled Combo and Cumulative Reference SD; 0% in the Pooled Chemo).
- The most common drug-related AEs leading to pembrolizumab discontinuation in the Pooled Pembro Combo were *Pneumonitis* (2.5% vs 1.1% in Pooled Chemo) and *Acute kidney injury* (2% vs 0% in Pooled Chemo). The incidence of these drug-related AEs in the group treated with pembrolizumab in combination to chemotherapy was higher also in comparison to pembrolizumab monotherapy (1.2% and 0.1% for *Pneumonitis* and *Acute kidney injury*, respectively in the Reference dataset).

3.5. Uncertainties and limitations about unfavourable effects

- Differences in safety between elderly and younger patients were observed in all treatment arms, but appear partially more pronounced in the Pooled Combo SD (e.g. for subjects with 75-84 years 73.2% grade 3-5 AEs, 17.1% death due to AEs, 31.7% discontinuations due to an AE, 24.4% discontinuations due to SAEs). Moreover, for subjects with 75-84 years a high rate of CV events (34.1%) and cerebrovascular events (12.2%) was observed in the Pooled Combo SD (compared to

8.3% and 0%, respectively in the Pooled Chemo SD). Thus, the tolerability of the combination therapy in subjects of ≥75 year could be questioned, but the sample size in this subgroup might be not sufficient to draw reliable conclusions. This has been reflected in the SmPC.

3.6. Effects Table

Table 63: Keytruda in combination with pemetrexed and carboplatin for the of first-line treatment of patients with metastatic non-squamous NSCLC - Study KEYNOTE-189 (date cut-off: 08 Nov 2017)

Effect	Short description	Unit	pembro 200 mg pemetrexed / carboplatin	pemetrexed / carboplatin	Uncertainties / Strength of evidence	Ref
Favourable Effects						
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	Not Reached (...,...)	11.3 (8.7, 15.1)	HR (95% CI)= 0.49 (0.38, 0.64) Data Immaturity (updated analysis is requested to establish the magnitude of effect in the ITT) PD-L1-dependent magnitude of effect HR=2.09 [0.84,5.23] in pts ≥75-year-old	CSR
PFS	survival without progression from randomization to PD or death whichever occurred first BICRper RECIST 1.1	months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)	HR (95% CI)= 0.52 (0.43, 0.64) Lack of consistency across PD-L1 subgroups (no significant effect in TPS<1%) HR=1.73 [0.77,3.90] in pts ≥75-year-old	CSR
ORR	Confirmed CR + PR BICR per RECIST 1.1	% (95% CI)	48% (43, 53)	19% (14, 25)	PD-L1-dependent magnitude of effect ORR difference=14.4% [-11.1,36.4] in pts ≥75-year-old	CSR
DoR		Median in months (range)	11.2 (1.1, 18.0)	7.8 (2.1, 16.4)		
Unfavourable Effects						
Tolerability			Pooled Pembro	Pooled Chemo		
	drug related AEs	%	92.4	90.9		ISS
	drug related Gr≥3 AE	%	47.3	37.1		
	drug related SAEs	%	26.4	18.6		
	drug related deaths	%	2	1.5		

Abbreviations: CSR: Clinical Study report; ISS: Integrated analysis of safety; OS: overall survival; PFS: Progression-Free-Survival; ORR: Overall Response Rate

Notes: safety data are reported for the Pooled Pembro and Pooled Combo datasets

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Immune check-point inhibitors are expected to improve clinical outcomes in patients co-treated with chemotherapy, through a potentiating effect on the anti-tumour immunological activity induced by the cytotoxic agents. According with this, an add-on value of pembrolizumab to the platinum/pemetrexed treatment scheme has been generally demonstrated in the KEYNOYTE-189 trial, in term of both OS and PFS.

Pembrolizumab in co-administration to platinum/pemetrexed seems to potentiate the toxic effects of the cytotoxic agents, as demonstrated by an increased rate of drug-related myelosuppression, gastrointestinal effects, and renal disorders in patients exposed to the combined therapy compared to those receiving platinum/pemetrexed only. On the other hand, chemotherapy appears to increase the immunological toxicity of pembrolizumab, considering that a higher frequency of nephritis was observed in the experimental arm compared to control.

3.7.2. Balance of benefits and risks

Results from KEYNOTE-189 study are considered sufficient to establish a positive B/R in the sought indication for the first line treatment of metastatic non-squamous NSCLC in combination with pemetrexed and platinum. The efficacy and safety profile of pembrolizumab in combination with chemotherapy, particularly within the subgroups of patients with TPS≥50% and ≥75-year old has been adequately described in section 5.1 of the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of KEYTRUDA in combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations is positive.

4. Recommendations

Outcome

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

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

Extension of Indication to include 1st line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in adults whose tumours have no EGFR or ALK positive mutations, in combination with pemetrexed and platinum chemotherapy, based on the efficacy and safety data from pivotal study KEYNOTE-189, supported by data from KEYNOTE-021 cohorts C and G.

KEYNOTE-189 is a phase 3, randomized, placebo-controlled study undertaken to evaluate the efficacy and safety of pembrolizumab +pemetrexed + carboplatin or cisplatin (pembro combo) versus saline placebo + pemetrexed + carboplatin or cisplatin (control) in previously untreated subjects with advanced/metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance.

An updated RMP version 17.0 was agreed during the procedure.