EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/223846/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0060

Note

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

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central radiologist review
CI	Confidence interval
CSR	Clinical study report
CT	Computed tomography
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	Euopean Medicines Agency
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and drug Administration
HR	Hazard ratio
IA1	Interim Analysis 1
IA2	Interim Analysis 2
ITT	Intention-to-Treat
IV	Intravenous
KM	Kaplan-Meier
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NE	Not estimable
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
QoL	Quality of life
Q3W	Every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
TPS	Tumour proportion score
Vs	Versus

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 31 July 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 a new indication for Keytruda in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Additionally, editorial corrections to section 5.1 of the SmPC are introduced (concerning the procedure EMEA/H/C/003820/II/0052). The RMP version 20.1 has also been submitted.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The 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	31 July 2018
Start of procedure:	18 August 2018
CHMP Rapporteur Assessment Report	12 October 2018
CHMP Co-Rapporteur Assessment Report	12 October 2018
PRAC Rapporteur Assessment Report	18 October 2018
PRAC Outcome	31 October 2018
CHMP members comments	5 November 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 November 2018
Request for supplementary information (RSI)	15 November 2018
MAH's responses submitted on:	20 November 2018
PRAC Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	28 November 2018
CHMP members comments	03 December 2018
PRAC members comments	N/A
Updated CHMP Rapporteur Assessment Report	N/A
Request for supplementary information (RSI)	13 December 2018
MAH's responses submitted on:	19 December 2018
PRAC Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	16 January 2019
CHMP members comments	21 January 2019
PRAC members comments	N/A
Updated Joint Assessment Report	25 January 2019
CHMP opinion:	31 January 2019

2. Scientific discussion

2.1. Introduction

Pembrolizumab

Keytruda (pembrolizumab) 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 currently authorised in the EU:

- as monotherapy for first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations

- as monotherapy 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.

- 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

In addition, Keytruda is approved for melanoma, refractory classical Hodgkin lymphoma, urothelial carcinoma and HNSCC.

Squamous Non-small cell lung cancer

In both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths) (Bray F et al. CA Cancer J Clin. 2018). NSCLC accounts for more than 80% of all lung cancer cases. Of the patients with NSCLC, tumour histology is approximately 40% to 60% adenocarcinoma, 10% to 15% squamous, 5% neuroendocrine, and the rest, "not otherwise specified". Squamous NSCLC is a malignant epithelial tumour that shows either keratinisation and/or intercellular bridges. Over the last decades, in Europe squamous NSCLC decreased while adenocarcinoma has increased in men, while in women both squamous NSCLC and adenocarcinoma are still increasing (Forman D et al, IARC press 2013). Squamous NSCLC is most strongly associated with smoking in a dose-dependent manner, with nearly 90% of cases attributed to cigarette smoking.

Compared to non-squamous histologies, squamous disease presents at an older age and more advanced disease stage at diagnosis, and is also associated with a higher incidence of comorbidities such as COPD and heart disease. Squamous NSCLC is usually centrally located, typically arising in the proximal bronchi and as a consequence more likely to invade large blood vessels (Socinski et al, J Thor Oncol 2017).

A new edition of the AJCC Cancer Staging Manual (8th Edition) was published in late 2016 and will be effective for all cancer cases recorded on or after 1st Jan 2018. With the AJCC staging, locally advanced disease is stage III, advanced disease is stage IV (NCCN NSCLC guidelines 6.2018).

Cytology may be sufficient to distinguish adenocarcinomas from squamous cell carcinoma. In those cases where specific subtyping is not possible by morphology alone, a limited panel of IHC is recommended to determine the subtype: TTF1 positivity is associated with probable diagnosis of adenocarcinoma, p40 positivity with probable diagnosis of squamous NSCLC (ESMO Metastatic NSCLC Guidelines 2018).

Squamous NSCLC 1st line treatment

Molecular testing (EGFR, ALK) is not recommended in patients with squamous NSCLC due to the very low incidence of mutation, except in those rare circumstances when squamous cell cancer is identified in a never-, long-time ex- or light-smoker (<15 pack/years) (ESMO Metastatic NSCLC Guidelines 2018). In addition, in case of mixed histology (adenosquamous), the presence of any adenocarcinoma component in a biopsy specimen that is otherwise squamous should trigger molecular testing (NCCN NSCLC guidelines 6.2018).

Pembrolizumab monotherapy is considered a standard first-line treatment option for NSCLC patients with ≥50% PD-L1 Tumour Proportion Score (TPS) with no EGFR or ALK positive tumour mutations who do not otherwise have contraindications to the use of immunotherapy, including squamous histology (ESMO Metastatic NSCLC Guidelines 2018). The pivotal KEYNOTE-024 study leading to the approval of pembrolizumab in 1st line tested pembrolizumab vs platinum-based doublet chemotherapy (including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin; non-squamous patients could receive pemetrexed maintenance) in NSCLC with PD-L1 TPS ≥50%. The study included 18% of squamous cell lung cancer patients (i.e. 29 vs 27 subjects in pembro vs chemo arm). In the squamous subgroup, PFS HR was 0.35 (95%CI 0.17-0.71) (Reck M et al,

NEJM 2016). A variation to extend the first line indication of pembrolizumab in NSCLC with TPS ≥1% is currently under EMA review, based on the result of KEYNOTE-042 study (EMEA/H/C/003820/II/0057 procedure).

Most individual trials and meta-analyses evaluating chemotherapy options in the first-line treatment of advanced NSCLC did not report any differential efficacy in patients with squamous NCSLC. Therefore, platinum-based (cisplatin/carboplatin) doublets with the addition of a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced squamous cell cancer patients without major comorbidities and PS 0-2 (ESMO Metastatic NSCLC Guidelines 2018). Notably, pemetrexed is not indicated in squamous cell carcinoma of the lung. No particular platinum-based doublet regimen has been proved to confer a clinically significant advantage over the others, choice often being based on safety profile. The addition of a third chemotherapy agent is not recommended. No effective maintenance strategies are available in squamous NSCLC (Daaboul N, Curr Oncol 2018). Neither a large individual trial nor a meta-analysis found an overall survival benefit of six versus fewer cycles of first-line platinum-based doublets, although a longer PFS coupled with higher toxicity was reported in patients receiving six cycles (Rossi A, Lancet Oncol 2014). Therefore, four up to six cycles are currently recommended (ESMO Metastatic NSCLC Guidelines 2018).

Albumine-bound paclitaxel (nab-paclitaxel) is considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication (i.e. dexamethasone, H1 and H2 blockers) (ESMO Metastatic NSCLC Guidelines 2018, Ann Oncol 2016; NCCN NSCLC guidelines 6.2018). The randomized phase III study CA031 compared carboplatin + nab-paclitaxel vs carboplatin + paclitaxel, with primary efficacy endpoint ORR based on the blinded radiological review. The null hypothesis of this study was that the Abraxane/carboplatin regimen response rate was non-inferior to that of the paclitaxel/carboplatin. A non-inferior efficacy of Abraxane/carboplatin as for Taxol/carboplatin combination therapy for the treatment of NSCLC was showed. Abraxane/carboplatin combination had lower neurotoxicity but higher haematologic toxicity compared to Taxol/carboplatin (EPAR Abraxane II/67; Socinsky et al, JCO 2012). Abraxane in combination with carboplatin is indicated for the first-line treatment of NSCLC in adult patients who are not candidates for potentially curative surgery and/or radiation therapy (Abraxane SmPC).

Table 1: Summary of recent clinical studies with platinum-based chemotherapy in first-line metastatic squamous NSCLC

Study Name	Treatment Arms	N	ORR (%)	PFS (months)	HR (PFS) (95% CI)	OS (months)	HR (OS) (95% CI)
Socinski et al [Ref. 5.4: 03NGVX]	**All comers**						
	Carboplatin/nab-paclitaxel	521	33	6.3	0.902 (0.767, 1.060)	12.1	0.922 (0.797, 1.066)
	Carboplatin/paclitaxel	531	25	5.8		11.2	
	Squamous						
	Carboplatin/nab-paclitaxel	229	41	5.6	0.865	10.7	0.890 (0.719, 1.101)
	Carboplatin/paclitaxel	221	24	5.7		9.5	
Scagliotti et al [Ref. 5.4: 00VSVP]	**All comers**						
	Cisplatin/pemetrexed	862	30.6	4.8	1.04 (0.94, 1.15)	10.3	0.94 (0.84, 1.05)
	Cisplatin/gemcitabine	863	28.2	5.1		10.3	
	Squamous						
	Cisplatin/pemetrexed	244		4.4	1.36 (1.12, 1.65)	9.4	1.23 (1.00, 1.51)
	Cisplatin/gemcitabine	229		5.5		10.8	
SQUIRE [Ref. 5.4: 04C5NH]	**Squamous**						
	Necitumumab/cisplatin/gemcitabine	545	31	5.7	0·85 (0.74, 0.98)	11.5	0·84 (0.74, 0.96)
	Cisplatin/gemcitabine	548	29	5.5		9.9	

In EGFR expressing squamous NSCLC who have not received prior chemotherapy, necitumumab is indicated in combination with gemcitabine and cisplatin chemotherapy (EPAR Portrazza). The addition of necitumumab to cisplatin/gemcitabine has not been adopted as a standard in Europe for advanced squamous NSCLC and its use should be carefully evaluated (ESMO Metastatic NSCLC Guidelines 2018). The addition of necitumumab to the regimen cisplatin/gemcitabine was felt by NCCN Panel not beneficial based on toxicity, cost and limited improvement in efficacy vs chemotherapy alone (NCCN NSCLC guidelines 6.2018).

The following indication was adopted by the CHMP:

"KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults."

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

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), an ERA justifying the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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

Table 2: Clinical trial supporting the application

Trial ID	Phase	Country / Region	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
P407V01MK3475 [Ref. 5.3.5.1: P407V01MK3475] - nsclc6	3	Australia, Canada, China, France, Germany, Hungary, Italy, Japan, South Korea, Mexico, Netherlands, Poland, Russia, Spain, Thailand, Turkey, USA	A Randomized, Double Blind, Phase III Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non small Cell Lung Cancer Subjects (KEYNOTE-407)	Multicenter, randomized, parallel assignment, double blind, placebo controlled intervention study	Pembrolizumab Combination: Pembrolizumab 200 mg (Day 1) + carboplatin AUC 6 mg/mL/min (D1) + paclitaxel 200 mg/m2 (D1) OR nab-paclitaxel 100 mg/m2 (D1, D8, D15) Q3W for 4 cycles followed by pembrolizumab 200 mg (D1) Q3W until progression. Control: Saline placebo + carboplatin AUC 6 mg/mL/min (D1) + paclitaxel 200 mg/m2 (D1) OR nab - paclitaxel 100 mg/m2 (D1, D8, D15) Q3W for 4 cycles followed by saline placebo (D1) Q3W until progression.	Male and female participants ≥18 years of age with metastatic squamous non-small cell lung cancer (NSCLC) who have not previously received systemic therapy for metastatic disease.	As of 03-APR-2018: Pembrolizumab Combination (n=278) Control (n=280)

2.3.2. Pharmacokinetics

No new PK and immunogenicity data for pembrolizumab have been provided as part of this application. A description of the clinical pharmacology of pembrolizumab in subjects with previously untreated metastatic NSCLC was included in variation EMEA/H/C/003820/II/0048 (Commission Decision issued on 02 August 2018) to support 200 mg Q3W as the recommended dose of pembrolizumab in this patient population.

In addition, a description of the pharmacology of pembrolizumab in combination with chemotherapy was included as part of variation Keytruda/H/C/003820/II/43 (Commission Decision issued on 04 September 2018). This analysis demonstrated that the PK and immunogenicity of pembrolizumab are not impacted by concomitant chemotherapy.

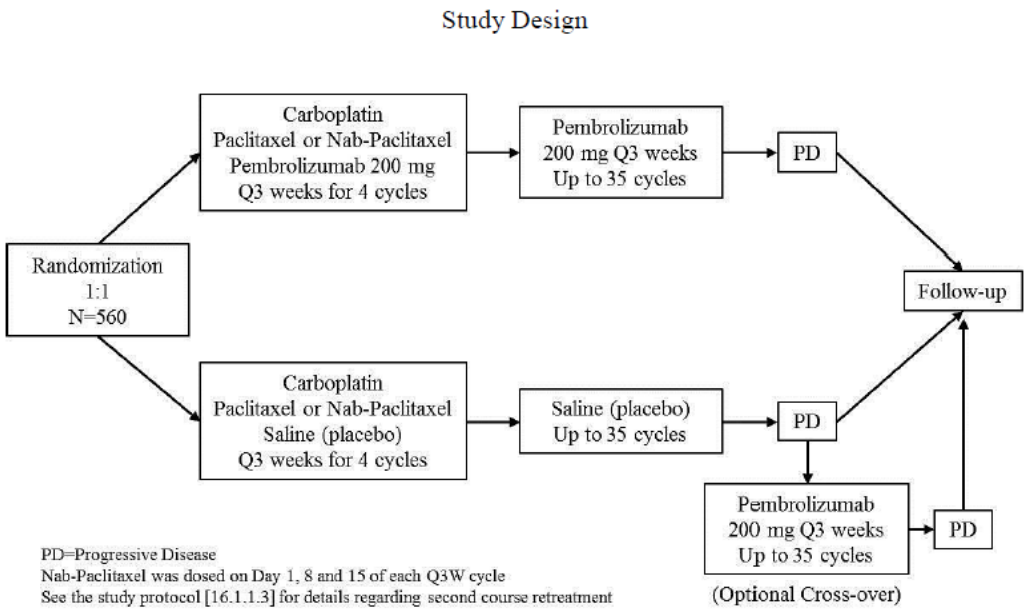
2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No specific dose-response study was conducted.

2.4.2. Main study

A Randomized, Double-Blind, Phase III Study of Carboplatin - Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)



Methods

Study participants

Key inclusion criteria included:

1. Had a histologically or cytologically confirmed diagnosis of Stage IV (M1a or M1b-AJCC 7th edition) squamous NSCLC. Patients with mixed histology (example adenosquamous) were allowed if there was squamous component in the specimen.

2. Had measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment.

3. Had not received prior systemic treatment for their metastatic NSCLC. Subjects who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease.

4. Had provided tumour tissue for determination of PD-L1 status prior to randomization.

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

6. Had an ECOG performance status of 0 or 1.

7. Had adequate organ function.

Key exclusion criteria included:

1. Had received 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.

2. Had received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of study treatment.

3. Had completed palliative radiotherapy within 7 days of the first dose of study treatment.

4. Had known active (ie, symptomatic) central nervous system (CNS) metastases and/or carcinomatous meningitis. (Subjects with previously treated brain metastases may participate if clinically stable for at least 2 weeks, no evidence of new or enlarging brain metastases and off steroids 3 days prior to dosing. Subjects with asymptomatic brain metastases (i.e., no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but require regular imaging of the brain as a site of disease).

5. Had pre-existing peripheral neuropathy that was ≥Grade 2 by CTCAE version 4 criteria.

6. Had active autoimmune disease that had required systemic treatment in the past 2 years.

7. Was on chronic systemic steroids. Participants who required intermittent use of bronchodilators, inhaled steroids, or local steroid injections were not excluded.

8. Had prior treatment targeting PD-1, PD-L1/PD-L2, or other immune-regulatory receptors or mechanisms.

9. Had an active infection requiring therapy.

10. Had interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management.

Treatments

Treatment Groups	Unit Dose and Frequency	Route of Administration
Pembro combo	Pembrolizumab 200 mg (Day 1) + carboplatin AUC 6 mg/mL/min (D1) + paclitaxel 200 mg/m2 (D1) OR nab-paclitaxel 100 mg/m2 (D1, D8, D15) Q3W for 4 cycles followed by pembrolizumab 200 mg (D1) Q3W until progression (up to a total of 35 cycles).	iv infusion
Control	Saline placebo + carboplatin AUC 6 mg/mL/min (D1) + paclitaxel 200 mg/m2 (D1) OR nab -paclitaxel 100 mg/m2 (D1, D8, D15) Q3W for 4 cycles followed by saline placebo (D1) Q3W until progression (up to a total of 35 cycles).	iv infusion

Pembrolizumab/Normal Saline to be administered prior to chemotherapy.
Investigator's choice of either paclitaxel or nab paclitaxel. Carboplatin dose should not to exceed 900 mg.

Treatment with pembrolizumab or placebo continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (BICR), unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients in the placebo arm were offered pembrolizumab as a single agent at the time of disease progression.

Objectives

Primary objectives:

- To evaluate PFS per RECIST 1.1, as assessed by BICR in participants treated with the pembro combo compared with the control.

- To evaluate OS in participants treated with the pembro combo compared with the control.

Secondary objectives:

- To evaluate ORR and DOR per RECIST 1.1, as assessed by BICR in participants treated with the pembro combo compared with the control.

- To evaluate the safety and tolerability profile of the pembro combo treatment.

Outcomes/endpoints

Dual primary endpoint:

- PFS defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first.

- OS defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis were censored at the date of last known contact.

Secondary endpoints:

- ORR defined as the proportion of participants who had a complete response (CR) or a partial response (PR).

- DOR defined as the time from first documented evidence of CR or PR until disease progression or death.

- Toxicities as defined by CTCAE v4.0

Exploratory Objectives

1. Evaluate the pembro combo compared with the control with respect to:

    a. PFS per RECIST 1.1, as assessed by investigator review in the next line of therapy (PFS2)

    b. PFS per irRECIST, as assessed by site investigator

    c. ORR and DOR per irRECIST, as assessed by site investigator

    d. PFS and ORR per RECIST 1.1 as assessed by central imaging vendor and OS by PD-L1 status (≥1% vs <1%) and by taxane (investigator's choice of paclitaxel or nab-paclitaxel)

2. To investigate the relationship between the pembro combo treatment and biomarkers predicting response (eg, PD-L2, genetic variation, serum sPD-L1) utilizing newly obtained or archival FFPE tumour tissue and blood, including serum and plasma.

3. To evaluate changes in health-related quality-of-life assessments from baseline in the overall study population and by PD-L1 expression level using the EORTC QLQ-C30 and EORTC QLQ-LC13.

4. To characterize utilities in participants treated with the pembro combo compared with the control using the EuroQoL(EQ)-5D.

5. To characterize the pharmacokinetic characteristics of carboplatin, paclitaxel or nab-paclitaxel, and pembrolizumab.

6. To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments

Imaging assessment

Initial tumour imaging at screening had to be performed within 28 days prior to the date of randomization. The site study team had to review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images had to be submitted to the central imaging vendor for retrospective confirmation of eligibility.

The imaging assessments were performed at approximately Week 6, Week 12, and Week 18 from the date of randomization. Subsequent tumour imaging was performed approximately every 9 weeks or more frequently if clinically indicated. After 45 weeks, imaging was performed every 12 weeks.

Sample size

With ~200 subjects, the study has ~ 84% power for detecting a 25% difference in ORR (50% vs 25%) or ~ 97% power for detecting a 30% difference in ORR (50% vs. 20%) at initially assigned 0.005 (one-sided) significance level. The study has ~ 94% power for detecting a 25% difference in ORR (50% vs 25%) or ~ 99% power for detecting a 30% difference in ORR (50% vs 20%) at 0.025 (one-sided) significance level.

With 415 PFS events, the study has ~ 90% power for detecting a HR of 0.7 at initially assigned 0.01 (one-sided) significance level, ~ 92% power for detecting a HR of 0.7 at 0.015 (one-sided) significance level, ~ 94% power for detecting a HR of 0.7 at 0.02 (one-sided) significance level, and ~ 95% power for detecting a HR of 0.7 at 0.025 (one-sided) significance level.

With 361 deaths, the study has ~ 85% power for detecting a hazard ratio (HR) of 0.7 at 0.01 (one-sided) significance level, ~ 90% power for detecting a HR of 0.7 at 0.02 (one-sided) significance level, and ~ 92% power for detecting a HR of 0.7 at 0.025 (one-sided) significance level.

The planned sample size is approximately 560 subjects assuming: (1) the enrollment period is 15.5 months and the ramp-up period of enrollment is 7 months; (2) median PFS is 6 months in the control group and the true hazard ratio is 0.7; (3) median OS is 12 months in the control group and the true hazard ratio is 0.7; (4) the annual dropout rate is 3% for PFS and 1% for OS; (5) the number of events and alpha levels of interim analyses and final analysis are as specified in the protocol.

Randomisation

Treatment allocation/randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Patients were randomized 1:1 to two treatment groups Stratification factors were:

- investigator's choice of chemotherapy regimen (paclitaxel vs nab-paclitaxel)

- PD-L1 status (TPS ≥1% vs <1%)

- geographic region of the enrolling site (East Asia vs non-East Asia)

The choice of paclitaxel or nab-paclitaxel treatment was determined prior to randomization.

Participants were required to provide tumour tissue for PD-L1 determination. However, enrollment was open to participants regardless of PD-L1 expression status.

Blinding (masking)

The study was double-blinded.

Statistical methods

The primary efficacy analysis was performed on intention-to-treat (ITT) population. The non-parametric Kaplan-Meier method was used to estimate the PFS and OS curve in each treatment group. The treatment difference in PFS and OS was assessed by the stratified log-rank test. For PFS and OS a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.

Sensitivity analyses were performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by a blinded independent central imaging vendor, sensitivity analyses with a different set of censoring rules was applied.

In case the proportional hazards assumption is not valid, supportive analyses using Restricted Mean Survival Time (RMST) method was planned for PFS and OS to account for the possible non-proportional hazards effect.

An exploratory analysis of PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, was planned.

Since subjects in the control arm are allowed to switch to the pembrolizumab treatment after progressive disease, adjustment for the effect of crossover on OS was planned based on recognized methods, e.g., a two-stage method or the Rank Preserving Structural Failure Time (RPSFT) model, based on an examination of the appropriateness of the data to the assumptions required by the methods.

The stratified Miettinen and Nurminen method was used for the comparison of the ORR between the two treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size with a single treatment covariate was reported. The stratification factors used for randomization were applied to the analysis.

If sample size permits, it was planned to summarize DOR descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who show a complete response or partial response will be included in this analysis.

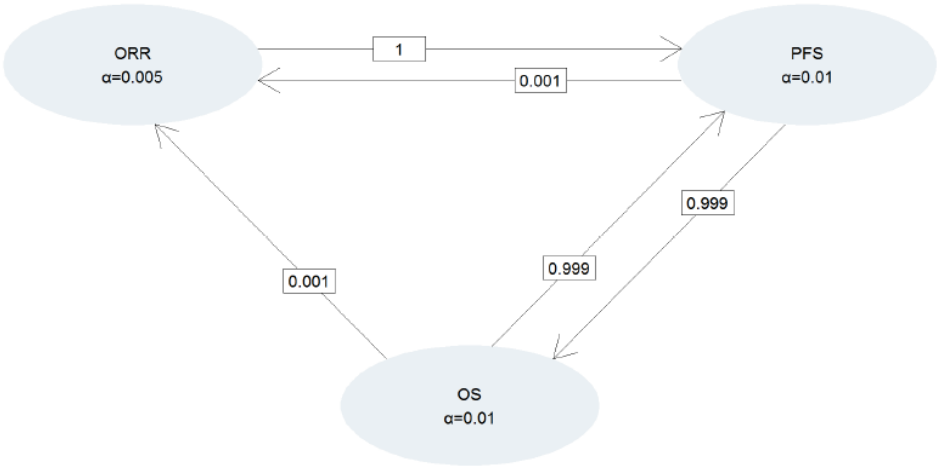
There are three planned interim analyses (IA) in addition to the final analysis for this study. The trial will continue until the number of death is approximately equal to the targeted number for the final analysis, irrespective of the outcome from the interim analyses. The analyses planned, endpoints evaluated, and drivers of timing are summarized in the table below:

Table 3: Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant	Primary Purpose of Analysis

IA1	ORR	~ 200 subjects are followed for ~ 28 weeks so that each patient has at least 4 tumour	~ 15 months	□ Demonstrate ORR superiority
IA2	PFS OS	~ 332 PFS events have been observed.	~ 20 months	□ Demonstrate PFS superiority □ Demonstrate OS superiority
IA3	PFS OS	~ 415 PFS events have been observed	~ 25 months	□ Demonstrate PFS superiority □ Demonstrate OS superiority
Final Analysis	OS	~ 361 deaths have occurred.	~ 31 months	□ Demonstrate OS superiority

The study uses the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests (see Figure below) shows the initial one-sided alpha allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.



Type I Error Reallocation Strategy Following Closed Testing Principle

The boundary properties for each of these alpha-levels for the interim analyses were derived using a Lan-DeMets O'Brien-Fleming spending function. If the OS null hypothesis is rejected at an interim or final analysis, each PFS interim and final analysis test may be compared to its updated bounds considering the alpha reallocation from the OS hypothesis.

The OS hypothesis may be tested at alpha=0.01 (initially allocated alpha), alpha=0.02 (if the PFS but not the ORR null hypothesis is rejected), or alpha=0.025 (if both the ORR and PFS null hypotheses are rejected).

Results

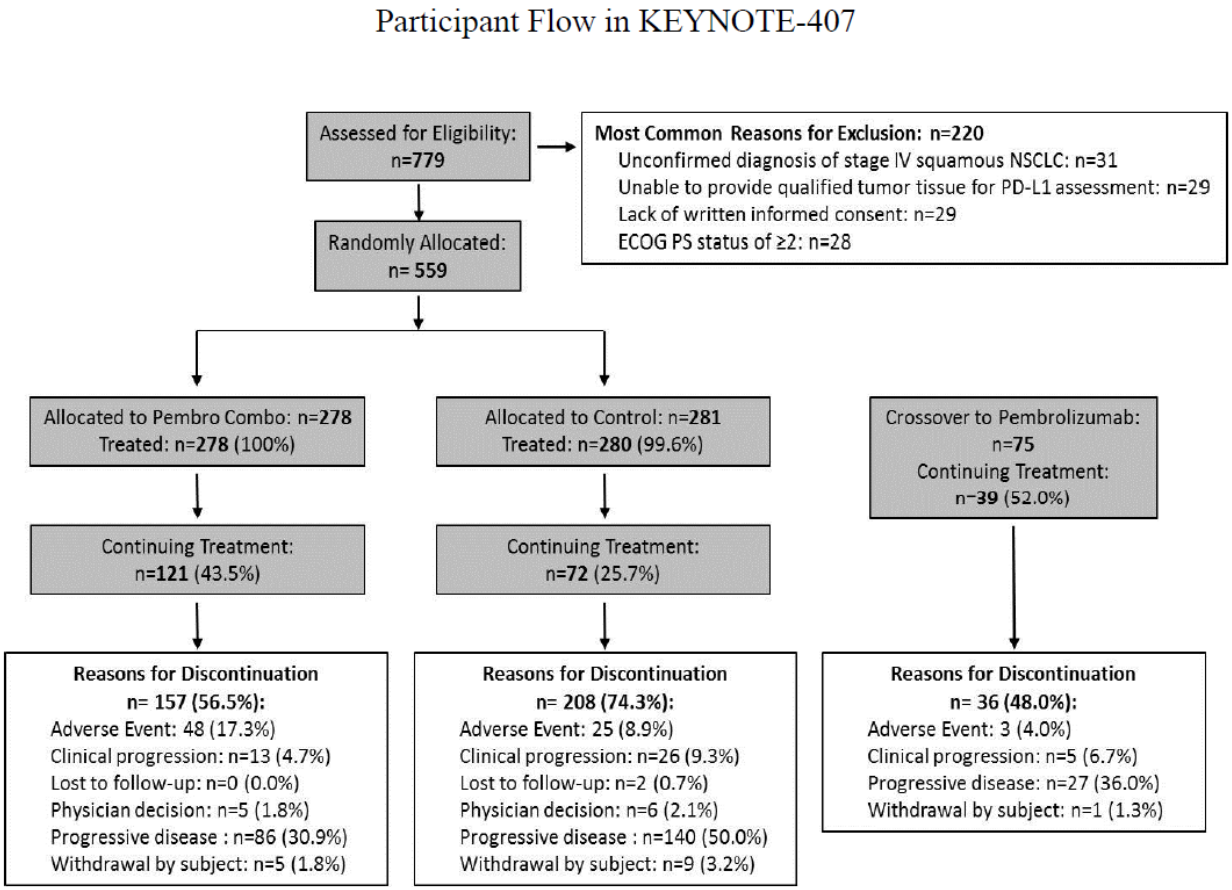
KEYNOTE-407 study is ongoing. The analyses reported in the submitted CSR were conducted using participants' data from the pre-specified **Interim Analysis 2** (IA2), and includes the evaluations of all primary and secondary objectives, as well as the following exploratory objectives:

1. PFS and ORR per RECIST 1.1 as assessed by central imaging vendor by PD-L1 status (≥1% vs <1%) and OS by PD-L1 status (≥1% vs <1%).
2. Changes in health-related quality-of-life assessments from baseline in the overall study population and by PD-L1 expression level using the EORTC QLQ-C30 and EORTC QLQ-LC13.

3. Utilities in participants treated with the pembro combo compared with the control using the EuroQoL(EQ)-5D.

The planned duration of KEYNOTE-407 is approximately 4 years. **Data cutoff date was 03-APR-2018**, at which time the overall median duration of follow-up was 7.8 months (range 0.1, 19.1).

Participant flow



Of the 220 participants who were assessed for eligibility, but not randomized in the study, 2 were due to physician decision and 218 were screen failures, the most frequent reasons being unconfirmed diagnosis of stage IV squamous NSCLC (14.3%), participant unable to provide qualified tumour tissue for PD-L1 assessment (13.4%) and lack of written informed consent (13.4%).

Table 4: Disposition of Subjects (ITT Population)

	Pembro Combo n (%)	Control n (%)
Subjects in population	278	281
Status for Study Medication of Treatment Phase		

Started	278	280
Discontinued	157 (56.5)	208 (74.3)
Adverse Event	48 (17.3)	25 (8.9)
Clinical Progression	13 (4.7)	26 (9.3)
Lost To Follow-Up	0 (0.0)	2 (0.7)
Physician Decision	5 (1.8)	6 (2.1)
Progressive Disease	86 (30.9)	140 (50.0)
Withdrawal By Subject	5 (1.8)	9 (3.2)
Ongoing[†]	121 (43.5)	72 (25.7)
Status for Study Medication of Crossover Phase		
Subjects who Crossed Over	0	75
Discontinued	0 (0.0)	36 (48.0)
Adverse Event	0 (0.0)	3 (4.0)
Clinical Progression	0 (0.0)	5 (6.7)
Progressive Disease	0 (0.0)	27 (36.0)
Withdrawal By Subject	0 (0.0)	1 (1.3)
Ongoing[‡]	0 (0.0)	39 (52.0)
Status for Trial		
Discontinued	86 (30.9)	126 (44.8)
Adverse Event	22 (7.9)	19 (6.8)
Death	61 (21.9)	99 (35.2)
Lost To Follow-Up	0 (0.0)	2 (0.7)
Physician Decision	0 (0.0)	1 (0.4)
Withdrawal By Subject	3 (1.1)	5 (1.8)
Ongoing[§]	192 (69.1)	155 (55.2)

[†] Status was not reported as of the cutoff date. Subjects could be ongoing with study treatment.
[‡] Status was not reported as of the cutoff date. Subjects could be ongoing with pembrolizumab monotherapy treatment.
[§] Status was not reported as of the cutoff date. Subjects could be ongoing with study.
For the status for study medication of treatment phase, subjects treated with study medication is used as the denominator for percentage calculation.
For the status for study medication of crossover phase, subjects who crossed over is used as the denominator for percentage calculation.
For the status for trial, subjects in population is used as the denominator for percentage calculation.
Database Cutoff Date: 03APR2018

Recruitment

The study was conducted at 125 centres in 17 countries worldwide. Patients were recruited from 19 Aug 2016 to 28 Dec 2017 (16 months).

Conduct of the study

Protocol amendments

The original protocol is dated 24 March 2016. Protocol amendments up to the cut-off date 3 April 2018 are presented below:

Table 5: Summary of Key Changes in Protocol Amendments

Amendment Nb	Global or Local	Date	Rationale and Key Changes
01	China	27-Jul-2017	• Extended the enrollment period to achieve the required numbers of participants and events to investigate the efficacy and safety in Chinese patients with NSCLC.

02	Global	26-Oct-2017	• Updated the statistical design for the evaluation of long term treatment effect in OS and PFS. • This amendment was never officially published
03	Global	13-Nov-2017	• Updated the statistical design to optimize the evaluation of long term treatment effect in OS and PFS.
04	China	20-Nov-2017	• Updated the statistical design to optimize the evaluation of long term treatment effect in OS and PFS.
Note: Table includes protocol amendments implemented up to the data cutoff date 03-APR-2018			

Primary reason for Amendment 3 (13 Nov 2017)

Description of changes: Alpha allocation scheme was updated. Added an interim analysis, extended the study duration and increased the number of PFS and OS events.

Rationale: The statistical design was updated to optimize the study for the identification of long term treatment effect in OS and PFS.

Protocol deviations

Subjects with important protocol deviations were 46 (16.5%) and 47 (16.7%) in pembro-combo and chemo arms, respectively.

Deviations were reported across the following categories:

- Discontinuation criteria (n=2 for pembro combo; n=0 for control)
- Inclusion/exclusion criteria (n=4 for pembro combo; n=5 for control)
- Informed consent form (n=3 for pembro combo; n=5 for control)
- Prohibited Medications (n=2 for pembro combo; n=7 for control)
- Safety reporting (n=16 for pembro combo; n=17 for control)
- Study intervention (n=15 for pembro combo; n=10 for control)
- Trial procedures (n=10 for pembro combo; n=6 for control)

Of these important protocol deviations, the MAH deemed 2 to be clinically significant. One participant (in the control group) was inadvertently administered blinded pembrolizumab/placebo for KEYNOTE-355 (another study open at the site) rather than the assigned placebo for KEYNOTE-407 on Day 1 of Cycle 1. The infusion was stopped after 10 minutes (approximately one third the planned dose) when the error was identified. Another participant incorrectly received placebo instead of pembrolizumab at Cycle 6 only. Both patients are included in the ITT analysis.

Unblinding

As of the data cutoff date, there were 2 participants who were inadvertently unblinded of their treatment assignment. Both unblinding events happened at the site level only, and had no impact on data analyses per evaluation by the Sponsor's Significant Quality Issues process. Therefore, these 2 participants were not excluded from the efficacy and safety analyses in IA2.

Baseline data

Table 6: Subject Characteristics (ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)

Subjects in population	278		281		559	
Gender						
Male	220	(79.1)	235	(83.6)	455	(81.4)
Female	58	(20.9)	46	(16.4)	104	(18.6)
Age (Years)						
< 65	127	(45.7)	127	(45.2)	254	(45.4)
>= 65	151	(54.3)	154	(54.8)	305	(54.6)
Mean	65.0		64.8		64.9	
SD	8.8		8.7		8.7	
Median	65.0		65.0		65.0	
Range	29 to 87		36 to 88		29 to 88	
Race						
American Indian Or Alaska Native	0	(0.0)	2	(0.7)	2	(0.4)
Asian	56	(20.1)	52	(18.5)	108	(19.3)
Black Or African American	3	(1.1)	4	(1.4)	7	(1.3)
Native Hawaiian Or Other Pacific Islander	1	(0.4)	0	(0.0)	1	(0.2)
White	216	(77.7)	214	(76.2)	430	(76.9)
Missing	2	(0.7)	9	(3.2)	11	(2.0)
Ethnicity						
Hispanic Or Latino	31	(11.2)	24	(8.5)	55	(9.8)
Not Hispanic Or Latino	237	(85.3)	245	(87.2)	482	(86.2)
Not Reported	7	(2.5)	9	(3.2)	16	(2.9)
Unknown	3	(1.1)	3	(1.1)	6	(1.1)
Geographic Region						
US	13	(4.7)	22	(7.8)	35	(6.3)
Ex US	265	(95.3)	259	(92.2)	524	(93.7)
Geographic Region						
East-Asia	54	(19.4)	52	(18.5)	106	(19.0)
Non-East Asia	224	(80.6)	229	(81.5)	453	(81.0)
Geographic region						
EU	125	(45.0)	115	(40.9)	240	(42.9)
Non-EU	153	(55.0)	166	(59.1)	319	(57.1)
Smoking Status						
Never Smoker	22	(7.9)	19	(6.8)	41	(7.3)
Former Smoker	174	(62.6)	199	(70.8)	373	(66.7)
Current Smoker	82	(29.5)	63	(22.4)	145	(25.9)
ECOG						
0	73	(26.3)	90	(32.0)	163	(29.2)
1	205	(73.7)	191	(68.0)	396	(70.8)
Histology						
Squamous	272	(97.8)	274	(97.5)	546	(97.7)
Adenosquamous	6	(2.2)	7	(2.5)	13	(2.3)
Metastatic Stage						
M1A	111	(39.9)	107	(38.1)	218	(39.0)
M1B	167	(60.1)	174	(61.9)	341	(61.0)
Brain Metastasis Status at Baseline						
Yes	20	(7.2)	24	(8.5)	44	(7.9)
No	258	(92.8)	257	(91.5)	515	(92.1)

Baseline Tumour Size						
Subjects with data	273		279		552	
Mean	112.47		107.24		109.83	
SD	71.84		66.69		69.27	
Median	94.50		94.10		94.20	
Range	13.3 to 424.3		10.3 to 376.5		10.3 to 424.3	
PD-L1 Status (Cut Point: 1%)						
TPS < 1%	95	(34.2)	99	(35.2)	194	(34.7)
TPS >= 1%	176	(63.3)	177	(63.0)	353	(63.1)
Unknown	7	(2.5)	5	(1.8)	12	(2.1)
PD-L1 Status (Cut Point: 1% and 50%)						
TPS < 1%	95	(34.2)	99	(35.2)	194	(34.7)
TPS 1-49%	103	(37.1)	104	(37.0)	207	(37.0)
TPS >= 50%	73	(26.3)	73	(26.0)	146	(26.1)
Unknown	7	(2.5)	5	(1.8)	12	(2.1)
Taxane Chemotherapy						
+Paclitaxel	169	(60.8)	167	(59.4)	336	(60.1)
+Nab-Paclitaxel	109	(39.2)	114	(40.6)	223	(39.9)
Prior Adjuvant/Neo-adjuvant Therapy						
Yes	5	(1.8)	8	(2.8)	13	(2.3)
No	273	(98.2)	273	(97.2)	546	(97.7)
Prior Radiation						
Yes	35	(12.6)	38	(13.5)	73	(13.1)
No	243	(87.4)	243	(86.5)	486	(86.9)
Prior Thoracic Radiation						
Yes	17	(6.1)	22	(7.8)	39	(7.0)
No	261	(93.9)	259	(92.2)	520	(93.0)
Database Cutoff Date: 03APR2018						

Numbers analysed

The ITT Population (all randomized subjects) was used for all efficacy analyses.

Table 7: Study population

	Pembro Combo	Control	Total
Number of Subjects Screened			779
Number of Subjects Randomized (Planned Treatment) (ITT)	278	281	559
Number of Subjects Received Treatment (Actual Treatment) (ASaT)	278	280	558
Number of Subjects Randomized and Did not Receive Treatment	0	1	1
Number of Subjects Discontinued Study Medication† (Actual Treatment)	157	133	290
Number of Subjects Crossed Over to Pembrolizumab		75	75

†Excluded Subjects who crossed over to Pembrolizumab.
Database Cutoff Date: 03APR2018.

Outcomes and estimation

The dual primary efficacy endpoints were OS and PFS per RECIST 1.1 by BICR. The secondary endpoints included ORR and DOR per RECIST 1.1.

The median follow-up time for participants was 8.3 months (range: 0.4 to 18.9 months) in the pembro combo and 7.4 months (range: 0.1 to 19.1 months) in the control at the cut-off date 3 Apr 2018.

Assessment of tumour status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter.

Overall survival

OS events occurred at 3 Apr 2018 cut-off date were 205 (37% of the overall population, 57% of the final planned 361 OS events).

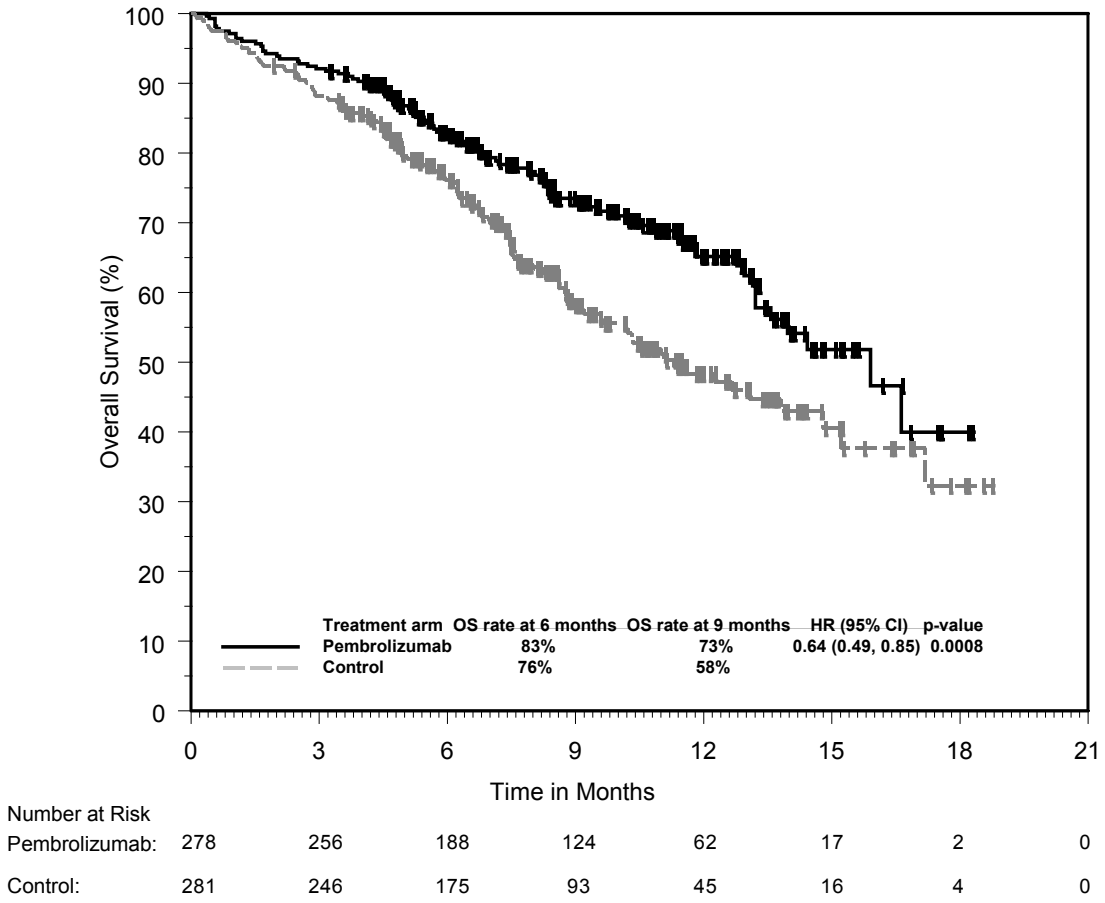


Figure 1: Kaplan-Meier Estimates of Overall Survival (ITT Population) – Data cut: 3 April 2018

Table 8: 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	278	85 (30.6)	2362.3	3.6	15.9 (13.2, .)	82.6 (77.4, 86.6)	0.64 (0.49, 0.85)	0.0008
Control	281	120 (42.7)	2160.0	5.6	11.3 (9.5, 14.8)	76.1 (70.5, 80.8)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Progression Free Survival (based on BICR by RECIST 1.1)

A total of 349 PFS events (62% of the overall population) occurred at 3 Apr 2018 cut-off date.

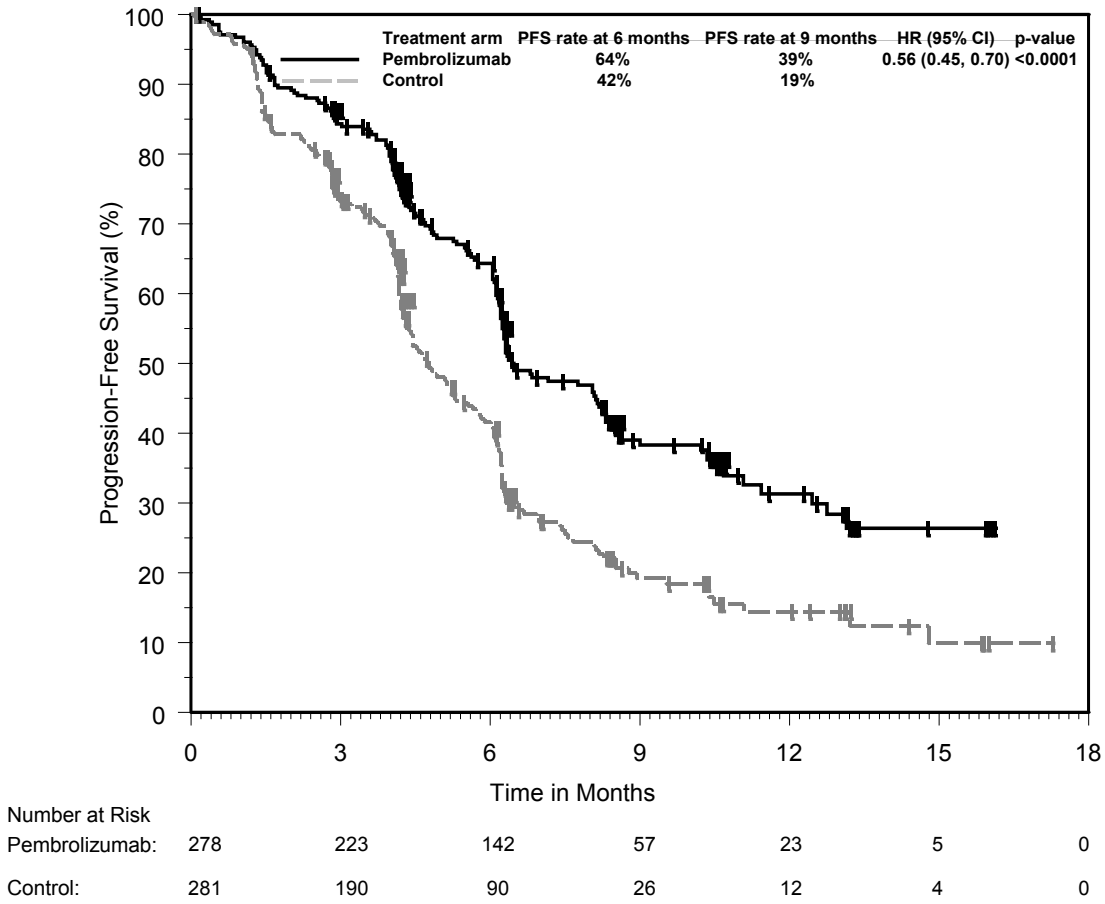


Figure 2: Kaplan-Meier Estimates of Progression-Free-Survival (PrimaryAnalysis) based on BICR Assessment per RECIST 1.1 (ITT Population) – Data cut: 3 April 2018

Table 9: Analysis of Progression-Free Survival (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	278	152 (54.7)	1716.9	8.9	6.4 (6.2, 8.3)	64.3 (58.0, 69.9)	0.56 (0.45, 0.70)	<0.0001
Control	281	197 (70.1)	1358.1	14.5	4.8 (4.3, 5.7)	41.6 (35.3, 47.7)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Table 10: Summary of PFS Rate Over Time Based on BICR per RECIST 1.1 (ITT Population)

	Pembro Combo (N=278) % (95% CI)†	Control (N=281) % (95% CI)†
Summary of PFS rate at time point		
6 months	64.3 (58.0, 69.9)	41.6 (35.3, 47.7)
9 months	39.0 (32.4, 45.6)	19.2 (13.9, 25.0)
12 months	31.3 (24.1, 38.7)	14.4 (9.4, 20.5)

† From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded independent central review.
Database cutoff date: 03APR2018

PFS based on investigator assessment per RECIST 1.1 was HR=0.55 (95%CI 0.45, 0.68; p<0.0001).

PFS based on BICR Assessment per RECIST 1.1 Sensitivity Analyses 1: HR=0.54 (95%CI 0.44, 0.68); PFS Sensitivity Analysis 2: HR=0.59 (0.49, 0.73).

Objective Response (confirmed, based on BICR by RECIST 1.1)

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	278	161	57.9 (51.9,63.8)	19.5 (11.2,27.5)	<0.0001
Control	281	108	38.4 (32.7,44.4)		

[†] Based on Miettinen & Nurminen method stratified by PD-L1 status (TPS ≥ 1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
[††] 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: 03APR2018

Table 12: Summary of Objective Response (Confirmed) based on BICR Assessment per RECIST 1.1 (ITT Population)

	Pembro Combo			Control		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	278			281		
Complete Response (CR)	4	1.4	(0.4, 3.6)	6	2.1	(0.8, 4.6)
Partial Response (PR)	157	56.5	(50.4, 62.4)	102	36.3	(30.7, 42.2)
Overall Response (CR+PR)	**161**	**57.9**	**(51.9, 63.8)**	**108**	**38.4**	**(32.7, 44.4)**
Stable Disease (SD)	78	28.1	(22.9, 33.7)	104	37.0	(31.4, 42.9)
Disease Control (CR+PR+SD)	**239**	**86.0**	**(81.3, 89.8)**	**212**	**75.4**	**(70.0, 80.4)**
Progressive Disease (PD)	17	6.1	(3.6, 9.6)	39	13.9	(10.1, 18.5)
Not Evaluable (NE)	6	2.2	(0.8, 4.6)	7	2.5	(1.0, 5.1)
No Assessment	16	5.8	(3.3, 9.2)	23	8.2	(5.3, 12.0)

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 03APR2018.

ORR (confirmed) based on Investigator assessment per RECIST 1.1 was 55% (95%CI 49, 61) vs 31.7% (95%CI 26.3, 37.5), with 153 vs 89 objective responses, in pembro combo vs control, respectively.

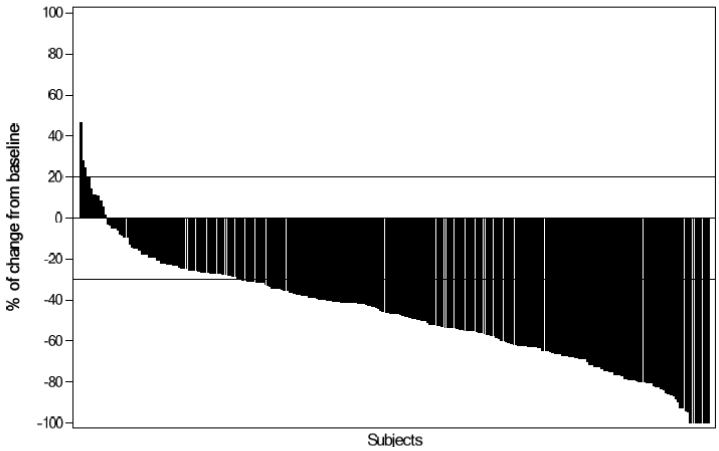


Figure 3: Waterfall Plot of Maximum Tumour Change from Baseline in Pembro Combo Arm based on BICR Assessment per RECIST 1.1 (ITT Population-Subjects with Measurable Disease at Baseline and at Least One Post-baseline Measurement) – Data cut: 3 April 2018

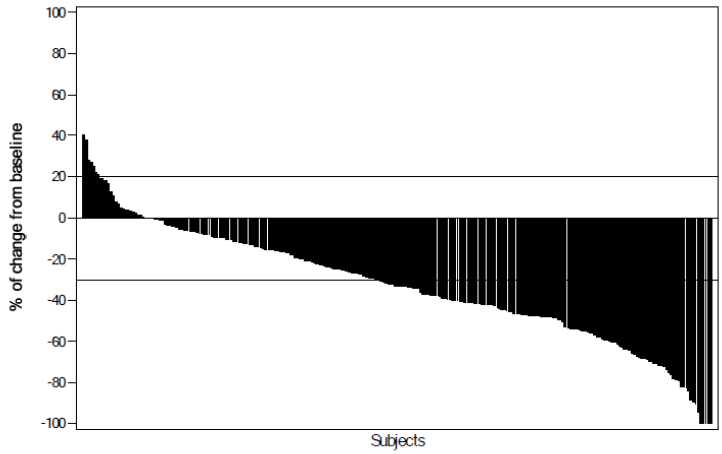


Figure 4: Waterfall Plot of Maximum Tumour Change from Baseline in Control Arm based on BICR Assessment per RECIST 1.1 (ITT Population-Subjects with Measurable Disease at Baseline and at Least One Post-baseline Measurement) – Data cut: 3 April 2018

Duration of Response

Table 13: Summary of Time to Response and Duration of Response Based on BICR Assessment per RECIST 1.1 (ITT Population - Subjects with Confirmed Response)

	Pembro Combo (N=278)	Control (N=281)
Number of Subjects with Response[†]	161	108
Time to Response[†] (months)		
Mean (SD)	1.9 (0.9)	1.7 (0.7)
Median (Range)	1.4 (1.1-6.1)	1.4 (1.0-4.5)
Response Duration[‡] (months)		
Median (Range)[§]	7.7 (1.1+ - 14.7+)	4.8 (1.3+ - 15.8+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥ 3 months	120 (86.3)	69 (76.9)
≥ 6 months	65 (61.8)	25 (40.4)
≥ 9 months	27 (46.5)	10 (33.6)
≥ 12 months	5 (39.1)	3 (30.2)

[†] 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.
NR = Not Reached.
BICR = Blinded independent central review.
Database Cutoff Date: 03APR2018

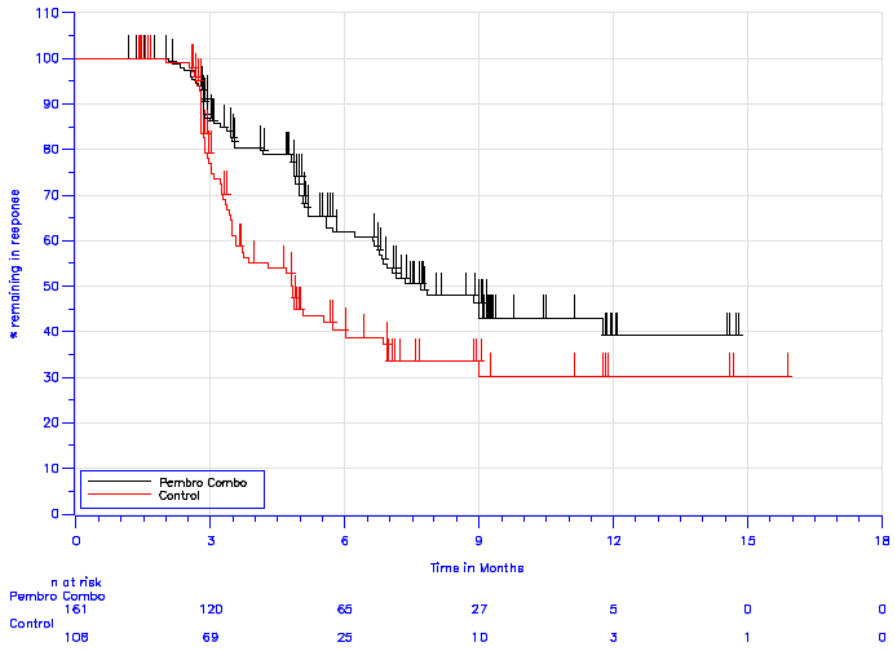


Figure 5: Kaplan-Meier Estimates of Duration of Response Based on BICR Assessment per RECIST 1.1 (ITT Population - Subjects with Confirmed Response) – Data cut: 3 April 2018

Median duration of response based on investigator assessment per RECIST 1.1 was 7.3 (range 1.1+ - 14.5+) vs 4.9 (1.2+ - 14.6+) months in pembro combo vs control, respectively.

Patients Reported Outcomes

Three PRO questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L) were used. All PRO endpoints were analysed up to Week 18.

Compliance rates for the EORTC QLQ-C30 at baseline until Week 18 were in a range from 79.0% through 95.0% in both treatment groups. The compliance rate for EORTC QLQ-LC13 and EQ-5D-3L were consistent with that for EORTC QLQ-C30. Completion rates decreased at each time point as more participants discontinued the study treatment.

Table 14: Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 9 - FAS Population

	Baseline		Week 9		Change from Baseline at Week 9	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembro Combo	254	63.91 (20.441)	187	65.95 (18.540)	276	1.76 (-0.86, 4.37)
Control	264	62.69 (21.323)	199	62.10 (19.600)	278	-1.84 (-4.40, 0.71)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	3.60 (0.28, 6.92)	0.0337

† 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%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia)) as covariates.
For baseline and Week 9, 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: 03APR2018

Table 15: Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 18 - FAS Population

	Baseline		Week 18		Change from Baseline at Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembro Combo	254	63.91 (20.441)	191	68.85 (19.317)	276	4.28 (1.65, 6.91)
Control	264	62.69 (21.323)	162	65.17 (17.149)	278	-0.57 (-3.34, 2.20)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	4.85 (1.40, 8.30)	0.0060

† 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%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia)) as covariates.
For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
P-value is based on two-sided t test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adplda]

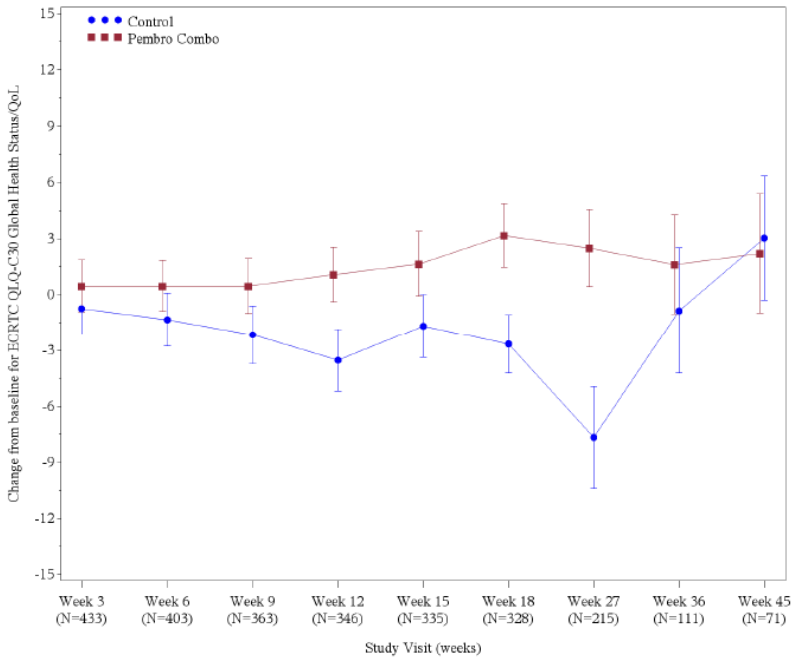


Figure 6: Summary of change from baseline for EORTC QLQ-C30 Global Health Status/QoL by Study Visit (Mean +/- SE) - FAS Population – Data cut: 3 April 2018

Table 16: Time to True Deterioration for Cough (LC13-Q1) Chest Pain (LC13-Q10) or Dyspnea (C30-Q8) - FAS Population

Treatment	N	True Deterioration Events(%)	Pembrolizumab vs. Control	
			Hazard Ratio[§](95% CI)[‡]	p-Value[§]
Pembro Combo	276	81 (29.3)	0.79 (0.58, 1.06)	0.125
Control	278	94 (33.8)	---	---

True deterioration is defined as the time to first onset of 10 or more increase 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%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
[‡] Two-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adttd]

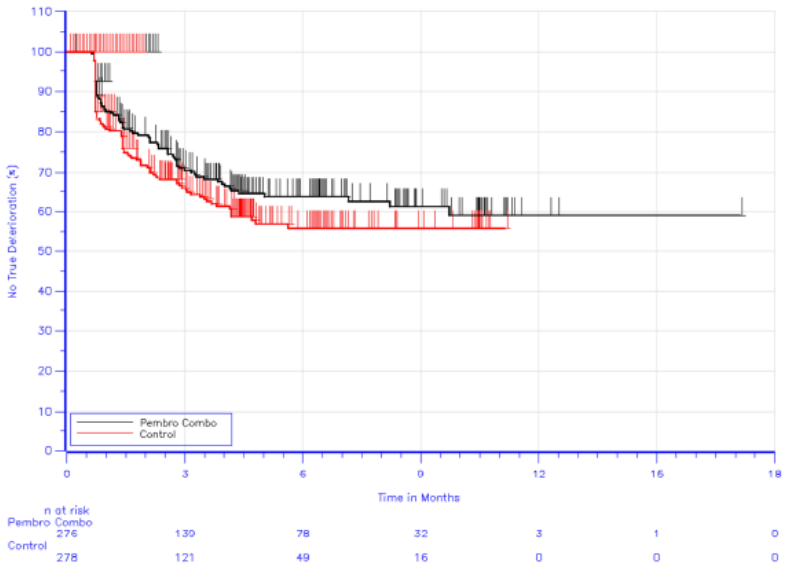
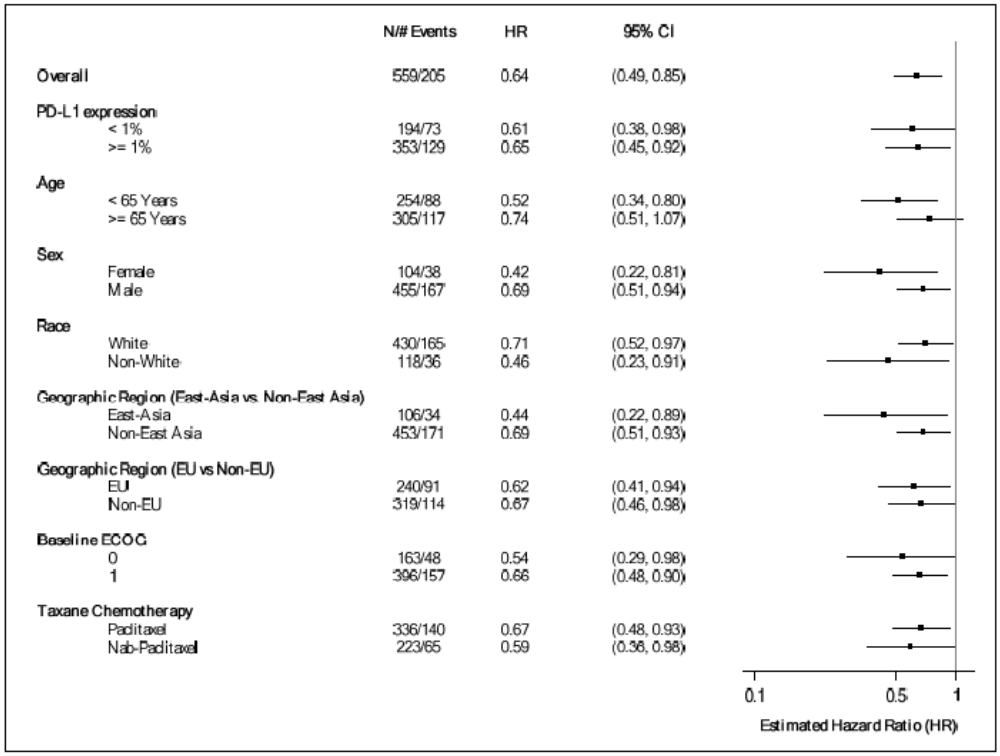


Figure 7: Time to True Deterioration for Cough (LC13-Q1) Chest Pain (LC13-Q10) or Dyspnea (C30-Q8) - FAS Population – Data cut: 3 April 2018

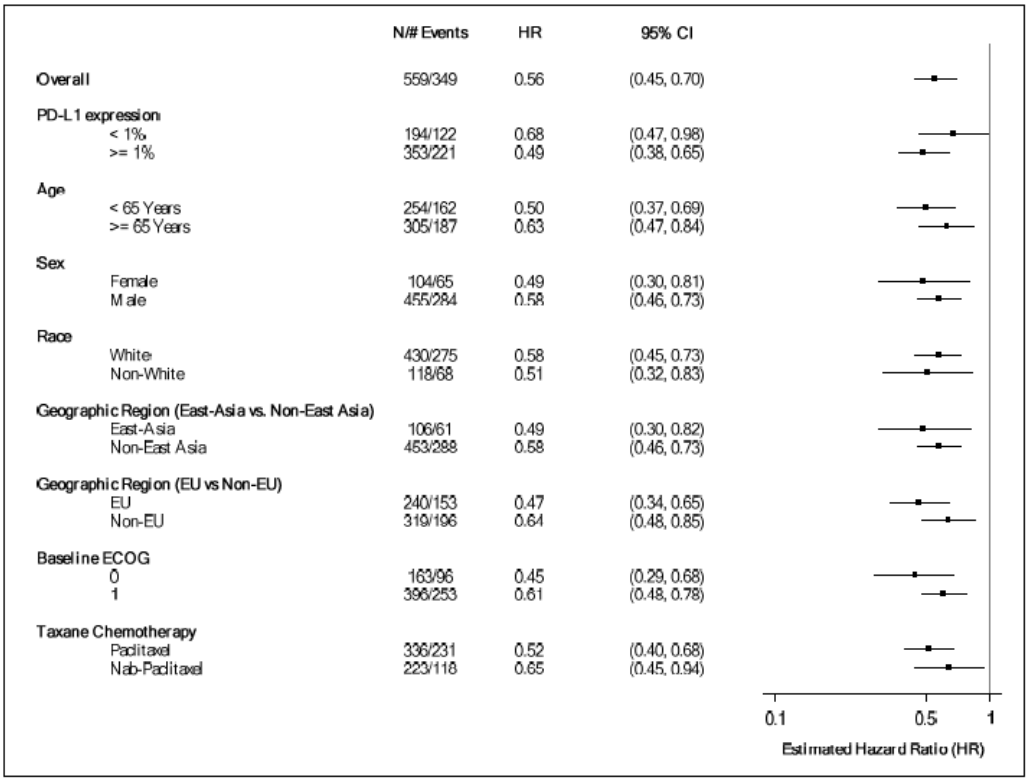
Ancillary analyses

Subgroup analyses



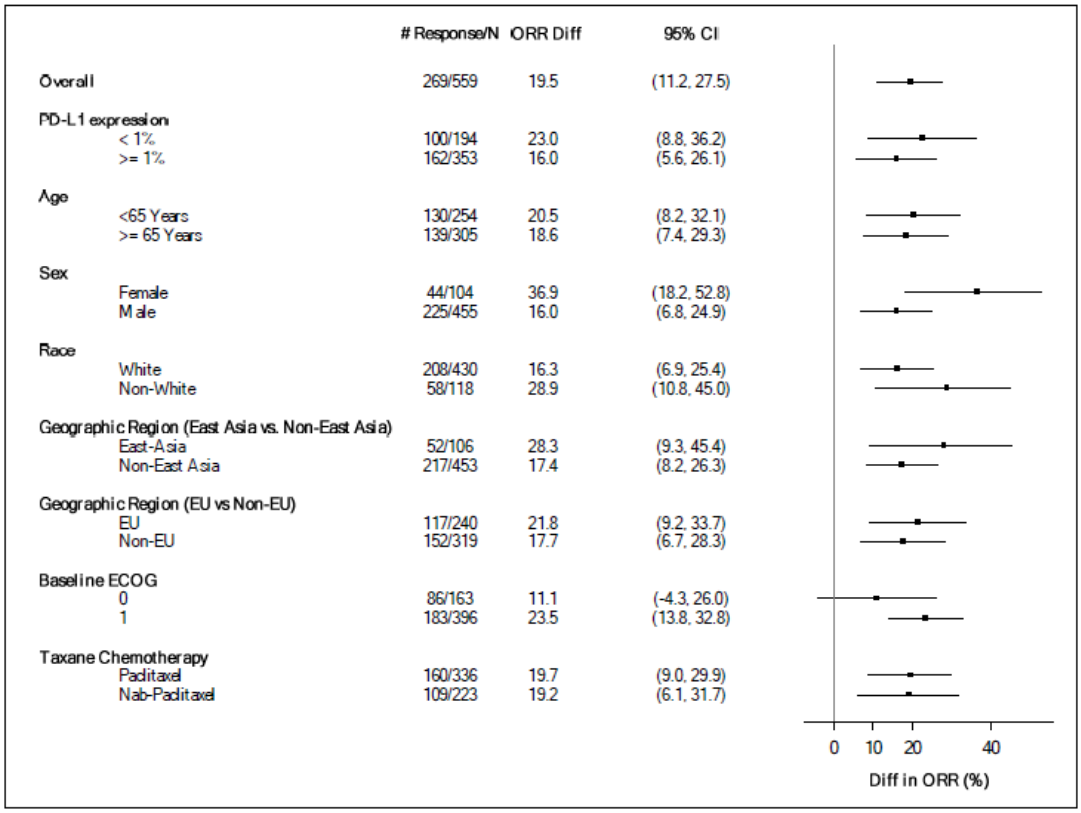
For overall population and the PD-L1 subgroup, analysis is based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. Non-East Asia). For other subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
Subjects with PD-L1 not evaluable are not included in the analysis for PD-L1 subgroup.
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.

Figure 8: Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population) – Data cut: 3 April 2018



For overall population and the PD-L1 subgroup, analysis is based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. Non-East Asia). For other subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
Subjects with PD-L1 not evaluable are not included in the analysis for PD-L1 subgroup.
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.

Figure 9: Forest Plot of PFS Hazard Ratio by Subgroup Factors Based on BICR Assessment per RECIST 1.1 (ITT Population) – Data cut: 3 April 2018



Analysis (ORR difference and 95% CI) for the overall population and the PD-L1 subgroup is based on the stratified Miettinen & Nurminen method; analysis for the other 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 analysis for PD-L1 subgroup variable.

Figure 10: Forest Plot of Objective Response Rate (Confirmed) by Subgroup Factors based on BICR Assessment per RECIST 1.1 (ITT Population) – Data cut: 3 April 2018

Subgroup analysis by PD-L1 expression

Table 17: Efficacy results by PD-L1 Expression in KEYNOTE-407

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1%		TPS 1 to 49%		TPS ≥ 50%	
OS HR* (95% CI)	0.61 (0.38, 0.98)		0.57 (0.36, 0.90)		0.64 (0.37, 1.10)	
PFS HR* (95% CI)	0.68 (0.47, 0.98)		0.56 (0.39, 0.80)		0.37 (0.24, 0.58)	
ORR %	63%	40%	50%	41%	60%	33%

* Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model

- Overall survival

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	95	29 (30.5)	788.4	3.7	15.9 (13.1, .)	80.7 (70.7, 87.5)	0.61 (0.38, 0.98)	0.0188
Control	99	44 (44.4)	762.0	5.8	10.2 (8.6, 13.8)	79.4 (69.6, 86.4)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: 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	103	31 (30.1)	891.5	3.5	14.0 (12.8, .)	84.5 (75.6, 90.4)	0.57 (0.36, 0.90)	0.0079
Control	104	45 (43.3)	811.6	5.5	11.6 (8.9, 17.2)	76.0 (66.3, 83.3)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: 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	73	23 (31.5)	616.8	3.7	Not Reached (11.3, .)	81.9 (70.9, 89.1)	0.64 (0.37, 1.10)	0.0523
Control	73	30 (41.1)	536.4	5.6	Not Reached (7.4, .)	71.3 (59.0, 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 (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adtte]

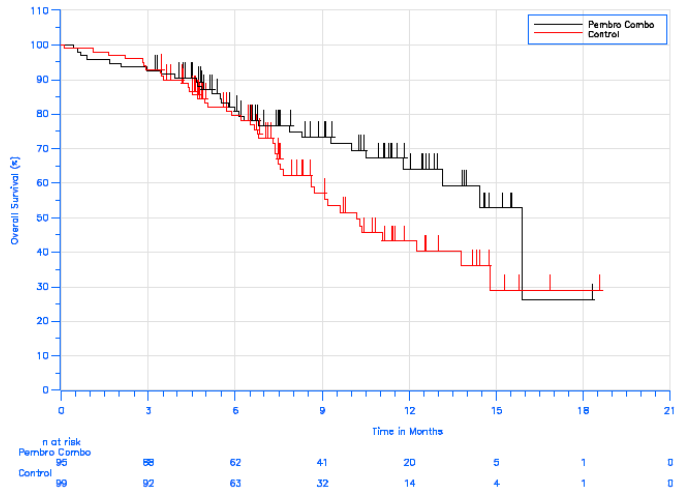


Figure 11: Kaplan-Meier Estimates of Overall Survival with TPS < 1% (ITT Population) – Data cut: 3 April 2018

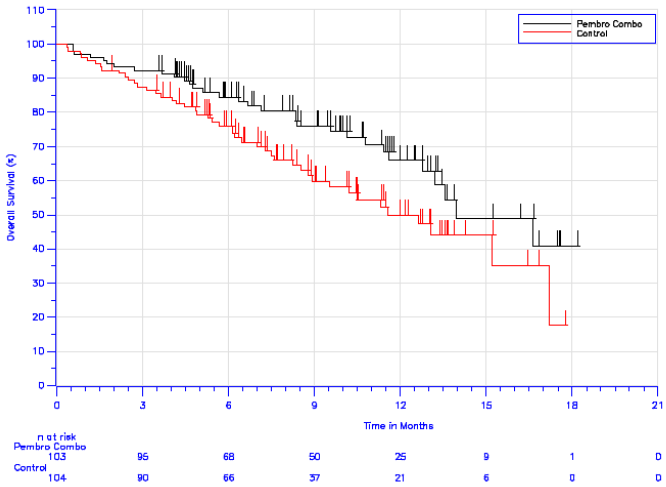
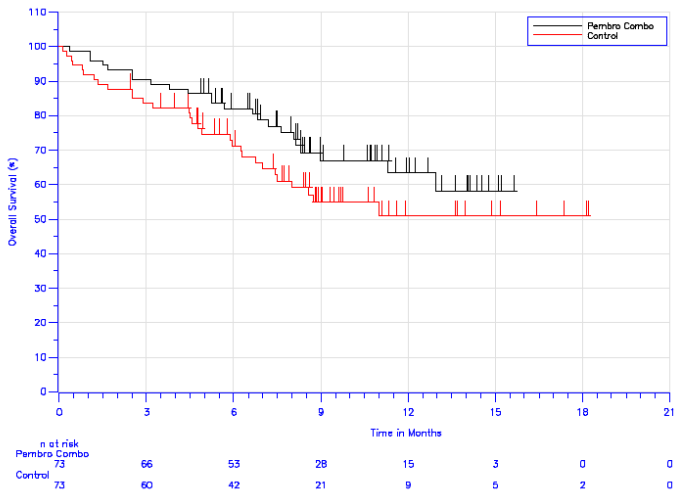


Figure 12: Kaplan-Meier Estimates of Overall Survival with TPS 1-49% (ITT Population) – Data cut: 3 April 2018



Database Cutoff Date: 03APR2018
Source: [P407V01MK3475: adam-adsl; adtte]

Figure 13: Kaplan-Meier Estimates of Overall Survival with TPS ≥ 50% (ITT Population) – Data cut: 3 April 2018

- Progression Free Survival

Table 21: Analysis of Progression-Free Survival (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	95	55 (57.9)	557.1	9.9	6.3 (6.1, 6.5)	65.7 (54.6, 74.7)	0.68 (0.47, 0.98)	0.0177
Control	99	67 (67.7)	508.9	13.2	5.3 (4.4, 6.2)	46.7 (35.8, 57.0)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adtte]

Table 19: Analysis of Progression-Free Survival (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	103	54 (52.4)	656.7	8.2	7.2 (6.0, 11.4)	61.9 (51.1, 71.0)	0.56 (0.39, 0.80)	0.0008
Control	104	73 (70.2)	526.5	13.9	5.2 (4.2, 6.2)	48.8 (38.3, 58.4)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adtte]

Table 20: Analysis of Progression-Free Survival (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	73	39 (53.4)	449.4	8.7	8.0 (6.1, 10.3)	67.0 (54.2, 77.0)	0.37 (0.24, 0.58)	<0.0001
Control	73	55 (75.3)	296.8	18.5	4.2 (2.8, 4.6)	23.0 (13.3, 34.2)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adtte]

- Overall Response Rate

Table 21: ORR by PD-L1 expression subgroup (ITT population)

	Pembro Combo (N=278)				Control (N=281)				Difference[†]	
	N	n	(%)	95% CI (%)	N	n	(%)	95% CI (%)	(%)	95% CI (%)
Overall	278	161	(57.9)	(51.9, 63.8)	281	108	(38.4)	(32.7, 44.4)	(19.5)	(11.2, 27.5)
PD-L1 (TPS cut point: 1%)										
TPS < 1%	95	60	(63.2)	(52.6, 72.8)	99	40	(40.4)	(30.7, 50.7)	(23.0)	(8.8, 36.2)
TPS ≥ 1%	176	95	(54.0)	(46.3, 61.5)	177	67	(37.9)	(30.7, 45.4)	(16.0)	(5.6, 26.1)
PD-L1 (TPS cut point: 50% and 1%)										
TPS < 1%	95	60	(63.2)	(52.6, 72.8)	99	40	(40.4)	(30.7, 50.7)	(23.0)	(8.8, 36.2)
TPS 1 - 49%	103	51	(49.5)	(39.5, 59.5)	104	43	(41.3)	(31.8, 51.4)	(8.0)	(-5.5, 21.3)
TPS ≥ 50%	73	44	(60.3)	(48.1, 71.5)	73	24	(32.9)	(22.3, 44.9)	(27.5)	(11.3, 42.3)

Post-study treatments

At the time of data cutoff, 208 (74.3%) subjects discontinued study treatment in the control arm. Of them, 75 eligible subjects with PD verified by BICR crossed over to pembrolizumab monotherapy within the study. An additional 14 subjects received a checkpoint inhibitor (pembrolizumab, atezolizumab, or nivolumab) as subsequent therapy outside of the study. Therefore, a total of 42.8% (89/208) of subjects in the control group who discontinued study treatment crossed over to a checkpoint inhibitor. In the chemotherapy group, only 110 subjects (53%, 110/208) received any subsequent anti-neoplastic therapy and the majority of these (89/110 subjects, 81%) received a subsequent checkpoint inhibitor. Among 98 subjects in the chemotherapy group who did not receive second-line therapy, 62 died within 3 months after their last dose of study treatment.

Table 22: Subjects With Specific Concomitant Medications (Incidence > 0% in One or More Treatment Groups) Subsequent Antineoplastic Therapy (ITT Population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		281	
With one or more concomitant medications	44	(15.8)	45	(16.0)
With no concomitant medication	234	(84.2)	236	(84.0)
antineoplastic and immunomodulating agents				
antineoplastic agents	**44**	**(15.8)**	**43**	**(15.3)**
atezolizumab	1	(0.4)	2	(0.7)
carboplatin	7	(2.5)	7	(2.5)
cisplatin	10	(3.6)	5	(1.8)
docetaxel	18	(6.5)	7	(2.5)
etoposide	1	(0.4)	0	(0.0)
gefitinib	1	(0.4)	0	(0.0)
gemcitabine	24	(8.6)	16	(5.7)
gimeracil (+) oteracil potassium (+) tegafur	4	(1.4)	2	(0.7)
hydrazine sulfate	0	(0.0)	2	(0.7)
nedaplatin	1	(0.4)	0	(0.0)
nivolumab	2	(0.7)	10	(3.6)
paclitaxel	2	(0.7)	4	(1.4)
paclitaxel albumin	1	(0.4)	0	(0.0)
pembrolizumab	1	(0.4)	3	(1.1)
pemetrexed disodium	0	(0.0)	1	(0.4)
ramucirumab	3	(1.1)	1	(0.4)
vinorelbine tartrate	7	(2.5)	3	(1.1)
various				
all other therapeutic products	**1**	**(0.4)**	**1**	**(0.4)**
investigational drug	1	(0.4)	1	(0.4)
(unspecified) **therapeutic**	**0**	**(0.0)**	**1**	**(0.4)**
radiopharmaceuticals	0	(0.0)	1	(0.4)
strontium chloride Sr 89				

Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

1 participant crossed over to pembrolizumab monotherapy within the study before receiving atezolizumab outside of the study; thus, a total of 14 participants were included in the crossover calculations.

Database Cutoff Date: 03APR2018

Summary of main study

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

Table 23: Summary of Efficacy for trial KEYNOTE-407

Title: A Randomized, Double-Blind, Phase III Study of Carboplatin- Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)			
Study identifier	KEYNOTE-407 (IND: 116,833 EudraCT: 2016-000229-38 Protocol Number: MK-3475-407)		
Design	phase III, randomized, double-blind, placebo controlled with active treatment		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Planned duration of the study is ~ 4 years. Study is ongoing (event-driven study). not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Pembro combo		Pembrolizumab 200 mg (Day 1) + carboplatin AUC 6 mg/mL/min (D1) + paclitaxel 200 mg/m2 (D1) OR nab-paclitaxel 100 mg/m2 (D1, D8, D15) Q3W for 4 cycles followed by pembrolizumab 200 mg (D1) Q3W until progression (Pembrolizumab up to a total of 35 cycles).
	Control		Saline placebo + carboplatin AUC 6 mg/mL/min (D1) + paclitaxel 200 mg/m2 (D1) OR nab-paclitaxel 100 mg/m2 (D1, D8, D15) Q3W for 4 cycles followed by saline placebo (D1) Q3W until progression (Saline placebo up to a total of 35 cycles).
Endpoints and definitions	Dual Primary endpoint	PFS (by BICR per RECIST 1.1)	Time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first.
	Dual Primary endpoint	OS	Time from randomization to death due to any cause. Participants without documented death at the time of analysis were censored at the date of last known contact.
	Secondary endpoint	ORR (by BICR per RECIST 1.1)	proportion of participants who had complete response (CR) or partial response (PR).
	Secondary endpoint	DOR	Time from first documented evidence of CR or PR until disease progression or death.
	Secondary endpoint	Safety	Toxicities as defined by CTCAE v4.0
Database lock	Data cut-off date: 3 April 2018 (Interim Analysis 2)		

Results and Analysis			
Analysis description	**Primary Analysis** (Interim Analysis 2)		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembro combo	Control
	Number of subject	278	281
	OS events, n (%)	85 (30.6)	120 (42.7)
	median in months (95%CI)	15.9 (13.2,-)	11.3 (9.5, 14.8)
	PFS events, n (%)	152 (54.7)	197 (70.1)
	median in months (95%CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
	ORR (%) (95%CI)	57.9% (51.9, 63.8)	38.4 (32.7, 44.4)
Effect estimate per comparison	Dual Primary endpoint **OS**	Comparison groups	pembro combo vs control
		HR	0.64
		95%CI	0.49, 0.85
		P-value	0.0008
	Dual Primary endpoint **PFS**	Comparison groups	pembro combo vs control
		HR	0.56
		95%CI	0.45, 0.70
		P-value	<0.0001
	Secondary endpoint **ORR**	Comparison groups	pembro combo vs control
		difference in %	19.5
		95%CI	11.2, 27.5

		P-value	<0.0001
Notes			

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

Clinical studies in special populations

Table 24: Subgroups analysis by age category for OS

	Pembro Combo (N=278)		Control (N=281)		Pembro Combo vs. Control
	N	Number (%) of Events	N	Number (%) of Events	Hazard Ratio (95% CI)†
Age (cutoff: 65, 75 and 85)					
< 65 Years	127	34 (26.8)	127	54 (42.5)	0.52 (0.34, 0.80)
≥ 65 to < 75 Years	117	40 (34.2)	123	56 (45.5)	0.66 (0.44, 1.00)
≥ 75 to < 85 Years	32	9 (28.1)	30	10 (33.3)	0.99 (0.40, 2.47)
≥ 85 Years	2	2 (100.0)	1	0 (0.00)	.(.,.)

Analysis based on unstratified Cox regression model with treatment as a covariate.

Table 25: Subgroups analysis by age category for PFS based on BICR assessment per RECIST 1.1

	Pembro Combo (N=278)		Control (N=281)		Pembro Combo vs. Control
	N	Number (%) of Events	N	Number (%) of Events	Hazard Ratio (95% CI)†
Age (cutoff: 65, 75 and 85)					
< 65 Years	127	69 (54.3)	127	93 (73.2)	0.50 (0.37, 0.69)
≥ 65 to < 75 Years	117	66 (56.4)	123	83 (67.5)	0.60 (0.43, 0.82)
≥ 75 to < 85 Years	32	15 (46.9)	30	20 (66.7)	0.72 (0.37, 1.41)
≥ 85 Years	2	2 (100.0)	1	1 (100.0)	0.71 (0.04, 11.79)

Analysis based on unstratified Cox regression model with treatment as a covariate.

Table 26: Subgroups analysis by age category for ORR (confirmed) based on BICR assessment per RECIST 1.1

	Pembro Combo (N=278)			Control (N=281)			Pembro Combo vs. Control	
	N	Number (%) of Events		N	Number (%) of Events		Hazard Ratio (95% CI)†	
Age (Cutoff: 65, 75 and 85)								
< 65 Years	127	78 (61.4)	(52.4, 69.9)	127	52 (40.9)	(32.3, 50.0)	(20.5)	(8.2, 32.1)
≥ 65 to < 75 Years	117	67 (57.3)	(47.8, 66.4)	123	43 (35.0)	(26.6, 44.1)	(22.3)	(9.7, 34.2)
≥ 75 to < 85 Years	32	15 (46.9)	(29.1, 65.3)	30	13 (43.3)	(25.5, 62.6)	(3.5)	(-20.9, 27.5)
≥ 85 Years	2	1 (50.0)	(1.3, 98.7)	1	0 (0.0)	(0.0, 97.5)	(50.0)	(-64.2, 93.1)

Analysis based on the unstratified Miettinen & Nurminen method.

Table 27: Summary of efficacy endpoints by age (<65, 65-74, 75-84) for KN407 alone and with the pooled data of KN407, KN189 and KN21G.

	KEYNOTE-407			KEYNOTE-189			Pooled KEYNOTE-407, 189, 021-G*		
Endpoint	<65 years	65-74 years	75-84 years	<65 years	65-74 years	75-84 years	<65 years	65-74 years	75-84 years
OS HR† (95% CI)	0.53 (0.34, 0.82)	0.68 (0.45, 1.03)	0.85 (0.31, 2.31)	0.43 (0.31, 0.61)	0.51 (0.32, 0.81)	2.09 (0.84, 5.23)	0.44 (0.34, 0.56)	0.61 (0.46, 0.83)	1.19 (0.66, 2.14)
PFS HR† (95% CI)	0.50 (0.36, 0.69)	0.56 (0.40, 0.78)	0.61 (0.30, 1.26)	0.43 (0.32, 0.56)	0.64 (0.45, 0.91)	1.73 (0.77, 3.90)	0.45 (0.37, 0.54)	0.61 (0.49, 0.77)	0.97 (0.61, 1.54)
ORR difference %‡ (95% CI)	20.6 (8.2, 32.3)	23.0 (10.3, 34.9)	-1.2 (-26.2, 25.3)	27.1 (16.9, 36.4)	32.2 (19.0, 43.4)	14.4 (-11.1, 36.4)	24.7 (17.3, 31.8)	27.5 (18.9, 35.5)	7.0 (-10.0, 23.4)

* Includes all subjects in the global ITT populations for KEYNOTE-021-G, KEYNOTE-189, and KEYNOTE-407.
†Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model
‡Analysis (ORR difference [pembro combo – control] and 95% CI) is based on the stratified Miettinen & Nurminen method.
Source: [Ref. 5.3.5.1: P407V01MK3475: Table 14.2-3, 14.2-13, 14.2-22] [Table 17] [Table 18] [Table 19]

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study supporting the sought indication is the ongoing KEYNOTE-407, a phase III randomized double-blind placebo-controlled trial with active treatment of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab in first line metastatic (stage IV M1a or M1b-AJCC 7th edition) squamous NSCLC. No Scientific Advice to CHMP was requested on this study.

Overall, patients' selection criteria are considered reflective of the target population in the indication.

Pembrolizumab 200 mg Q3W or saline placebo were administered in association with carboplatin + paclitaxel or nab-paclitaxel for a total of 4 cycles, followed by pembrolizumab/saline placebo until progression for maximum 2 years (i.e. 35 cycles) of treatment. Currently, the 200 mg Q3W dose is being evaluated in multiple clinical studies, is the approved monotherapy dose in patients with previously untreated NSCLC based on KEYNOTE-024, and is the dose used in combination with chemotherapy in patients with non-squamous NSCLC in KEYNOTE-189.

Participants who had PD verified by BICR could be unblinded and crossover to or continue to receive pembrolizumab monotherapy. Re-treatment with open-label pembrolizumab at progression was allowed in case the drug had been previously stopped for CR or after 35 administrations for reasons other than PD or intolerability. Carboplatin with either paclitaxel or nab-paclitaxel is one of the accepted standard treatment option for 1st line squamous cell lung cancer. Cisplatin, although indicated and used in squamous disease, was not included in this study. Therefore, no data are available for pembrolizumab in combination with cisplatin-based chemotherapy in squamous histology, contrary to non-squamous NSCLC (KEYNOTE-189 study) where both cisplatin and carboplatin (with pemetrexed) have been investigated and approved in association with Keytruda. On the other hand, nab-paclitaxel is approved in combination with carboplatin only.

International guidelines recommend the use of 4 to 6 cycles of treatment (Planchard et al, 2018). The number of cycles of chemotherapy used in this study was four. Investigators choice of number of cycles (up to six) could have been appropriate. Indeed, even acknowledging that no OS benefit has been demonstrated for six versus fewer cycles of first-line platinum-based doublets, a longer PFS was reported in patients receiving six cycles (Rossi A, Lancet Oncol 2014).

OS and PFS per RECIST 1.1 by BICR as dual primary efficacy endpoints for this study are considered appropriate. ORR and DOR per RECIST 1.1 by BICR were evaluated as secondary endpoints. Among the exploratory endpoints included in this submission, the MAH presented OS, PFS, and ORR by PD-L1 status as well as Quality of Life evaluation.

Sample size calculation was driven by number of required PFS and OS events. However, the overall 1-sided 2.5% type 1 error was split between the two primary endpoints and the ORR. The pre-allocated alpha was 0.005, 0.01 and 0.01 for ORR, PFS and OS, respectively. The graphical method of Maurer and Bretz was applied to control multiplicity for multiple hypotheses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. Therefore, the power of the study depends on the allocated alpha and several scenarios were proposed. The sample size calculations result congruent with the assumptions made.

Stratification factors used at randomization (PD-L1 status <1% vs ≥1%, investigator's choice of paclitaxel vs nab-paclitaxel, East-Asia vs non-East Asia) are considered appropriate.

The statistical methods used for time to events and binary endpoints are considered adequate. The graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses and O'Brien-Fleming approach to allocate Type I error rate across interim analyses are appropriate as well.

Two global protocol amendments (02 and 03) are reported up to the cut-off date. The content of Amendment 03 is the same as Amendment 02; the latter was retracted due to clerical and typographical errors. From the statistical point of view, an additional IA for PFS and OS was added and the alpha allocation scheme was updated. In the original protocol version, the type I error was controlled at 0.025 (one sided) for the hypothesis testing of ORR, PFS and OS and the pre-allocated alpha was 0.005, 0.015 and 0.005 for ORR, PFS and OS, respectively. ORR was tested first and the alpha was subject to rollover to PFS (i.e., PFS will be tested at 0.020 if ORR is positive or at 0.015 otherwise). The alpha for PFS was subject to rollover to OS (i.e., the overall OS alpha was 0.005 if PFS was negative, or 0.020 or 0.025 if PFS was positive and ORR was negative or positive, respectively). However, the same Lan-DeMets O'Brien-Fleming approximation spending function defined in the original protocol was used for the calculation of efficacy bounds for PFS (IA2 and IA3) and for OS (IA2, IA3 and final) that are more conservative due the introduction of a new IA and a new allocation scheme. Amendment 03 was approved and released prior to IA1 results being available to the independent DMC which is reassuring on the timing of the protocol amendment.

Important protocol deviations occurred in a similar rate in both arms (16.5% vs 16.7%), and are not expected to have significantly impacted the trial results.

Efficacy data and additional analyses

A total of 559 patients were recruited worldwide across 168 sites in 17 countries. Subjects were allocated 1:1 to pembro combo arm (n=278) or control (n=281). Eligibility was assessed in 779 patients, for a total of 220 participants not randomized in the study. Of them, 2 were due to physician decision and 218 were screen failures (among which 217 failed to meet eligibility requirements based on the inclusion/exclusion criteria). The most frequent reasons for exclusion were unconfirmed diagnosis of stage IV squamous NSCLC (31 subjects, 14.3%), participant unable to provide qualified tumour tissue for PD-L1 assessment (29 subjects, 13.4%) and lack of written informed consent (29 subjects, 13.4%).

All randomized patients received the allocated treatment, except one subject in the control arm who was not treated. At the cut-off date, more subjects in the pembrolizumab combination arm were still receiving treatment compared to the control (43.5% vs 25.7%). Most common reason for discontinuation was progressive disease in both arms, more frequent in the control arm (30.9% vs 50%). The rate of discontinuation due to adverse events was on the contrary higher in the group receiving combination therapy compared to chemotherapy alone, as expected (17.3% vs 8.9%), which is approximately comparable to the discontinuation rate due to AEs seen in the combination arm of study KN189 (19.3% vs 10.4%) supporting the approval of pembrolizumab in combination with pemetrexed and platinum chemotherapy in the first-line treatment of metastatic non-squamous NSCLC patients. There was an imbalance in the number of patients who discontinued any drug due to a drug-related adverse event

(pembro combo: 50 / 278 (18.0%), control: 20 / 280 (7.1%)). Treatment discontinuation due to withdrawal by subjects + physician decision + lost to follow-up was more common in the control arm (3.6% vs 6%).

A total of 75 (27%) patients in the control arm crossed over to pembrolizumab at progression, which appeared quite low taking into account the current authorized indication after chemotherapy. However, an additional 14 subjects received a checkpoint inhibitor (pembrolizumab, atezolizumab, or nivolumab) as subsequent therapy outside of the study. Therefore, 42.8% of subjects in the control group who discontinued study treatment crossed over to a checkpoint inhibitor (i.e. 75 within the trial and 14 outside the trial). This is similar to crossover rates in other first line NSCLC trials (e.g. 54% in KEYNOTE-24, 50% in KEYNOTE-189, 42.1% in IMpower-131). Specific reasons for not receiving a subsequent checkpoint inhibitor were not collected. In the chemotherapy group, only 110 subjects (53% of the 208 subjects in this group who discontinued from study treatment) received any subsequent anti-neoplastic therapy and the majority of these (89/110 subjects, 81%) received a subsequent checkpoint inhibitor.

In the pembrolizumab combination arm, the most common subsequent anti-neoplastic therapies were gemcitabine (8.6%) and docetaxel (6.5%). In the chemotherapy arm, the most common subsequent anti-neoplastic therapy excluding checkpoint inhibitors was gemcitabine (5.7%).

Baseline characteristics of enrolled subjects appeared overall balanced between the two arms. Median age was 65 years, ECOG was 0 (29%) or 1 (71%). As expected for squamous histology, the majority of subjects were male (81.4%) and former or current smokers (92% overall). According to international guidelines, patients with squamous NSCLC who are never or former light smokers should be considered for molecular testing (Planchard et al, 2018). It is acknowledged that the 2015 Guideline (College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology Guideline (AMP)) that was in place at the time of trial start did not recommend molecular testing for squamous histology (regardless of smoking status). Also a small number of patients with adenosquamous carcinomas have been included in KN407 study (13 patients, 2.3%). These patients are also recommended to undergo molecular analysis. Although EGFR and ALK analyses were recommended in 2015 Guidelines in the presence of an adenocarcinoma component in the tumour specimen, no data on molecular testing was available for those 13 subjects.

According to PD-L1 status, approximately 63% of patients in both arms were PD-L1 positive (i.e. TPS≥1%, which was a stratification factor) and 35% PD-L1 negative, only 2% were PD-L1 unknown. Patients remained well balanced in both arms also in each PD-L1 expression subgroup TPS<1% (35%), 1-49% (37%) and ≥50% (26%).

Paclitaxel and nab-paclitaxel were used overall by 60% and 40% of the subjects in each arm, respectively. Overall, subjects with prior radiation were 13.1%, with no meaningful imbalances between the two arms: prior thoracic radiation was reported only in 7%.

This application is based on the results of the IA2 with a data cut-off date 3 April 2018, at which time the overall median duration of follow-up time was 7.8 months (range 0.1, 19.1). A statistically significant improvement in both PFS and OS was shown for pembrolizumab combination vs chemotherapy alone at the IA2. With a total of 349 PFS events (62% of the overall population), a reduction in disease progression by 44% (HR=0.56; 95%CI 0.45, 0.70; p<0.0001) was shown for pembrolizumab combination vs control arm, for a median PFS of 6.4 vs 4.8 months. OS HR was 0.64 (95%CI 0.49, 0.85; p=0.0008) in favour of pembrolizumab combination, with a gain of about 4.6 months in median survival over chemotherapy alone (15.9 vs 11.3 months). However, maturity level of OS (i.e. number of OS events at IA2/number of OS events planned at final analysis) is 57%, (corresponding to 37% of the overall population experiencing an OS event) at this analysis and due to the high rate of censoring curves are hardly interpretable after month 3. A subsequent database lock for the prespecified IA3 was not available or planned in the near future, as along with statistically significant results for ORR at the IA1, all alpha-controlled analyses as specified in the protocol were completed at IA2.

Overall, a consistent treatment benefit could be observed across all endpoints at the time of the interim analysis. However more mature OS data are needed. The MAH will submit the final CSR for KEYNOTE-407 as an Annex II condition by September 2021 in order to confirm the survival advantage of pembrolizumab plus chemotherapy vs chemotherapy alone in 1L squamous NSCLC with longer follow-up.

To assess the impact of cross-over on OS, proper statistical methods have been applied (e.g. analysis censoring at time of cross-over, Inverse Probability of Censoring Weighting (IPCW), Rank Preserving Structural Failure Time models (RPSFT), and two-stage methods) taking into account the assumptions required by the methods. The results were consistent with the primary OS analysis.

Results from PFS sensitivity analysis 1 and 2, as well as PFS based on investigator assessment, were consistent with the primary analysis.

The advantage of pembro combo over chemotherapy alone is also observed in terms of response rate (confirmed ORR based on BICR per RECIST 1.1: 57.9% vs 38.4%), although there was a similar number of complete responses in the two arms (1.4% vs 2.1%). Median DOR was also longer for pembro combo (7.7 vs 4.8 months).

With regards to subgroup analyses, it appears that the advantage of pembro combo is maintained in most of the subgroups analysed. For all subgroups except the PD-L1 subgroups, OS, PFS and ORR results were presented based on unstratified analyses. Results of the stratified subgroup analyses were overall comparable with unstratified data.

Clinically meaningful improvement in outcomes from treatment with the combination in previously untreated patients with metastatic squamous NSCLC was observed in patients from both East Asia and non-East-Asia regions. However, the treatment effect was more pronounced in the East Asia population and no satisfying explanation could be given by the MAH. No meaningful differences in OS could be detected for never smokers vs smokers and patients with or without liver metastasis compared to the control group. Nevertheless, only limited data are available.

In the KEYNOTE-189 combination study in non-squamous NSCLC, a clear relation between efficacy and increasing PD-L1 tumour expression was noted in all endpoints. In KEYNOTE-407, a trend for a better PFS HR of pembro combo vs chemo the higher the PD-L1 score has been observed. Differently, this trend is not evident in OS or ORR. OS HR appeared similar across all three subgroups. By looking at the KM curves, in the PD-L1 negative population (TPS<1%), curves of the two treatment arms appeared overlapping up to about month 6 before dividing in favour of pembro combo. Updated analyses will be provided with the final CSR (see Annex II).

The available efficacy results of pembro combo in the different subgroups (TPS<1%, 1-49%, ≥50%) have been included in the SmPC. Unfortunately we can observe a crossing of the OS KM-curves at 3 month in patients with TPS<1%. The baseline characteristics for subjects with TPS<1% and early death within the first 3 months from randomization in both treatment arms were submitted, however due to the small number of patients, no relevant conclusion could be drawn from this data.

KEYNOTE-407 study started before the approval of pembrolizumab as monotherapy in first line metastatic NSCLC (including squamous histology) with TPS≥50%. At the time of approval of pembrolizumab in combination with pemetrexed and platinum chemotherapy in non-squamous NSCLC, a wording was introduced in section 4.2 of the SmPC for stating that *in patients whose tumours have high PD-L1 expression, the risk of adverse reactions with combination therapy relative to pembrolizumab monotherapy should be considered and the benefit/risk ratio of the combined therapy evaluated on an individual basis of the combination regimen*, along with a warning in section 4.4 underlining the *lack of direct comparison between pembrolizumab in combination with chemotherapy and pembrolizumab alone*. Both statements are considered applicable to the sought indication of pembrolizumab in combination with chemotherapy in squamous disease. Furthermore, as pembrolizumab monotherapy could be regarded as SOC in first line for

the PD-L1 high subpopulation, the MAH was requested to present a comparison of efficacy between the combination therapy and pembrolizumab monotherapy in the squamous histology and provide a B/R discussion for subjects with TPS ≥50% considering the higher toxicity of the combination therapy. Since no trials provide a direct comparison between chemotherapy + pembrolizumab versus pembrolizumab alone in 1L NSCLC with PD-L1 expression TPS ≥50%, it is unclear whether patients with high PD-L1 expression would benefit from the addition of chemotherapy to pembrolizumab. In the absence of a clinical trial that would allow direct, definitive analysis comparing efficacy for pembrolizumab combined with chemotherapy to pembrolizumab monotherapy, the observed differences in efficacy should be interpreted with caution.

An advantage of the combination with pembrolizumab vs chemotherapy alone was shown regardless the drug used (paclitaxel or nab-paclitaxel). It was however noted that the number of both OS and PFS events was higher in paclitaxel-based treatment compared to nab-paclitaxel-based subgroup.

A trend toward reduced PFS and OS performance of pembro combo vs chemotherapy according with increase in age was noted. The MAH was asked to provide a summary of efficacy endpoints by age (<65, 65-74, 75-84) for KN407 and for KN407 with the pooled data of KN189 and KN21G. Efficacy data for NSCLC patients ≥75 years receiving combination therapy in KEYNOTE-407 (squamous) and KEYNOTE-189 (non-squamous) are reported in section 5.1 of the SmPC in order to better guide physicians in the choice of treatment in elderly population. Furthermore, a warning that efficacy and safety data from patients ≥75 years are limited, and that pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis, was included in section 4.4 of the SmPC based on the pembrolizumab plus chemotherapy data in 1st line non-squamous NSCLC (KEYNOTE-189). Such wording is considered applicable also to the applied indication.

The analysis of PRO/HRQoL was included among exploratory endpoints, with no pre-specified hypotheses. Health-related QoL appeared to be maintained for the pembro combo arm.

2.4.4. Conclusions on the clinical efficacy

The results of the Interim Analysis 2 of the pivotal study KEYNOTE-407 showed a consistent treatment benefit in all efficacy endpoints for pembrolizumab in combination with carboplatin/paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous NSCLC.

The CHMP considers the following measures necessary to address issues related to efficacy:

Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P407: A Randomized, Double-Blind, Phase III Study of Carboplatin - Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects – Final Study Report.

2.5. Clinical safety

Introduction

In addition to the individual analysis of study KEYNOTE-407, data on clinical safety were derived from the following datasets:

- KEYNOTE-407 Combo + KEYNOTE-021-A Combo Safety Dataset (N = 303): Pooled data from 278 participants with previously untreated metastatic squamous NSCLC who received pembrolizumab in combination with carboplatin/paclitaxel (or nab-paclitaxel) in KEYNOTE-407 (data from IA2), and 25 participants with NSCLC of any histology type in Cohort A of KEYNOTE-021 and were treated with pembrolizumab in combination with carboplatin/paclitaxel.
- KEYNOTE-407 Chemo Dataset (N = 280): Data from participants with metastatic squamous NSCLC who

received carboplatin/paclitaxel (or nab-paclitaxel) in KEYNOTE-407 (data from IA2).

- KEYNOTE-189 Combo + KEYNOTE-021-G/C Combo Safety Dataset (N = 488): Pooled data from participants with previously untreated metastatic nonsquamous NSCLC who participated in KEYNOTE-189 or KEYNOTE-021 (Cohorts G and C) who received a combination of pembrolizumab and pemetrexed and either cisplatin or carboplatin.
- KEYNOTE-189 Chemo + KEYNOTE-021-G Chemo Safety Dataset (N = 264): Pooled data from participants with previously untreated metastatic nonsquamous NSCLC who participated in KEYNOTE-189 or KEYNOTE-021 (Cohort G) and were treated with pemetrexed and either cisplatin or carboplatin.
- Pembrolizumab Monotherapy RSD (N = 3830): Participants who received at least 1 dose of pembrolizumab in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3 (NSCLC, melanoma), KEYNOTE-002 (original phase, melanoma), KEYNOTE-006 (melanoma), KEYNOTE-010 (NSCLC), KEYNOTE-013 Cohort 3 (Hodgkin's lymphoma), KEYNOTE-024 (NSCLC), KEYNOTE-045 and KEYNOTE-052 (urothelial cancer), and KEYNOTE-087 (classical Hodgkin's lymphoma). This dataset represents the established safety profile for pembrolizumab monotherapy based on the currently approved indications in the European Union.

Safety analysis used a tiered approach as illustrated below:

Table 28: Analysis strategy for safety parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset and Duration of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification Due to AE		X	X
	Discontinuation Due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X
There are no Tier 1 AEs pre-specified in this protocol.				

Patient exposure

KEYNOTE-407

Table 29: Summary of drug exposure of any study treatment component (ASaT population)

	Pembro Combo (N=278)	Control (N=280)
Number of Days on Therapy		
Mean	191.4	143.7
Median	169	127
SD	124.5	106.3
Range	1 to 545	1 to 545
Number of Cycles		
Mean	9.3	7.3
Median	8	6
SD	5.8	5.0
Range	1 to 27	1 to 27
Database Cutoff Date: 03APR2018		

Source: [P407V01MK3475: adam-adsl; adexsum]

Table 30: Summary of drug administration by dose regimen (ASaT population – carboplatin/paclitaxel)

	Pembro Combo (N = 169)			Control (N = 167)		
Number of Administrations	Pembrolizumab n (%)	Paclitaxel n (%)	Carboplatin n (%)	Placebo n (%)	Paclitaxel n (%)	Carboplatin n (%)
Subjects with at least one administration of the drug	169	169	169	167	167	167
1	8 (4.7)	9 (5.3)	8 (4.7)	12 (7.2)	13 (7.8)	12 (7.2)
2	10 (5.9)	12 (7.1)	11 (6.5)	19 (11.4)	21 (12.6)	19 (11.4)
3	7 (4.1)	15 (8.9)	12 (7.1)	9 (5.4)	14 (8.4)	14 (8.4)
4	10 (5.9)	133 (78.7)	138 (81.7)	16 (9.6)	119 (71.3)	122 (73.1)
>=5	134 (79.3)	0 (0.00)	0 (0.00)	111 (66.5)	0 (0.00)	0 (0.00)
Mean	9.6	3.6	3.7	7.5	3.4	3.5
SD	5.9	0.8	0.8	5.3	1.0	1.0
Median	8.0	4.0	4.0	7.0	4.0	4.0
Range	1 to 27	1 to 4	1 to 4	1 to 27	1 to 4	1 to 4
For subjects who crossed over to pembrolizumab from the Control Group, doses administered after crossover are excluded. Subjects with at least one administration of the drug will be taken as the denominator. The maximum allowed number of administrations for carboplatin and paclitaxel is 4. Database Cutoff Date: 03APR2018						

Source: [P407V01MK3475: adam-adsl; adexsum]

Table 31: Summary of drug administration by dose regimen (ASaT population – carboplatin/Nab-paclitaxel)

	Pembro Combo (N = 109)			Control (N = 113)		
Number of Administrations	Pembrolizumab n (%)	Nab-Paclitaxel n (%)	Carboplatin n (%)	Placebo n (%)	Nab-Paclitaxel n (%)	Carboplatin n (%)
Subjects with at least one administration of the drug	109	109	109	113	113	113
1	12 (11.0)	5 (4.6)	10 (9.2)	9 (8.0)	4 (3.5)	10 (8.8)
2	4 (3.7)	5 (4.6)	4 (3.7)	5 (4.4)	6 (5.3)	8 (7.1)
3	8 (7.3)	0 (0.00)	14 (12.8)	11 (9.7)	2 (1.8)	12 (10.6)
4	5 (4.6)	2 (1.8)	81 (74.3)	10 (8.8)	4 (3.5)	83 (73.5)
5-11	49 (45.0)	72 (66.1)	0 (0.00)	63 (55.8)	73 (64.6)	0 (0.00)
>=12	31 (28.4)	25 (22.9)	0 (0.00)	15 (13.3)	24 (21.2)	0 (0.00)
Mean	8.8	9.0	3.5	7.0	8.7	3.5
SD	5.8	3.1	0.9	4.5	3.2	1.0
Median	8.0	10.0	4.0	6.0	10.0	4.0
Range	1 to 25	1 to 12	1 to 4	1 to 23	1 to 12	1 to 4
For subjects who crossed over to pembrolizumab from the Control Group, doses administered after crossover are excluded. Subjects with at least one administration of the drug will be taken as the denominator. The maximum allowed number of administrations for carboplatin is 4. The maximum allowed number of administrations for nab-paclitaxel is 12. Database Cutoff Date: 03APR2018						

Source: [P407V01MK3475: adam-adsl; adexsum]

Dataset comparison

Table 32: Summary of drug exposure (subjects in ASaT population)

	KN407 + KN021-A combo[†] (N=303)	KN407 chemo[‡] (N=280)	KN189 + KN021-G/C combo[§] (N=488)	KN189 + KN021-G chemo[¶] (N=264)	Reference Safety Dataset for Pembrolizumab monotherapy[‡‡] (N=3830)
Study Days On-Therapy (days)					
Mean	201.25	143.74	245.41	177.97	202.56
Median	169.00	127.00	231.00	134.50	143.50
SD	145.74	106.32	168.58	152.85	184.44
Range	1.00 to 785.00	1.00 to 545.00	1.00 to 862.00	1.00 to 760.00	1.00 to 988.00
Number of Cycles					
Mean	9.76	7.29	11.68	8.79	11.06
Median	8.00	6.00	11.00	7.00	8.00
SD	6.77	4.98	7.48	6.89	9.56
Range	1.00 to 35.00	1.00 to 27.00	1.00 to 35.00	1.00 to 37.00	1.00 to 59.00

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
[†] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN407 and KN021 cohort A.
[‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.
[§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087
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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adexsum]

Adverse events

Adverse events (AE) were monitored throughout the study and for a minimum of 30 days after the end of study treatment. Serious adverse events (SAEs) were collected for up to 90 days after the end of treatment or 30 days following cessation of treatment if the participant initiated new cancer therapy, whichever was earlier. All AEs were graded in severity according to the guideline outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

AEs summary

KEYNOTE-407

Table 33: Adverse event summary (ASaT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	273	(98.2)	274	(97.9)
with no adverse event	5	(1.8)	6	(2.1)
with drug-related[†] adverse events	265	(95.3)	249	(88.9)
with toxicity grade 3-5 adverse events	194	(69.8)	191	(68.2)
with toxicity grade 3-5 drug-related adverse events	152	(54.7)	154	(55.0)
with serious adverse events	113	(40.6)	107	(38.2)
with serious drug-related adverse events	70	(25.2)	51	(18.2)
who died	23	(8.3)	18	(6.4)
who died due to a drug-related adverse event	10	(3.6)	6	(2.1)
discontinued any drug due to an adverse event	65	(23.4)	33	(11.8)
discontinued pembrolizumab or placebo	48	(17.3)	22	(7.9)
discontinued any chemotherapy	44	(15.8)	29	(10.4)
discontinued all drugs	23	(8.3)	16	(5.7)
discontinued any drug due to a drug-related adverse event	50	(18.0)	20	(7.1)
discontinued pembrolizumab or placebo	33	(11.9)	9	(3.2)
discontinued any chemotherapy	32	(11.5)	20	(7.1)
discontinued all drugs	14	(5.0)	9	(3.2)
discontinued any drug due to a serious adverse event	46	(16.5)	23	(8.2)
discontinued pembrolizumab or placebo	40	(14.4)	19	(6.8)
discontinued any chemotherapy	30	(10.8)	20	(7.1)
discontinued all drugs	22	(7.9)	15	(5.4)
discontinued any drug due to a serious drug-related adverse event	31	(11.2)	11	(3.9)
discontinued pembrolizumab or placebo	26	(9.4)	8	(2.9)
discontinued any chemotherapy	19	(6.8)	11	(3.9)
discontinued all drugs	14	(5.0)	8	(2.9)

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

For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.

Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Dataset comparison

Table 34: Adverse event summary (subjects in ASaT population)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	298	(98.3)	274	(97.9)	487	(99.8)	261	(98.9)	3,720	(97.1)
with no adverse event	5	(1.7)	6	(2.1)	1	(0.2)	3	(1.1)	110	(2.9)
with drug-related[†] adverse events	290	(95.7)	249	(88.9)	451	(92.4)	240	(90.9)	2,751	(71.8)
with toxicity grade 3-5 adverse events	209	(69.0)	191	(68.2)	323	(66.2)	167	(63.3)	1,802	(47.0)
with toxicity grade 3-5 drug-related adverse events	162	(53.5)	154	(55.0)	231	(47.3)	98	(37.1)	577	(15.1)
with non-serious adverse events	296	(97.7)	272	(97.1)	483	(99.0)	259	(98.1)	3,647	(95.2)
with serious adverse events	125	(41.3)	107	(38.2)	244	(50.0)	115	(43.6)	1,450	(37.9)
with serious drug-related adverse events	77	(25.4)	51	(18.2)	129	(26.4)	49	(18.6)	403	(10.5)
with any dose modification[‡] due to an adverse event	224	(73.9)	178	(63.6)	329	(67.4)	146	(55.3)	1,256	(32.8)
pembrolizumab or placebo dose modification	177	(58.4)	123	(43.9)	298	(61.1)	109	(41.3)	1,256	(32.8)
any chemotherapy dose modification	46	(15.2)	29	(10.4)	110	(22.5)	35	(13.3)	0	(0.0)
all drugs dose modification	24	(7.9)	16	(5.7)	27	(5.5)	11	(4.2)	1,256	(32.8)
who died	23	(7.6)	18	(6.4)	30	(6.1)	14	(5.3)	157	(4.1)
who died due to a drug-related adverse event	10	(3.3)	6	(2.1)	10	(2.0)	4	(1.5)	17	(0.4)
discontinued any drug due to an adverse event	68	(22.4)	33	(11.8)	129	(26.4)	39	(14.8)	452	(11.8)
discontinued pembrolizumab or placebo	50	(16.5)	22	(7.9)	93	(19.1)	21	(8.0)	452	(11.8)
discontinued any chemotherapy	46	(15.2)	29	(10.4)	110	(22.5)	35	(13.3)	0	(0.0)
discontinued all drugs	24	(7.9)	16	(5.7)	27	(5.5)	11	(4.2)	452	(11.8)
discontinued any drug due to a drug-related adverse event	51	(16.8)	20	(7.1)	100	(20.5)	26	(9.8)	224	(5.8)
discontinued pembrolizumab or placebo	33	(10.9)	9	(3.2)	68	(13.9)	10	(3.8)	224	(5.8)
discontinued any chemotherapy	33	(10.9)	20	(7.1)	85	(17.4)	25	(9.5)	0	(0.0)
discontinued all drugs	14	(4.6)	9	(3.2)	15	(3.1)	7	(2.7)	224	(5.8)
discontinued any drug due to a serious adverse event	49	(16.2)	23	(8.2)	86	(17.6)	22	(8.3)	338	(8.8)
discontinued pembrolizumab or placebo	42	(13.9)	19	(6.8)	72	(14.8)	16	(6.1)	338	(8.8)
discontinued any chemotherapy	32	(10.6)	20	(7.1)	73	(15.0)	19	(7.2)	0	(0.0)
discontinued all drugs	23	(7.6)	15	(5.4)	26	(5.3)	10	(3.8)	338	(8.8)
discontinued any drug due to a serious drug-related adverse event	32	(10.6)	11	(3.9)	62	(12.7)	10	(3.8)	149	(3.9)
discontinued pembrolizumab or placebo	26	(8.6)	8	(2.9)	49	(10.0)	6	(2.3)	149	(3.9)
discontinued any chemotherapy	20	(6.6)	11	(3.9)	52	(10.7)	9	(3.4)	0	(0.0)
discontinued all drugs	14	(4.6)	8	(2.9)	14	(2.9)	6	(2.3)	149	(3.9)

[†] 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.

[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Overall AEs

KEYNOTE-407

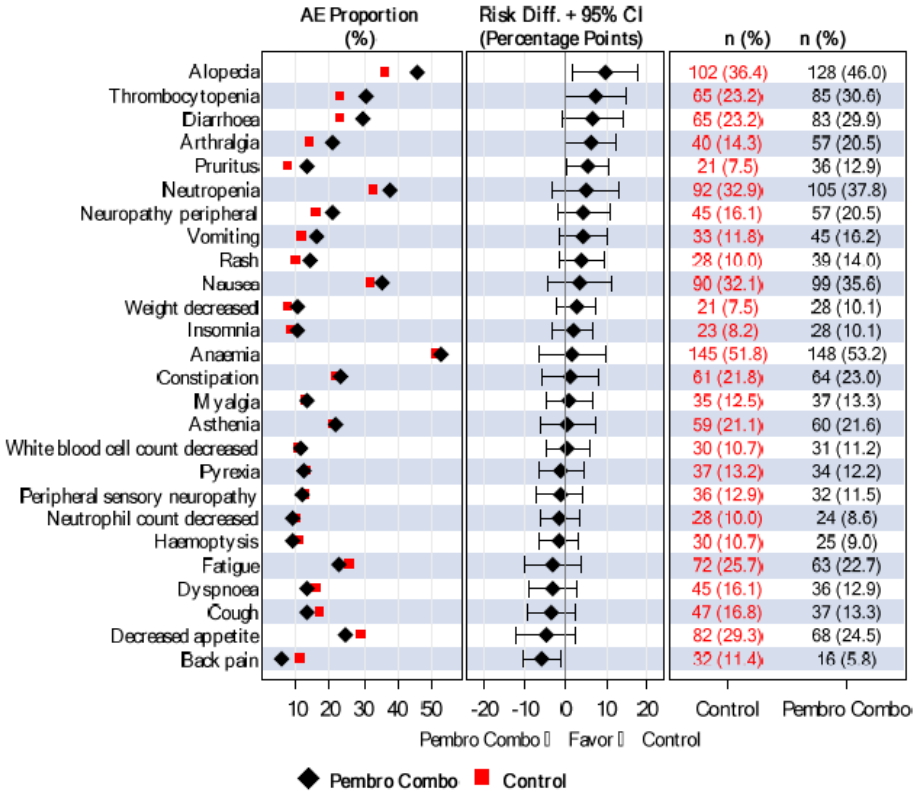


Figure 14: Between treatment comparisons in adverse events – selected adverse events (≥10% incidence) and sorted by risk difference (ASaT population) – Pembro combo (N=278) vs. control (N=280)

Table 35: 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[‡]	278	238	143	37	280	225	97	17
Total exposure[§] person-months	783.06	583.00	509.86	70.14	767.29	481.59	267.91	41.42
Total events (rate)	2732 (348.89)	553 (94.85)	311 (61.00)	30 (42.77)	2533 (330.12)	447 (92.82)	161 (60.09)	11 (26.56)
AE Category								
Blood and lymphatic system disorders	**548 (70.0)**	**66 (11.3)**	**9 (1.8)**	**0 (0.0)**	**466 (60.7)**	**34 (7.1)**	**3 (1.1)**	**0 (0.0)**
Anaemia	156 (19.9)	23 (3.9)	6 (1.2)	0 (0.0)	163 (21.2)	14 (2.9)	2 (0.7)	0 (0.0)
Neutropenia	198 (25.3)	12 (2.1)	0 (0.0)	0 (0.0)	161 (21.0)	7 (1.5)	0 (0.0)	0 (0.0)
Thrombocytopenia	111 (14.2)	19 (3.3)	3 (0.6)	0 (0.0)	85 (11.1)	6 (1.2)	0 (0.0)	0 (0.0)
Endocrine disorders	**20 (2.6)**	**21 (3.6)**	**9 (1.8)**	**0 (0.0)**	**5 (0.7)**	**1 (0.2)**	**1 (0.4)**	**0 (0.0)**
Gastrointestinal disorders	**415 (53.0)**	**62 (10.6)**	**46 (9.0)**	**6 (8.6)**	**377 (49.1)**	**40 (8.3)**	**21 (7.8)**	**2 (4.8)**
Constipation	66 (8.4)	6 (1.0)	9 (1.8)	1 (1.4)	60 (7.8)	7 (1.5)	6 (2.2)	0 (0.0)
Diarrhoea	92 (11.7)	12 (2.1)	12 (2.4)	2 (2.9)	71 (9.3)	5 (1.0)	5 (1.9)	0 (0.0)
Nausea	122 (15.6)	11 (1.9)	6 (1.2)	1 (1.4)	120 (15.6)	6 (1.2)	4 (1.5)	1 (2.4)
Vomiting	44 (5.6)	5 (0.9)	5 (1.0)	2 (2.9)	42 (5.5)	5 (1.0)	2 (0.7)	0 (0.0)
General disorders and administration site conditions	**239 (30.5)**	**43 (7.4)**	**24 (4.7)**	**1 (1.4)**	**286 (37.3)**	**41 (8.5)**	**13 (4.9)**	**2 (4.8)**
Asthenia	66 (8.4)	10 (1.7)	4 (0.8)	0 (0.0)	59 (7.7)	7 (1.5)	2 (0.7)	0 (0.0)
Fatigue	75 (9.6)	2 (0.3)	6 (1.2)	0 (0.0)	89 (11.6)	8 (1.7)	3 (1.1)	0 (0.0)
Pyrexia	29 (3.7)	7 (1.2)	4 (0.8)	0 (0.0)	38 (5.0)	6 (1.2)	1 (0.4)	0 (0.0)

Infections and infestations	**126 (16.1)**	**39 (6.7)**	**33 (6.5)**	**5 (7.1)**	**110 (14.3)**	**27 (5.6)**	**17 (6.3)**	**1 (2.4)**
Investigations	**227 (29.0)**	**62 (10.6)**	**43 (8.4)**	**5 (7.1)**	**214 (27.9)**	**59 (12.3)**	**9 (3.4)**	**0 (0.0)**
Neutrophil count decreased	42 (5.4)	4 (0.7)	0 (0.0)	0 (0.0)	51 (6.6)	7 (1.5)	0 (0.0)	0 (0.0)
Weight decreased	23 (2.9)	4 (0.7)	1 (0.2)	0 (0.0)	15 (2.0)	3 (0.6)	3 (1.1)	0 (0.0)
White blood cell count decreased	55 (7.0)	4 (0.7)	0 (0.0)	0 (0.0)	45 (5.9)	10 (2.1)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**188 (24.0)**	**51 (8.7)**	**21 (4.1)**	**2 (2.9)**	**216 (28.2)**	**43 (8.9)**	**8 (3.0)**	**0 (0.0)**
Decreased appetite	82 (10.5)	14 (2.4)	8 (1.6)	1 (1.4)	87 (11.3)	11 (2.3)	3 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	**172 (22.0)**	**39 (6.7)**	**32 (6.3)**	**2 (2.9)**	**153 (19.9)**	**38 (7.9)**	**17 (6.3)**	**0 (0.0)**
Arthralgia	60 (7.7)	10 (1.7)	9 (1.8)	1 (1.4)	42 (5.5)	4 (0.8)	3 (1.1)	0 (0.0)
Back pain	7 (0.9)	4 (0.7)	5 (1.0)	0 (0.0)	17 (2.2)	10 (2.1)	5 (1.9)	0 (0.0)
Myalgia	38 (4.9)	1 (0.2)	6 (1.2)	1 (1.4)	33 (4.3)	6 (1.2)	2 (0.7)	0 (0.0)
Nervous system disorders	**206 (26.3)**	**31 (5.3)**	**20 (3.9)**	**2 (2.9)**	**186 (24.2)**	**31 (6.4)**	**14 (5.2)**	**1 (2.4)**
Neuropathy peripheral	56 (7.2)	5 (0.9)	1 (0.2)	0 (0.0)	45 (5.9)	7 (1.5)	0 (0.0)	1 (2.4)
Peripheral sensory neuropathy	30 (3.8)	3 (0.5)	0 (0.0)	0 (0.0)	36 (4.7)	1 (0.2)	0 (0.0)	0 (0.0)
Psychiatric disorders	**39 (5.0)**	**11 (1.9)**	**6 (1.2)**	**0 (0.0)**	**39 (5.1)**	**12 (2.5)**	**5 (1.9)**	**0 (0.0)**
Insomnia	20 (2.6)	6 (1.0)	3 (0.6)	0 (0.0)	17 (2.2)	7 (1.5)	2 (0.7)	0 (0.0)
Renal and urinary disorders	**29 (3.7)**	**9 (1.5)**	**5 (1.0)**	**1 (1.4)**	**24 (3.1)**	**7 (1.5)**	**3 (1.1)**	**1 (2.4)**
Respiratory, thoracic and mediastinal disorders	**189 (24.1)**	**41 (7.0)**	**33 (6.5)**	**3 (4.3)**	**162 (21.1)**	**65 (13.5)**	**30 (11.2)**	**1 (2.4)**
Cough	22 (2.8)	8 (1.4)	11 (2.2)	0 (0.0)	28 (3.6)	20 (4.2)	6 (2.2)	0 (0.0)
Dyspnoea	26 (3.3)	3 (0.5)	7 (1.4)	1 (1.4)	36 (4.7)	9 (1.9)	2 (0.7)	0 (0.0)
Haemoptysis	20 (2.6)	5 (0.9)	1 (0.2)	0 (0.0)	26 (3.4)	9 (1.9)	6 (2.2)	0 (0.0)
Skin and subcutaneous tissue disorders	**244 (31.2)**	**36 (6.2)**	**18 (3.5)**	**2 (2.9)**	**183 (23.9)**	**19 (3.9)**	**8 (3.0)**	**0 (0.0)**
Alopecia	127 (16.2)	1 (0.2)	0 (0.0)	0 (0.0)	101 (13.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pruritus	25 (3.2)	11 (1.9)	4 (0.8)	0 (0.0)	19 (2.5)	3 (0.6)	3 (1.1)	0 (0.0)
Rash	37 (4.7)	7 (1.2)	3 (0.6)	0 (0.0)	25 (3.3)	4 (0.8)	3 (1.1)	0 (0.0)
Vascular disorders	**33 (4.2)**	**16 (2.7)**	**4 (0.8)**	**1 (1.4)**	**46 (6.0)**	**11 (2.3)**	**2 (0.7)**	**0 (0.0)**

† 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 crossover 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 20.1 terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Drug-related AEs

KEYNOTE-407

Table 36: Exposure-adjusted drug-related adverse events (including multiple occurrences of events) Incidence >0% in one or more treatment groups (ASaT population)

	Event Count and Rate (Events/100 person-months)†	
	Pembro Combo	Control
Number of subjects exposed	278	280
Total exposure‡ person-months	1946.05	1558.21
Total events (rate)	2205 (113.31)	1678 (107.69)
AE Category		
Blood and lymphatic system disorders	**554 (28.5)**	**433 (27.8)**
Anaemia	150 (7.7)	139 (8.9)
Anaemia macrocytic	1 (0.1)	0 (0.0)
Coagulopathy	1 (0.1)	0 (0.0)
Febrile neutropenia	14 (0.7)	12 (0.8)
Hypofibrinogenaemia	1 (0.1)	0 (0.0)
Iron deficiency anaemia	2 (0.1)	1 (0.1)
Leukocytosis	0 (0.0)	2 (0.1)
Leukopenia	57 (2.9)	33 (2.1)
Lymphopenia	9 (0.5)	4 (0.3)
Neutropenia	195 (10.0)	158 (10.1)
Neutrophilia	0 (0.0)	3 (0.2)
Thrombocytopenia	124 (6.4)	81 (5.2)

Gastrointestinal disorders	**344 (17.7)**	**257 (16.5)**
Abdominal discomfort	1 (0.1)	0 (0.0)
Abdominal distension	1 (0.1)	1 (0.1)
Abdominal pain	4 (0.2)	3 (0.2)
Abdominal pain upper	4 (0.2)	2 (0.1)
Anorectal discomfort	0 (0.0)	1 (0.1)
Cheilitis	1 (0.1)	1 (0.1)
Colitis	7 (0.4)	3 (0.2)
Constipation	39 (2.0)	28 (1.8)
Diarrhoea	77 (4.0)	56 (3.6)
Diarrhoea haemorrhagic	1 (0.1)	0 (0.0)
Dry mouth	4 (0.2)	1 (0.1)
Duodenitis	3 (0.2)	0 (0.0)
Dyschezia	1 (0.1)	0 (0.0)
Dyspepsia	2 (0.1)	0 (0.0)
Dysphagia	1 (0.1)	1 (0.1)
Enteritis	0 (0.0)	1 (0.1)
Enterocolitis	0 (0.0)	1 (0.1)
Epigastric discomfort	0 (0.0)	1 (0.1)
Faeces soft	1 (0.1)	1 (0.1)
Flatulence	1 (0.1)	1 (0.1)
Investigations	**243 (12.5)**	**184 (11.8)**
Alanine aminotransferase increased	15 (0.8)	8 (0.5)
Amylase increased	1 (0.1)	0 (0.0)
Aspartate aminotransferase increased	18 (0.9)	5 (0.3)
Endocrine disorders	**40 (2.1)**	**5 (0.3)**
Autoimmune thyroiditis	2 (0.1)	0 (0.0)
Hyperthyroidism	17 (0.9)	2 (0.1)
Hypophysitis	1 (0.1)	0 (0.0)
Hypopituitarism	1 (0.1)	0 (0.0)
Hypothyroidism	16 (0.8)	3 (0.2)
Thyroid disorder	3 (0.2)	0 (0.0)

Table 37: Exposure-adjusted drug-related adverse events by maximum toxicity grade - Incidence >0% in one or more treatment groups (ASaT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	265	(95.3)	249	(88.9)
Grade 1	12	(4.3)	17	(6.1)
Grade 2	101	(36.3)	78	(27.9)
Grade 3	97	(34.9)	106	(37.9)
Grade 4	45	(16.2)	42	(15.0)
Grade 5	10	(3.6)	6	(2.1)
with no adverse events	13	(4.7)	31	(11.1)
Blood and lymphatic system disorders	**191**	**(68.7)**	**163**	**(58.2)**
Grade 1	23	(8.3)	14	(5.0)
Grade 2	69	(24.8)	45	(16.1)
Grade 3	68	(24.5)	77	(27.5)
Grade 4	31	(11.2)	27	(9.6)
Gastrointestinal disorders	**154**	**(55.4)**	**127**	**(45.4)**
Grade 1	84	(30.2)	70	(25.0)
Grade 2	53	(19.1)	44	(15.7)
Grade 3	15	(5.4)	12	(4.3)
Grade 4	2	(0.7)	1	(0.4)
Nervous system disorders	**142**	**(51.1)**	**115**	**(41.1)**
Grade 1	81	(29.1)	71	(25.4)
Grade 2	52	(18.7)	36	(12.9)
Grade 3	9	(3.2)	8	(2.9)
General disorders and administration site conditions	**124**	**(44.6)**	**110**	**(39.3)**
Grade 1	56	(20.1)	50	(17.9)
Grade 2	52	(18.7)	45	(16.1)
Grade 3	14	(5.0)	14	(5.0)
Grade 5	2	(0.7)	1	(0.4)

Investigations	**78**	**(28.1)**	**72**	**(25.7)**
Grade 1	23	(8.3)	16	(5.7)
Grade 2	30	(10.8)	21	(7.5)
Grade 3	12	(4.3)	22	(7.9)
Grade 4	13	(4.7)	13	(4.6)
Musculoskeletal and connective tissue disorders	**75**	**(27.0)**	**64**	**(22.9)**
Grade 1	37	(13.3)	34	(12.1)
Grade 2	35	(12.6)	27	(9.6)
Grade 3	3	(1.1)	3	(1.1)
Respiratory, thoracic and mediastinal disorders	**44**	**(15.8)**	**32**	**(11.4)**
Grade 1	19	(6.8)	21	(7.5)
Grade 2	16	(5.8)	6	(2.1)
Grade 3	5	(1.8)	3	(1.1)
Grade 4	1	(0.4)	1	(0.4)
Grade 5	3	(1.1)	1	(0.4)
Infections and infestations	**34**	**(12.2)**	**19**	**(6.8)**
Grade 1	6	(2.2)	4	(1.4)
Grade 2	12	(4.3)	7	(2.5)
Grade 3	9	(3.2)	5	(1.8)
Grade 4	3	(1.1)	0	(0.0)
Grade 5	4	(1.4)	3	(1.1)
Endocrine disorders	**33**	**(11.9)**	**5**	**(1.8)**
Grade 1	10	(3.6)	5	(1.8)
Grade 2	20	(7.2)	0	(0.0)
Grade 3	3	(1.1)	0	(0.0)
Renal and urinary disorders	**13**	**(4.7)**	**4**	**(1.4)**
Grade 1	5	(1.8)	0	(0.0)
Grade 2	4	(1.4)	1	(0.4)
Grade 3	4	(1.4)	2	(0.7)
Grade 5	0	(0.0)	1	(0.4)
Cardiac disorders	**7**	**(2.5)**	**2**	**(0.7)**
Grade 1	3	(1.1)	2	(0.7)
Grade 3	4	(1.4)	0	(0.0)
Hepatobiliary disorders	**6**	**(2.2)**	**2**	**(0.7)**
Grade 1	0	(0.0)	1	(0.4)
Grade 3	4	(1.4)	1	(0.4)
Grade 4	1	(0.4)	0	(0.0)
Grade 5	1	(0.4)	0	(0.0)

Dataset comparison

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

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	290	(95.7)	249	(88.9)	451	(92.4)	240	(90.9)	2,751	(71.8)
with no adverse events	13	(4.3)	31	(11.1)	37	(7.6)	24	(9.1)	1,079	(28.2)
Alopecia	138	(45.5)	100	(35.7)	30	(6.1)	11	(4.2)	30	(0.8)
Anaemia	130	(42.9)	117	(41.8)	182	(37.3)	111	(42.0)	122	(3.2)
Neutropenia	100	(33.0)	86	(30.7)	107	(21.9)	51	(19.3)	20	(0.5)
Nausea	93	(30.7)	71	(25.4)	229	(46.9)	118	(44.7)	395	(10.3)
Thrombocytopenia	85	(28.1)	58	(20.7)	72	(14.8)	31	(11.7)	29	(0.8)
Diarrhoea	65	(21.5)	47	(16.8)	98	(20.1)	31	(11.7)	445	(11.6)
Fatigue	65	(21.5)	52	(18.6)	185	(37.9)	89	(33.7)	826	(21.6)
Neuropathy peripheral	61	(20.1)	37	(13.2)	12	(2.5)	4	(1.5)	31	(0.8)
Decreased appetite	50	(16.5)	57	(20.4)	101	(20.7)	54	(20.5)	337	(8.8)
Asthenia	46	(15.2)	41	(14.6)	54	(11.1)	33	(12.5)	260	(6.8)
Arthralgia	42	(13.9)	24	(8.6)	21	(4.3)	11	(4.2)	324	(8.5)
Vomiting	38	(12.5)	25	(8.9)	93	(19.1)	50	(18.9)	146	(3.8)
Peripheral sensory neuropathy	37	(12.2)	36	(12.9)	10	(2.0)	4	(1.5)	17	(0.4)
Myalgia	34	(11.2)	26	(9.3)	12	(2.5)	4	(1.5)	171	(4.5)
Rash	34	(11.2)	20	(7.1)	72	(14.8)	26	(9.8)	485	(12.7)
White blood cell count decreased	33	(10.9)	28	(10.0)	28	(5.7)	17	(6.4)	19	(0.5)
Constipation	32	(10.6)	25	(8.9)	82	(16.8)	30	(11.4)	121	(3.2)
Pruritus	30	(9.9)	15	(5.4)	49	(10.0)	15	(5.7)	608	(15.9)
Dysgeusia	28	(9.2)	7	(2.5)	49	(10.0)	21	(8.0)	62	(1.6)
Neutrophil count decreased	27	(8.9)	28	(10.0)	21	(4.3)	11	(4.2)	17	(0.4)
Leukopenia	25	(8.3)	19	(6.8)	23	(4.7)	14	(5.3)	17	(0.4)
Platelet count decreased	24	(7.9)	16	(5.7)	12	(2.5)	7	(2.7)	23	(0.6)
Hypothyroidism	18	(5.9)	3	(1.1)	30	(6.1)	3	(1.1)	309	(8.1)
Hyperthyroidism	17	(5.6)	2	(0.7)	16	(3.3)	7	(2.7)	116	(3.0)
Febrile neutropenia	16	(5.3)	10	(3.6)	26	(5.3)	4	(1.5)	0	(0.0)
Hypomagnesaemia	16	(5.3)	9	(3.2)	28	(5.7)	4	(1.5)	23	(0.6)
Paraesthesia	16	(5.3)	13	(4.6)	13	(2.7)	8	(3.0)	31	(0.8)
Aspartate aminotransferase increased	15	(5.0)	5	(1.8)	46	(9.4)	18	(6.8)	127	(3.3)
Alanine aminotransferase increased	11	(3.6)	8	(2.9)	55	(11.3)	24	(9.1)	132	(3.4)
Dry skin	10	(3.3)	5	(1.8)	16	(3.3)	14	(5.3)	119	(3.1)
Blood creatinine increased	9	(3.0)	6	(2.1)	45	(9.2)	16	(6.1)	51	(1.3)
Oedema peripheral	9	(3.0)	6	(2.1)	38	(7.8)	15	(5.7)	72	(1.9)
Stomatitis	9	(3.0)	11	(3.9)	31	(6.4)	19	(7.2)	48	(1.3)
Mucosal inflammation	8	(2.6)	6	(2.1)	36	(7.4)	15	(5.7)	28	(0.7)
Pyrexia	8	(2.6)	11	(3.9)	30	(6.1)	5	(1.9)	197	(5.1)
Lacrimation increased	1	(0.3)	1	(0.4)	62	(12.7)	21	(8.0)	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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Grade 3-5 AEs

KEYNOTE-407

Table 39: Subjects with grade 3-5 adverse events by decreasing incidence - Incidence ≥1% in one or more treatment groups (ASaT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	194	(69.8)	191	(68.2)
with no adverse events	84	(30.2)	89	(31.8)
Neutropenia	63	(22.7)	69	(24.6)
Anaemia	43	(15.5)	57	(20.4)
Thrombocytopenia	19	(6.8)	18	(6.4)
Pneumonia	18	(6.5)	17	(6.1)
Neutrophil count decreased	17	(6.1)	24	(8.6)
Febrile neutropenia	15	(5.4)	11	(3.9)
Leukopenia	13	(4.7)	12	(4.3)
White blood cell count decreased	12	(4.3)	11	(3.9)
Diarrhoea	11	(4.0)	6	(2.1)
Hyponatraemia	10	(3.6)	5	(1.8)
Fatigue	9	(3.2)	11	(3.9)
Pneumonitis	7	(2.5)	1	(0.4)
Asthenia	6	(2.2)	10	(3.6)
Colitis	6	(2.2)	2	(0.7)
Decreased appetite	6	(2.2)	5	(1.8)
Autoimmune hepatitis	5	(1.8)	0	(0.0)
Hyperkalaemia	5	(1.8)	4	(1.4)
Hypertension	5	(1.8)	5	(1.8)
Hypotension	5	(1.8)	5	(1.8)
Lung infection	5	(1.8)	3	(1.1)
Platelet count decreased	5	(1.8)	7	(2.5)
Arthralgia	4	(1.4)	2	(0.7)
Death	4	(1.4)	3	(1.1)
Dyspnoea	4	(1.4)	3	(1.1)
Haemoptysis	4	(1.4)	3	(1.1)
Pleural effusion	4	(1.4)	3	(1.1)
Sepsis	4	(1.4)	3	(1.1)
Syncope	4	(1.4)	3	(1.1)
Acute kidney injury	3	(1.1)	5	(1.8)
Gamma-glutamyltransferase increased	3	(1.1)	4	(1.4)
Hypokalaemia	3	(1.1)	1	(0.4)
Infusion related reaction	3	(1.1)	1	(0.4)
Nausea	3	(1.1)	4	(1.4)
Neuropathy peripheral	3	(1.1)	2	(0.7)
Pulmonary embolism	3	(1.1)	4	(1.4)
Pulmonary haemorrhage	3	(1.1)	1	(0.4)
Pyrexia	3	(1.1)	3	(1.1)
Respiratory failure	3	(1.1)	0	(0.0)
Aspartate aminotransferase increased	2	(0.7)	3	(1.1)
Back pain	2	(0.7)	5	(1.8)
Constipation	2	(0.7)	3	(1.1)
Cough	2	(0.7)	3	(1.1)
Hypercalcaemia	2	(0.7)	5	(1.8)
Hypophosphataemia	2	(0.7)	3	(1.1)
Lymphocyte count decreased	2	(0.7)	3	(1.1)
Alopecia	1	(0.4)	3	(1.1)
Hypomagnesaemia	1	(0.4)	4	(1.4)
Septic shock	1	(0.4)	3	(1.1)
Vomiting	1	(0.4)	6	(2.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

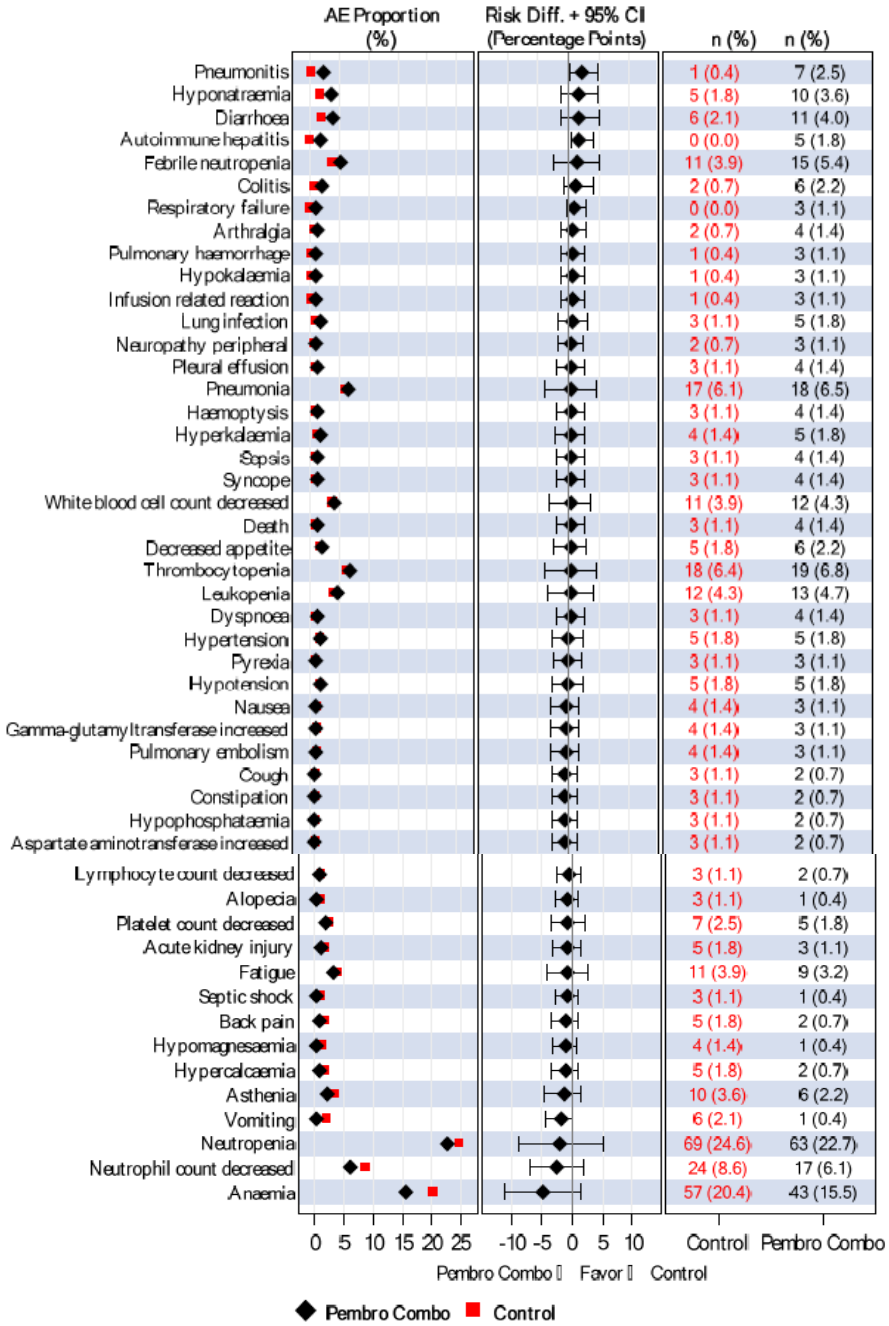


Figure 15: Between-treatment comparisons in grade 3-5 adverse events – selected adverse events (≥1% incidence) and sorted by risk difference (ASaT population) – Pembro combo (N=278) vs. control (N=280)

Dataset comparison

Table 40: Subjects with grade 3-5 adverse events (Incidence ≥1% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	209	(69.0)	191	(68.2)	323	(66.2)	167	(63.3)	1,802	(47.0)
with no adverse events	94	(31.0)	89	(31.8)	165	(33.8)	97	(36.7)	2,028	(53.0)
Neutropenia	65	(21.5)	69	(24.6)	66	(13.5)	26	(9.8)	11	(0.3)
Anaemia	47	(15.5)	57	(20.4)	77	(15.8)	40	(15.2)	159	(4.2)
Pneumonia	23	(7.6)	17	(6.1)	27	(5.5)	16	(6.1)	102	(2.7)
Thrombocytopenia	19	(6.3)	18	(6.4)	34	(7.0)	16	(6.1)	15	(0.4)
Febrile neutropenia	17	(5.6)	11	(3.9)	28	(5.7)	5	(1.9)	4	(0.1)
Neutrophil count decreased	17	(5.6)	24	(8.6)	12	(2.5)	4	(1.5)	5	(0.1)
Leukopenia	14	(4.6)	12	(4.3)	9	(1.8)	1	(0.4)	7	(0.2)
White blood cell count decreased	13	(4.3)	11	(3.9)	9	(1.8)	6	(2.3)	3	(0.1)
Fatigue	12	(4.0)	11	(3.9)	26	(5.3)	5	(1.9)	103	(2.7)
Diarrhoea	11	(3.6)	6	(2.1)	23	(4.7)	7	(2.7)	55	(1.4)
Hyponatraemia	11	(3.6)	5	(1.8)	9	(1.8)	7	(2.7)	91	(2.4)
Decreased appetite	7	(2.3)	5	(1.8)	7	(1.4)	1	(0.4)	45	(1.2)
Pneumonitis	7	(2.3)	1	(0.4)	12	(2.5)	4	(1.5)	49	(1.3)
Asthenia	6	(2.0)	10	(3.6)	26	(5.3)	7	(2.7)	45	(1.2)
Colitis	6	(2.0)	2	(0.7)	3	(0.6)	0	(0.0)	47	(1.2)
Hypertension	6	(2.0)	5	(1.8)	11	(2.3)	5	(1.9)	50	(1.3)
Hypotension	6	(2.0)	5	(1.8)	4	(0.8)	0	(0.0)	15	(0.4)
Autoimmune hepatitis	5	(1.7)	0	(0.0)	1	(0.2)	0	(0.0)	9	(0.2)
Dyspnoea	5	(1.7)	3	(1.1)	20	(4.1)	11	(4.2)	95	(2.5)
Hyperkalaemia	5	(1.7)	4	(1.4)	0	(0.0)	2	(0.8)	17	(0.4)
Lung infection	5	(1.7)	3	(1.1)	3	(0.6)	0	(0.0)	15	(0.4)
Platelet count decreased	5	(1.7)	7	(2.5)	7	(1.4)	2	(0.8)	6	(0.2)
Arthralgia	4	(1.3)	2	(0.7)	4	(0.8)	2	(0.8)	22	(0.6)
Death	4	(1.3)	3	(1.1)	5	(1.0)	1	(0.4)	19	(0.5)
Haemoptysis	4	(1.3)	3	(1.1)	3	(0.6)	2	(0.8)	10	(0.3)
Nausea	4	(1.3)	4	(1.4)	15	(3.1)	7	(2.7)	40	(1.0)
Pleural effusion	4	(1.3)	3	(1.1)	8	(1.6)	6	(2.3)	48	(1.3)
Sepsis	4	(1.3)	3	(1.1)	7	(1.4)	4	(1.5)	21	(0.5)
Syncope	4	(1.3)	3	(1.1)	12	(2.5)	3	(1.1)	19	(0.5)
Acute kidney injury	3	(1.0)	5	(1.8)	13	(2.7)	2	(0.8)	41	(1.1)
Chronic obstructive pulmonary disease	3	(1.0)	2	(0.7)	7	(1.4)	4	(1.5)	22	(0.6)
Gamma-glutamyltransferase increased	3	(1.0)	4	(1.4)	4	(0.8)	2	(0.8)	23	(0.6)

Hypokalaemia	3	(1.0)	1	(0.4)	15	(3.1)	6	(2.3)	33	(0.9)
Infusion related reaction	3	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	3	(1.0)	2	(0.7)	0	(0.0)	0	(0.0)	2	(0.1)
Pulmonary embolism	3	(1.0)	4	(1.4)	6	(1.2)	7	(2.7)	58	(1.5)
Pulmonary haemorrhage	3	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)	3	(0.1)
Pyrexia	3	(1.0)	3	(1.1)	2	(0.4)	1	(0.4)	21	(0.5)
Respiratory failure	3	(1.0)	0	(0.0)	1	(0.2)	3	(1.1)	18	(0.5)
Alanine aminotransferase increased	2	(0.7)	2	(0.7)	5	(1.0)	4	(1.5)	38	(1.0)
Aspartate aminotransferase increased	2	(0.7)	3	(1.1)	4	(0.8)	3	(1.1)	41	(1.1)
Back pain	2	(0.7)	5	(1.8)	6	(1.2)	4	(1.5)	53	(1.4)
Chest pain	2	(0.7)	1	(0.4)	0	(0.0)	3	(1.1)	15	(0.4)
Constipation	2	(0.7)	3	(1.1)	4	(0.8)	2	(0.8)	20	(0.5)
Cough	2	(0.7)	3	(1.1)	0	(0.0)	0	(0.0)	8	(0.2)
Dehydration	2	(0.7)	2	(0.7)	14	(2.9)	4	(1.5)	42	(1.1)
Hypercalcaemia	2	(0.7)	5	(1.8)	0	(0.0)	0	(0.0)	19	(0.5)
Hyperglycaemia	2	(0.7)	0	(0.0)	6	(1.2)	2	(0.8)	45	(1.2)
Hypophosphataemia	2	(0.7)	3	(1.1)	11	(2.3)	3	(1.1)	19	(0.5)
Lymphocyte count decreased	2	(0.7)	3	(1.1)	6	(1.2)	2	(0.8)	16	(0.4)
Upper respiratory tract infection	2	(0.7)	0	(0.0)	6	(1.2)	2	(0.8)	4	(0.1)
Urinary tract infection	2	(0.7)	1	(0.4)	7	(1.4)	2	(0.8)	67	(1.7)
Vomiting	2	(0.7)	6	(2.1)	16	(3.3)	6	(2.3)	33	(0.9)
Alopecia	1	(0.3)	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Atrial fibrillation	1	(0.3)	2	(0.7)	6	(1.2)	1	(0.4)	15	(0.4)
Blood alkaline phosphatase increased	1	(0.3)	1	(0.4)	0	(0.0)	3	(1.1)	30	(0.8)
General physical health deterioration	1	(0.3)	1	(0.4)	5	(1.0)	3	(1.1)	29	(0.8)
Hypocalcaemia	1	(0.3)	1	(0.4)	5	(1.0)	1	(0.4)	4	(0.1)
Hypomagnesaemia	1	(0.3)	4	(1.4)	7	(1.4)	0	(0.0)	0	(0.0)
Lower respiratory tract infection	1	(0.3)	1	(0.4)	2	(0.4)	3	(1.1)	13	(0.3)
Myocardial infarction	1	(0.3)	0	(0.0)	5	(1.0)	0	(0.0)	7	(0.2)
Rash	1	(0.3)	0	(0.0)	9	(1.8)	3	(1.1)	16	(0.4)
Septic shock	1	(0.3)	3	(1.1)	1	(0.2)	1	(0.4)	8	(0.2)
Cellulitis	0	(0.0)	0	(0.0)	11	(2.3)	2	(0.8)	17	(0.4)
Pancytopenia	0	(0.0)	0	(0.0)	7	(1.4)	5	(1.9)	1	(0.0)

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

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

Non-serious adverse events up to 30 days 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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Drug-related Grade 3-5 AEs

KEYNOTE-407

Table 41: Subjects with drug-related grade 3-5 adverse events by decreasing incidence - Incidence ≥1% in one or more treatment groups (ASaT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	152	(54.7)	154	(55.0)
with no adverse events	126	(45.3)	126	(45.0)
Neutropenia	59	(21.2)	63	(22.5)
Anaemia	38	(13.7)	43	(15.4)
Thrombocytopenia	18	(6.5)	16	(5.7)
Neutrophil count decreased	17	(6.1)	24	(8.6)
Febrile neutropenia	14	(5.0)	10	(3.6)
Leukopenia	12	(4.3)	12	(4.3)
White blood cell count decreased	11	(4.0)	10	(3.6)
Diarrhoea	8	(2.9)	4	(1.4)
Pneumonia	8	(2.9)	3	(1.1)
Fatigue	7	(2.5)	7	(2.5)
Colitis	6	(2.2)	2	(0.7)
Autoimmune hepatitis	5	(1.8)	0	(0.0)
Decreased appetite	5	(1.8)	4	(1.4)
Hyponatraemia	5	(1.8)	1	(0.4)
Platelet count decreased	5	(1.8)	6	(2.1)
Pneumonitis	5	(1.8)	0	(0.0)
Asthenia	3	(1.1)	6	(2.1)
Infusion related reaction	3	(1.1)	1	(0.4)
Neuropathy peripheral	3	(1.1)	2	(0.7)
Sepsis	3	(1.1)	0	(0.0)
Hypotension	2	(0.7)	3	(1.1)
Nausea	2	(0.7)	3	(1.1)
Acute kidney injury	1	(0.4)	3	(1.1)
Alopecia	1	(0.4)	3	(1.1)
Vomiting	1	(0.4)	3	(1.1)
Gamma-glutamyltransferase increased	0	(0.0)	3	(1.1)

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

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

For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.

Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Dataset comparison

Table 42: Subjects with drug-related grade 3-5 adverse events (Incidence ≥1% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	162	(53.5)	154	(55.0)	231	(47.3)	98	(37.1)	577	(15.1)
with no adverse events	141	(46.5)	126	(45.0)	257	(52.7)	166	(62.9)	3,253	(84.9)
Neutropenia	61	(20.1)	63	(22.5)	61	(12.5)	24	(9.1)	8	(0.2)
Anaemia	40	(13.2)	43	(15.4)	64	(13.1)	36	(13.6)	18	(0.5)
Thrombocytopenia	18	(5.9)	16	(5.7)	33	(6.8)	15	(5.7)	4	(0.1)
Neutrophil count decreased	17	(5.6)	24	(8.6)	11	(2.3)	4	(1.5)	3	(0.1)
Febrile neutropenia	16	(5.3)	10	(3.6)	25	(5.1)	4	(1.5)	0	(0.0)
Leukopenia	13	(4.3)	12	(4.3)	9	(1.8)	1	(0.4)	3	(0.1)
White blood cell count decreased	12	(4.0)	10	(3.6)	8	(1.6)	6	(2.3)	1	(0.0)
Fatigue	9	(3.0)	7	(2.5)	22	(4.5)	3	(1.1)	45	(1.2)
Diarrhoea	8	(2.6)	4	(1.4)	16	(3.3)	5	(1.9)	40	(1.0)
Pneumonia	8	(2.6)	3	(1.1)	5	(1.0)	1	(0.4)	9	(0.2)
Colitis	6	(2.0)	2	(0.7)	3	(0.6)	0	(0.0)	41	(1.1)
Autoimmune hepatitis	5	(1.7)	0	(0.0)	1	(0.2)	0	(0.0)	9	(0.2)
Decreased appetite	5	(1.7)	4	(1.4)	5	(1.0)	1	(0.4)	11	(0.3)
Hyponatraemia	5	(1.7)	1	(0.4)	3	(0.6)	1	(0.4)	16	(0.4)
Platelet count decreased	5	(1.7)	6	(2.1)	6	(1.2)	1	(0.4)	2	(0.1)
Pneumonitis	5	(1.7)	0	(0.0)	11	(2.3)	3	(1.1)	45	(1.2)
Asthenia	3	(1.0)	6	(2.1)	16	(3.3)	3	(1.1)	17	(0.4)
Infusion related reaction	3	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	3	(1.0)	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Sepsis	3	(1.0)	0	(0.0)	2	(0.4)	1	(0.4)	0	(0.0)
Hypotension	2	(0.7)	3	(1.1)	1	(0.2)	0	(0.0)	1	(0.0)
Lymphocyte count decreased	2	(0.7)	2	(0.7)	5	(1.0)	2	(0.8)	5	(0.1)
Nausea	2	(0.7)	3	(1.1)	13	(2.7)	4	(1.5)	12	(0.3)
Acute kidney injury	1	(0.3)	3	(1.1)	10	(2.0)	1	(0.4)	4	(0.1)
Alanine aminotransferase increased	1	(0.3)	1	(0.4)	5	(1.0)	4	(1.5)	20	(0.5)
Alopecia	1	(0.3)	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypomagnesaemia	1	(0.3)	2	(0.7)	5	(1.0)	0	(0.0)	0	(0.0)
Vomiting	1	(0.3)	3	(1.1)	8	(1.6)	4	(1.5)	10	(0.3)
Cellulitis	0	(0.0)	0	(0.0)	7	(1.4)	0	(0.0)	1	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	3	(1.1)	3	(0.6)	1	(0.4)	9	(0.2)
Pancytopenia	0	(0.0)	0	(0.0)	7	(1.4)	5	(1.9)	1	(0.0)
Rash	0	(0.0)	0	(0.0)	7	(1.4)	3	(1.1)	12	(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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Adverse Drug Reactions (ADRs)

The Applicant has provided a Table of ADRs for the use of pembrolizumab in combination with chemotherapy for first-line treatment of patients with NSCLC deriving from the pooled safety data of studies KEYNOTE-189, KEYNOTE-021, and KEYNOTE-407.

Table 43: Adverse Reactions in Patients Treated with Pembrolizumab

	Combination Therapy	Frequency (n=791)	Grade of Severity (Grade 3-5) (n)
Infections and infestations			
Common	pneumonia	8.8% (70)	50
Blood and lymphatic system disorders			
Very common	neutropenia anaemia thrombocytopeni	28.6% (226) 47.7% (377) 21.0% (166)	131 124 53
Common	febrile neutropenia leukopenia lymphopenia	5.9% (47) 6.4% (51) 1.4% (11)	45 23 2
Uncommon	eosinophilia	0.1% (1)	1
Immune system disorders			
Common	infusion related reaction[a]	2.8% (22)	6
Endocrine disorders			
Common	hypothyroidism hyperthyroidism	8.0% (63) 5.2% (41)	3 1
Uncommon	hypophysitis[c] thyroiditis adrenal insufficiency	0.8% (6) 0.5% (4) 0.3% (2)	2 1 1
Metabolism and nutrition disorders			
Very common	decreased appetite	28.3% (224)	14
Common	hyponatraemia hypokalaemia hypocalcaemi	4.6% (36) 9.7% (77) 3.7% (29)	20 18 6
Uncommon	type 1 diabetes mellitus	0.1% (1)	1
Psychiatric disorders			
Common	insomnia	9.0% (71)	1
Nervous system disorders			
Very common	dizziness neuropathy peripheral dysgeusia	11.6% (92) 12.1% (96) 11.5% (91) 12.1% (96)	3 3 1 1
Common	lethargy	2.0% (16)	0
Uncommon	epilepsy	0.3% (2)	1
Eye disorders			
Common	dry eye	4.0% (32)	0
Cardiac disorders			
Uncommon	pericardial effusion pericarditis	0.3% (2) 0.1% (1)	2 1
Vascular disorders			
Common	hypertension	5.9% (47)	17
Respiratory, thoracic and mediastinal			
Very common	dyspnoea cough	20.0% (158) 20.1% (159)	25 2
Common	pneumonitis	5.2% (41)	19
Gastrointestinal disorders			
Very common	diarrhoea nausea vomiting constipation abdominal	31.4% (248) 49.4% (391) 22.1% (175) 33.8% (267) 15.2% (120)	34 19 18 6 4
Common	colitis[k] dry mouth	2.9% (23) 3.4% (27)	11 0
Uncommon	pancreatitis[l]	0.4% (3)	2
Hepatobiliary disorders			
Common	hepatitis[m]	1.3% (10)	9
Skin and subcutaneous tissue disorders			

Very common	rash[n] alopecia pruritus	27.4% (217) 22.4% (177) 15.7% (124)	14 1 1
Common	severe skin reactions[p] erythema dermatitis acneiform dry skin	1.9% (15) 3.8% (30) 1.0% (8) 5.1% (40)	13 1 0 0
Uncommon	psoriasis dermatitis eczema hair colour changes lichenoid keratosis papule vitiligo[q]	0.5% (4) 0.6% (5) 0.4% (3) 0.1% (1) 0.1% (1) 0.1% (1) 0.5% (4)	2 0 0 0 0 0 0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[s] arthralgia	23.0% (182) 15.5% (123)	9 8
Common	myositis[t] pain in extremity	7.8% (62) 9.1% (72) 2.1% (17)	3 2 0
Uncommon	tenosynovitis[v]	0.4% (3)	1
Renal and urinary disorders			
Common	nephritis[w] acute kidney injury	1.1% (9) 5.1% (40)	8 16
Uncommon			
General disorders and administration site			
Very common	fatigue asthenia oedema[x] pyrexia	38.4% (304) 18.5% (146) 23.3% (184) 16.1% (127)	38 32 5 5
Common	Chills influenza like illness	2.0% (16) 2.4% (19)	0 0
Investigations			
Very common	alanine aminotransferase increased blood creatinine increased	10.4% (82) 11.3% (89)	7 3
Common	aspartate aminotransferase increased hypercalcaemia blood alkaline phosphatase increased	9.7% (77) 1.8% (14) 3.4% (27)	6 2 1
Uncommon	amylase increased blood bilirubin increased	0.3% (2) 0.8% (6)	1 0

The following terms represent a group of related events that describe a medical condition rather than a single event.
a. infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome)
b. hypothyroidism (myxoedema)
c. hypophysitis (hypopituitarism)
d. thyroiditis (autoimmune thyroiditis and thyroid disorder)
e. type 1 diabetes mellitus (diabetic ketoacidosis)
f. Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
g. myasthenic syndrome (myasthenia gravis)
h. uveitis (iritis and iridocyclitis)
i. pneumonitis (interstitial lung disease)
j. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
k. colitis (colitis microscopic, enterocolitis, and autoimmune colitis)
l. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
m. hepatitis (autoimmune hepatitis and drug induced liver injury)
n. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
o. pruritus (urticaria, urticaria papular, pruritus generalised and pruritus genital)
p. severe skin reactions (dermatitis bullous, dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigus, skin necrosis, toxic skin eruption and Grade ≥ 3 of the following: acute febrile neutropenic dermatosis, contusion, decubitus ulcer, dermatitis psoriasiform, drug eruption, jaundice, pemphigoid, pruritus, pruritus generalised, rash, rash erythematous, rash generalised, rash maculo papular, rash pruritic, rash pustular and skin lesion)
q. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
r. lichenoid keratosis (lichen planus and lichen sclerosus)
s. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
t. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis)
u. arthritis (joint swelling, polyarthritis and joint effusion)
v. tenosynovitis (tendonitis, synovitis and tendon pain)
w. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome)
x. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema)

Serious adverse event/deaths/other significant events

SAEs

KEYNOTE-407

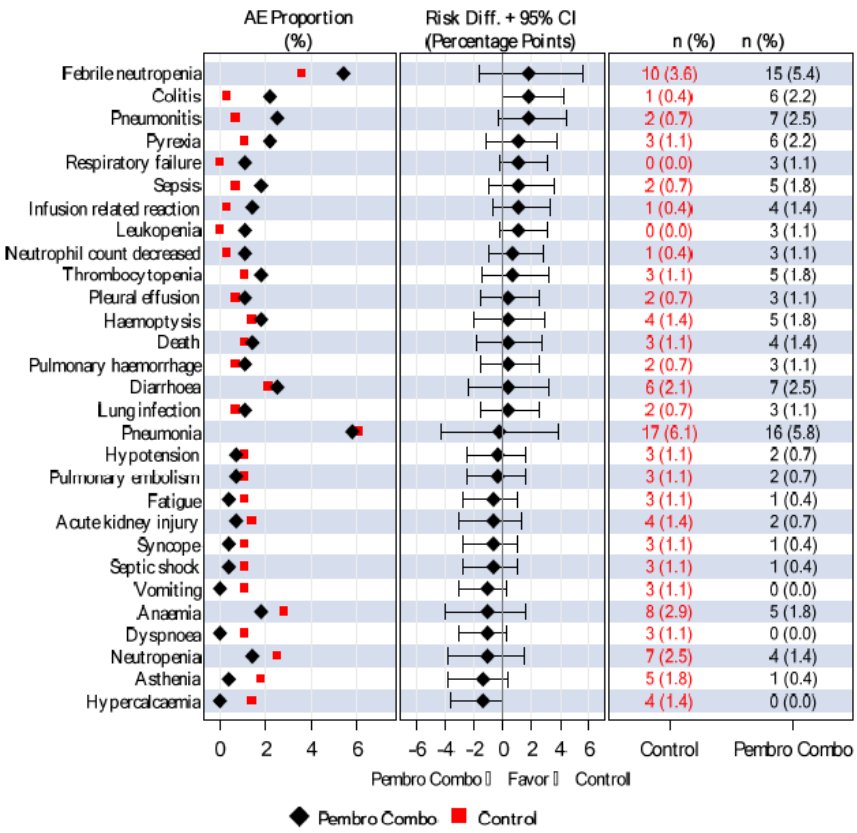


Figure 16: Between-treatment comparisons in serious adverse events – selected adverse events (≥1% incidence) and sorted by risk difference (ASaT population) – Pembro combo (N=278) vs. control (N=280)

Dataset comparison

Table 44: Subjects with serious adverse events up to 90 days of last dose (Incidence ≥1% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	125	(41.3)	107	(38.2)	244	(50.0)	115	(43.6)	1,450	(37.9)
with no adverse events	178	(58.7)	173	(61.8)	244	(50.0)	149	(56.4)	2,380	(62.1)
Pneumonia	21	(6.9)	17	(6.1)	27	(5.5)	17	(6.4)	114	(3.0)
Febrile neutropenia	17	(5.6)	10	(3.6)	24	(4.9)	5	(1.9)	2	(0.1)
Colitis	7	(2.3)	1	(0.4)	4	(0.8)	0	(0.0)	41	(1.1)
Diarrhoea	7	(2.3)	6	(2.1)	15	(3.1)	7	(2.7)	37	(1.0)
Pneumonitis	7	(2.3)	2	(0.7)	13	(2.7)	4	(1.5)	69	(1.8)
Anaemia	6	(2.0)	8	(2.9)	15	(3.1)	12	(4.5)	48	(1.3)
Pyrexia	6	(2.0)	3	(1.1)	11	(2.3)	4	(1.5)	51	(1.3)
Haemoptysis	5	(1.7)	4	(1.4)	4	(0.8)	2	(0.8)	14	(0.4)
Sepsis	5	(1.7)	2	(0.7)	7	(1.4)	3	(1.1)	21	(0.5)
Thrombocytopenia	5	(1.7)	3	(1.1)	14	(2.9)	6	(2.3)	6	(0.2)
Death	4	(1.3)	3	(1.1)	5	(1.0)	1	(0.4)	19	(0.5)
Infusion related reaction	4	(1.3)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.1)
Neutropenia	4	(1.3)	7	(2.5)	10	(2.0)	2	(0.8)	1	(0.0)
Chronic obstructive pulmonary disease	3	(1.0)	2	(0.7)	6	(1.2)	4	(1.5)	22	(0.6)
Leukopenia	3	(1.0)	0	(0.0)	1	(0.2)	1	(0.4)	0	(0.0)
Lung infection	3	(1.0)	2	(0.7)	3	(0.6)	0	(0.0)	13	(0.3)
Neutrophil count decreased	3	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.0)
Pleural effusion	3	(1.0)	2	(0.7)	9	(1.8)	4	(1.5)	56	(1.5)
Pulmonary haemorrhage	3	(1.0)	2	(0.7)	0	(0.0)	0	(0.0)	3	(0.1)
Respiratory failure	3	(1.0)	0	(0.0)	1	(0.2)	3	(1.1)	16	(0.4)
Acute kidney injury	2	(0.7)	4	(1.4)	14	(2.9)	1	(0.4)	41	(1.1)
Arthralgia	2	(0.7)	0	(0.0)	5	(1.0)	0	(0.0)	9	(0.2)
Hypotension	2	(0.7)	3	(1.1)	0	(0.0)	0	(0.0)	7	(0.2)
Pulmonary embolism	2	(0.7)	3	(1.1)	6	(1.2)	5	(1.9)	48	(1.3)
Upper respiratory tract infection	2	(0.7)	0	(0.0)	7	(1.4)	2	(0.8)	4	(0.1)
Urinary tract infection	2	(0.7)	1	(0.4)	5	(1.0)	1	(0.4)	53	(1.4)
Asthenia	1	(0.3)	5	(1.8)	8	(1.6)	0	(0.0)	14	(0.4)
Dyspnoea	1	(0.3)	3	(1.1)	8	(1.6)	5	(1.9)	57	(1.5)
Fatigue	1	(0.3)	3	(1.1)	5	(1.0)	0	(0.0)	17	(0.4)
Lower respiratory tract infection	1	(0.3)	1	(0.4)	2	(0.4)	3	(1.1)	15	(0.4)
Myocardial infarction	1	(0.3)	0	(0.0)	5	(1.0)	0	(0.0)	8	(0.2)
Nausea	1	(0.3)	2	(0.7)	5	(1.0)	7	(2.7)	20	(0.5)
Septic shock	1	(0.3)	3	(1.1)	1	(0.2)	1	(0.4)	6	(0.2)
Syncope	1	(0.3)	3	(1.1)	2	(0.4)	3	(1.1)	11	(0.3)
Vomiting	1	(0.3)	3	(1.1)	9	(1.8)	5	(1.9)	20	(0.5)
Cellulitis	0	(0.0)	0	(0.0)	10	(2.0)	1	(0.4)	17	(0.4)
Dehydration	0	(0.0)	1	(0.4)	7	(1.4)	3	(1.1)	31	(0.8)
Hypercalcaemia	0	(0.0)	4	(1.4)	0	(0.0)	0	(0.0)	16	(0.4)
Pancytopenia	0	(0.0)	0	(0.0)	5	(1.0)	4	(1.5)	1	(0.0)

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

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

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

[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Drug-related SAEs

KEYNOTE-407

Table 45: Subjects with drug-related serious adverse events up to 90 days of last dose by decreasing incidence (Incidence >0% in one or more treatment groups) - ASaT population

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	70	(25.2)	51	(18.2)
with no adverse events	208	(74.8)	229	(81.8)
Febrile neutropenia	14	(5.0)	9	(3.2)
Pneumonia	7	(2.5)	3	(1.1)
Colitis	6	(2.2)	1	(0.4)
Anaemia	5	(1.8)	5	(1.8)
Pneumonitis	5	(1.8)	1	(0.4)
Thrombocytopenia	5	(1.8)	3	(1.1)
Diarrhoea	4	(1.4)	4	(1.4)
Infusion related reaction	4	(1.4)	1	(0.4)
Neutropenia	4	(1.4)	7	(2.5)
Sepsis	4	(1.4)	0	(0.0)
Leukopenia	3	(1.1)	0	(0.0)
Neutrophil count decreased	3	(1.1)	1	(0.4)
Pyrexia	3	(1.1)	0	(0.0)
Autoimmune hepatitis	2	(0.7)	0	(0.0)
Death	2	(0.7)	0	(0.0)
Duodenitis	2	(0.7)	0	(0.0)
Interstitial lung disease	2	(0.7)	2	(0.7)
Acute kidney injury	1	(0.4)	3	(1.1)
Asthenia	1	(0.4)	4	(1.4)
Atrial flutter	1	(0.4)	0	(0.0)
Autoimmune thyroiditis	1	(0.4)	0	(0.0)
Biliary tract infection	1	(0.4)	0	(0.0)
Cerebrovascular accident	1	(0.4)	0	(0.0)
Decreased appetite	1	(0.4)	1	(0.4)
Drug hypersensitivity	1	(0.4)	0	(0.0)
Fatigue	1	(0.4)	3	(1.1)
General physical health deterioration	1	(0.4)	0	(0.0)
Hepatic failure	1	(0.4)	0	(0.0)
Hyperthyroidism	1	(0.4)	0	(0.0)
Hyponatraemia	1	(0.4)	1	(0.4)
Hypopituitarism	1	(0.4)	0	(0.0)
Hypotension	1	(0.4)	2	(0.7)
Lung abscess	1	(0.4)	0	(0.0)

Lung infection	1	(0.4)	0	(0.0)
Myocardial infarction	1	(0.4)	0	(0.0)
Necrotising fasciitis	1	(0.4)	0	(0.0)
Nephritis	1	(0.4)	1	(0.4)
Neuropathy peripheral	1	(0.4)	0	(0.0)
Pericardial effusion	1	(0.4)	0	(0.0)
Platelet count decreased	1	(0.4)	0	(0.0)
Psoriasis	1	(0.4)	0	(0.0)
Pulmonary haemorrhage	1	(0.4)	1	(0.4)
Respiratory failure	1	(0.4)	0	(0.0)
Tubulointerstitial nephritis	1	(0.4)	0	(0.0)
Urosepsis	1	(0.4)	0	(0.0)
Vasculitis	1	(0.4)	0	(0.0)
White blood cell count decreased	1	(0.4)	0	(0.0)
Alanine aminotransferase increased	0	(0.0)	1	(0.4)
Arterial disorder	0	(0.0)	1	(0.4)
Candida infection	0	(0.0)	1	(0.4)
Cholangitis	0	(0.0)	1	(0.4)
Dehydration	0	(0.0)	1	(0.4)
Device related infection	0	(0.0)	1	(0.4)
Enterocolitis	0	(0.0)	1	(0.4)
Epistaxis	0	(0.0)	1	(0.4)
Gastric ulcer haemorrhage	0	(0.0)	1	(0.4)
Hyperkalaemia	0	(0.0)	1	(0.4)
Malaise	0	(0.0)	1	(0.4)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.4)
Myalgia	0	(0.0)	1	(0.4)
Nausea	0	(0.0)	1	(0.4)
Oedema peripheral	0	(0.0)	1	(0.4)
Pneumonia bacterial	0	(0.0)	1	(0.4)
Septic shock	0	(0.0)	2	(0.7)
Tumour necrosis	0	(0.0)	1	(0.4)
Uraemic encephalopathy	0	(0.0)	1	(0.4)
Vomiting	0	(0.0)	1	(0.4)

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.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Dataset comparison

Table 46: Subjects with drug-related serious adverse events up to 90 days of last dose (Incidence >1% in one or more treatment groups) by decreasing frequency of preferred term – Subjects in ASaT population

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	77	(25.4)	51	(18.2)	129	(26.4)	49	(18.6)	403	(10.5)
with no adverse events	226	(74.6)	229	(81.8)	359	(73.6)	215	(81.4)	3,427	(89.5)
Febrile neutropenia	16	(5.3)	9	(3.2)	22	(4.5)	4	(1.5)	0	(0.0)
Colitis	7	(2.3)	1	(0.4)	4	(0.8)	0	(0.0)	34	(0.9)
Pneumonia	7	(2.3)	3	(1.1)	5	(1.0)	1	(0.4)	10	(0.3)
Anaemia	5	(1.7)	5	(1.8)	10	(2.0)	12	(4.5)	4	(0.1)
Pneumonitis	5	(1.7)	1	(0.4)	12	(2.5)	3	(1.1)	65	(1.7)
Thrombocytopenia	5	(1.7)	3	(1.1)	14	(2.9)	6	(2.3)	2	(0.1)
Diarrhoea	4	(1.3)	4	(1.4)	12	(2.5)	6	(2.3)	24	(0.6)
Infusion related reaction	4	(1.3)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.1)
Neutropenia	4	(1.3)	7	(2.5)	7	(1.4)	2	(0.8)	1	(0.0)
Sepsis	4	(1.3)	0	(0.0)	2	(0.4)	1	(0.4)	0	(0.0)
Leukopenia	3	(1.0)	0	(0.0)	1	(0.2)	1	(0.4)	0	(0.0)
Neutrophil count decreased	3	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	3	(1.0)	0	(0.0)	6	(1.2)	1	(0.4)	13	(0.3)
Acute kidney injury	1	(0.3)	3	(1.1)	10	(2.0)	0	(0.0)	6	(0.2)
Asthenia	1	(0.3)	4	(1.4)	3	(0.6)	0	(0.0)	4	(0.1)
Fatigue	1	(0.3)	3	(1.1)	5	(1.0)	0	(0.0)	5	(0.1)
Cellulitis	0	(0.0)	0	(0.0)	6	(1.2)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	1	(0.4)	4	(0.8)	4	(1.5)	6	(0.2)
Pancytopenia	0	(0.0)	0	(0.0)	5	(1.0)	4	(1.5)	1	(0.0)
Vomiting	0	(0.0)	1	(0.4)	6	(1.2)	4	(1.5)	6	(0.2)

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

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

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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Deaths

KEYNOTE-407

Table 47: Subjects with adverse events resulting in death by decreasing incidence (Incidence >0% in one or more treatment groups) - ASaT population

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	23	(8.3)	18	(6.4)
with no adverse events	255	(91.7)	262	(93.6)
Death	4	(1.4)	3	(1.1)
Respiratory failure	3	(1.1)	0	(0.0)
Sepsis	3	(1.1)	1	(0.4)
Cardiac arrest	2	(0.7)	1	(0.4)
Pulmonary haemorrhage	2	(0.7)	1	(0.4)
Cardiac failure	1	(0.4)	0	(0.0)
Circulatory collapse	1	(0.4)	0	(0.0)
Hepatic failure	1	(0.4)	0	(0.0)
Intestinal perforation	1	(0.4)	0	(0.0)
Lung abscess	1	(0.4)	0	(0.0)
Necrotising fasciitis	1	(0.4)	0	(0.0)
Pneumonia	1	(0.4)	1	(0.4)
Pneumonitis	1	(0.4)	1	(0.4)
Pulmonary sepsis	1	(0.4)	0	(0.0)
Acute kidney injury	0	(0.0)	1	(0.4)
Cardio-respiratory arrest	0	(0.0)	2	(0.7)
Haemothorax	0	(0.0)	1	(0.4)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.4)
Pleural effusion	0	(0.0)	1	(0.4)
Pulmonary mycosis	0	(0.0)	1	(0.4)
Septic shock	0	(0.0)	3	(1.1)

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

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

For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.

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: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Dataset comparison

Table 48: Subjects with adverse events resulting in death up to 90 days of last dose (Incidence >1% in one or more treatment groups) by decreasing frequency of preferred term – Subjects in ASaT population

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	23	(7.6)	18	(6.4)	30	(6.1)	14	(5.3)	157	(4.1)
with no adverse events	280	(92.4)	262	(93.6)	458	(93.9)	250	(94.7)	3,673	(95.9)
Death	4	(1.3)	3	(1.1)	5	(1.0)	1	(0.4)	19	(0.5)
Respiratory failure	3	(1.0)	0	(0.0)	1	(0.2)	2	(0.8)	8	(0.2)
Sepsis	3	(1.0)	1	(0.4)	1	(0.2)	1	(0.4)	3	(0.1)
Septic shock	0	(0.0)	3	(1.1)	1	(0.2)	1	(0.4)	5	(0.1)

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

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

Non-serious adverse events up to 30 days 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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Adverse Events of Special Interest (AEOSI)

Dataset comparison

Table 49: Adverse event summary – AEOSI including all risk categories (subjects in ASaT population)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	85	(28.1)	24	(8.6)	117	(24.0)	30	(11.4)	857	(22.4)
with no adverse event	218	(71.9)	256	(91.4)	371	(76.0)	234	(88.6)	2,973	(77.6)
with drug-related[†] adverse events	68	(22.4)	20	(7.1)	95	(19.5)	20	(7.6)	744	(19.4)
with toxicity grade 3-5 adverse events	30	(9.9)	9	(3.2)	41	(8.4)	9	(3.4)	229	(6.0)
with toxicity grade 3-5 drug-related adverse events	24	(7.9)	6	(2.1)	37	(7.6)	7	(2.7)	196	(5.1)
with non-serious adverse events	61	(20.1)	17	(6.1)	93	(19.1)	25	(9.5)	698	(18.2)
with serious adverse events	30	(9.9)	9	(3.2)	33	(6.8)	5	(1.9)	227	(5.9)
with serious drug-related adverse events	26	(8.6)	7	(2.5)	31	(6.4)	3	(1.1)	199	(5.2)
with any dose modification[‡] due to an adverse event	45	(14.9)	7	(2.5)	62	(12.7)	6	(2.3)	312	(8.1)
pembrolizumab or placebo dose modification	40	(13.2)	3	(1.1)	60	(12.3)	5	(1.9)	312	(8.1)
any chemotherapy dose modification	7	(2.3)	5	(1.8)	19	(3.9)	3	(1.1)	0	(0.0)
all drugs dose modification	2	(0.7)	2	(0.7)	4	(0.8)	1	(0.4)	312	(8.1)
who died	1	(0.3)	1	(0.4)	3	(0.6)	0	(0.0)	7	(0.2)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)	3	(0.6)	0	(0.0)	7	(0.2)
discontinued any drug due to an adverse event	20	(6.6)	5	(1.8)	32	(6.6)	4	(1.5)	129	(3.4)
discontinued pembrolizumab or placebo	17	(5.6)	3	(1.1)	29	(5.9)	3	(1.1)	129	(3.4)
discontinued any chemotherapy	7	(2.3)	5	(1.8)	19	(3.9)	3	(1.1)	0	(0.0)
discontinued all drugs	2	(0.7)	2	(0.7)	4	(0.8)	1	(0.4)	129	(3.4)
discontinued any drug due to a drug-related adverse event	19	(6.3)	4	(1.4)	31	(6.4)	4	(1.5)	127	(3.3)
discontinued pembrolizumab or placebo	16	(5.3)	2	(0.7)	28	(5.7)	3	(1.1)	127	(3.3)
discontinued any chemotherapy	7	(2.3)	4	(1.4)	19	(3.9)	3	(1.1)	0	(0.0)
discontinued all drugs	2	(0.7)	2	(0.7)	4	(0.8)	1	(0.4)	127	(3.3)
discontinued any drug due to a serious adverse event	16	(5.3)	4	(1.4)	24	(4.9)	3	(1.1)	99	(2.6)
discontinued pembrolizumab or placebo	14	(4.6)	3	(1.1)	23	(4.7)	3	(1.1)	99	(2.6)
discontinued any chemotherapy	5	(1.7)	4	(1.4)	15	(3.1)	2	(0.8)	0	(0.0)
discontinued all drugs	2	(0.7)	2	(0.7)	4	(0.8)	1	(0.4)	99	(2.6)
discontinued any drug due to a serious drug-related adverse event	15	(5.0)	3	(1.1)	23	(4.7)	3	(1.1)	97	(2.5)
discontinued pembrolizumab or placebo	13	(4.3)	2	(0.7)	22	(4.5)	3	(1.1)	97	(2.5)
discontinued any chemotherapy	5	(1.7)	3	(1.1)	15	(3.1)	2	(0.8)	0	(0.0)
discontinued all drugs	2	(0.7)	2	(0.7)	4	(0.8)	1	(0.4)	97	(2.5)

[†] 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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Table 50: Subjects with AEOSI (Incidence >0% in one or more treatment groups) by AEOSI category and preferred term – Subjects in ASaT population

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	85	(28.1)	24	(8.6)	117	(24.0)	30	(11.4)	857	(22.4)
with no adverse events	218	(71.9)	256	(91.4)	371	(76.0)	234	(88.6)	2,973	(77.6)
Adrenal Insufficiency	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**	**1**	**(0.4)**	**30**	**(0.8)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	2	(0.4)	1	(0.4)	28	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Colitis	**9**	**(3.0)**	**4**	**(1.4)**	**14**	**(2.9)**	**0**	**(0.0)**	**74**	**(1.9)**
Autoimmune colitis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.0)
Colitis	7	(2.3)	3	(1.1)	11	(2.3)	0	(0.0)	68	(1.8)
Colitis microscopic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Enterocolitis	2	(0.7)	1	(0.4)	2	(0.4)	0	(0.0)	5	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Encephalitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatitis	**5**	**(1.7)**	**0**	**(0.0)**	**5**	**(1.0)**	**0**	**(0.0)**	**24**	**(0.6)**
Autoimmune hepatitis	5	(1.7)	0	(0.0)	1	(0.2)	0	(0.0)	13	(0.3)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Hepatitis	0	(0.0)	0	(0.0)	4	(0.8)	0	(0.0)	9	(0.2)
Hyperthyroidism	**20**	**(6.6)**	**2**	**(0.7)**	**21**	**(4.3)**	**7**	**(2.7)**	**134**	**(3.5)**
Hyperthyroidism	20	(6.6)	2	(0.7)	21	(4.3)	7	(2.7)	134	(3.5)
Hypophysitis	**3**	**(1.0)**	**0**	**(0.0)**	**3**	**(0.6)**	**0**	**(0.0)**	**21**	**(0.5)**
Hypophysitis	2	(0.7)	0	(0.0)	1	(0.2)	0	(0.0)	12	(0.3)
Hypopituitarism	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	9	(0.2)
Hypothyroidism	**24**	**(7.9)**	**5**	**(1.8)**	**39**	**(8.0)**	**7**	**(2.7)**	**347**	**(9.1)**
Hypothyroidism	24	(7.9)	5	(1.8)	39	(8.0)	7	(2.7)	346	(9.0)
Hypothyroidism	**24**	**(7.9)**	**5**	**(1.8)**	**39**	**(8.0)**	**7**	**(2.7)**	**347**	**(9.1)**
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**10**	**(3.3)**	**6**	**(2.1)**	**12**	**(2.5)**	**5**	**(1.9)**	**102**	**(2.7)**
Anaphylactic reaction	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	4	(0.1)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	8	(0.2)
Drug hypersensitivity	2	(0.7)	3	(1.1)	3	(0.6)	0	(0.0)	14	(0.4)
Hypersensitivity	3	(1.0)	0	(0.0)	3	(0.6)	2	(0.8)	33	(0.9)
Infusion related reaction	4	(1.3)	3	(1.1)	4	(0.8)	3	(1.1)	43	(1.1)
Serum sickness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**
Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Myocarditis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Myocarditis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Myositis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**	**17**	**(0.4)**
Myopathy	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.1)
Myositis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	12	(0.3)
Rhabdomyolysis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	**2**	**(0.7)**	**2**	**(0.7)**	**7**	**(1.4)**	**0**	**(0.0)**	**15**	**(0.4)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Autoimmune nephritis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	2	(0.1)
Glomerulonephritis membranous	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nephritis	1	(0.3)	1	(0.4)	3	(0.6)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)	3	(0.6)	0	(0.0)	7	(0.2)
Pancreatitis	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.6)**	**0**	**(0.0)**	**10**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	8	(0.2)
Pancreatitis acute	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.0)

Pneumonitis	**19**	**(6.3)**	**6**	**(2.1)**	**22**	**(4.5)**	**5**	**(1.9)**	**142**	**(3.7)**
Interstitial lung disease	3	(1.0)	2	(0.7)	0	(0.0)	0	(0.0)	11	(0.3)
Pneumonitis	16	(5.3)	4	(1.4)	22	(4.5)	5	(1.9)	132	(3.4)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Severe Skin Reactions	**5**	**(1.7)**	**1**	**(0.4)**	**10**	**(2.0)**	**5**	**(1.9)**	**54**	**(1.4)**
Dermatitis bullous	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Dermatitis exfoliative	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Erythema multiforme	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Pemphigoid	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pruritus	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	6	(0.2)
Pruritus generalised	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash	1	(0.3)	0	(0.0)	9	(1.8)	3	(1.1)	16	(0.4)
Rash erythematous	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Rash maculo-papular	2	(0.7)	0	(0.0)	0	(0.0)	1	(0.4)	9	(0.2)
Rash pruritic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash pustular	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Toxic skin eruption	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.4)	2	(0.1)
Thyroiditis	**3**	**(1.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**	**27**	**(0.7)**
Autoimmune thyroiditis	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.2)
Thyroid disorder	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Thyroiditis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	19	(0.5)
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**	**12**	**(0.3)**
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Type 1 diabetes mellitus	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	9	(0.2)
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**17**	**(0.4)**
Iridocyclitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Iritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**17**	**(0.4)**
Uveitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.3)

Every subject is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
†† Includes all subjects who received at least one dose of treatment in pembro combo arm of KN407 and KN021 cohort A.
‡‡ Includes all subjects who received at least one dose of treatment in control arm of KN407.
§§ 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087
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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

The MAH also provided an updated safety analysis of AEOSI in a pooled pembro combo dataset comprising all combination studies of pembrolizumab+chemotherapy in NSCLC in comparison with an up-to-date RSD, as follows:

Table 51: Subjects With Adverse Events of Special Interest (Incidence > 0% in One or More Treatment Groups) By AEOSI Category and Preferred Term (Subjects in ASaT Population)

	All Combination Therapy Studies in NSCLC for MK-3475[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[§§]	
	n	(%)	n	(%)
Subjects in population	791		5,584	
with one or more adverse events	202	(25.5)	1,354	(24.2)
with no adverse events	589	(74.5)	4,230	(75.8)
Adrenal Insufficiency	**2**	**(0.3)**	**43**	**(0.8)**
Adrenal insufficiency	2	(0.3)	40	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	1	(0.0)
Colitis	**23**	**(2.9)**	**104**	**(1.9)**

	All Combination Therapy Studies in NSCLC for MK-3475[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[§§]	
	n	(%)	n	(%)
Autoimmune colitis	1	(0.1)	6	(0.1)
Colitis	18	(2.3)	91	(1.6)
Colitis microscopic	0	(0.0)	4	(0.1)
Enterocolitis	4	(0.5)	6	(0.1)
Encephalitis	**0**	**(0.0)**	**1**	**(0.0)**
Encephalitis	0	(0.0)	1	(0.0)
Guillain-Barre	**0**	**(0.0)**	**4**	**(0.1)**
Syndrome	0	(0.0)	1	(0.0)
Axonal neuropathy	0	(0.0)	1	(0.0)
Demyelinating	0	(0.0)	2	(0.0)
polyneuropathy	**10**	**(1.3)**	**48**	**(0.9)**
Guillain-Barre syndrome	6	(0.8)	22	(0.4)
Hepatitis	0	(0.0)	5	(0.1)
Autoimmune hepatitis	4	(0.5)	21	(0.4)
Drug-induced liver injury	0	(0.0)	1	(0.0)
Hepatitis	**41**	**(5.2)**	**236**	**(4.2)**
Hepatitis acute	41	(5.2)	236	(4.2)
Hyperthyroidism	**6**	**(0.8)**	**35**	**(0.6)**
Hyperthyroidism	3	(0.4)	22	(0.4)
Hypophysitis	3	(0.4)	13	(0.2)
Hypophysitis	**63**	**(8.0)**	**591**	**(10.6)**
Hypopituitarism	63	(8.0)	590	(10.6)
Hypothyroidism	0	(0.0)	1	(0.0)
Hypothyroidism	0	(0.0)	1	(0.0)
Myxoedema				
Primary hypothyroidism				
Infusion Reactions	**22**	**(2.8)**	**130**	**(2.3)**
Anaphylactic reaction	3	(0.4)	9	(0.2)
Anaphylactoid reaction	0	(0.0)	1	(0.0)
Cytokine release syndrome	1	(0.1)	8	(0.1)
Drug hypersensitivity	5	(0.6)	18	(0.3)
Hypersensitivity	6	(0.8)	43	(0.8)
Infusion related reaction	8	(1.0)	53	(0.9)
Myasthenic Syndrome	**0**	**(0.0)**	**3**	**(0.1)**
Myasthenia gravis	0	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	2	(0.0)
Myocarditis	**0**	**(0.0)**	**5**	**(0.1)**
Myocarditis	0	(0.0)	5	(0.1)
Myositis	**1**	**(0.1)**	**19**	**(0.3)**
Myopathy	1	(0.1)	4	(0.1)
Myositis	0	(0.0)	14	(0.3)
Rhabdomyolysis	0	(0.0)	1	(0.0)
Nephritis	**9**	**(1.1)**	**20**	**(0.4)**
Acute kidney injury	0	(0.0)	2	(0.0)
Autoimmune nephritis	1	(0.1)	3	(0.1)
Glomerulonephritis membranous	0	(0.0)	1	(0.0)
Nephritis	4	(0.5)	3	(0.1)
Nephrotic syndrome	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	2	(0.0)
Tubulointerstitial nephritis	4	(0.5)	8	(0.1)
Pancreatitis	**3**	**(0.4)**	**14**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	1	(0.0)
Pancreatitis	2	(0.3)	12	(0.2)
Pancreatitis acute	1	(0.1)	2	(0.0)
Pneumonitis	**41**	**(5.2)**	**235**	**(4.2)**
Interstitial lung disease	3	(0.4)	19	(0.3)
Organising pneumonia	0	(0.0)	1	(0.0)
Pneumonitis	38	(4.8)	217	(3.9)
Sarcoidosis	**0**	**(0.0)**	**10**	**(0.2)**
Sarcoidosis	0	(0.0)	10	(0.2)
Severe Skin Reactions	**15**	**(1.9)**	**81**	**(1.5)**
Dermatitis bullous	1	(0.1)	6	(0.1)
Dermatitis exfoliative	1	(0.1)	7	(0.1)
Erythema multiforme	0	(0.0)	4	(0.1)
Exfoliative rash	0	(0.0)	2	(0.0)
Pemphigoid	0	(0.0)	3	(0.1)
Pemphigus	0	(0.0)	2	(0.0)
Pruritus	0	(0.0)	9	(0.2)

	All Combination Therapy Studies in NSCLC for MK-3475[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[§§]	
	n	(%)	n	(%)
Pruritus generalised	0	(0.0)	2	(0.0)
Pruritus genital	0	(0.0)	1	(0.0)
Rash	10	(1.3)	23	(0.4)
Rash erythematous	0	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	4	(0.1)
Rash maculo-papular	2	(0.3)	15	(0.3)
Rash pruritic	0	(0.0)	1	(0.0)
Rash pustular	0	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	3	(0.1)
Toxic skin eruption	1	(0.1)	2	(0.0)
Thyroiditis	**4**	**(0.5)**	**56**	**(1.0)**
Autoimmune thyroiditis	2	(0.3)	13	(0.2)
Thyroid disorder	1	(0.1)	5	(0.1)
Thyroiditis	1	(0.1)	40	(0.7)
Type 1 Diabetes Mellitus	**1**	**(0.1)**	**20**	**(0.4)**
Diabetic ketoacidosis	0	(0.0)	9	(0.2)
Type 1 diabetes mellitus	1	(0.1)	16	(0.3)
Uveitis	**0**	**(0.0)**	**19**	**(0.3)**
Iridocyclitis	0	(0.0)	4	(0.1)
Iritis	0	(0.0)	3	(0.1)
Uveitis	**0**	**(0.0)**	**19**	**(0.3)**
Uveitis	0	(0.0)	12	(0.2)

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

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

Non-serious adverse events up to 30 days 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 KN407, KN021 cohort A, KN189 and KN021 cohort G/C.

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

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016) MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

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

With reference to pneumonitis, a safety analysis was restricted to the NSCLC setting across all indication lines, as shown below:

Table 52: Subjects With Adverse Events by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) AEOSI-Pneumonitis (ASaT Population)

	All Approved Monotherapy Studies in NSCLC for MK-3475[¶]		All Combination Therapy Studies in NSCLC for MK-3475[††]		All Approved Studies in NSCLC for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	1,386		791		2,177	
with one or more adverse events	66	(4.8)	41	(5.2)	107	(4.9)
with no adverse events	1,320	(95.2)	750	(94.8)	2,070	(95.1)
Pneumonitis	**66**	**(4.8)**	**41**	**(5.2)**	**107**	**(4.9)**
Grade 1	13	(0.9)	6	(0.8)	19	(0.9)
Grade 2	23	(1.7)	16	(2.0)	39	(1.8)
Grade 3	16	(1.2)	14	(1.8)	30	(1.4)
Grade 4	9	(0.6)	1	(0.1)	10	(0.5)
Grade 5	5	(0.4)	4	(0.5)	9	(0.4)
Interstitial lung disease	5	(0.4)	3	(0.4)	8	(0.4)
Grade 1	2	(0.1)	1	(0.1)	3	(0.1)
Grade 2	2	(0.1)	2	(0.3)	4	(0.2)
Grade 5	1	(0.1)	0	(0.0)	1	(0.0)
Pneumonitis	61	(4.4)	38	(4.8)	99	(4.5)
Grade 1	11	(0.8)	5	(0.6)	16	(0.7)
Grade 2	21	(1.5)	14	(1.8)	35	(1.6)
Grade 3	16	(1.2)	14	(1.8)	30	(1.4)
Grade 4	9	(0.6)	1	(0.1)	10	(0.5)
Grade 5	4	(0.3)	4	(0.5)	8	(0.4)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

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.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

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

[¶] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part C, F1, F2, F3; KN010; and KN024.

[††] Includes all subjects who received at least one dose of treatment in pembro combo arm of KN407, KN021 cohort A, KN189 and KN021 cohort G/C.

[§§] Includes all subjects who received at least one dose of Pembrolizumab in KN001 C, F1, F2, F3; KN024 and KN010; and all subjects who received at least one dose of treatment in pembro combo arm of KN407, KN021 cohort A, KN189 and KN021 cohort G/C.

MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

Laboratory findings

Table 53: Summary of subjects with increases from baseline in laboratory test toxicity grade based on highest post-baseline toxicity grade (overall incidence >0% in one or more treatment groups) – Subjects with baseline and post-baseline measurements (ASaT population)

Laboratory Test	Pembro Combo (N=278) n	(%)	Control (N=280) n	(%)
Leukocytes Decreased (White blood cell decreased)				
Subjects with Baseline and Post-baseline Measurements	273		270	
Grade 1	53	(19.4)	42	(15.6)
Grade 2	70	(25.6)	62	(23.0)
Grade 3	38	(13.9)	41	(15.2)
Grade 4	16	(5.9)	12	(4.4)
Grade 3-4	54	(19.8)	53	(19.6)
All Grades	177	(64.8)	157	(58.1)
Platelets Decreased (Platelet count decreased)				
Subjects with Baseline and Post-baseline Measurements	273		270	
Grade 1	112	(41.0)	85	(31.5)
Grade 2	37	(13.6)	31	(11.5)
Grade 3	14	(5.1)	13	(4.8)
Grade 4	12	(4.4)	13	(4.8)
Grade 3-4	26	(9.5)	26	(9.6)
All Grades	175	(64.1)	142	(52.6)
Alanine Aminotransferase Increased (Alanine aminotransferase increased)				
Subjects with Baseline and Post-baseline Measurements	270		267	
Grade 1	53	(19.6)	45	(16.9)
Grade 2	10	(3.7)	3	(1.1)
Grade 3	8	(3.0)	5	(1.9)
Grade 4	1	(0.4)	0	(0.0)
Grade 3-4	9	(3.3)	5	(1.9)
All Grades	72	(26.7)	53	(19.9)
Aspartate Aminotransferase Increased (Aspartate aminotransferase increased)				
Subjects with Baseline and Post-baseline Measurements	269		266	
Grade 1	57	(21.2)	37	(13.9)
Grade 2	10	(3.7)	7	(2.6)
Grade 3	8	(3.0)	5	(1.9)
Grade 4	3	(1.1)	0	(0.0)
Grade 3-4	11	(4.1)	5	(1.9)
All Grades	78	(29.0)	49	(18.4)
Bilirubin Increased (Blood bilirubin increased)				
Subjects with Baseline and Post-baseline Measurements	270		266	
Grade 1	24	(8.9)	14	(5.3)
Grade 2	6	(2.2)	6	(2.3)
Grade 3	1	(0.4)	1	(0.4)
Grade 4	1	(0.4)	2	(0.8)
Grade 3-4	2	(0.7)	3	(1.1)
All Grades	32	(11.9)	23	(8.6)

In patients treated with pembrolizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 23.8% for neutrophils decreased, 20.2% for lymphocytes decreased, 16.2% for haemoglobin decreased, 14.6% for leucocytes decreased, 10.3% for platelets decreased, 7.9% for glucose increased, 7.8% for phosphate decreased, 7.4% for sodium decreased, 4.6% for potassium decreased, 3.7% for ALT increased, 3.6% for creatinine increased, 3.5% for AST increased, 2.9% for calcium decreased, 2.6% for potassium increased, 2.5% for albumin decreased, 1.7% for calcium increased, 1.2% for alkaline phosphatase increased, 0.9% for glucose decreased, 0.7% for bilirubin increased, and 0.1% for sodium increased (see section 4.8 of the SmPC).

Safety in special populations

Age

KEYNOTE-407

Table 54: Adverse event summary by age category (EU age categories) – Subjects in ASaT population

	KN407 + KN021-A combo††								KN407 chemo‡‡							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	137		131		33		2		126		123		30		1	
with one or more adverse events	136	(99.3)	128	(97.7)	32	(97.0)	2	(100.0)	124	(98.4)	119	(96.7)	30	(100.0)	1	(100.0)
with no adverse event	1	(0.7)	3	(2.3)	1	(3.0)	0	(0.0)	2	(1.6)	4	(3.3)	0	(0.0)	0	(0.0)
with drug-related† adverse events	133	(97.1)	124	(94.7)	31	(93.9)	2	(100.0)	110	(87.3)	109	(88.6)	29	(96.7)	1	(100.0)
with toxicity grade 3-5 adverse events	87	(63.5)	97	(74.0)	23	(69.7)	2	(100.0)	82	(65.1)	84	(68.3)	24	(80.0)	1	(100.0)
with toxicity grade 3-5 drug-related adverse events	62	(45.3)	80	(61.1)	18	(54.5)	2	(100.0)	62	(49.2)	71	(57.7)	20	(66.7)	1	(100.0)
with non-serious adverse events	134	(97.8)	128	(97.7)	32	(97.0)	2	(100.0)	123	(97.6)	118	(95.9)	30	(100.0)	1	(100.0)
with serious adverse events	44	(32.1)	65	(49.6)	14	(42.4)	2	(100.0)	42	(33.3)	50	(40.7)	15	(50.0)	0	(0.0)
with serious drug-related adverse events	25	(18.2)	40	(30.5)	10	(30.3)	2	(100.0)	16	(12.7)	29	(23.6)	6	(20.0)	0	(0.0)
with dose modification‡ due to an adverse event	93	(67.9)	104	(79.4)	25	(75.8)	2	(100.0)	71	(56.3)	80	(65.0)	26	(86.7)	1	(100.0)
who died	9	(6.6)	8	(6.1)	4	(12.1)	2	(100.0)	5	(4.0)	8	(6.5)	5	(16.7)	0	(0.0)
who died due to a drug-related adverse event	2	(1.5)	4	(3.1)	2	(6.1)	2	(100.0)	2	(1.6)	3	(2.4)	1	(3.3)	0	(0.0)
discontinued drug due to an adverse event	23	(16.8)	32	(24.4)	11	(33.3)	2	(100.0)	11	(8.7)	16	(13.0)	6	(20.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	15	(10.9)	25	(19.1)	9	(27.3)	2	(100.0)	6	(4.8)	10	(8.1)	4	(13.3)	0	(0.0)
discontinued drug due to a serious adverse event	17	(12.4)	22	(16.8)	8	(24.2)	2	(100.0)	7	(5.6)	10	(8.1)	6	(20.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	9	(6.6)	15	(11.5)	6	(18.2)	2	(100.0)	3	(2.4)	5	(4.1)	3	(10.0)	0	(0.0)

† 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 KN407 and KN021 cohort A.
‡‡ Includes all subjects who received at least one dose of treatment in control arm of KN407.
§§ 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087
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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Table 55: Adverse event summary for elderly subjects by age (EU age categories) – AsaT population

	KN407 + KN021-A combo††								KN407 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	137		131		33		2		126		123		30		1	
with one or more adverse events	136	(99.3)	128	(97.7)	32	(97.0)	2	(100)	124	(98.4)	119	(96.7)	30	(100)	1	(100)
Who died	9	(6.6)	8	(6.1)	4	(12.1)	2	(100)	5	(4.0)	8	(6.5)	5	(16.7)	0	(0.0)
with serious adverse events	44	(32.1)	65	(49.6)	14	(42.4)	2	(100)	42	(33.3)	50	(40.7)	15	(50.0)	0	(0.0)
discontinued due to an adverse event	23	(16.8)	32	(24.4)	11	(33.3)	2	(100)	11	(8.7)	16	(13.0)	6	(20.0)	0	(0.0)
CNS (confusion/extrapyramidal)	6	(4.4)	15	(11.5)	7	(21.2)	0	(0.0)	10	(7.9)	5	(4.1)	4	(13.3)	0	(0.0)
AE related to falling	3	(2.2)	7	(5.3)	4	(12.1)	0	(0.0)	4	(3.2)	8	(6.5)	1	(3.3)	0	(0.0)
CV events	35	(25.5)	26	(19.8)	8	(24.2)	2	(100)	23	(18.3)	30	(24.4)	8	(26.7)	0	(0.0)
Cerebrovascular events	4	(2.9)	2	(1.5)	2	(6.1)	0	(0.0)	4	(3.2)	4	(3.3)	1	(3.3)	0	(0.0)
Infections	60	(43.8)	65	(49.6)	16	(48.5)	0	(0.0)	42	(33.3)	49	(39.8)	17	(56.7)	1	(100)

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 control arm of KN407.
†† Includes all subjects who received at least one dose of treatment in pembro combo arm of KN407 and KN021 cohort A.
MK-3475 Database Cutoff Date for Lung (KN021 Cohort A: 07NOV2016, KN407: 03APR2018)

Source: [ISS: adam-adsl; adae]

Dataset comparison

Table 56: Adverse event summary by age category (<65, ≥65 years) - Subjects in ASaT population

	KN407 + KN021-A combo[††]				KN407 chemo[‡‡]				KN189 + KN021-G/C combo[§§]				KN189 + KN021-G chemo[†††]				Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	137		166		126		154		245		243		141		123		2,056		1,774	
with one or more adverse events	136	(99.3)	162	(97.6)	124	(98.4)	150	(97.4)	244	(99.6)	243	(100.0)	141	(100.0)	120	(97.6)	1,997	(97.1)	1,723	(97.1)
with no adverse event	1	(0.7)	4	(2.4)	2	(1.6)	4	(2.6)	1	(0.4)	0	(0.0)	0	(0.0)	3	(2.4)	59	(2.9)	51	(2.9)
with drug-related[†] adverse events	133	(97.1)	157	(94.6)	110	(87.3)	139	(90.3)	219	(89.4)	232	(95.5)	126	(89.4)	114	(92.7)	1,475	(71.7)	1,276	(71.9)
with toxicity grade 3-5 adverse events	87	(63.5)	122	(73.5)	82	(65.1)	109	(70.8)	156	(63.7)	167	(68.7)	86	(61.0)	81	(65.9)	880	(42.8)	922	(52.0)
with toxicity grade 3-5 drug-related adverse events	62	(45.3)	100	(60.2)	62	(49.2)	92	(59.7)	108	(44.1)	123	(50.6)	49	(34.8)	49	(39.8)	271	(13.2)	306	(17.2)
with non-serious adverse events	134	(97.8)	162	(97.6)	123	(97.6)	149	(96.8)	241	(98.4)	242	(99.6)	141	(100.0)	118	(95.9)	1,963	(95.5)	1,684	(94.9)
with serious adverse events	44	(32.1)	81	(48.8)	42	(33.3)	65	(42.2)	107	(43.7)	137	(56.4)	56	(39.7)	59	(48.0)	688	(33.5)	762	(43.0)
with serious drug-related adverse events	25	(18.2)	52	(31.3)	16	(12.7)	35	(22.7)	53	(21.6)	76	(31.3)	23	(16.3)	26	(21.1)	191	(9.3)	212	(12.0)
with any dose modification[‡] due to an adverse event	93	(67.9)	131	(78.9)	71	(56.3)	107	(69.5)	154	(62.9)	175	(72.0)	78	(55.3)	68	(55.3)	602	(29.3)	654	(36.9)
pembrolizumab or placebo dose modification	71	(51.8)	106	(63.9)	48	(38.1)	75	(48.7)	138	(56.3)	160	(65.8)	64	(45.4)	45	(36.6)	602	(29.3)	654	(36.9)
any chemotherapy dose modification	16	(11.7)	30	(18.1)	9	(7.1)	20	(13.0)	43	(17.6)	67	(27.6)	16	(11.3)	19	(15.4)	0	(0.0)	0	(0.0)
all drugs dose modification	8	(5.8)	16	(9.6)	5	(4.0)	11	(7.1)	14	(5.7)	13	(5.3)	5	(3.5)	6	(4.9)	602	(29.3)	654	(36.9)
who died	9	(6.6)	14	(8.4)	5	(4.0)	13	(8.4)	8	(3.3)	22	(9.1)	5	(3.5)	9	(7.3)	61	(3.0)	96	(5.4)
who died due to a drug-related adverse event	2	(1.5)	8	(4.8)	2	(1.6)	4	(2.6)	3	(1.2)	7	(2.9)	1	(0.7)	3	(2.4)	7	(0.3)	10	(0.6)
discontinued any drug due to an adverse event	23	(16.8)	45	(27.1)	11	(8.7)	22	(14.3)	51	(20.8)	78	(32.1)	18	(12.8)	21	(17.1)	205	(10.0)	247	(13.9)
discontinued pembrolizumab or placebo	16	(11.7)	34	(20.5)	7	(5.6)	15	(9.7)	38	(15.5)	55	(22.6)	12	(8.5)	9	(7.3)	205	(10.0)	247	(13.9)
discontinued any chemotherapy	16	(11.7)	30	(18.1)	9	(7.1)	20	(13.0)	43	(17.6)	67	(27.6)	16	(11.3)	19	(15.4)	0	(0.0)	0	(0.0)
discontinued all drugs	8	(5.8)	16	(9.6)	5	(4.0)	11	(7.1)	14	(5.7)	13	(5.3)	5	(3.5)	6	(4.9)	205	(10.0)	247	(13.9)
discontinued any drug due to a drug-related adverse event	15	(10.9)	36	(21.7)	6	(4.8)	14	(9.1)	43	(17.6)	57	(23.5)	11	(7.8)	15	(12.2)	92	(4.5)	132	(7.4)
discontinued pembrolizumab or placebo	8	(5.8)	25	(15.1)	2	(1.6)	7	(4.5)	32	(13.1)	36	(14.8)	6	(4.3)	4	(3.3)	92	(4.5)	132	(7.4)
discontinued any chemotherapy	12	(8.8)	21	(12.7)	6	(4.8)	14	(9.1)	36	(14.7)	49	(20.2)	11	(7.8)	14	(11.4)	0	(0.0)	0	(0.0)
discontinued all drugs	4	(2.9)	10	(6.0)	2	(1.6)	7	(4.5)	10	(4.1)	5	(2.1)	4	(2.8)	3	(2.4)	92	(4.5)	132	(7.4)
discontinued any drug due to a serious adverse event	17	(12.4)	32	(19.3)	7	(5.6)	16	(10.4)	36	(14.7)	50	(20.6)	10	(7.1)	12	(9.8)	154	(7.5)	184	(10.4)
discontinued pembrolizumab or placebo	14	(10.2)	28	(16.9)	6	(4.8)	13	(8.4)	30	(12.2)	42	(17.3)	8	(5.7)	8	(6.5)	154	(7.5)	184	(10.4)
discontinued any chemotherapy	11	(8.0)	21	(12.7)	6	(4.8)	14	(9.1)	28	(11.4)	45	(18.5)	9	(6.4)	10	(8.1)	0	(0.0)	0	(0.0)
discontinued all drugs	8	(5.8)	15	(9.0)	5	(4.0)	10	(6.5)	13	(5.3)	13	(5.3)	4	(2.8)	6	(4.9)	154	(7.5)	184	(10.4)
discontinued any drug due to a serious drug-related adverse event	9	(6.6)	23	(13.9)	3	(2.4)	8	(5.2)	29	(11.8)	33	(13.6)	4	(2.8)	6	(4.9)	63	(3.1)	86	(4.8)
discontinued pembrolizumab or placebo	6	(4.4)	20	(12.0)	2	(1.6)	6	(3.9)	24	(9.8)	25	(10.3)	3	(2.1)	3	(2.4)	63	(3.1)	86	(4.8)
discontinued any chemotherapy	7	(5.1)	13	(7.8)	3	(2.4)	8	(5.2)	22	(9.0)	30	(12.3)	4	(2.8)	5	(4.1)	0	(0.0)	0	(0.0)
discontinued all drugs	4	(2.9)	10	(6.0)	2	(1.6)	6	(3.9)	9	(3.7)	5	(2.1)	3	(2.1)	3	(2.4)	63	(3.1)	86	(4.8)

[†] 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 KN407 and KN021 cohort A.

[‡‡] Includes all subjects who received at least one dose of treatment in control arm of KN407.

[§§] 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Sex

In the ASaT

Table 57: Adverse event summary by gender (male, female) – Subjects in ASaT population

	KN407 + KN021-A combo††				KN407 chemo‡‡				KN189 + KN021-G/C combo§§				KN189 + KN021-G chemo†††				Reference 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	232		71		234		46		284		204		134		130		2,366		1,464	
with one or more adverse events	228	(98.3)	70	(98.6)	229	(97.9)	45	(97.8)	283	(99.6)	204	(100.0)	132	(98.5)	129	(99.2)	2,297	(97.1)	1,423	(97.2)
with no adverse event	4	(1.7)	1	(1.4)	5	(2.1)	1	(2.2)	1	(0.4)	0	(0.0)	2	(1.5)	1	(0.8)	69	(2.9)	41	(2.8)
with drug-related† adverse events	222	(95.7)	68	(95.8)	207	(88.5)	42	(91.3)	259	(91.2)	192	(94.1)	117	(87.3)	123	(94.6)	1,713	(72.4)	1,038	(70.9)
with toxicity grade 3-5 adverse events	160	(69.0)	49	(69.0)	155	(66.2)	36	(78.3)	184	(64.8)	139	(68.1)	83	(61.9)	84	(64.6)	1,124	(47.5)	678	(46.3)
with toxicity grade 3-5 drug-related adverse events	122	(52.6)	40	(56.3)	126	(53.8)	28	(60.9)	134	(47.2)	97	(47.5)	50	(37.3)	48	(36.9)	379	(16.0)	198	(13.5)
with non-serious adverse events	227	(97.8)	69	(97.2)	227	(97.0)	45	(97.8)	280	(98.6)	203	(99.5)	131	(97.8)	128	(98.5)	2,257	(95.4)	1,390	(94.9)
with serious adverse events	98	(42.2)	27	(38.0)	93	(39.7)	14	(30.4)	144	(50.7)	100	(49.0)	63	(47.0)	52	(40.0)	924	(39.1)	526	(35.9)
with serious drug-related adverse events	60	(25.9)	17	(23.9)	44	(18.8)	7	(15.2)	79	(27.8)	50	(24.5)	29	(21.6)	20	(15.4)	269	(11.4)	134	(9.2)
with any dose modification‡ due to an adverse event	175	(75.4)	49	(69.0)	143	(61.1)	35	(76.1)	186	(65.5)	143	(70.1)	78	(58.2)	68	(52.3)	776	(32.8)	480	(32.8)
pembrolizumab or placebo dose modification	138	(59.5)	39	(54.9)	100	(42.7)	23	(50.0)	174	(61.3)	124	(60.8)	60	(44.8)	49	(37.7)	776	(32.8)	480	(32.8)
any chemotherapy dose modification	42	(18.1)	4	(5.6)	23	(9.8)	6	(13.0)	57	(20.1)	53	(26.0)	18	(13.4)	17	(13.1)	0	(0.0)	0	(0.0)
all drugs dose modification	22	(9.5)	2	(2.8)	13	(5.6)	3	(6.5)	17	(6.0)	10	(4.9)	6	(4.5)	5	(3.8)	776	(32.8)	480	(32.8)
who died	18	(7.8)	5	(7.0)	15	(6.4)	3	(6.5)	24	(8.5)	6	(2.9)	6	(4.5)	8	(6.2)	106	(4.5)	51	(3.5)
who died due to a drug-related adverse event	8	(3.4)	2	(2.8)	4	(1.7)	2	(4.3)	8	(2.8)	2	(1.0)	1	(0.7)	3	(2.3)	13	(0.5)	4	(0.3)
discontinued any drug due to an adverse event	58	(25.0)	10	(14.1)	26	(11.1)	7	(15.2)	70	(24.6)	59	(28.9)	20	(14.9)	19	(14.6)	284	(12.0)	168	(11.5)
discontinued pembrolizumab or placebo	42	(18.1)	8	(11.3)	17	(7.3)	5	(10.9)	54	(19.0)	39	(19.1)	11	(8.2)	10	(7.7)	284	(12.0)	168	(11.5)
discontinued any chemotherapy	42	(18.1)	4	(5.6)	23	(9.8)	6	(13.0)	57	(20.1)	53	(26.0)	18	(13.4)	17	(13.1)	0	(0.0)	0	(0.0)
discontinued all drugs	22	(9.5)	2	(2.8)	13	(5.6)	3	(6.5)	17	(6.0)	10	(4.9)	6	(4.5)	5	(3.8)	284	(12.0)	168	(11.5)
discontinued any drug due to a drug-related adverse event	44	(19.0)	7	(9.9)	15	(6.4)	5	(10.9)	51	(18.0)	49	(24.0)	13	(9.7)	13	(10.0)	152	(6.4)	72	(4.9)
discontinued pembrolizumab or placebo	28	(12.1)	5	(7.0)	6	(2.6)	3	(6.5)	35	(12.3)	33	(16.2)	6	(4.5)	4	(3.1)	152	(6.4)	72	(4.9)
discontinued any chemotherapy	29	(12.5)	4	(5.6)	15	(6.4)	5	(10.9)	42	(14.8)	43	(21.1)	12	(9.0)	13	(10.0)	0	(0.0)	0	(0.0)
discontinued all drugs	12	(5.2)	2	(2.8)	6	(2.6)	3	(6.5)	8	(2.8)	7	(3.4)	3	(2.2)	4	(3.1)	152	(6.4)	72	(4.9)
discontinued any drug due to a serious adverse event	41	(17.7)	8	(11.3)	18	(7.7)	5	(10.9)	52	(18.3)	34	(16.7)	12	(9.0)	10	(7.7)	216	(9.1)	122	(8.3)
discontinued pembrolizumab or placebo	34	(14.7)	8	(11.3)	15	(6.4)	4	(8.7)	43	(15.1)	29	(14.2)	9	(6.7)	7	(5.4)	216	(9.1)	122	(8.3)
discontinued any chemotherapy	30	(12.9)	2	(2.8)	15	(6.4)	5	(10.9)	43	(15.1)	30	(14.7)	11	(8.2)	8	(6.2)	0	(0.0)	0	(0.0)
discontinued all drugs	21	(9.1)	2	(2.8)	12	(5.1)	3	(6.5)	17	(6.0)	9	(4.4)	6	(4.5)	4	(3.1)	216	(9.1)	122	(8.3)
discontinued any drug due to a serious drug-related adverse event	27	(11.6)	5	(7.0)	7	(3.0)	4	(8.7)	35	(12.3)	27	(13.2)	6	(4.5)	4	(3.1)	103	(4.4)	46	(3.1)
discontinued pembrolizumab or placebo	21	(9.1)	5	(7.0)	5	(2.1)	3	(6.5)	26	(9.2)	23	(11.3)	5	(3.7)	1	(0.8)	103	(4.4)	46	(3.1)
discontinued any chemotherapy	18	(7.8)	2	(2.8)	7	(3.0)	4	(8.7)	29	(10.2)	23	(11.3)	5	(3.7)	4	(3.1)	0	(0.0)	0	(0.0)
discontinued all drugs	12	(5.2)	2	(2.8)	5	(2.1)	3	(6.5)	8	(2.8)	6	(2.9)	3	(2.2)	3	(2.3)	103	(4.4)	46	(3.1)

† 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.

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 KN407 and KN021 cohort A.

‡‡ Includes all subjects who received at least one dose of treatment in control arm of KN407.

§§ 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

As stratified by taxane group:

Table 58: Adverse event summary by gender (Carboplatin/Nab-paclitaxel) – AsaT population

	Pembro Combo				Control			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	86		23		89		24	
with one or more adverse events	86	(100.0)	22	(95.7)	88	(98.9)	23	(95.8)
with no adverse event	0	(0.0)	1	(4.3)	1	(1.1)	1	(4.2)
with drug-related† adverse events	84	(97.7)	22	(95.7)	86	(96.6)	21	(87.5)
with toxicity grade 3-5 adverse events	69	(80.2)	17	(73.9)	72	(80.9)	20	(83.3)
with toxicity grade 3-5 drug-related adverse events	58	(67.4)	16	(69.6)	66	(74.2)	17	(70.8)
with serious adverse events	35	(40.7)	8	(34.8)	35	(39.3)	7	(29.2)
with serious drug-related adverse events	20	(23.3)	4	(17.4)	13	(14.6)	3	(12.5)
who died	9	(10.5)	3	(13.0)	4	(4.5)	1	(4.2)
who died due to a drug-related adverse event	5	(5.8)	1	(4.3)	1	(1.1)	0	(0.0)
discontinued any drug due to an adverse event	28	(32.6)	4	(17.4)	8	(9.0)	3	(12.5)
discontinued pembrolizumab or placebo	19	(22.1)	4	(17.4)	4	(4.5)	2	(8.3)
discontinued any chemotherapy	23	(26.7)	2	(8.7)	7	(7.9)	3	(12.5)
discontinued all drugs	11	(12.8)	2	(8.7)	3	(3.4)	1	(4.2)
discontinued any drug due to a drug-related adverse event	23	(26.7)	2	(8.7)	5	(5.6)	2	(8.3)
discontinued pembrolizumab or placebo	14	(16.3)	2	(8.7)	2	(2.2)	1	(4.2)
discontinued any chemotherapy	17	(19.8)	2	(8.7)	5	(5.6)	2	(8.3)
discontinued all drugs	8	(9.3)	2	(8.7)	2	(2.2)	1	(4.2)
discontinued any drug due to a serious adverse event	19	(22.1)	4	(17.4)	3	(3.4)	2	(8.3)
discontinued pembrolizumab or placebo	15	(17.4)	4	(17.4)	2	(2.2)	2	(8.3)
discontinued any chemotherapy	17	(19.8)	2	(8.7)	3	(3.4)	2	(8.3)
discontinued all drugs	11	(12.8)	2	(8.7)	2	(2.2)	1	(4.2)
discontinued any drug due to a serious drug-related adverse event	13	(15.1)	2	(8.7)	1	(1.1)	1	(4.2)
discontinued pembrolizumab or placebo	10	(11.6)	2	(8.7)	1	(1.1)	1	(4.2)
discontinued any chemotherapy	11	(12.8)	2	(8.7)	1	(1.1)	1	(4.2)
discontinued all drugs	8	(9.3)	2	(8.7)	1	(1.1)	1	(4.2)

† Determined by the investigator to be related to the drug.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Table 59: Adverse event summary by gender (Carboplatin/Paclitaxel) – AsaT population

	Pembro Combo				Control			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	134		35		145		22	
with one or more adverse events	130	(97.0)	35	(100.0)	141	(97.2)	22	(100.0)
with no adverse event	4	(3.0)	0	(0.0)	4	(2.8)	0	(0.0)
with drug-related† adverse events	126	(94.0)	33	(94.3)	121	(83.4)	21	(95.5)
with toxicity grade 3-5 adverse events	84	(62.7)	24	(68.6)	83	(57.2)	16	(72.7)
with toxicity grade 3-5 drug-related adverse events	60	(44.8)	18	(51.4)	60	(41.4)	11	(50.0)
with serious adverse events	55	(41.0)	15	(42.9)	58	(40.0)	7	(31.8)
with serious drug-related adverse events	36	(26.9)	10	(28.6)	31	(21.4)	4	(18.2)
who died	9	(6.7)	2	(5.7)	11	(7.6)	2	(9.1)
who died due to a drug-related adverse event	3	(2.2)	1	(2.9)	3	(2.1)	2	(9.1)
discontinued any drug due to an adverse event	27	(20.1)	6	(17.1)	18	(12.4)	4	(18.2)
discontinued pembrolizumab or placebo	21	(15.7)	4	(11.4)	13	(9.0)	3	(13.6)
discontinued any chemotherapy	17	(12.7)	2	(5.7)	16	(11.0)	3	(13.6)
discontinued all drugs	10	(7.5)	0	(0.0)	10	(6.9)	2	(9.1)
discontinued any drug due to a drug-related adverse event	20	(14.9)	5	(14.3)	10	(6.9)	3	(13.6)
discontinued pembrolizumab or placebo	14	(10.4)	3	(8.6)	4	(2.8)	2	(9.1)
discontinued any chemotherapy	11	(8.2)	2	(5.7)	10	(6.9)	3	(13.6)
discontinued all drugs	4	(3.0)	0	(0.0)	4	(2.8)	2	(9.1)
discontinued any drug due to a serious adverse event	19	(14.2)	4	(11.4)	15	(10.3)	3	(13.6)
discontinued pembrolizumab or placebo	17	(12.7)	4	(11.4)	13	(9.0)	2	(9.1)
discontinued any chemotherapy	11	(8.2)	0	(0.0)	12	(8.3)	3	(13.6)
discontinued all drugs	9	(6.7)	0	(0.0)	10	(6.9)	2	(9.1)
discontinued any drug due to a serious drug-related adverse event	13	(9.7)	3	(8.6)	6	(4.1)	3	(13.6)
discontinued pembrolizumab or placebo	11	(8.2)	3	(8.6)	4	(2.8)	2	(9.1)
discontinued any chemotherapy	6	(4.5)	0	(0.0)	6	(4.1)	3	(13.6)
discontinued all drugs	4	(3.0)	0	(0.0)	4	(2.8)	2	(9.1)

† Determined by the investigator to be related to the drug.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

ECOG

Table 60: Adverse event summary by ECOG category (0, 1) – Subjects in ASaT population

	KN407 + KN021-A combo††				KN407 chemo‡‡				KN189 + KN021-G/C combo§§				KN189 + KN021-G chemo†††				Reference Safety Dataset for Pembrolizumab monotherapy‡‡‡			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	84		219		90		190		215		272		107		157		1,811		1,851	
with one or more adverse events	83	(98.8)	215	(98.2)	89	(98.9)	185	(97.4)	215	(100.0)	271	(99.6)	106	(99.1)	155	(98.7)	1,770	(97.7)	1,789	(96.7)
with no adverse event	1	(1.2)	4	(1.8)	1	(1.1)	5	(2.6)	0	(0.0)	1	(0.4)	1	(0.9)	2	(1.3)	41	(2.3)	62	(3.3)
with drug-related† adverse events	80	(95.2)	210	(95.9)	83	(92.2)	166	(87.4)	204	(94.9)	246	(90.4)	98	(91.6)	142	(90.4)	1,400	(77.3)	1,261	(68.1)
with toxicity grade 3-5 adverse events	59	(70.2)	150	(68.5)	62	(68.9)	129	(67.9)	132	(61.4)	190	(69.9)	60	(56.1)	107	(68.2)	743	(41.0)	960	(51.9)
with toxicity grade 3-5 drug-related adverse events	46	(54.8)	116	(53.0)	47	(52.2)	107	(56.3)	103	(47.9)	127	(46.7)	34	(31.8)	64	(40.8)	263	(14.5)	285	(15.4)
with non-serious adverse events	82	(97.6)	214	(97.7)	89	(98.9)	183	(96.3)	215	(100.0)	267	(98.2)	104	(97.2)	155	(98.7)	1,750	(96.6)	1,741	(94.1)
with serious adverse events	32	(38.1)	93	(42.5)	33	(36.7)	74	(38.9)	90	(41.9)	153	(56.3)	39	(36.4)	76	(48.4)	587	(32.4)	780	(42.1)
with serious drug-related adverse events	20	(23.8)	57	(26.0)	16	(17.8)	35	(18.4)	57	(26.5)	72	(26.5)	15	(14.0)	34	(21.7)	193	(10.7)	192	(10.4)
with any dose modification‡ due to an adverse event	61	(72.6)	163	(74.4)	56	(62.2)	122	(64.2)	142	(66.0)	187	(68.8)	62	(57.9)	84	(53.5)	537	(29.7)	659	(35.6)
pembrolizumab or placebo dose modification	50	(59.5)	127	(58.0)	37	(41.1)	86	(45.3)	124	(57.7)	174	(64.0)	46	(43.0)	63	(40.1)	537	(29.7)	659	(35.6)
any chemotherapy dose modification	12	(14.3)	34	(15.5)	6	(6.7)	23	(12.1)	45	(20.9)	65	(23.9)	14	(13.1)	21	(13.4)	0	(0.0)	0	(0.0)
all drugs dose modification	6	(7.1)	18	(8.2)	4	(4.4)	12	(6.3)	8	(3.7)	19	(7.0)	5	(4.7)	6	(3.8)	537	(29.7)	659	(35.6)
who died	5	(6.0)	18	(8.2)	4	(4.4)	14	(7.4)	10	(4.7)	20	(7.4)	10	(9.3)	4	(2.5)	50	(2.8)	95	(5.1)
who died due to a drug-related adverse event	3	(3.6)	7	(3.2)	1	(1.1)	5	(2.6)	6	(2.8)	4	(1.5)	3	(2.8)	1	(0.6)	7	(0.4)	10	(0.5)
discontinued any drug due to an adverse event	16	(19.0)	52	(23.7)	7	(7.8)	26	(13.7)	55	(25.6)	74	(27.2)	16	(15.0)	23	(14.6)	182	(10.0)	244	(13.2)
discontinued pembrolizumab or placebo	11	(13.1)	39	(17.8)	5	(5.6)	17	(8.9)	38	(17.7)	55	(20.2)	10	(9.3)	11	(7.0)	182	(10.0)	244	(13.2)
discontinued any chemotherapy	12	(14.3)	34	(15.5)	6	(6.7)	23	(12.1)	45	(20.9)	65	(23.9)	14	(13.1)	21	(13.4)	0	(0.0)	0	(0.0)
discontinued all drugs	6	(7.1)	18	(8.2)	4	(4.4)	12	(6.3)	8	(3.7)	19	(7.0)	5	(4.7)	6	(3.8)	182	(10.0)	244	(13.2)
discontinued any drug due to a drug-related adverse event	14	(16.7)	37	(16.9)	3	(3.3)	17	(8.9)	49	(22.8)	51	(18.8)	9	(8.4)	17	(10.8)	105	(5.8)	106	(5.7)
discontinued pembrolizumab or placebo	9	(10.7)	24	(11.0)	2	(2.2)	7	(3.7)	34	(15.8)	34	(12.5)	4	(3.7)	6	(3.8)	105	(5.8)	106	(5.7)
discontinued any chemotherapy	10	(11.9)	23	(10.5)	3	(3.3)	17	(8.9)	40	(18.6)	45	(16.5)	9	(8.4)	16	(10.2)	0	(0.0)	0	(0.0)
discontinued all drugs	5	(6.0)	9	(4.1)	2	(2.2)	7	(3.7)	7	(3.3)	8	(2.9)	3	(2.8)	4	(2.5)	105	(5.8)	106	(5.7)
discontinued any drug due to a serious adverse event	11	(13.1)	38	(17.4)	6	(6.7)	17	(8.9)	39	(18.1)	47	(17.3)	13	(12.1)	9	(5.7)	128	(7.1)	190	(10.3)
discontinued pembrolizumab or placebo	8	(9.5)	34	(15.5)	4	(4.4)	15	(7.9)	32	(14.9)	40	(14.7)	8	(7.5)	8	(5.1)	128	(7.1)	190	(10.3)
discontinued any chemotherapy	9	(10.7)	23	(10.5)	6	(6.7)	14	(7.4)	32	(14.9)	41	(15.1)	11	(10.3)	8	(5.1)	0	(0.0)	0	(0.0)
discontinued all drugs	6	(7.1)	17	(7.8)	4	(4.4)	11	(5.8)	8	(3.7)	18	(6.6)	5	(4.7)	5	(3.2)	128	(7.1)	190	(10.3)
discontinued any drug due to a serious drug-related adverse event	8	(9.5)	24	(11.0)	3	(3.3)	8	(4.2)	34	(15.8)	28	(10.3)	6	(5.6)	4	(2.5)	66	(3.6)	74	(4.0)
discontinued pembrolizumab or placebo	6	(7.1)	20	(9.1)	2	(2.2)	6	(3.2)	28	(13.0)	21	(7.7)	2	(1.9)	4	(2.5)	66	(3.6)	74	(4.0)
discontinued any chemotherapy	7	(8.3)	13	(5.9)	3	(3.3)	8	(4.2)	28	(13.0)	24	(8.8)	6	(5.6)	3	(1.9)	0	(0.0)	0	(0.0)
discontinued all drugs	5	(6.0)	9	(4.1)	2	(2.2)	6	(3.2)	7	(3.3)	7	(2.6)	3	(2.8)	3	(1.9)	66	(3.6)	74	(4.0)

† 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 KN407 and KN021 cohort A.

‡‡ Includes all subjects who received at least one dose of treatment in control arm of KN407.

§§ 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087

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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Region

In the ASaT:

Table 61: Adverse event summary by region (EU, Ex-EU) – Subjects in ASaT population

	KN407 + KN021-A combo††				KN407 chemo‡‡				KN189 + KN021-G/C combo§§				KN189 + KN021-G chemo†††				Reference 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	125		178		115		165		240		248		130		134		1,384		2,446	
with one or more adverse events	120	(96.0)	178	(100.0)	111	(96.5)	163	(98.8)	239	(99.6)	248	(100.0)	128	(98.5)	133	(99.3)	1,334	(96.4)	2,386	(97.5)
with no adverse event	5	(4.0)	0	(0.0)	4	(3.5)	2	(1.2)	1	(0.4)	0	(0.0)	2	(1.5)	1	(0.7)	50	(3.6)	60	(2.5)
with drug-related† adverse events	115	(92.0)	175	(98.3)	99	(86.1)	150	(90.9)	215	(89.6)	236	(95.2)	115	(88.5)	125	(93.3)	946	(68.4)	1,805	(73.8)
with toxicity grade 3-5 adverse events	82	(65.6)	127	(71.3)	79	(68.7)	112	(67.9)	153	(63.8)	170	(68.5)	87	(66.9)	80	(59.7)	644	(46.5)	1,158	(47.3)
with toxicity grade 3-5 drug-related adverse events	65	(52.0)	97	(54.5)	60	(52.2)	94	(57.0)	109	(45.4)	122	(49.2)	53	(40.8)	45	(33.6)	213	(15.4)	364	(14.9)
with non-serious adverse events	119	(95.2)	177	(99.4)	111	(96.5)	161	(97.6)	236	(98.3)	247	(99.6)	127	(97.7)	132	(98.5)	1,295	(93.6)	2,352	(96.2)
with serious adverse events	45	(36.0)	80	(44.9)	47	(40.9)	60	(36.4)	112	(46.7)	132	(53.2)	65	(50.0)	50	(37.3)	550	(39.7)	900	(36.8)
with serious drug-related adverse events	27	(21.6)	50	(28.1)	20	(17.4)	31	(18.8)	60	(25.0)	69	(27.8)	30	(23.1)	19	(14.2)	163	(11.8)	240	(9.8)
with any dose modification‡ due to an adverse event	91	(72.8)	133	(74.7)	68	(59.1)	110	(66.7)	173	(72.1)	156	(62.9)	80	(61.5)	66	(49.3)	454	(32.8)	802	(32.8)
pembrolizumab or placebo dose modification	71	(56.8)	106	(59.6)	45	(39.1)	78	(47.3)	157	(65.4)	141	(56.9)	76	(58.5)	33	(24.6)	454	(32.8)	802	(32.8)
any chemotherapy dose modification	18	(14.4)	28	(15.7)	11	(9.6)	18	(10.9)	58	(24.2)	52	(21.0)	20	(15.4)	15	(11.2)	0	(0.0)	0	(0.0)
all drugs dose modification	9	(7.2)	15	(8.4)	4	(3.5)	12	(7.3)	17	(7.1)	10	(4.0)	8	(6.2)	3	(2.2)	454	(32.8)	802	(32.8)
who died	9	(7.2)	14	(7.9)	7	(6.1)	11	(6.7)	17	(7.1)	13	(5.2)	10	(7.7)	4	(3.0)	68	(4.9)	89	(3.6)
who died due to a drug-related adverse event	2	(1.6)	8	(4.5)	1	(0.9)	5	(3.0)	4	(1.7)	6	(2.4)	1	(0.8)	3	(2.2)	6	(0.4)	11	(0.4)
discontinued any drug due to an adverse event	29	(23.2)	39	(21.9)	13	(11.3)	20	(12.1)	68	(28.3)	61	(24.6)	24	(18.5)	15	(11.2)	160	(11.6)	292	(11.9)
discontinued pembrolizumab or placebo	21	(16.8)	29	(16.3)	7	(6.1)	15	(9.1)	48	(20.0)	45	(18.1)	18	(13.8)	3	(2.2)	160	(11.6)	292	(11.9)
discontinued any chemotherapy	18	(14.4)	28	(15.7)	11	(9.6)	18	(10.9)	58	(24.2)	52	(21.0)	20	(15.4)	15	(11.2)	0	(0.0)	0	(0.0)
discontinued all drugs	9	(7.2)	15	(8.4)	4	(3.5)	12	(7.3)	17	(7.1)	10	(4.0)	8	(6.2)	3	(2.2)	160	(11.6)	292	(11.9)
discontinued any drug due to a drug-related adverse event	23	(18.4)	28	(15.7)	7	(6.1)	13	(7.9)	50	(20.8)	50	(20.2)	14	(10.8)	12	(9.0)	84	(6.1)	140	(5.7)
discontinued pembrolizumab or placebo	15	(12.0)	18	(10.1)	1	(0.9)	8	(4.8)	32	(13.3)	36	(14.5)	9	(6.9)	1	(0.7)	84	(6.1)	140	(5.7)
discontinued any chemotherapy	13	(10.4)	20	(11.2)	7	(6.1)	13	(7.9)	43	(17.9)	42	(16.9)	13	(10.0)	12	(9.0)	0	(0.0)	0	(0.0)
discontinued all drugs	4	(3.2)	10	(5.6)	1	(0.9)	8	(4.8)	9	(3.8)	6	(2.4)	5	(3.8)	2	(1.5)	84	(6.1)	140	(5.7)
discontinued any drug due to a serious adverse event	20	(16.0)	29	(16.3)	8	(7.0)	15	(9.1)	46	(19.2)	40	(16.1)	15	(11.5)	7	(5.2)	127	(9.2)	211	(8.6)
discontinued pembrolizumab or placebo	18	(14.4)	24	(13.5)	6	(5.2)	13	(7.9)	37	(15.4)	35	(14.1)	13	(10.0)	3	(2.2)	127	(9.2)	211	(8.6)
discontinued any chemotherapy	11	(8.8)	21	(11.8)	7	(6.1)	13	(7.9)	38	(15.8)	35	(14.1)	12	(9.2)	7	(5.2)	0	(0.0)	0	(0.0)
discontinued all drugs	9	(7.2)	14	(7.9)	4	(3.5)	11	(6.7)	16	(6.7)	10	(4.0)	7	(5.4)	3	(2.2)	127	(9.2)	211	(8.6)
discontinued any drug due to a serious drug-related adverse event	14	(11.2)	18	(10.1)	3	(2.6)	8	(4.8)	31	(12.9)	31	(12.5)	6	(4.6)	4	(3.0)	60	(4.3)	89	(3.6)
discontinued pembrolizumab or placebo	12	(9.6)	14	(7.9)	1	(0.9)	7	(4.2)	22	(9.2)	27	(10.9)	5	(3.8)	1	(0.7)	60	(4.3)	89	(3.6)
discontinued any chemotherapy	6	(4.8)	14	(7.9)	3	(2.6)	8	(4.8)	25	(10.4)	27	(10.9)	5	(3.8)	4	(3.0)	0	(0.0)	0	(0.0)
discontinued all drugs	4	(3.2)	10	(5.6)	1	(0.9)	7	(4.2)	8	(3.3)	6	(2.4)	4	(3.1)	2	(1.5)	60	(4.3)	89	(3.6)

† 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 KN407 and KN021 cohort A.
‡‡ Includes all subjects who received at least one dose of treatment in control arm of KN407.
§§ 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, and KN010. KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087
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, KN024: 10JUL2017, KN021 Cohort A: 07NOV2016, KN021 Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)
MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

As stratified by taxane group:

Table 62: Adverse event summary by region (Carboplatin/Paclitaxel) – Subjects in ASaT population

	Pembro Combo				Control			
	EU		Non-EU		EU		Non-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	68		101		69		98	
with one or more adverse events	64	(94.1)	101	(100.0)	67	(97.1)	96	(98.0)
with no adverse event	4	(5.9)	0	(0.0)	2	(2.9)	2	(2.0)
with drug-related† adverse events	60	(88.2)	99	(98.0)	56	(81.2)	86	(87.8)
with toxicity grade 3-5 adverse events	40	(58.8)	68	(67.3)	43	(62.3)	56	(57.1)
with toxicity grade 3-5 drug-related adverse events	30	(44.1)	48	(47.5)	31	(44.9)	40	(40.8)
with serious adverse events	26	(38.2)	44	(43.6)	30	(43.5)	35	(35.7)
with serious drug-related adverse events	18	(26.5)	28	(27.7)	14	(20.3)	21	(21.4)
who died	4	(5.9)	7	(6.9)	5	(7.2)	8	(8.2)
who died due to a drug-related adverse event	2	(2.9)	2	(2.0)	1	(1.4)	4	(4.1)
discontinued any drug due to an adverse event	14	(20.6)	19	(18.8)	8	(11.6)	14	(14.3)
discontinued pembrolizumab or placebo	12	(17.6)	13	(12.9)	5	(7.2)	11	(11.2)
discontinued any chemotherapy	7	(10.3)	12	(11.9)	6	(8.7)	13	(13.3)
discontinued all drugs	4	(5.9)	6	(5.9)	3	(4.3)	9	(9.2)
discontinued any drug due to a drug-related adverse event	12	(17.6)	13	(12.9)	4	(5.8)	9	(9.2)
discontinued pembrolizumab or placebo	10	(14.7)	7	(6.9)	1	(1.4)	5	(5.1)
discontinued any chemotherapy	5	(7.4)	8	(7.9)	4	(5.8)	9	(9.2)
discontinued all drugs	2	(2.9)	2	(2.0)	1	(1.4)	5	(5.1)
discontinued any drug due to a serious adverse event	12	(17.6)	11	(10.9)	6	(8.7)	12	(12.2)
discontinued pembrolizumab or placebo	11	(16.2)	10	(9.9)	4	(5.8)	11	(11.2)
discontinued any chemotherapy	5	(7.4)	6	(5.9)	5	(7.2)	10	(10.2)
discontinued all drugs	4	(5.9)	5	(5.0)	3	(4.3)	9	(9.2)
discontinued any drug due to a serious drug-related adverse event	10	(14.7)	6	(5.9)	3	(4.3)	6	(6.1)
discontinued pembrolizumab or placebo	9	(13.2)	5	(5.0)	1	(1.4)	5	(5.1)
discontinued any chemotherapy	3	(4.4)	3	(3.0)	3	(4.3)	6	(6.1)
discontinued all drugs	2	(2.9)	2	(2.0)	1	(1.4)	5	(5.1)

† Determined by the investigator to be related to the drug.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Table 63: Adverse event summary by region (Carboplatin/Nab-paclitaxel) – Subjects in ASaT population

	Pembro Combo				Control			
	EU		Non-EU		EU		Non-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	57		52		46		67	
with one or more adverse events	56	(98.2)	52	(100.0)	44	(95.7)	67	(100.0)
with no adverse event	1	(1.8)	0	(0.0)	2	(4.3)	0	(0.0)
with drug-related† adverse events	55	(96.5)	51	(98.1)	43	(93.5)	64	(95.5)
with toxicity grade 3-5 adverse events	42	(73.7)	44	(84.6)	36	(78.3)	56	(83.6)
with toxicity grade 3-5 drug-related adverse events	35	(61.4)	39	(75.0)	29	(63.0)	54	(80.6)
with serious adverse events	19	(33.3)	24	(46.2)	17	(37.0)	25	(37.3)
with serious drug-related adverse events	9	(15.8)	15	(28.8)	6	(13.0)	10	(14.9)
who died	5	(8.8)	7	(13.5)	2	(4.3)	3	(4.5)
who died due to a drug-related adverse event	0	(0.0)	6	(11.5)	0	(0.0)	1	(1.5)
discontinued any drug due to an adverse event	15	(26.3)	17	(32.7)	5	(10.9)	6	(9.0)
discontinued pembrolizumab or placebo	9	(15.8)	14	(26.9)	2	(4.3)	4	(6.0)
discontinued any chemotherapy	11	(19.3)	14	(26.9)	5	(10.9)	5	(7.5)
discontinued all drugs	5	(8.8)	8	(15.4)	1	(2.2)	3	(4.5)
discontinued any drug due to a drug-related adverse event	11	(19.3)	14	(26.9)	3	(6.5)	4	(6.0)
discontinued pembrolizumab or placebo	5	(8.8)	11	(21.2)	0	(0.0)	3	(4.5)
discontinued any chemotherapy	8	(14.0)	11	(21.2)	3	(6.5)	4	(6.0)
discontinued all drugs	2	(3.5)	8	(15.4)	0	(0.0)	3	(4.5)
discontinued any drug due to a serious adverse event	8	(14.0)	15	(28.8)	2	(4.3)	3	(4.5)
discontinued pembrolizumab or placebo	7	(12.3)	12	(23.1)	2	(4.3)	2	(3.0)
discontinued any chemotherapy	6	(10.5)	13	(25.0)	2	(4.3)	3	(4.5)
discontinued all drugs	5	(8.8)	8	(15.4)	1	(2.2)	2	(3.0)
discontinued any drug due to a serious drug-related adverse event	4	(7.0)	11	(21.2)	0	(0.0)	2	(3.0)
discontinued pembrolizumab or placebo	3	(5.3)	9	(17.3)	0	(0.0)	2	(3.0)
discontinued any chemotherapy	3	(5.3)	10	(19.2)	0	(0.0)	2	(3.0)
discontinued all drugs	2	(3.5)	8	(15.4)	0	(0.0)	2	(3.0)

† Determined by the investigator to be related to the drug.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover 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.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

No DDI study has been submitted in this application.

Discontinuation due to adverse events

Overall AEs

Table 64: Subjects with adverse events resulting in treatment discontinuation of pembrolizumab/placebo (Incidence >0% in one or more treatment groups) by decreasing frequency of preferred term – Subjects in ASaT population (extract)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	50	(16.5)	22	(7.9)	93	(19.1)	21	(8.0)	452	(11.8)
with no adverse events	253	(83.5)	258	(92.1)	395	(80.9)	243	(92.0)	3,378	(88.2)
Autoimmune hepatitis	5	(1.7)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.1)
Pneumonitis	5	(1.7)	1	(0.4)	13	(2.7)	3	(1.1)	57	(1.5)
Colitis	3	(1.0)	1	(0.4)	4	(0.8)	0	(0.0)	19	(0.5)
Respiratory failure	3	(1.0)	0	(0.0)	0	(0.0)	1	(0.4)	9	(0.2)
Sepsis	3	(1.0)	0	(0.0)	1	(0.2)	0	(0.0)	3	(0.1)
Cardiac arrest	2	(0.7)	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.1)
Death	2	(0.7)	3	(1.1)	2	(0.4)	0	(0.0)	11	(0.3)
Pneumonia	2	(0.7)	0	(0.0)	1	(0.2)	1	(0.4)	10	(0.3)
Pulmonary haemorrhage	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.0)
Anaemia	1	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)	3	(0.1)
Biliary tract infection	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)	2	(0.1)
Cerebrovascular accident	1	(0.3)	0	(0.0)	1	(0.2)	1	(0.4)	3	(0.1)
Cholestasis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Circulatory collapse	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)	7	(0.2)
Diverticular perforation	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)
Headache	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Hypotension	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Interstitial lung disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Lung abscess	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal chest pain	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Necrotising fasciitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nephritis	1	(0.3)	1	(0.4)	2	(0.4)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Psoriasis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sepsis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Small cell lung cancer	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	3	(0.1)

Table 65: Subjects with adverse events resulting in treatment discontinuation of chemotherapy (Incidence >0% in one or more treatment groups) by decreasing frequency of preferred term – Subjects in ASaT population (extract)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264	
with one or more adverse events	46	(15.2)	29	(10.4)	110	(22.5)	35	(13.3)
with no adverse events	257	(84.8)	251	(89.6)	378	(77.5)	229	(86.7)
Neutropenia	5	(1.7)	3	(1.1)	0	(0.0)	0	(0.0)
Infusion related reaction	3	(1.0)	1	(0.4)	0	(0.0)	1	(0.4)
Sepsis	3	(1.0)	0	(0.0)	1	(0.2)	1	(0.4)
Cardiac arrest	2	(0.7)	0	(0.0)	2	(0.4)	0	(0.0)
Febrile neutropenia	2	(0.7)	0	(0.0)	4	(0.8)	0	(0.0)
Lung abscess	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
Pneumonia	2	(0.7)	0	(0.0)	1	(0.2)	2	(0.8)
Pulmonary haemorrhage	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
Rash	2	(0.7)	0	(0.0)	5	(1.0)	0	(0.0)
Anaemia	1	(0.3)	1	(0.4)	0	(0.0)	1	(0.4)
Anaphylactic reaction	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arrhythmia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arthralgia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)
Biliary tract infection	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)
Cerebrovascular accident	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)
Chest pain	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium difficile colitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Colitis	1	(0.3)	1	(0.4)	1	(0.2)	0	(0.0)
Delirium	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(0.3)	0	(0.0)	4	(0.8)	0	(0.0)
Diverticular perforation	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal chest pain	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Necrotising fasciitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neutrophil count decreased	1	(0.3)	0	(0.0)	1	(0.2)	1	(0.4)
Paraesthesia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(0.3)	1	(0.4)	7	(1.4)	2	(0.8)
Psoriasis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary sepsis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)
Abdominal pain	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)

Drug-related AEs

Table 66: 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 – Subjects in ASaT population (extract)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]		Reference Safety Dataset for Pembrolizumab monotherapy[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264		3,830	
with one or more adverse events	33	(10.9)	9	(3.2)	68	(13.9)	10	(3.8)	224	(5.8)
with no adverse events	270	(89.1)	271	(96.8)	420	(86.1)	254	(96.2)	3,606	(94.2)
Autoimmune hepatitis	5	(1.7)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.1)
Pneumonitis	4	(1.3)	0	(0.0)	12	(2.5)	3	(1.1)	56	(1.5)
Colitis	3	(1.0)	1	(0.4)	4	(0.8)	0	(0.0)	19	(0.5)
Sepsis	3	(1.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Anaemia	1	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Biliary tract infection	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebrovascular accident	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.0)
Cholestasis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Death	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Diarrhoea	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)	5	(0.1)
Duodenitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)
Headache	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Interstitial lung disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Necrotising fasciitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nephritis	1	(0.3)	1	(0.4)	2	(0.4)	0	(0.0)	0	(0.0)
Psoriasis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary haemorrhage	1	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	3	(0.1)
Abdominal pain	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Acute kidney injury	0	(0.0)	1	(0.4)	10	(2.0)	0	(0.0)	2	(0.1)
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adrenal insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alanine aminotransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Arterial thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Arthralgia	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.1)
Arthritis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	2	(0.1)

Table 67: 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 – Subjects in ASaT population (extract)

	KN407 + KN021-A combo[††]		KN407 chemo[‡‡]		KN189 + KN021-G/C combo[§§]		KN189 + KN021-G chemo[†††]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	303		280		488		264	
with one or more adverse events	33	(10.9)	20	(7.1)	85	(17.4)	25	(9.5)
with no adverse events	270	(89.1)	260	(92.9)	403	(82.6)	239	(90.5)
Neutropenia	5	(1.7)	3	(1.1)	0	(0.0)	0	(0.0)
Infusion related reaction	3	(1.0)	1	(0.4)	0	(0.0)	1	(0.4)
Sepsis	3	(1.0)	0	(0.0)	1	(0.2)	1	(0.4)
Febrile neutropenia	2	(0.7)	0	(0.0)	4	(0.8)	0	(0.0)
Peripheral sensory neuropathy	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
Rash	2	(0.7)	0	(0.0)	5	(1.0)	0	(0.0)
Anaphylactic reaction	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arrhythmia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arthralgia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)
Biliary tract infection	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebrovascular accident	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)
Colitis	1	(0.3)	1	(0.4)	1	(0.2)	0	(0.0)
Diarrhoea	1	(0.3)	0	(0.0)	4	(0.8)	0	(0.0)
Duodenitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Lung abscess	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Necrotising fasciitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neutrophil count decreased	1	(0.3)	0	(0.0)	1	(0.2)	1	(0.4)
Paraesthesia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(0.3)	0	(0.0)	7	(1.4)	2	(0.8)
Psoriasis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	1	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)
Respiratory failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Acute kidney injury	0	(0.0)	2	(0.7)	13	(2.7)	1	(0.4)
Anaemia	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)
Arthritis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Asthenia	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
Autoimmune hepatitis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Blood creatine increased	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	4	(0.8)	2	(0.8)
Cellulitis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Cholangitis sclerosing	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Creatinine renal clearance decreased	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
Death	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2017 through 03-MAR-2018.

2.5.1. Discussion on clinical safety

The safety data in support of this application were derived from the individual analysis of the pivotal Phase III study KN-407 (n=278 in pembro combo and 280 in control), in addition to a pooled dataset of patients with squamous NSCLC who received pembrolizumab in combination with (nab)/paclitaxel-carboplatin (including patients treated with pembrolizumab in combination with carboplatin/paclitaxel (or nab-paclitaxel) from Study KN-407 (n=278) and in patients from Study KN-021-A (n=25, including 9 with NSCLC of squamous histology). Data were compared to prior databases comprising non-squamous NSCLC

patients treated with pembrolizumab as add-on therapy to platinum/pemetrexed-based doublets (KN-189+KN-021-G/C pooled; n=488) and a reference database (RSD; n=3830) including all pembrolizumab monotherapy indications currently approved in the EU.

The KN-407 showed a median exposure of 8 cycles in the experimental arm vs 6 cycles in the control group. Length of treatment with pembrolizumab was independent of the combination regimen (8 administrations in median in both the paclitaxel and nab-paclitaxel subgroup). Exposure to carboplatin/paclitaxel (or nab-paclitaxel) was similar between treatment arms.

Compared with the other safety datasets, KN-407+KN-021-A pooled combo showed a shorter exposure to pembrolizumab than KN-189 +KN-021-G/C pooled combo (8 vs 11 administrations in median; exposure to chemotherapy is not directly comparable considering the different therapeutic schemes used in the two clinical settings). This is likely explained by the shorter follow-up of KN-407 at data cut-off (7.8 months) compared to the 10.5 month follow-up in KN-189 at the time of dossier submission.

In study KN-407, the frequency of overall AEs was generally similar between treatment arms (98.2% vs 97.2% in pembro combo vs control, respectively), with the exception of drug-related AEs (95.3% vs 88.9%), serious drug-related AEs (25.2% vs 18.2%) and discontinuation of any drug due to either AEs (23.4% vs 11.8%) or drug-related AEs (18% vs 7.1%) that occurred more frequently on combined therapy than chemotherapy alone. Moreover, more patients died in the combo arm than chemo group (8.3% vs 6.4%), including those for whom fatalities were subsequent to drug-related AEs (3.6% vs 2.1%). This is in line with what has been previously reported in the non-squamous histology (KN-189+KN-021-G/C pooled group). As expected, the combined regimen compares unfavourably with the RSD for pembrolizumab monotherapy across all different AE categories.

Most common AEs (incidence $\geqslant$30%) were those characteristic for chemotherapy (anaemia, alopecia, neutropenia, nausea, and thrombocytopenia in the Pembro combo group). Some of these incidences typically attributable to chemotherapy were reported with higher incidences in the Pembro combo group than in the control group (such as thrombocytopenia 30.6% vs. 23.2%, neutropenia 37.8% vs. 32.9%, and alopecia 46% vs. 36.4%).

Exposure-adjusted analysis by observation period revealed that the majority of AEs in KN-407 occurred during the first 3 months of therapy in both arms, with a progressive and similar decline in incidence rate up to 6-12-month follow-up between groups; this is expected given that exposure to chemotherapy, either alone or in combination, was limited to the first 4 cycles of therapy. A higher frequency of AEs beyond 12 months was observed in the pembrolizumab arm likely due to the maintenance therapy not administered in the control group.

In terms of SOC categories, the two treatments displayed a similar AEs pattern with blood and lymphatic system disorders as the prevailing events, followed by gastrointestinal, skin disorders and neurotoxicity. However, their occurrence was higher in the pembro than control group, the majority of events being registered during the first 6 months of treatment. This temporal pattern suggests that events were mainly associated with cytotoxic agents with an additive effect of pembrolizumab co-treatment. On the contrary, endocrine disorders were commonly reported in the combo group with a peak between 3-6 months but were rare in the control arm at all time points. Infections and infestations as well as respiratory and mediastinal disorders were generally similar between pembro combo and control up to 6-12 months; beyond 12 months, their incidence was higher in the experimental group (7.1% vs 2.4% and 4.3% vs 2.4% for infections and respiratory disorders, respectively) indicating a likely association with pembrolizumab maintenance therapy.

In KN-407, the incidence of drug-related AEs was increased in the combined therapy compared to chemotherapy only (95.3% vs 88.9%). Blood and lymphatic system disorders were the most frequent events (68.7% vs 58.2%) with pembrolizumab increasing the rate of Grade 1, Grade 2 and Grade 4 toxicities. Among the most prominent differences, a higher incidence of drug-related AEs were reported in

the experimental arm within the SOCs endocrine disorders (11.9% vs. 1.8%), nervous system disorders (51.1% vs 41.1%), skin and subcutaneous tissue disorders (54.3% vs 43.9%), gastrointestinal disorders (55.4 vs. 45.4%), general disorders (44.6% vs. 39.3%), infections and infestations (12.2% vs. 6.8%), musculoskeletal disorders (27.0% vs 22.9%), renal and urinary disorders (4.7% vs. 1.4%), and respiratory disorders (15.8 vs. 11.4%). The fact that subjects with drug-related AEs were more numerous in the pembro combo supports the concept that pembrolizumab has an additive effect on chemotherapy toxicity, as also previously observed in KN-189.

As expected, the comparison of the pooled KN-407+KN-021-A combo database with the clinical datasets of pembrolizumab used as monotherapy or in combination with platinum-pemetrexed in non-squamous NSCLC revealed an increased frequency of alopecia, myelosuppression and neuropathy that is consistent with the known toxicity profile of the carboplatin-paclitaxel association and that, as previously mentioned, is worsened by pembrolizumab co-treatment. Moreover, serious infusion-related reactions occurred with a common frequency in the pooled KN-407+KN-021-A group compared with no event reported in the pooled KN-187+KN-021-A database. A safety analysis in the AsAT as stratified by either paclitaxel or nab-paclitaxel use, revealed that IRR only occurred in patients who received paclitaxel, either with (2.4%) or without (1.8%) pembrolizumab co-administration, and that the majority of these events were causally related to the taxane. The remaining drug-related events as distinguished by the different PTs were overall in line with the prior experience of pembrolizumab including thyroid dysfunction, renal and liver function abnormalities.

While overall Grade 3-5 AEs occurred with a similar frequency between treatment arms, febrile neutropenia, hyponatraemia, diarrhoea, pneumonitis, colitis, autoimmune hepatitis and infusion-related reactions were more frequent in the combined therapy than control. Causality with treatment was reported in the majority of these events. All of these events were reported with increased frequency in the KN-407+KN-021-A pooled combo compared to the RSD but at a similar rate than KN-189+KN-021-G/C pooled combo, with the exception of colitis, autoimmune hepatitis and infusion-related reactions that occurred more often than previously observed in the combined therapy (0.6%, 0.2% and 0%, respectively). Colitis was reported for 4 (2.4%) subjects in the pembro/paclitaxel combination group and 2 subjects (1.8%) in the pembro/nab-paclitaxel combination group; five subjects (1.8%) experienced autoimmune hepatitis in KN-407, all in the pembro/nab-paclitaxel combination group. Of note, the incidence of these events in KN-407 was similar to the RSD. The SmPC currently list them among the AEOSI and correctly reports the need for patient monitoring with suggested dose modifications should they occur.

Febrile neutropenia, pneumonitis and colitis were also among the most frequent SAEs reported with a higher incidence in the pembro combo than control; also, infusion-related reactions were observed with a common frequency in the combined but not the control therapy (1.4% vs 0.4%).

In KN-407, more fatalities due to AEs were reported in the pembro combo than control group (8.3% vs 6.4%). With respect to the comparator, pembro combo increased the incidence of fatal respiratory failure (1.1% vs 0%), cardiac arrest (0.7% vs 0.4%) and sepsis (1.1% vs 0.4%). The pooled KN-407+KN-021-A dataset comparison with pembrolizumab monotherapy was unfavourable (7.6% vs 4.1%), although a similar rate of deaths was reported in the pembrolizumab combination with platinum-pemetrexed (6.1%) which is consistent with the expected increased rate of toxicities in combined regimens.

In line with the known safety profile of pembrolizumab, AEOSIs occurred more frequently in the experimental arm than control. Their incidence in the KN-407 pooled combo was overall comparable with the RSD, except for colitis (3% vs 1.9%), hepatitis (1.7% vs 0.6%), hyperthyroidism (6.6% vs 3.5%)hypophysitis (1% vs 0.5%) and pneumonitis (6.3% vs 3.7%). To better evaluate the clinical relevance of these differences, incidence rates in a pooled data set comprising all pembro combination studies (KN189, KN407, KN021) compared to an updated RSD were requested and confirmed these trends although with an attenuation of differences between the combined therapy in the NSCLC setting and monotherapy in the overall pembrolizumab indications as regards colitis (2.9% vs 1.9%), hepatitis (1.3% vs 0.9%),

hyperthyroidism (5.2% vs 4.2%), hypophysitis (0.8% vs 0.6%) and pneumonitis (5.2% vs 4.2%). The SmPC has been amended accordingly with the new updated RSD rates for all AEOSIs.

The MAH provided analyses of pneumonitis in NSCLC indicating a small, but numerically higher rate of pneumonitis compared with the currently reported ones for pembrolizumab monotherapy across all approved indications. The updated rates of pneumonitis in NSCLC have been reflected in section 4.8 of the SmPC.

As regards the other AEOSIs as listed above, their frequency is overall within the same range as previously observed in KN-189, showing that cytotoxic agents increase the toxicity associated to pembrolizumab therapy. Indeed, a worse safety profile of the combined regimen compared to monotherapy can be recognised and this needs to be considered by physicians in treatment-decision making (see section 4.2 of the SmPC). No differences in deaths due to AEOSIs were reported across datasets.

In terms of laboratory abnormalities, differences between pembro combo and control were observed in leukocyte and platelet count decrease, and liver function tests with a more unfavourable profile in the experimental arm (see section 4.8 of the SmPC).

Safety analysis by age category revealed a higher rate of drug discontinuation due to AEs in the pembro combo than control across all groups. Of note, cardiovascular events occurred more frequently in the youngest patients, which is quite unexpected. However, the group of patients ≥75-year-old was constituted of 33 and 30 patients in the experimental and control arm, respectively. Moreover, only three patients were aged ≥85 years. Therefore, data in the very elderly population remain very limited, as already stated in section 4.2 of the SmPC. When analysing the population by the cut-off value of 65 years, a clear tendency towards worse tolerability to the combined therapy in ≥ 65 year-old than younger patients (≤ 65-year old) can be recognised. Age-dependency of safety emerges across all datasets, including combo and monotherapy studies. The same trend can be observed, as expected, within the chemotherapy group although the association of pembrolizumab to the cytotoxic agents clearly enhances the rate of AEs compared to both chemotherapy only and pembrolizumab monotherapy. Therefore, careful consideration should be given to the treatment decision making for elderly patients (see section 4.4 of the SmPC).

To overcome the limitations of the small numbers and to better characterize the safety profile in the elderly patients, the MAH was asked to provide analysis by age (< 65 vs. ⩾ 65 years and using additional age categories (65 to 74 years old, 75 to 84 years old, and ⩾85 years old)) in the pooled data set for pembro /chemotherapy combination therapy in 1L NSCLC. It emerged that 17% of deaths were due to an AE, 34.2% of discontinuations were AE-related, and cardiovascular and cerebrovascular events were reported with a frequency of 31.6% and 9.2%, respectively, in patients ≥75-year-old. These rates are of concern, since they are notably higher compared to the same age group of the chemotherapy arms.

Further analyses of pooled dataset showed that the proportion of patients with AEs in each AE category was mostly higher for the pembrolizumab plus chemotherapy arms compared with the chemo arms and among subjects ≥65 years compared with <65 years. However the differences between both age categories were generally similar in both treatment groups apart from SAEs and discontinuations that were more pronounced in the elderly patients of the pembrolizumab combination arm. The analysis of AE categories of particular interest in the elderly population did not reveal categories with a notably larger difference in the elderly compared to the <65 years age category. No dose adjustment is necessary in patients ≥65 years (see section 4.2 of the SmPC).

Overall similar incidences for the age category of 75-84 years are seen between both treatment arms; however rates of serious drug-related SAEs, discontinuations due to an AE and death due to an AE were higher in the pembrolizumab combination arm compared to chemotherapy arm. Nevertheless pooled NSCLC combination therapy data in the age group beyond 75 years are still considered too small to draw reliable conclusions or to provide more detailed information in the SmPC.

Unexpectedly and unlike the control therapy, the combined regimen seemed to be associated with an apparent lower tolerability in men than female, specifically with regard to dose modifications due to AEs, discontinuations due to AEs. The rate of drug modifications and discontinuations were also influenced by ECOG score, as expected. Overall, from the additional analyses submitted by the MAH, no significant clinical findings emerged in terms of sex-related tolerability of pembrolizumab in combination to chemotherapy.

It was also investigated whether the use of nab-paclitaxel vs paclitaxel differed between region groups and, if it is the case, to what extent this could explain the region-dependent difference observed between EU and ex-EU. No major differences were observed in terms of baseline characteristics between treatment arms in both EU and ex-EU. The choice of the taxane was similar between regions. A few disparities could be recognised in the incidence of certain AE categories between regions (i.e. discontinuation of pembrolizumab due to adverse drug reactions in the group of carbo/paclitaxel; discontinuation of any drug due to adverse drug reactions in the group of carbo/nab-paclitaxel). However it is agreed that specific subgroups of patients were numerically very limited to plausibly be indicative of region-dependent differences in tolerability of the combined therapy.

Finally, common AEs leading to pembrolizumab discontinuation in the combined therapy group included autoimmune hepatitis and pneumonitis (both with an incidence of 1.7%), colitis, respiratory failure and sepsis (1%) as well as cardiovascular events (including cardiac arrest 0.7%, cardiac failure 0.3%, cerebrovascular accident 0.3%). All of these events were deemed drug-related and occurred with a higher incidence than previously reported in KN-189+KN-021-G/C pooled combo and RSD , with the exception of pneumonitis. Neutropenia (1.7%), infusion-related reactions and sepsis (1%) and cardiovascular events (cardiac arrest 0.7%, cardiac failure 0.3%, cerebrovascular accident 0.3%) were also among the main reasons for AE-related chemotherapy discontinuation in the experimental arm, their rate being higher than the other safety datasets.

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. 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. Systemic corticosteroids, or other immunosuppressants, can be used during pembrolizumab treatment to treat immune-related adverse reactions. Similarly, the potential of DDI between pembrolizumab and chemotherapy agents is expected to be low. No impact of co-administered chemotherapy on pembrolizumab PK was observed in KN-021-G.

2.5.2. Conclusions on clinical safety

Pembrolizumab in combination to (nab)/paclitaxel-carboplatin therapy for squamous NSCLC compared unfavourable with chemotherapy alone. The increased toxicity of pembrolizumab as add-on to chemotherapy vs chemotherapy alone in the intended population is consistent with the prior experience and already authorised indication of pembrolizumab co-treatment with cytotoxic agents in non-squamous NSCLC patients. Moreover, a worse safety profile of the combined regimen emerged in comparison with pembrolizumab monotherapy that should be considered for treatment decision making, particularly in elderly patients for whom data remain limited. The proposed SmPC reflects the available data and warnings. No changes to the RMP have been considered necessary as part of this procedure.

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 23.0 is acceptable.

No changes to the list of safety concerns, pharmacovigilance plan and risk minimisations measures were required as a result of this extension of indication.

The CHMP endorsed the Risk Management Plan version 23.0 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

Summary of safety concerns	
	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

Pharmacovigilance plan

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 tumours 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 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 (KN042)	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) -Long term safety	Final Study Report	Dec 2019
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	Final Study Report	Mar 2019

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
			patients with a history of allogeneic SCT;Immunogenicity)		
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
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 tumour 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 tumours 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

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
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
Started	Clinical Trial 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 (KN189)	To evaluate the antitumour activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy and to evaluate the antitumour 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
Started	Clinical Trial A randomized, activecontrolled, multicenter, openlabel Phase III clinical trial to examine the efficacy and safety of Pembrolizumab versus the choice of 3 different standard treatment options in subjects with recurrent	To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, Immunogenicity) -Long term safety	Final Study Report	May 2020

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) whose disease has progressed on or after prior platinum-containing chemotherapy (KN040)				

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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types
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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types
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. Additional risk minimisation measures: ▪ Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
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. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
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: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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. 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. Additional risk minimisation measures: ▪ Educational materials	Additional pharmacovigilance including: · Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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 tumour 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 Concern	Risk minimisation Measures	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 tumour 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	Additional pharmacovigilance including: • Safety monitoring in ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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 Concern	Risk minimisation Measures	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: T questionnaire for spontaneous postmarketing reports of all adverse events

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.

The MAH also took the opportunity to introduce two minor editorial corrections to section 5.1 of the SmPC regarding the procedure EMEA/H/C/003820/II/0052, in relation to KEYNOTE-052 (urothelial carcinoma indication) which obtained a Commission Decision on the 6th of July 2018.

2.7.1. User consultation

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

The only change in the leaflet is the addition of one paragraph regarding the combination products in section 1 "What KEYTRUDA is and what it is used for". There are no other proposed changes to the content of the package leaflet. In particular the key messages for the safe use of the medicinal product are not impacted. Furthermore the design, layout and format of the package leaflet is not affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is seeking an extension of indication for KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC in adults, based on the interim results of the pivotal study KEYNOTE-407.

Squamous NSCLC is a malignant epithelial tumour comprising approximately 30-40% of the NSCLC that shows either keratinisation and/or intercellular bridges, which is strongly associated with cigarette smoking.

3.1.2. Available therapies and unmet medical need

In advanced squamous NSCLC disease, molecular testing (EGFR, ALK) is not usually recommended due to the very low incidence of mutation, unless subject is a never or former light smokers (<15 pack/years). In case of mixed adenosquamous tumours, the adenocarcinoma component should trigger molecular analysis. Four to six cycles of platinum-based doublets chemotherapy with the addition of a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in first line advanced squamous cell cancer patients without major comorbidities and PS 0-2 according to the ESMO guideline (Planchard et al, 2018). Albumine-bound paclitaxel (nab-paclitaxel) is an option particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel

premedication (i.e. dexamethasone, H1 and H2 blockers). Nab-paclitaxel/carboplatin regimen response rate was shown to be non-inferior to that of the paclitaxel/carboplatin (Socinski et al, 2012).

Pembrolizumab as monotherapy is currently indicated in first-line NSCLC with PD-L1 TPS≥50% expression, including squamous histology.

3.1.3. Main clinical studies

The application is based upon results of KEYNOTE-407 trial, an international, randomized, double-blind, phase III study, placebo-controlled with active treatment of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab in first line metastatic squamous NSCLC subjects.

A total of 559 patients with previously untreated metastatic squamous NSCLC were randomized. This study is ongoing and data presented are coming from the IA2 with data cut-off date 3 April 2018. OS and PFS per RECIST 1.1 by BICR were dual primary endpoints. The secondary endpoints included ORR and DOR per RECIST 1.1 by BICR.

3.2. Favourable effects

- Statistically significant advantage of pembrolizumab combination over chemotherapy alone in the ITT population in OS (HR 0.64, 95%CI 0.49, 0.85, p<0.0008) as well as in PFS per BICR by RECIST 1.1 (HR 0.56, 95%CI 0.45, 0.70, p<0.0001).
- Higher confirmed ORR by RECIST 1.1 according to BICR in the pembro combo arm compared to chemotherapy (57.9% vs 38.4%, p<0.0001) with longer median DOR (7.7 vs 4.8 months).
- Overall consistent results across subgroups, including PD-L1 subgroups.

3.3. Uncertainties and limitations about favourable effects

- Immaturity of OS data (OS events occurred account for 57% of that planned for the final analysis) and limited follow-up time (median 7.8 months). Due to the short follow-up, there is a need to confirm the efficacy of the combination also on later events. The MAH will submit the final study report for study KN-407 in order to confirm the benefit of the combination vs chemotherapy with longer FU (annex II condition).
- Lack of comparison with pembrolizumab monotherapy for NSCLC patients with TPS≥50% is reflected in section 4.4 of the SmPC.
- Due to the limited sample size, the magnitude of the benefit of pembrolizumab in combination with chemotherapy patients aged ≥ 75 years is difficult to characterise (see section 5.1 of the SmPC).

3.4. Unfavourable effects

- In study KN-407, the safety of pembrolizumab in combination with chemotherapy compared unfavourably against chemotherapy alone. Drug-related AEs, serious drug-related AEs, discontinuations due to either AEs or drug-related AEs and deaths, including those for whom fatalities were subsequent to drug-related AEs (3.6% vs 2.1%), were more frequently reported on combined therapy than chemotherapy alone.
- While overall Grade 3-5 AEs occurred with a similar frequency between treatment arms (69.8% vs 68.2%) febrile neutropenia (5.4% vs 3.9%), hyponatremia (3.6% vs 1.8%), diarrhoea (4% vs 2.1%), pneumonitis (2.5% vs 0.4%), colitis (2.2% vs 0.7%), autoimmune hepatitis (1.8% vs 0%) and infusion-related reactions (1.1% vs 0.4%) were more frequent in the combined therapy than control.

Febrile neutropenia (5.4% vs 3.6%), pneumonitis (2.5% vs 0.7%) and colitis (2.2% vs 0.4%) were also among the most frequent SAEs reported with a higher incidence in the pembro combo than control.

- With respect to the comparator, pembro combo slightly increased the incidence of fatal respiratory failure (1.1% vs 0%), cardiac arrest (0.7% vs 0.4%) and sepsis (1.1% vs 0.4%).
- The indirect comparison with the reference safety database also showed a worse toxicity profile than pembrolizumab in monotherapy.

3.5. Uncertainties and limitations about unfavourable effects

- The combination therapy appears less tolerable in elderly (≥75 years); however final conclusions are limited by the small patient numbers (see section 4.4 of the SmPC).

3.6. Effects Table

Table 68: Effects Table for Keytruda in 1st line treatment of metastatic squamous NSCLC in combination with carboplatin/paclitaxel or carboplatin/nab paclitaxel (study KEYNOTE-407, data cut-off: 03-APR-2018, Interim Analysis 2)

Effect	Short description	Unit	pembro + (nab)/pacli taxel	placebo + (nab)/pacli taxel	Uncertainties / Strength of evidence
Favourable Effects					
OS *dual primary*	Time from randomization to death (whatever the cause)	median months (95%CI)	15.9 (13.2,-)	11.3 (9.5, 14.8)	immature data (57% of the final planned OS event, 37% of ITT population), short follow up
		HR	0.64 (0.49-0.85)		
PFS (by BICR per RECIST 1.1) *dual primary*	time from randomization to first documented PD per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first.	median months	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)	
		HR	0.56 (0.45, 0.70)		
ORR *secondary endpoint*	proportion of participants who had CR or PR per RECIST 1.1 by BICR.	% (95%CI)	57.9 (51.9, 63.8)	38.4 (32.7, 44.4)	same rate of CR
DOR *secondary endpoint*	time from first documented evidence of CR or PR until PD or death.	median months (range)	7.7 (1.1+, 14.7+)	4.8 (1.3+,15.8+)	
Unfavourable Effects					
Tolerability					
	Gr≥3 AEs	%	69.8	68.2	
	drug related SAEs	%	25.2	18.2	
	drug related deaths	%	3.6	2.1	
	discontinuation drug related AEs	%	18.0	7.1	
	discontinuation drug related SAEs	%	11.2	3.9	
AEs	Alopecia	%	46.0	36.4	
	Anaemia	%	53.2	51.8	
	Neutropenia	%	37.8	32.9	
	Febrile Neutropenia	%	5.4	3.9	
	Hypothyroidism	%	7.9	1.8	
	Hyperthyroidism	%	7.2	0.7	

Effect	Short description	Unit	pembro + (nab)/pacli taxel	placebo + (nab)/pacli taxel	Uncertainties / Strength of evidence
	Neuropathy peripheral	%	20.5	16.1	
	Diarrhoea	%	29.9	23.2	
	Vomiting	%	16.2	11.8	
	Pneumonitis	%	5.4	1.4	
	Colitis	%	2.2	1.1	
	Autoimmune hepatitis	%	1.8	0	

Abbreviations: OS=overall survival; PFS=progression free survival; ORR=objective response rate (confirmed); DOR=duration of response; PD=progressive disease; CR=complete response; PR=partial response; HR=hazard ratio. Notes: data from CSR KEYNOTE-407 study

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KEYNOTE-407 study interim results have shown a relevant clinical advantage of the addition of pembrolizumab to carboplatin+paclitaxel/nab-paclitaxel compared to chemotherapy alone in all efficacy endpoints OS, PFS ORR and DOR.

Compared with chemotherapy alone, the combined therapy was associated with a worse tolerability profile, particularly in terms of increased rate of certain drug-related events, including fatalities, although the incidence of grade 3-5 ADRs was similar across treatment groups. As expected, an additive effect of pembrolizumab has been observed on myelosuppression, neurotoxicity and alopecia which are known toxicities associated with carboplatin-paclitaxel combination; additionally, a higher frequency of infections (including sepsis), infusion-related reactions and gastrointestinal disorders were observed in pembro combo compared to control. The increased toxicity of pembrolizumab as add-on to chemotherapy vs chemotherapy alone in the intended population is consistent with the prior experience and already authorised indication of pembrolizumab co-treatment with cytotoxic agents in non-squamous NSCLC patients, although some specific ADRs were noted to occur with increased frequency in KN-407 than KN-187 in relation to the different therapeutic association. AEOSIs, with particular reference to thyroid dysfunctions, hepatitis and pneumonitis were common events in the experimental, but not in the control arm. The indirect comparison with pembrolizumab monotherapy showed that the pembrolizumab/chemotherapy combination carries an increased toxicity across all AE categories. Therefore, careful consideration is recommended in treatment-decision making, particularly in the elderly patients considering that age-dependent tolerability has been observed as reflected in the SmPC.

3.7.2. Balance of benefits and risks

Although OS data are not yet fully mature, there is a statistically significant survival advantage and increased PFS of pembrolizumab in combination with chemotherapy vs chemotherapy alone (4.6 months and 1.6 month difference respectively). This is considered to outweigh the worse tolerability profile of pembrolizumab in combination with chemotherapy.

Results from KEYNOTE-407 study are considered sufficient to establish a positive B/R in the sought indication for the first line treatment of metastatic squamous NSCLC in combination with carboplatin/(nab)paclitaxel. The MAH is expected to submit the final CSR of study KN-407 to further characterise the OS benefit from the combination treatment.

3.8. Conclusions

The overall B/R of Keytruda in combination with carboplatin and either paclitaxel/nab-paclitaxel for the

first-line treatment of metastatic squamous NSCLC in adults is positive.

The CHMP considers the following measures necessary to address issues related to efficacy:

- in order to confirm the advantage of the combination compared to chemotherapy alone, including primary and secondary outcomes by ITT and subgroups, the MAH should submit the final CSR of KEYNOTE-407 study post-approval (Annex II) (projected by September 2021).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults for Keytruda; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Additionally, editorial corrections to section 5.1 of the SmPC are introduced (concerning the procedure EMEA/H/C/003820/II/0052). The RMP version 23 has also been submitted.

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

This CHMP recommendation is subject to the following new condition:

Conditions and requirements of the marketing authorisation

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P407: A Randomized, Double-Blind, Phase III Study of Carboplatin - Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects – Final Study Report	3Q 2021

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for

the first-line treatment of metastatic squamous NSCLC in adults for Keytruda; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Additionally, editorial corrections to section 5.1 of the SmPC are introduced (concerning the procedure EMEA/H/C/003820/II/0052). The RMP version 23 has also been submitted.

Summary

Please refer to the Scientific Discussion EMEA/H/C/003820/II/0060.

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