30 April 2020
EMA/CHMP/299815/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0057

Note

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

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List of abbreviations

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

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 3 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

Extension of Indication to include 1st line treatment of locally advanced or metastatic non-small cell lung cancer tumours expressing PD-L1 with a ≥ 1% tumour proportion score (TPS), based on data from study KEYNOTE-042; an international, randomized, open-label Phase 3 study investigating KEYTRUDA monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC, and on supportive data from the final planned analysis of KEYNOTE-024; a Phase 3 randomized open-label study of KEYTRUDA monotherapy compared to platinum-based chemotherapy in metastatic NSCLC with PD-L1 TPS ≥50%. As a result, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. An updated RMP version 18.1 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0043/2018 was 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	3 July 2018
Start of procedure	21 July 2018
CHMP Rapporteur's preliminary assessment report circulated on	25 September 2018
CHMP Co-Rapporteur's preliminary assessment report circulated on	14 September 2018
PRAC Rapporteur's preliminary assessment report circulated on	13 September 2018
PRAC Rapporteur's updated assessment report circulated on	25 September 2018
PRAC RMP advice and assessment overview adopted by PRAC	4 October 2018
CHMP Rapporteurs' preliminary joint assessment report circulated on	11 October 2018
Request for supplementary information and extension of timetable adopted by the CHMP on	18 October 2018
MAH's responses submitted to the CHMP on	24 January 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	5 March 2019
CHMP Rapporteurs' updated joint assessment report on the MAH's responses circulated on	21 March 2019
2nd Request for supplementary information and extension of timetable adopted by the CHMP on	28 March 2019
MAH's responses submitted to the CHMP on	19 July 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	27 August 2019
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	10 September 2019
CHMP Rapporteurs' updated joint assessment report on the MAH's responses circulated on	12 September 2019
3rd Request for supplementary information and extension of timetable adopted by the CHMP on	19 September 2019
MAH's responses submitted to the CHMP on	17 December 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	28 January 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	30 January 2020
PRAC RMP advice and assessment overview adopted by PRAC	13 February 2020
CHMP Rapporteurs' updated joint assessment report on the MAH's responses circulated on	20 February 2020
4th Request for supplementary information and extension of timetable adopted by the CHMP on	27 February 2020
MAH's responses submitted to the CHMP on	25 March 2020
CHMP Rapporteurs' preliminary joint assessment report on the MAH's	1 April 2020

Timetable	Actual dates
responses circulated on	
CHMP opinion adopted on	30 April 2020

2. Scientific discussion

2.1. Introduction

Pembrolizumab (Keytruda) is a highly selective humanized monoclonal antibody that binds to human programmed cell death 1 (PD 1) and blocks the interaction between the PD-1 pathway receptor and its ligands, programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2) expressed on antigen presenting tumour cells. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T-cell receptor, thus overcoming the active anti-tumour specific T cell immune surveillance. The high expression of PD-L1 on tumour cells has been found to correlate with poor prognosis and survival in various cancers and suggests that the PD-1/PD-L1 pathway plays a critical role in tumour evasion and is thus an attractive target for therapeutic intervention.

In the setting of lung cancer, which currently represents the main cause of malignancy-related mortality worldwide accounting for 1.76 million of deaths globally (Globocan 2018), pembrolizumab-based immunotherapy is a consolidated therapeutic option in clinical practice. Current guidelines recommend the use of Keytruda monotherapy for the treatment of non-small cell lung cancer (NSCLC), i.e. the prevailing histological subtype (85%-90%) of all lung malignancies, as follows (ESMO, 2019):

- First-line treatment of patients with metastatic NSCLC in patients whose tumours have high PD-L1 expression [Tumour Proportion Score (TPS) ≥ 50%] with no EGFR or ALK positive tumour aberrations
- Advanced or metastatic NSCLC in patients whose tumours express PD-L1 (TPS ≥1%) and who have received prior platinum-based therapy, and if the tumours express EGFR or ALK genomic tumour aberrations should have disease progression on approved therapy before receiving Keytruda

Moreover, Keytruda has been recently approved in combination with chemotherapy as first line treatment in metastatic NSCLC irrespective of the PD-L1 level of expression. The chemotherapy regimen associated with pembrolizumab depends on the histology: pemetrexed and a platinum compound in non-squamous NSCLC with negative ALK/EGFR disease (EMEA/H/C/003820/II/0043) or carboplatin and either paclitaxel or nab-paclitaxel in squamous NSCLC (EMEA/H/C/003820/II/0060).

Chemotherapy regimens used in NSCLC include cisplatin or carboplatin in combination with paclitaxel, nab-paclitaxel, gemcitabine, pemetrexed, or docetaxel (ESMO, 2019). Multiple Phase 3 studies have demonstrated similar efficacy for most platinum-based chemotherapy in the 1st line treatment of patients with advanced NSCLC (Schiller JH. et al, 2002); response rates have ranged from 15% to 33%, with median PFS of approximately 4.5 to 6.3 months, and median OS of 10.3 to 12.1 months [Socinski et al. 2012, Sandler et al 2006, Scagliotti et al 2008, Thatcher et al 2015]. Treatment-related mortality (deaths due to AEs) in these studies has ranged from 0% to 3%. However, the overall 5-year survival rate of 9% to 13%. Over the past 4 years, immune checkpoint inhibitors, such as PD-1/PD-L1 blocking antibodies, have emerged as effective alternatives to chemotherapy for many tumour types. In 1L and 2L+ NSCLC, PD-1 and PD-L1 inhibitors have demonstrated efficacy as monotherapy or in combination depending on the setting.

With this submission, the MAH intends to further extend the clinical indication of Keytruda as monotherapy in the NSCLC setting to include previously untreated patients with metastatic disease (including both squamous and non-squamous subtypes) not expressing EGFR or ALK tumour aberrations,

in the presence of a PD-L1 positive score with TPS ≥ 1%.

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 conducting Environmental Risk Assessment studies as the product and excipients are not expected to pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

The only new clinical study that has been submitted in support of this application is study KEYNOTE-042.

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

Clinical Development Program for Pembrolizumab in Non-small Cell Lung Cancer

Study	Design	Subject Population	Primary Endpoint	Status
KEYNOTE-001	Phase 1, open label study of pembrolizumab in multiple expansion cohorts	Progressive locally advanced/metastatic carcinomas, primarily melanoma or NSCLC; 5 parts with unique study designs: Parts C and F enrolled only subjects with NSCLC	ORR	Enrollment complete; treatment ongoing
KEYNOTE-010	Phase 2/3, randomized study of 2 doses of pembrolizumab vs. docetaxel	NSCLC with PD-L1 TPS ≥1%; experienced disease progression after platinum-containing systemic therapy	OS, PFS	Enrollment complete; treatment ongoing
KEYNOTE-021	Phase 1/2, open-label study of 2 dose schedules of pembrolizumab in combination with chemotherapy or immunotherapy (multiple cohorts); 2 parts	Locally advanced/metastatic NSCLC; no prior systemic therapy for metastatic disease	ORR	Enrollment complete; treatment ongoing
KEYNOTE-024	Phase 3, randomized, open-label study of pembrolizumab vs. platinum chemotherapy	Metastatic NSCLC with PD-L1 TPS ≥50%; no prior systemic therapy for metastatic disease	PFS	Enrollment complete; treatment ongoing
KEYNOTE-042	Phase 3, randomized, open-label study of pembrolizumab vs. platinum chemotherapy	Advanced/metastatic NSCLC with PD-L1 TPS ≥1%; no prior systemic therapy for advanced/ metastatic disease	OS	Enrollment complete; treatment ongoing
KEYNOTE-091	Phase 3, randomized, placebo-controlled study of pembrolizumab vs. placebo for 1 year after completion of surgical resection and adjuvant chemotherapy (if received)	Early stage NSCLC (Stage IB [T ≥4 cm] to stages II-IIIA) with complete surgical resection	DFS	Enrollment ongoing
KEYNOTE-189	Phase 3, randomized, placebo-controlled study of platinum + pemetrexed chemotherapy +/- pembrolizumab	Metastatic nonsquamous NSCLC eligible for first-line therapy	PFS, OS	Enrollment complete; treatment ongoing
KEYNOTE-407	Phase 3, randomized, double-blind study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy +/- pembrolizumab	Metastatic squamous NSCLC eligible for first-line therapy	PFS, OS	Enrollment complete; treatment ongoing
KEYNOTE-598	Phase 3, randomized, double-blind study of pembrolizumab + ipilimumab vs. pembrolizumab alone	Stage IV, metastatic NSCLC; TPS ≥50%; no prior systemic anticancer therapy	PFS, OS	Enrollment ongoing
KEYNOTE-654	Phase 3, randomized, double-blind study of pembrolizumab + epacadostat vs. pembrolizumab alone	metastatic NSCLC; TPS ≥50%; no prior systemic anticancer therapy; no known *EGFR* sensitizing or *ROS-1* mutations or *ALK* gene rearrangements	PFS, OS	Enrollment ongoing
KEYNOTE-715	Phase 3, randomized, active-controlled, partial double-blind, 3 parallel-group study comparing the combination of pembrolizumab + epacadostat alone or with platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy + placebo	Stage IV, metastatic NSCLC; no prior systemic therapy for metastatic disease; not eligible for *EGFR*-, *ALK*-, or *ROS1*-directed therapy	PFS, OS	Enrollment ongoing
KEYNOTE-671	Phase 3, randomized, double-blind study of platinum chemotherapy +/- pembrolizumab as perioperative therapy	Resectable Stage IIB or IIIA NSCLC; neoadjuvant/adjuvant therapy	EFS, OS	Enrollment pending

EFS=event-free survival; DFS=disease-free survival; NSCLC=non-small cell lung cancer; PD-L1=programmed cell death-1 ligand-1; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; TPS=tumor proportion score.

2.3.2. Discussion and conclusion on clinical pharmacology

No new clinical pharmacology studies have been submitted with this application which is acceptable considering substantial characterizations of the PK and immunogenicity of pembrolizumab have been provided in previous submissions. A description of the clinical pharmacology of pembrolizumab in patients with previously untreated metastatic NSCLC was included in the KEYNOTE-024 submission to support 200 mg Q3W as the recommended dosing regimen of pembrolizumab in this patient population (EMEA/H/C/003820/II/0011, 27 January 2017). No new clinical pharmacology analyses beyond those provided in previous submissions have been generated.

2.4. Clinical efficacy

This submission is based on the second interim analysis (IA2; date cut-off: 26-FEB-2018) of the Phase 3 trial KEYNOTE-042, a multicentre, international, randomized, open-label, controlled clinical study of pembrolizumab versus platinum-based chemotherapy in previously untreated adult subjects with locally advanced or metastatic TPS ⩾1% NSCLC with no EGFR or ALK genomic tumour aberrations. During the procedure, final analysis results of the study were also submitted (FA; date cut-off: 4-SEP-2018); a subsequent updated OS analysis with database date cut-off of 25-OCT-2019 was also presented.

The MAH also included supporting data from the final planned analysis of OS (data cut-off: 10-JUL-2017) and primary analysis of PFS, ORR, and DOR (IA2, data cut-off: 09-MAY-2016) of the phase 3 trial KEYNOTE-024, i.e. the pivotal study for pembrolizumab in treatment-naïve metastatic NSCLC patients negative for ALK/EGFR tumour aberrations and highly expressing PD-L1 (TPS≥50%). Detailed information on the main pivotal study (KEYNOTE-042) are summarised in the following table:

Study ID/ centres/locations	Study design	Treatment	No of pts planned/ random/ treated	Demographics	Primary endpoint	Secondary endpoints
KEYNOTE-042						
196 enrolling centers in 32 countries: Argentina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Estonia, Guatemala, Hongkong, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, Vietnam.	Multicenter, international, randomized, open-label, active-controlled, parallel group In male/female subjects, at least 18 years of age with NSCLC who did not have an EGFR sensitizing mutation and were ALK translocation negative, whose tumors demonstrated PDL1 expression, who have not received systemic anti-cancer therapy for their advanced or metastatic NSCLC	**Pembrolizumab** group: Pembrolizumab 200 mg IV Q3W until 35 cycles **Chemotherapy** group: Carboplatin AUC 5 or 6 + paclitaxel 200 mg/m2 IV Q3W for 4-6 cycles, followed by optional pemetrexed 500 mg/m2 IV Q3W (non-squamous histologies only) until progression **OR** **Chemotherapy** group: Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 Q3W for 4-6 cycles, followed by optional pemetrexed 500 mg/m2 IV Q3W until progression (non-squamous histologies only)	620/638/ 636 620/637/ 615	Sex: 450 M/187 F Median age (min/max): 63 years (25-89) Sex: 452 M/185 F Median age (min/max): 63 years (31-90)	**OS**	**PFS** **ORR** **DOR**

2.4.1. Dose response study(ies)

No dose-response studies were submitted as part of this application. The dose of pembrolizumab for the sought indication corresponds to the already licensed 200 mg IV Q3W that is currently in use for the treatment of previously untreated NSCLC highly expressing PD-L1, as derived from prior clinical studies submitted as part of the dossier at the time of the former MA.

2.4.2. Main study

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 (KEYNOTE 042)

This was a Phase 3, multicenter, international, randomized, open-label, controlled study of pembrolizumab monotherapy versus platinum-based chemotherapy in previously untreated subjects with advanced or metastatic TPS≥1% NSCLC without EGFR or ALK genomic tumour aberrations.

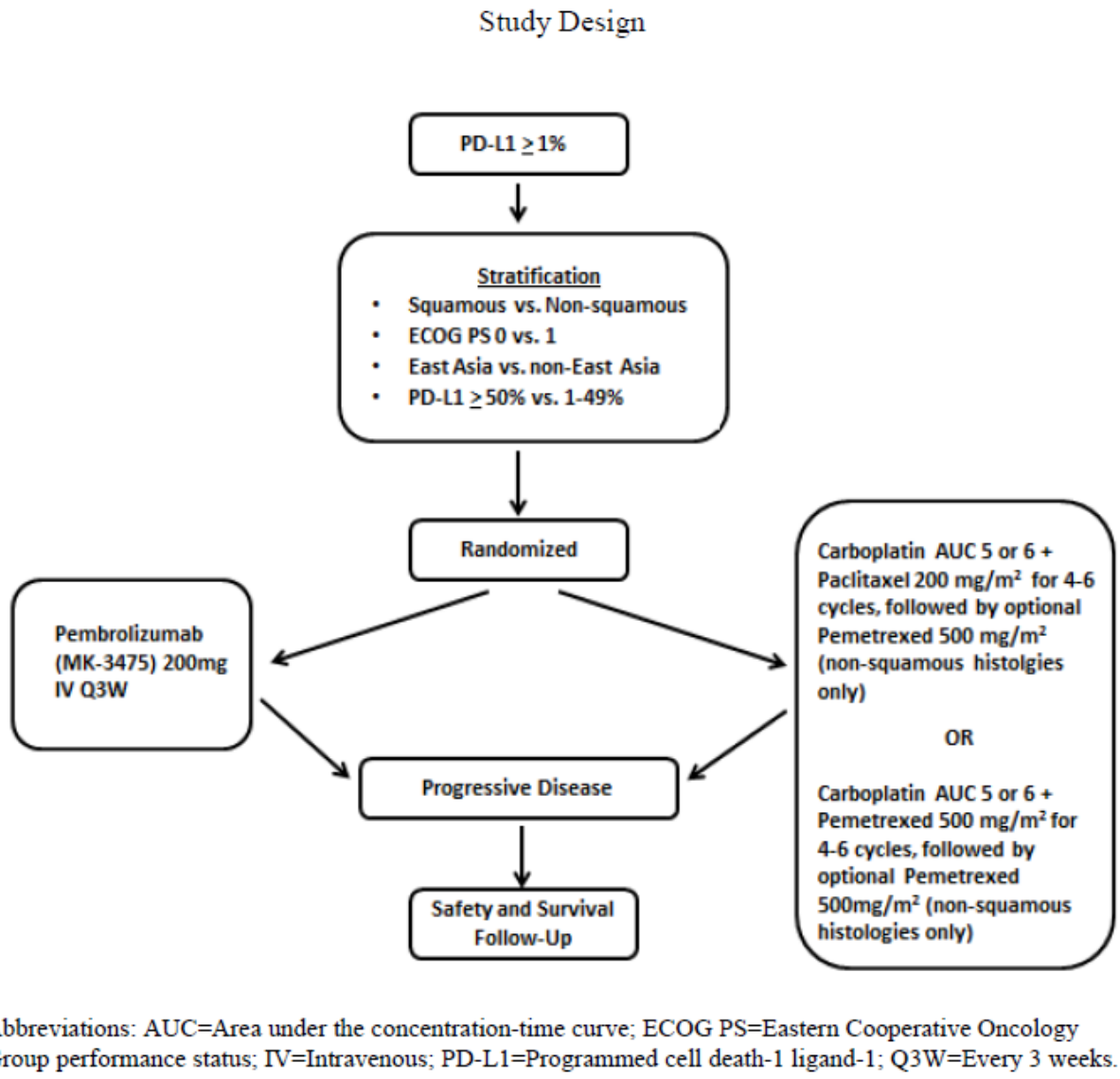


Figure 1: Study design of KEYNOTE-042

Methods

Study participants

Main inclusion criteria:

1. Had measurable disease based on RECIST 1.1 as determined by the site.

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

3. Had a life expectancy of at least 3 months.

4. Had not received prior systemic chemotherapy treatment for their advanced or metastatic NSCLC.

Note: Treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy was allowed as long as therapy was completed at least 6 months prior to the diagnosis of advanced or metastatic disease.

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

6. Had adequate organ function as indicated by the laboratory values listed in Section 5.1.2 of the protocol.

7. Had no history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancer, or had undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

8. Had provided formalin-fixed tumour tissue sample from a biopsy of a tumour lesion either at the time of or after the diagnosis of advanced or metastatic disease had been made AND from a site not previously irradiated to assess for PD-L1 status.

Note: Biopsies obtained PRIOR to the administration of any systemic therapy administered for the treatment of a subject's tumour (such as adjuvant therapy) were not permitted for analysis. The tissue sample was received by the central vendor prior to randomization. Fine needle aspirates were not acceptable. Core needle or excisional biopsies or resected tissue was required.

9. Had a histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC without an EGFR-sensitizing (activating) mutation or an ALK translocation.

10. Had a PD-L1 positive (TPS =1%) tumour as determined by IHC at a central laboratory.

Main exclusion criteria:

1. Had an EGFR-sensitizing mutation and/or ALK translocation.

2. Tumour specimen was not evaluable for PD-L1 expression by the central laboratory.

3. Subjects with squamous histology who received carboplatin in combination with paclitaxel in the adjuvant setting.

4. Was receiving systemic steroid therapy =3 days prior to the first dose of study treatment or receiving any other form of immunosuppressive medication.

5. The subject's NSCLC could have been treated with curative intent with either surgical resection and/or chemoradiation.

6. Was expected to require any other form of systemic or localized antineoplastic therapy while on study (including maintenance therapy, radiation therapy, and/or surgical resection).

7. Had received any prior systemic cytotoxic chemotherapy, biological therapy OR had major surgery within 3 weeks of the first dose of study treatment; received lung radiation therapy of >30 Gy within 6 months of the first dose of study treatment.

8. Had received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated protein 4 antibody.

9. Had known central nervous system metastases and/or carcinomatous meningitis.

Note: Subjects with previously treated brain metastases may have participated provided they were clinically stable (neurologically asymptomatic) and had no evidence of new or enlarging brain metastasis by imaging at least 4 weeks after treatment of the brain metastases (e.g., surgery, radiation therapy) and were off steroids for at least 3 days prior to the first dose of study treatment.

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

Treatments

Table 1: Treatment schedule in study Keynote 042

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200 mg	Q3W	IV	Day 1 of each 21-day cycle
Paclitaxel	200 mg/m^2	Q3W	IV	Day 1 of each 21-day cycle
Pemetrexed	500 mg/m^2	Q3W	IV	Day 1 of each 21-day cycle
Carboplatin	AUC 5 or 6 mg/mL/min	Q3W	IV	Day 1 of each 21-day cycle
AUC=Area under the concentration-time curve; IV=Intravenous; Q3W=Every 3 weeks				

Chemotherapy was administered in the following order, as applicable: paclitaxel OR pemetrexed, followed by carboplatin.

Pemetrexed maintenance therapy was optional and for patients with non-squamous NSCLC who did not demonstrate PD after completion of at least 4 cycles of platinum doublet.

Objectives

Primary Objectives
1. To evaluate overall survival (OS) in subjects with first-line advanced/metastatic TPS ≥50% NSCLC treated with pembrolizumab compared to chemotherapy.
2. To evaluate OS in subjects with first-line advanced/metastatic TPS ≥20% NSCLC treated with pembrolizumab compared to chemotherapy.
3. To evaluate OS in subjects with first-line advanced/metastatic TPS ≥1% NSCLC treated with pembrolizumab compared to chemotherapy.

Secondary Objectives
1. To evaluate the PFS by RECIST 1.1 as assessed by BICR in subjects with first-line advanced/metastatic TPS ≥50% NSCLC treated with pembrolizumab compared to chemotherapy.
2. To evaluate the PFS by RECIST 1.1 as assessed by BICR in subjects with first-line advanced/metastatic TPS ≥20% NSCLC treated with pembrolizumab compared to chemotherapy.
3. To evaluate the PFS by RECIST 1.1 as assessed by BICR in subjects with first-line advanced/metastatic TPS ≥1% NSCLC treated with pembrolizumab compared to chemotherapy.
4. To evaluate the ORR by RECIST 1.1 as assessed by BICR in subjects with first-line advanced/metastatic TPS ≥50% NSCLC treated with pembrolizumab compared to chemotherapy.
5. To evaluate the ORR by RECIST 1.1 as assessed by BICR in subjects with first-line advanced/metastatic TPS ≥20% NSCLC treated with pembrolizumab compared to chemotherapy.
6. To evaluate the ORR by RECIST 1.1 as assessed by BICR in subjects with first-line advanced/metastatic TPS ≥1% NSCLC treated with pembrolizumab compared to chemotherapy.
7. To evaluate the safety and tolerability profile of pembrolizumab in subjects with first-line advanced/metastatic TPS ≥1% NSCLC.

Exploratory Objectives

1. To evaluate PFS per investigator-assessed RECIST 1.1 response criteria in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

2. To evaluate ORR per investigator-assessed RECIST 1.1 response criteria in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

3. To evaluate response duration per RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

4. To evaluate the PFS as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to SOC chemotherapy.

5. To evaluate genomic signatures that predict for response in subjects treated with pembrolizumab.

6. To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (e.g., PD-L1, genetic variation, serum sPDL1) utilizing newly obtained or archival FFPE tumour tissue and blood, including serum and plasma.

Outcomes/endpoints

Table 2: Efficacy endpoints in study Keynote 042

Endpoints		Populations	Definitions
Primary	OS	ITT, TPS ≥50%	Time from randomization to death due to any cause. Subjects without documented death at the time of the analysis were censored at the date of the last follow-up.
		ITT, TPS ≥20%	
		ITT, TPS ≥1%	
Secondary	PFS	ITT, TPS ≥50%	Time from randomization to first documented PD (per RECIST 1.1 based on BICR) or death due to any cause.
		ITT, TPS ≥20%	
		ITT, TPS ≥1%	
	ORR	ITT, TPS ≥50%	Proportion of subjects who had a confirmed CR or PR (per RECIST 1.1 based on BICR).
		ITT, TPS ≥20%	
		ITT, TPS ≥1%	

Abbreviations: BICR=blinded independent central review; CR=complete response; ITT; Intention-to-treat; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PR=partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; TPS=tumor proportion score

Sample size

The study randomized subjects in a 1:1 ratio into the pembrolizumab arm and the SOC arm. The sample size for the subjects with TPS≥50% was targeted at approximately 530 and drove the end of enrolment, the overall sample size for this study was projected to be approximately 1240. The final analysis of the study was planned to occur about 45 months after the first subject randomized (study start), at which time approximately 398 deaths (projections updated in November 2017) were expected between the two arms in the subjects with TPS≥50%. With 398 deaths, the study had approximately 99% power to detect a 0.65 piece-wise hazard ratio on OS at alpha=2.5% (one-sided) in the subjects with TPS≥50%. By the same time, the expected numbers of deaths were about 557 and 900 in the subjects with TPS≥ 20% and TPS≥1%, respectively. With 557 deaths, the study had approximately 98% power to detect a piecewise hazard ratio on OS with 0.8 before month 6 and 0.64 after month 6 at alpha=2.5% (one-

sided) in the subjects with TPS≥20%. With 900 deaths, the study had approximately 91% power to detect a piecewise hazard ratio with 0.92 by month 6 and 0.73 after month 6 at alpha=2.5% (one-sided) in the subjects with TPS≥1%.

The assumed hazard ratios were based on results from studies KN010 and KN024. The above calculations were based on the following assumptions: 1) OS in the standard of care arm follows an exponential distribution with a median of 13 months, 2) hazard ratio on OS between pembrolizumab and control is 0.65 in the subjects with TPS≥50%, 3) an enrolment period of ~26 months and a minimal 19-month follow-up period after enrolment completion, 4) a dropout rate of 0.003 per month for OS.

Randomisation

Randomization was centralized using an interactive voice response system / integrated web response system (IVRS/IWRS). There were 2 treatment arms. Subjects were assigned randomly in a 1:1 ratio to pembrolizumab and SOC, respectively.

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

1) Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1)

2) Histology (squamous vs. non-squamous)

3) Geographic region of the enrolling site (East Asia vs. non-East Asia)

4) PD-L1 expression status (TPS ≥50% vs. TPS 1-49%) prior to randomization.

Blinding (masking)

This was an open-label study. Imaging data for the primary analysis were centrally reviewed by independent radiologists without knowledge of subject treatment assignment. The subject level PD-L1 biomarker (TPS) results were masked in the database to the study team at the Sponsor including clinical, statistical, statistical programming, and data management personnel. Access to the TPS results was limited to an unblinded Sponsor clinical scientist and an unblinded data management analyst who were responsible for data review to ensure validity of results but who had no other responsibilities associated with the study. Even though the Sponsor was unblinded to individual treatment assignments, the Sponsor did not conduct any analysis upon aggregate data until the required number of events were reached and did not become aware of such results until the external DMC advised the Executive Oversight Committee that the endpoint of OS had been achieved.

Statistical methods

Efficacy analyses were conducted in the TPS ≥50%, ≥20%, and ≥1% sub-populations using the intention-to-treat (ITT) population.

All safety analyses were conducted using data from the All-Subjects-as-Treated (ASaT) population, i.e., all randomized subjects who received at least 1 dose of study treatment.

The treatment difference in OS (primary efficacy endpoint) was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., the HR). The Kaplan-Meier method was used to estimate the survival curves. The hypotheses for PFS were evaluated using the same methods used for OS assessment. The hypotheses for ORR were evaluated using a stratified Miettinen and Nurminen method with weights proportional to the stratum size. Stratification factors were the same used for randomization (ECOG performance scale, histology, geographic region of the enrolling site, and PD-L1 expression).

As an exploratory analysis, recognized methods, e.g., the Rank Preserving Structural Failure Time (RPSFT) model, two-stage method, etc., were to be used to adjust for the effect of crossover on OS based upon the appropriateness of the data to the assumption required by the methods.

To further account for the possible confounding effect, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy was planned and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate was also to be conducted. In case the proportional hazards assumption did not hold, Fleming and Harrington's weighted log-rank test, Restricted Mean Survival Time (RMST) method or other methods, as appropriate, were planned, possibly after proper adjustment of the crossover effect over time.

In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses with a different set of censoring rules were planned (Table below).

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

Subgroup analyses

The estimate of the treatment effect was provided for the following subgroups:
age (≤65 vs. >65 years); sex (female vs. male); race (white vs. non-white); ECOG status (0 vs. 1); geographic region of enrolling site (East Asia vs. non-East Asia and East Asia vs. Europe vs. Latin America vs. Other); histology (squamous vs. non-squamous); smoking status (never vs. former vs. current); PD-L1 status (TPS≥50% vs. TPS 1-49%, TPS≥20% vs. TPS 1-19%, and TPS≥50% vs. TPS 20-49% vs. TPS 1-19%); Investigators' choice of SOC chemotherapy prior to randomization (Pemetrexed vs. No Pemetrexed); disease stage (advanced vs. metastatic); brain metastasis status (yes vs. no); baseline tumour size (at/above median vs. below median).

Interim analyses

According to the last version of the protocol, two interim analyses were planned in this trial. The Table below provides the summary of the strategy and timing of the interim and final analyses.

Table 3: Decision guidance for the primary OS hypotheses at the interim analyses and final analysis under a hypothetical scenario

Analysis	Targeted Number of Events/Targeted Study Time	Cumulative Alpha	Efficacy Bars in Subjects with TPS≥50%[1]	Efficacy Bars in Subjects with TPS≥20% (if OS positive in TPS≥50%)[1]	Efficacy Bars in Subjects with TPS≥1% (if OS positive in both TPS≥50% and TPS≥20%)[1]
IA1	• At least 250 deaths observed in two arms in the subjects with TPS≥50% AND at least 6 month after last subject is enrolled (~32 months after study start) • At IA1, 293 deaths were observed in the subjects with TPS≥50%	• 1.576%	• (One-sided) p-value for OS < 1.576%, i.e., observed HR < ~0.78 (~3.7-month improvement)	• (One-sided) p-value for OS < 1.576%, i.e., observed HR < ~0.81 (~3.1-month improvement)	• (One-sided) p-value for OS < 1.576%, i.e., an observed HR < ~0.85 (2.3-month improvement)
IA2	• About 38 months after study start[2]	• 1.94%	• (One-sided) p-value for OS < 1.233%, i.e., observed HR < ~0.78 (3.6-month improvement)	• (One-sided) p-value for OS < 1.197%, i.e., observed HR < ~0.81 (3.0-month improvement)	• (One-sided) p-value for OS < 1.228%, i.e., observed HR < ~0.85 (2.3-month improvement)
FA	• About 45 months after study start[2]	• 2.5%	• (One-sided) p-value for OS < 1.521%, i.e., observed HR < ~0.80 (3.2-month improvement)	• (One-sided) p-value for OS < 1.497%, i.e., observed HR < ~0.83 (2.6-month improvement)	• (One-sided) p-value for OS < 1.556%, i.e., observed HR < ~0.87 (2.0-month improvement)

[1] Nominal alpha and boundaries will be re-calculated if the actual number of events at analyses is altered from the expected. In this hypothetical scenario, the numbers of death at IA2 and final are assumed to be the same as the projected, i.e., 340 and 398 in the subjects with TPS≥50%, 474 and 557 in the subjects with TPS≥20%, and 780 and 900 in the subjects with TPS≥1%. The actual boundaries will need to be recalculated based on the observed number of deaths.
[2] Study start is defined as the date when the first subject was randomized.

Multiplicity strategy

The primary and secondary efficacy hypotheses were analysed using a sequential testing strategy, testing a hypothesis only if superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was as follows: OS in subjects with TPS ≥50%, TPS ≥20%, and TPS ≥1%; PFS in TPS ≥50%, TPS ≥20%, and TPS ≥1%; and ORR in TPS ≥50%, TPS ≥20%, and TPS ≥1%. The alpha spending at IA2 and FA was determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter -0.9023.

Change in the planned analysis and study design

During the conduct of KEYNOTE-042 and prior to any analysis being performed, the study protocol was amended several times. The major changes are summarized below:

In the original protocol (18 Jun 2014), the hypothesis was formulated on the basis of the supposed OS in strongly positive patients (TPS ≥50%); analyses were event-driven (final analysis at 354 OS events, supposed HR=0.70) and three interim analyses were contemplated (IA1 at 75 OS events observed in the weakly positive PD-L1 stratum; IA2 at 315 PFS events and IA3 at 283 OS events in TPS ⩾50%); the type I error rate was split between OS (2%, one-sided) and PFS (0.5%, that was a key secondary endpoint).

With Amendment 02 (21 Dec 2015), the hypothesis also included TPS≥1%; changes in the target number of events were introduced (from the initial 354 OS events to 340 for the FA in TPS≥50%); the number of IA were reduced from 3 to 2 (IA1 at 187 OS events and IA2 at 272 OS events); the type I error was totally spent for OS (2.5%).

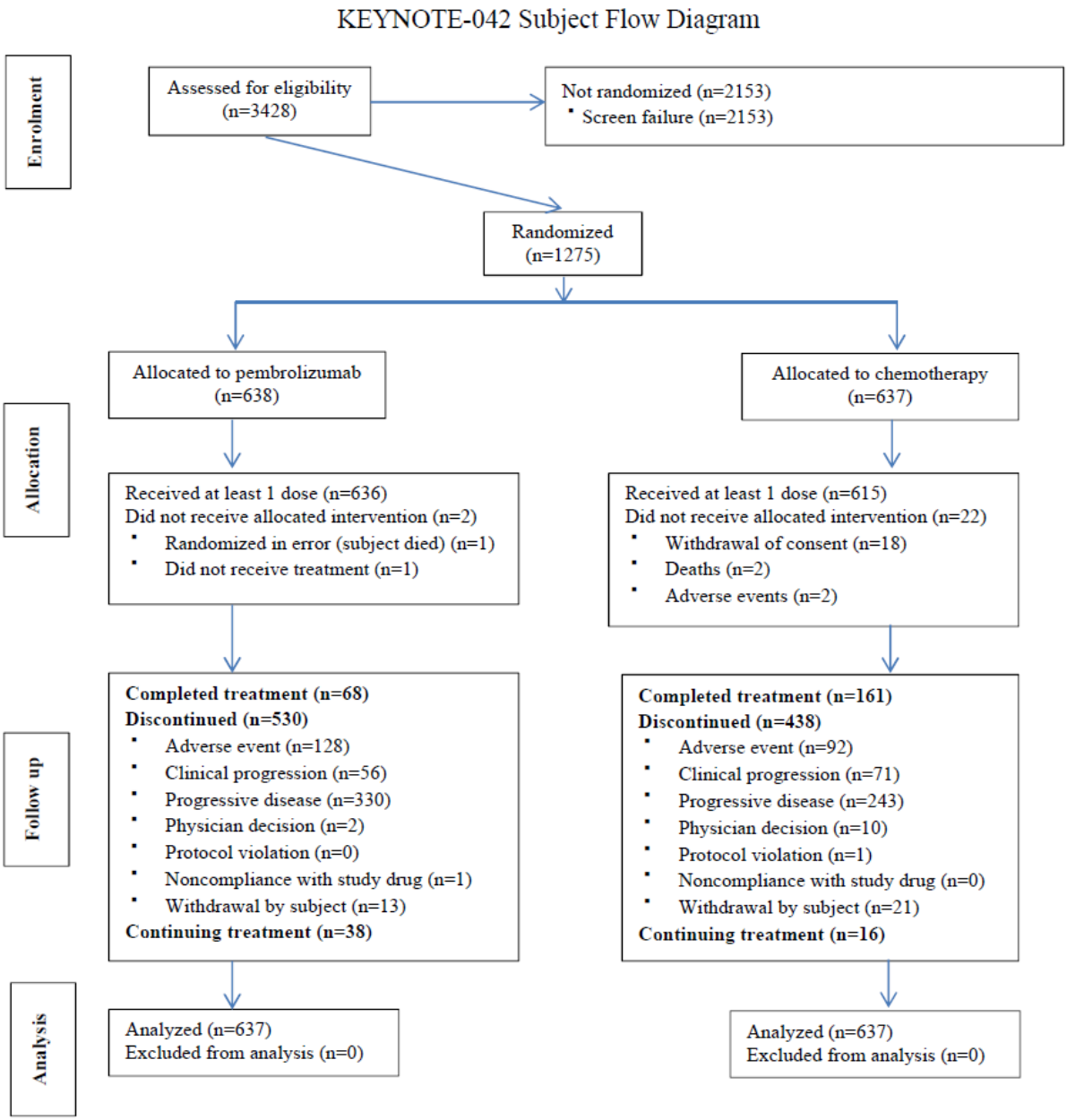
In Amendment 03 (12 Apr 2017) an intermediate cut-off value of TPS≥20% was introduced; a single IA was planned at 250 OS events and with a conserved totality of OS events of 340 for FA, the HR was changed from 0.70 to 0.65.

Finally, Amendment 06 (09 Jan 2018), that followed the conduction of IA1 (30 Aug 2017), re-introduced IA2 with an updated FA based on calendar time at 45 months and an additional IA based on calendar time at 38 months in order to maintain a minimum follow-up duration of 12 months. Timing and control of multiplicity were changed accordingly. Under the revised alpha allocation, the alpha spending was

determined by the Hwang-Shih-DeCani with the gamma parameter -0.9023 instead of the initially set value -5. With this spending, the alpha level at IA1 was the same as the actual spent at IA1 (one-sided 1.576%) based on the scale of calendar time fraction 0.729 (i.e., 986/1353). The cumulative alpha (one-sided) spending at the planned time of IA2 and FA became 1.94% and 2.5%, regardless of the actual number of deaths observed at the IA2 and FA.

Results

Participant flow



Main reasons for screen failure were the following (note that a subject may have had more than one trial entry criteria resulting in screen failure):

- tumour samples PD-L1 negative: n=1062

- No histologically or cytologically confirmed advanced/metastatic NSCLC and had an EGFR sensitizing

mutation or ALK translocation: n=291

- Had an EGFR sensitizing mutation or ALK translocation: n=272

- Tumour specimen not evaluable for PD-L1 expression: n=165

- ECOG score >1: n=161

Disposition

Table 4: **Disposition of Subjects (ITT Population with TPS>=1%)**

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	637		637	
Status for Trial				
Discontinued	424	(66.6)	493	(77.4)
Adverse Event	120	(18.8)	72	(11.3)
Death	301	(47.3)	409	(64.2)
Lost To Follow-Up	0	(0.0)	2	(0.3)
Withdrawal By Parent/Guardian	0	(0.0)	1	(0.2)
Withdrawal By Subject	3	(0.5)	9	(1.4)
Status Not Recorded	213	(33.4)	144	(22.6)
Status for Study medication in Trial Segment Treatment				
Started	636		615	
Completed	68	(10.7)	161	(26.2)
Discontinued	530	(83.3)	438	(71.2)
Adverse Event	128	(20.1)	92	(15.0)
Clinical Progression	56	(8.8)	71	(11.5)
Non-Compliance With Study Drug	1	(0.2)	0	(0.0)
Physician Decision	2	(0.3)	10	(1.6)
Progressive Disease	330	(51.9)	243	(39.5)
Protocol Violation	0	(0.0)	1	(0.2)
Withdrawal By Subject	13	(2.0)	21	(3.4)
Status Not Recorded	38	(6.0)	16	(2.6)
Each subject is counted once for Study Medication Disposition. Status not Recorded for subjects that are continuing in trial or trial segment. Database Cutoff Date: 04SEP2018				

Disposition for subjects with TPS ⩾50% and ⩾20% NSCLC was similar to that observed for the entire study population (TPS ⩾1% NSCLC).

Recruitment

The study was conducted at 196 centres in 32 countries across Europe (22.4%), Latin America (21.1%), East Asia (29.0%) and other (27.5%). Randomization started on 19 Dec 2014 and was completed on 27 Feb 2017.

Conduct of the study

Protocol amendments

There were 7 protocol amendments; of them, 4 were country-specific (amendment 01 for Sweden, amendments 04, 05 and 07 were related to the China Extension Study). A summary of the relevant

changes to KEYNOTE-042 protocol, including updates to the statistical analysis plan (SAP), are outlined below:

Amendment-02: An amendment to modify the SAP based on new efficacy data from KEYNOTE-010. As a consequence, the futility analysis for the PD-L1 1-49% subgroup was removed from KEYNOTE-042. The primary objective was updated to include the primary endpoint for OS in the overall TPS ⩾1% population in addition to the PD-L1 TPS ⩾50% subgroup. The full alpha was allocated to OS, instead of splitting it between OS and PFS.

Amendment-03: An amendment to update the SAP based on KEYNOTE-010 results (2L+ treatment), evaluating efficacy at different PD-L1 cutpoints, and new data from KEYNOTE-024 (1L treatment), showing a very strong overall survival signal. As a result, the KEYNOTE-042 SAP changed the OS primary endpoint to a sequential stepdown from TPS ⩾50% to a new intermediate cutpoint of TPS ⩾20%, to TPS ⩾1%. Based on the updated projected timing of events and power calculations for IA1 and IA2, the number of planned interim analyses was reduced to one. The exponential spending function was changed to O'Brien-Fleming as requested by the FDA.

Amendment-06: An amendment to update the SAP. The rate of event accrual was faster than originally anticipated and the FA was expected to occur in February 2018 when the elapsed time would only be about 38 months. In order to preserve the data maturity at the FA, a new IA was added for February 2018 and a new FA that preserved the originally anticipated 45 months of follow-up. These changes required a revised alpha spending allocation that was retrospectively consistent with the alpha spent at IA1. Given the alpha spend of 1.576% (one-sided) at IA1, the new cumulative alpha spending follows the Hwang-Shih-Decani spending function with the gamma parameter -0.9023, so that the alpha actually spent at the IA1 will be kept intact. The power calculations were updated based on the revised alpha allocation and analysis timing.

Protocol deviations

The following table provides a summary of the most important protocol deviations by category:

Table 5: Summary of the most important protocol deviations (Database lock: 26 February 2018)

Deviation Category	Number of Subjects
Inclusion Criteria	
Inclusion #4 - prior chemotherapy for advanced/metastatic NSCLC	1
Inclusion #6 - adequate organ function lab values	2
Inclusion #9 – EGFR-sensitizing mutation	1
Exclusion Criteria	
Exclusion #11 - active autoimmune disease requiring therapy	2
Discontinuation Criteria	
Treatment discontinuation requirement not followed	3
Trial Procedures	
Dose modification guidance not followed	5
Study Intervention	
Squamous subject received pemetrexed maintenance therapy	2
Subject received 3 simultaneous chemotherapeutic agents (carboplatin, paclitaxel, and pemetrexed)	1

In addition, important administrative protocol deviations were noted for 66 subjects without SAE reporting within 24 hours of learning of the event, 9 subjects with a delay in signing the initial consent, and 113 subjects that did not sign the updated safety consent following a significant safety change to the risk language prior to performing study procedures and/or the next cycle of treatment. At a subsequent visit, all subjects signed the initial consent or safety consent except for 8 subjects that either died or withdrew from the study. According to the MAH, no subject's safety was endangered due to the delay in reporting SAEs or to the delay in signing the informed consent. No subjects were excluded from the efficacy analyses.

At the updated database lock (01-OCT-2018), there were 4 additional patients with important protocol deviations compared to the prior cut-off date (2 patients: Inclusion #9-EGFR sensitizing mutation; 1 patient: treatment discontinuation requirement not followed; 1 patient administration of prohibited medication (Tarceva) during the study).

Baseline data

Table 6: Subject characteristics (ITT population with TPS≥ 1%)

	Pembrolizumab		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	637		637		1,274	
Gender						
Male	450	(70.6)	452	(71.0)	902	(70.8)
Female	187	(29.4)	185	(29.0)	372	(29.2)
Age (Years)						

< 65	359	(56.4)	348	(54.6)	707	(55.5)
>= 65	278	(43.6)	289	(45.4)	567	(44.5)
Mean	62.5		63.1		62.8	
SD	9.9		9.4		9.7	
Median	63.0		63.0		63.0	
Range	25 to 89		31 to 90		25 to 90	
Race						
American Indian Or Alaska Native	10	(1.6)	5	(0.8)	15	(1.2)
Asian	189	(29.7)	187	(29.4)	376	(29.5)
Black Or African American	10	(1.6)	13	(2.0)	23	(1.8)
Multiple	30	(4.7)	19	(3.0)	49	(3.8)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.2)	1	(0.1)
White	398	(62.5)	412	(64.7)	810	(63.6)
Ethnicity						
Hispanic Or Latino	120	(18.8)	122	(19.2)	242	(19.0)
Not Hispanic Or Latino	512	(80.4)	508	(79.7)	1,020	(80.1)
Not Reported	5	(0.8)	7	(1.1)	12	(0.9)
Age Group (Years)						
< 65	359	(56.4)	348	(54.6)	707	(55.5)
65 - 74	213	(33.4)	225	(35.3)	438	(34.4)
75 - 84	59	(9.3)	57	(8.9)	116	(9.1)
>= 85	6	(0.9)	7	(1.1)	13	(1.0)
PD-L1 Tumor Proportion Score						
TPS>=50%	299	(46.9)	300	(47.1)	599	(47.0)
TPS=20-49%	114	(17.9)	105	(16.5)	219	(17.2)
TPS=1-19%	224	(35.2)	232	(36.4)	456	(35.8)

	Pembrolizumab		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
ECOG						
0	198	(31.1)	192	(30.1)	390	(30.6)
1	438	(68.8)	445	(69.9)	883	(69.3)
2	1	(0.2)	0	(0.0)	1	(0.1)
Cancer Stage at Screening						
IB	0	(0.0)	1	(0.2)	1	(0.1)
IIIA	10	(1.6)	10	(1.6)	20	(1.6)
IIIB	60	(9.4)	70	(11.0)	130	(10.2)
IV	567	(89.0)	556	(87.3)	1,123	(88.1)
Disease Status						
Metastatic	567	(89.0)	556	(87.3)	1,123	(88.1)
Advanced	70	(11.0)	81	(12.7)	151	(11.9)
Geographic Region of Enrolling Site						
East Asia	185	(29.0)	185	(29.0)	370	(29.0)
Non-East Asia	452	(71.0)	452	(71.0)	904	(71.0)
Geographic Region of Enrolling Site						
East Asia	185	(29.0)	185	(29.0)	370	(29.0)
EU	149	(23.4)	137	(21.5)	286	(22.4)
Latin America	136	(21.4)	133	(20.9)	269	(21.1)
Other	167	(26.2)	182	(28.6)	349	(27.4)
Histology						
Squamous	242	(38.0)	249	(39.1)	491	(38.5)
Non-Squamous	395	(62.0)	388	(60.9)	783	(61.5)
Smoking Status						
Current	125	(19.6)	146	(22.9)	271	(21.3)
Former	370	(58.1)	351	(55.1)	721	(56.6)
Never	142	(22.3)	140	(22.0)	282	(22.1)
Brain Metastasis Status at Baseline						
Y	35	(5.5)	35	(5.5)	70	(5.5)
N	602	(94.5)	602	(94.5)	1,204	(94.5)

	Pembrolizumab		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Baseline Tumor Size (mm)						
Subjects with data	635		636		1271	
Mean	108.3		110.9		109.6	
SD	60.3		62.8		61.6	
Median	101		99		100	
Range	14 to 420		10 to 394		10 to 420	
Baseline Weight (kg)						
Subjects with data	637		637		1274	
Mean	67.9		67.5		67.7	
SD	14.1		14.4		14.2	
Median	67		67		67	
Range	34 to 140		37 to 121		34 to 140	
Prior Adjuvant Therapy						
Yes	18	(2.8)	12	(1.9)	30	(2.4)
No	619	(97.2)	625	(98.1)	1,244	(97.6)
Prior Neo-adjuvant Therapy						
Yes	3	(0.5)	7	(1.1)	10	(0.8)
No	634	(99.5)	630	(98.9)	1,264	(99.2)
Prior Radiation Therapy						
Yes	74	(11.6)	81	(12.7)	155	(12.2)
No	563	(88.4)	556	(87.3)	1,119	(87.8)
For disease status, Advanced = Stage IIIA and IIIB, Metastatic = Stage IV. Database Cutoff Date: 04SEP2018						

Source: [P042V02MK3475: adam-adsl]

Demographics for subjects with TPS ≥50% and ≥20% NSCLC were similar to those of the entire population (TPS ≥1% NSCLC), with no meaningful imbalances between treatment arms.

Chemotherapy by histology

The majority of the 375/388 subjects with non-squamous NSCLC that actually started treatment received pemetrexed + carboplatin, while all subjects with squamous NSCLC received paclitaxel + carboplatin. Of these 375 subjects, 196 (52.3%) received pemetrexed maintenance following induction chemotherapy. Of the 179 subjects with non-squamous NSCLC who did not receive pemetrexed maintenance, 50.3% experienced PD/clinical progression prior to the maintenance phase, 19.0% discontinued treatment due to AEs prior to the maintenance phase, and 23.5% did not receive pemetrexed maintenance because maintenance was not planned/specified at the time of randomization.

Table 7: Breakdown of chemotherapy by histology ASaT in chemotherapy arm

	Non-squamous		Squamous		Total	
	N	(%)	N	(%)	N	(%)
Overall	375		240		615	
Paclitaxel and carboplatin with pemetrexed maintenance	18	(4.8)	2	(0.8)	20	(3.3)
Paclitaxel and carboplatin without pemetrexed maintenance	45	(12.0)	238	(99.2)	283	(46.0)
Pemetrexed and carboplatin with pemetrexed maintenance	178	(47.5)	0	(0.0)	178	(28.9)
Pemetrexed and carboplatin without pemetrexed maintenance	134	(35.7)	0	(0.0)	134	(21.8)
Database Cutoff Date: 04SEP2018						

Source: [P042V02MK3475: adam-adsl]

Table 8: Disposition of subjects non-squamous subjects without pemetrexed maintenance (ITT population with TPS⩾ 1%)

	Paclitaxel and Carboplatin Without Pemetrexed Maintenance		Pemetrexed and Carboplatin Without Pemetrexed Maintenance		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	45		134		179	
Status for Study medication in Trial Segment Treatment						
Discontinued	45	(100.0)	134	(100.0)	179	(100.0)
Adverse Event	3	(6.7)	30	(22.4)	33	(18.4)
Clinical Progression	3	(6.7)	16	(11.9)	19	(10.6)
Maintenance Not Planned At Randomization	30	(66.7)	12	(9.0)	42	(23.5)
Other	0	(0.0)	4	(3.0)	4	(2.2)
Physician Decision	1	(2.2)	3	(2.2)	4	(2.2)
Progressive Disease	7	(15.6)	65	(48.5)	72	(40.2)
Withdrawal By Subject	1	(2.2)	4	(3.0)	5	(2.8)
Each subject is counted once for Study Medication Disposition. Database Cutoff Date: 04SEP2018						

Source: [P042V02MK3475: adam-adsl]

Numbers analysed

Table 9: Study population – Keynote 042

	Pembrolizumab	Chemotherapy	Total
Number of Subjects Screened			3428
Number of Subjects in the Intent to Treat Population (Planned Treatment) (ITT)	637	637	1274
Number of Subjects in the ITT population with TPS>=1%	637	637	1274
Number of Subjects in the ITT population with TPS>=20%	413	405	818
Number of Subjects in the ITT population with TPS>=50%	299	300	599
Number of Subjects Received Treatment (Actual Treatment) (ASaT)	636	615	1251
Number of Subjects Did not Receive Treatment	1	22	23
Number of Subjects Discontinued Study Medication (Actual Treatment)	530	438	968
Database Cutoff Date: 04SEP2018			

Source: [P042V02MK3475: adam-adsl]

Outcomes and estimation

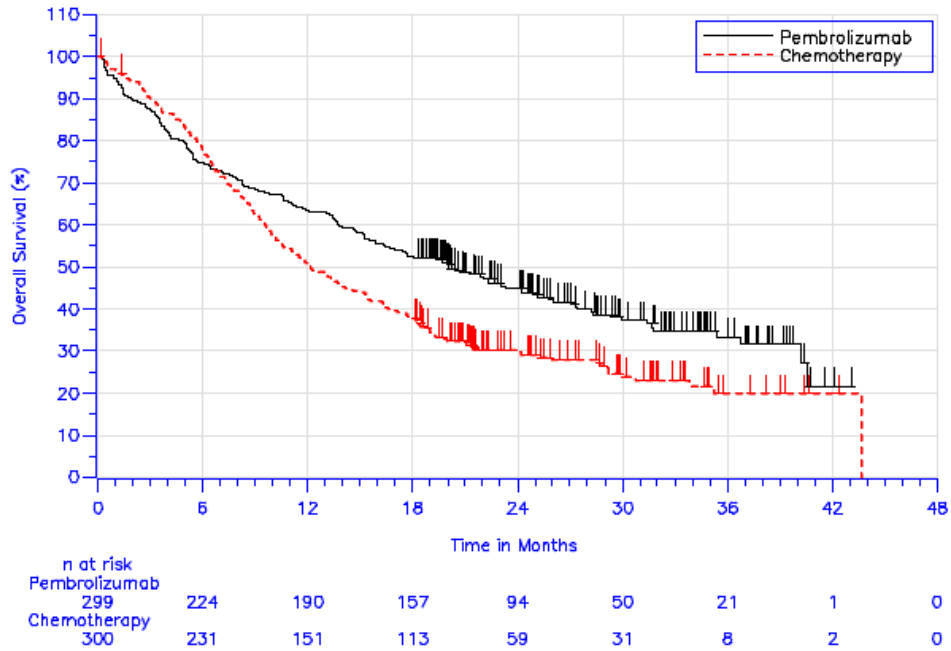
Results from the second interim analysis (cut-off date 26-Feb-2018) were provided at the time of submission of this application. As of the data cut-off date, the median duration of follow-up was 12.8 months (range: 0.1 to 38.3 months) in the ITT population.

During the procedure, results of OS, PFS and ORR based on the Final Analysis (FA, cut-off date 4-Sep-2018) were submitted. An updated OS analysis was also provided with cut-off date of 25-OCT-2019. The presentation of the efficacy results is focusing on the final analysis even though results from other cut-off dates could presented for selected endpoints.

Primary Efficacy Endpoints

Overall Survival

TPS ≥50% NSCLC



Database Cutoff Date: 04SEP2018

Figure 2: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 50%) - cutoff date 4-Sep-2018

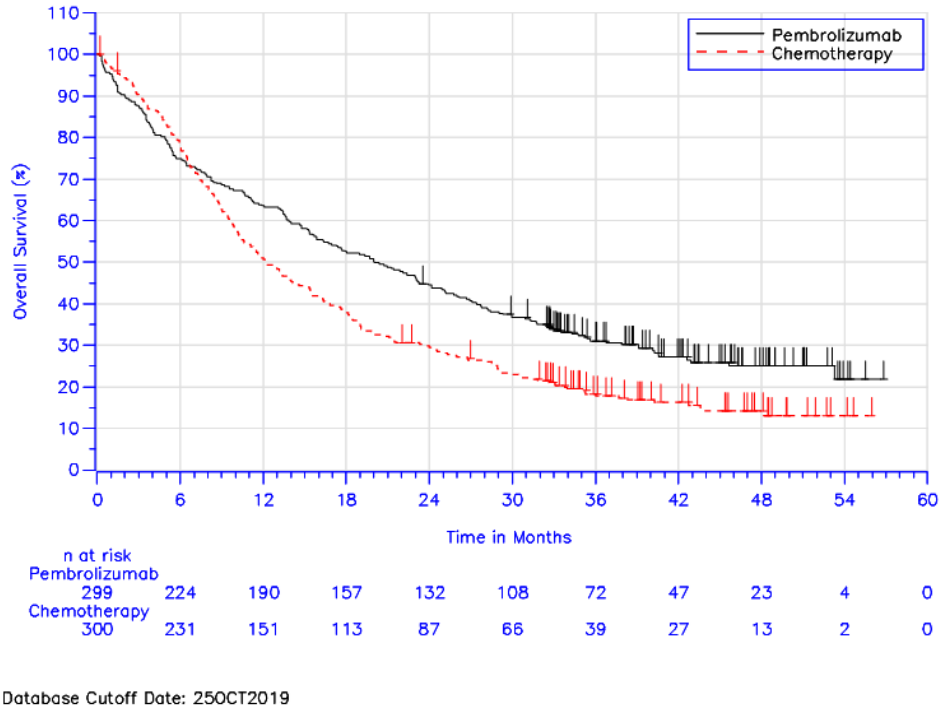


Figure 3: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 50%) - cutoff date 25-Oct-2019

Table 10: Analysis of Overall survival (ITT population with TPS ≥ 50%) - cutoff date 4-Sep-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	299	180 (60.2)	5248.3	3.4	20.0 (15.9, 24.2)	63.5 (57.8, 68.7)	0.70 (0.58, 0.86)	0.0003
Chemotherapy	300	220 (73.3)	4430.8	5.0	12.2 (10.4, 14.6)	50.7 (44.9, 56.2)	---	---

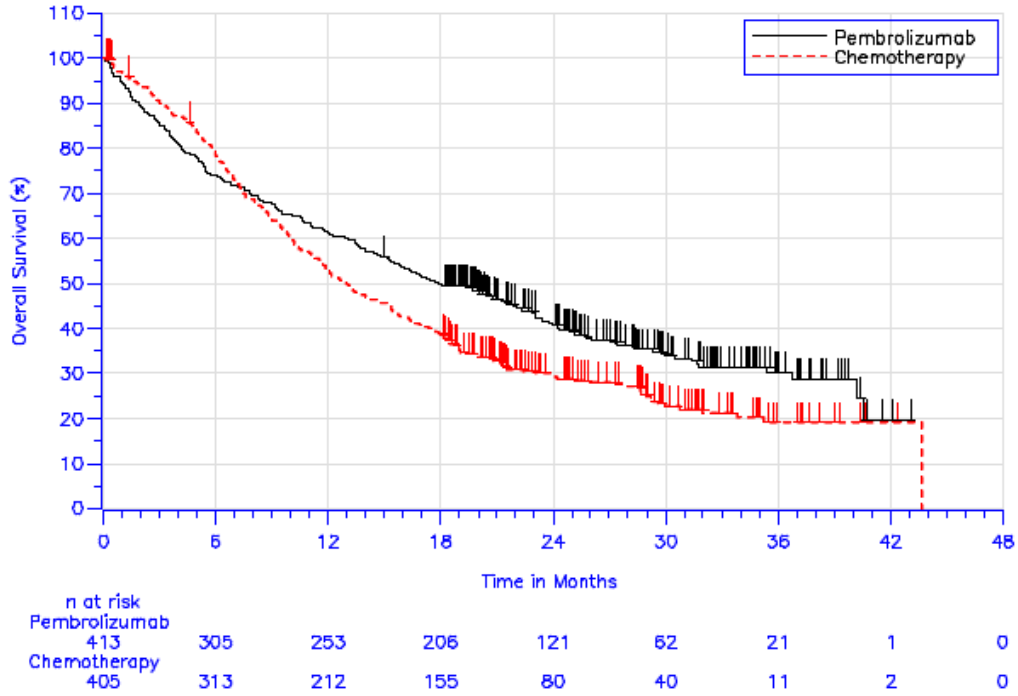
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 04SEP2018

Table 11: Analysis of Overall survival (ITT population with TPS ≥ 50%) - cutoff date 25-Oct-2019

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	299	216 (72.2)	6629.9	3.3	20.0 (15.9, 24.2)	63.5 (57.8, 68.7)	0.70 (0.58, 0.84)	0.0001
Chemotherapy	300	249 (83.0)	5240.5	4.8	12.2 (10.4, 14.6)	50.7 (44.9, 56.2)	---	---

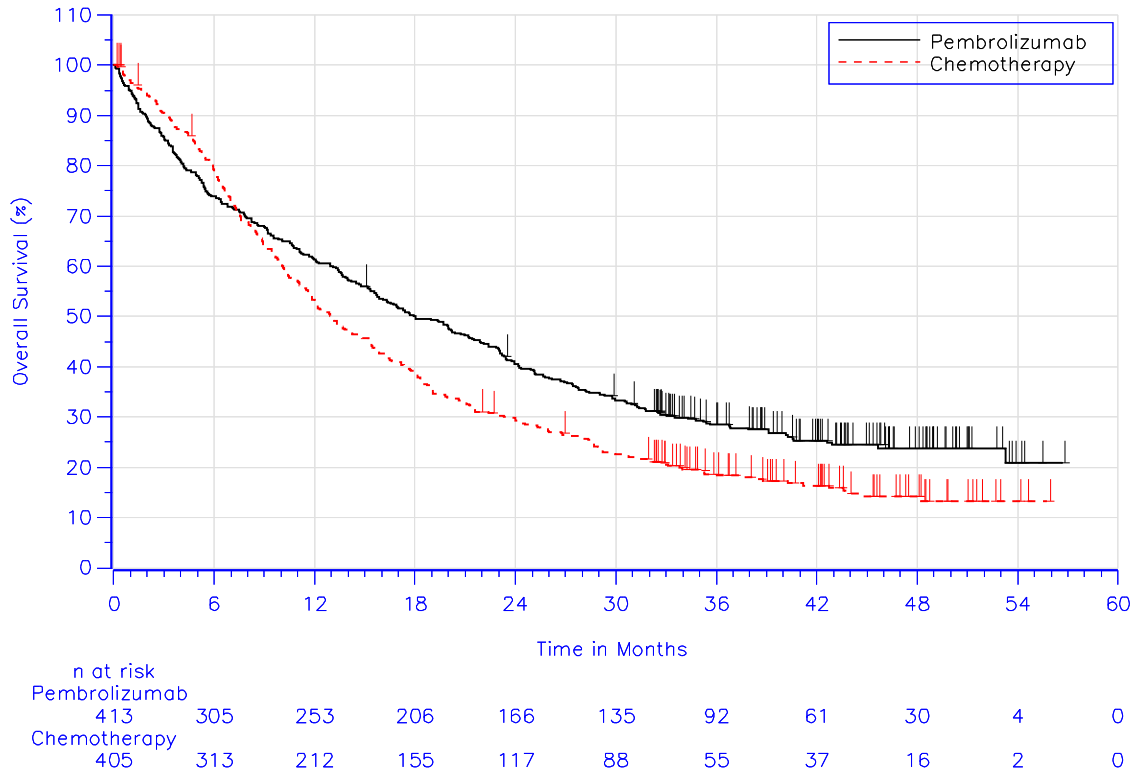
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 25OCT2019

TPS ≥20% NSCLC



Database Cutoff Date: 04SEP2018

Figure 4: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 20%) - cutoff date 4-Sep-2018



Database Cutoff Date: 25OCT2019

Figure 5: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 20%) - cutoff date 25-Oct-2019

Table 12: Analysis of Overall survival (ITT population with TPS ≥ 20%) - cutoff date 4-Sep-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	413	261 (63.2)	6977.2	3.7	18.0 (15.4, 21.9)	61.3 (56.4, 65.8)	0.77 (0.65, 0.91)	0.0012
Chemotherapy	405	296 (73.1)	6022.5	4.9	13.0 (11.6, 15.3)	53.2 (48.1, 57.9)	---	---

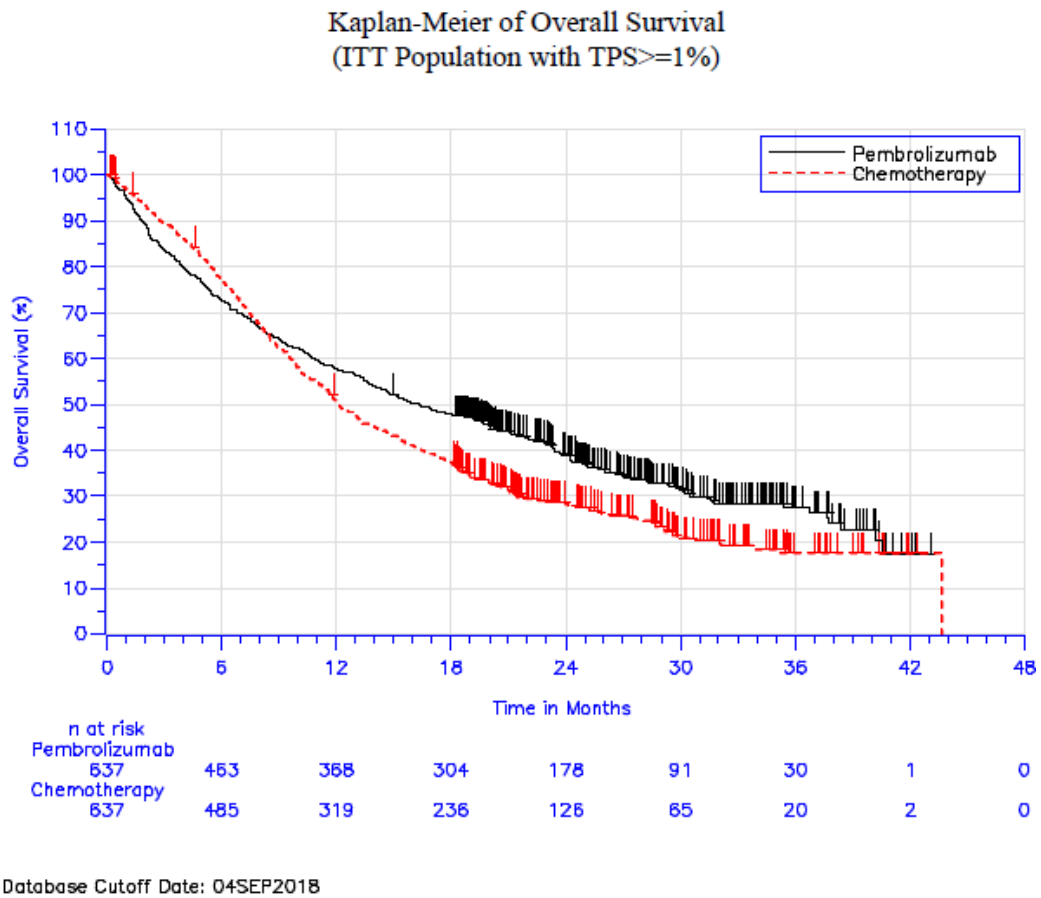
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 04SEP2018

Table 13: Analysis of Overall survival (ITT population with TPS ≥ 20%) - cutoff date 25-Oct-2019

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	413	306 (74.1)	8720.7	3.5	18.0 (15.5, 21.5)	61.3 (56.4, 65.8)	0.76 (0.65, 0.89)	0.0003
Chemotherapy	405	333 (82.2)	7106.7	4.7	13.0 (11.6, 15.3)	53.2 (48.1, 57.9)	---	---

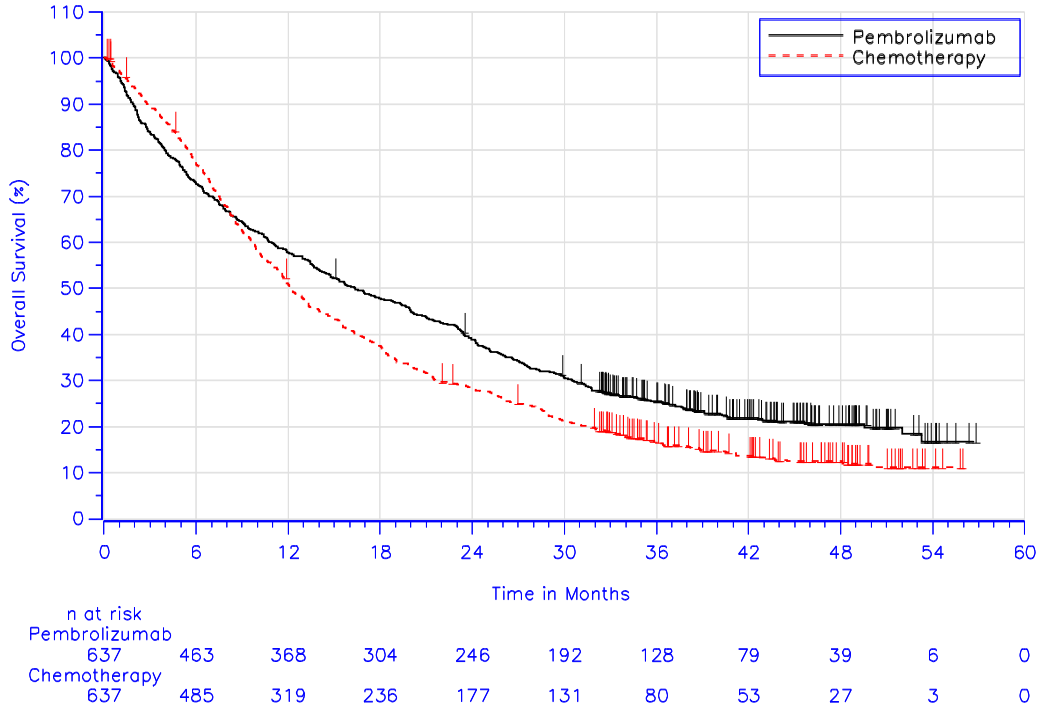
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 25OCT2019

TPS ≥1% NSCLC



Database Cutoff Date: 04SEP2018

Figure 6: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 1%) - cutoff date 4-Sep-2018



Database Cutoff Date: 25OCT2019

Figure 7: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 1%) - cutoff date 25-Oct-2019

Table 14: Analysis of Overall survival (ITT population with TPS ≥ 1%) - cutoff date 4-Sep-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	637	422 (66.2)	10351.0	4.1	16.4 (14.0, 19.7)	57.8 (53.8, 61.5)	0.82 (0.71, 0.93)	0.0013
Chemotherapy	637	481 (75.5)	9365.7	5.1	12.1 (11.3, 13.3)	50.7 (46.8, 54.6)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 04SEP2018

Table 15: Analysis of Overall survival (ITT population with TPS ≥ 1%) - cutoff date 25 Oct-2019

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	637	495 (77.7)	12734.3	3.9	16.4 (14.0, 19.6)	57.8 (53.8, 61.5)	0.80 (0.71, 0.91)	0.0002
Chemotherapy	637	541 (84.9)	10892.6	5.0	12.1 (11.3, 13.3)	50.7 (46.8, 54.6)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 25OCT2019

The hypotheses for OS across all 3 TPS cut-points (TPS ≥50%, ≥20%, and ≥1%) were met at the previous IA2.

As of the data cut-off date of the FA, the median duration of follow-up was 14.0 months (range: 0.1-43.7 months) in the ITT population. In the most up-to-date OS analysis, additional 14 months of follow-up were included with extension of the median follow-up period in the ITT population up to 43 months (range: 32-58 months).

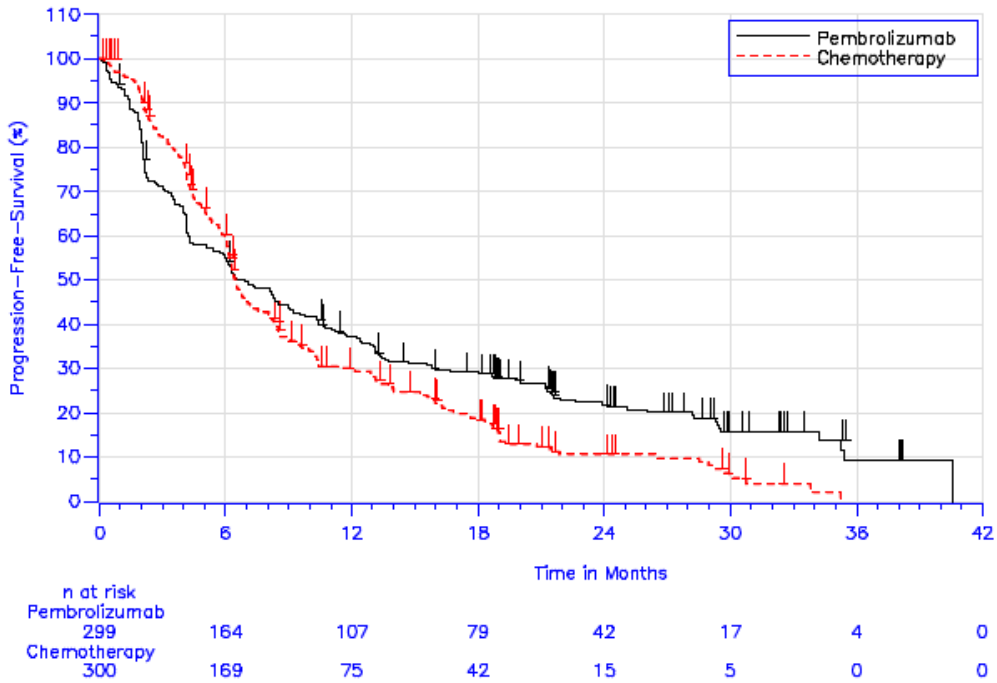
The OS rate was higher in the pembrolizumab group than in the chemotherapy group at 18 months (48.3% vs 37.4%, respectively).

Secondary Efficacy Endpoints

Progression Free Survival

TPS ≥50% NSCLC

PFS was not significantly improved with pembrolizumab compared with chemotherapy (tested at the p-value boundary of 0.01455) in subjects with TPS ≥50% NSCLC. Therefore, subsequent secondary efficacy hypotheses beyond subjects with TPS ≥50% NSCLC were not formally tested at this interim analysis and would be tested at the final analysis.



Database Cutoff Date: 04SEP2018

Figure 8: Kaplan-Meier of PFS based on BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS ≥ 50% - cutoff date 4-Sep-2018

Table 16: Analysis of PFS based on BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS ≥ 50% - cutoff date 4-Sep-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	299	238 (79.6)	3228.1	7.4	6.5 (5.9, 8.5)	37.2 (31.8, 42.7)	0.83 (0.69, 1.00)	0.0260
Chemotherapy	300	250 (83.3)	2618.3	9.5	6.4 (6.2, 7.2)	29.6 (24.3, 35.0)	---	---

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 geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 04SEP2018

The following secondary efficacy hypotheses were not formally tested neither at the interim analysis nor at the final one.

TPS ≥20% NSCLC

PFS was comparable for pembrolizumab and chemotherapy, with an HR of 0.94 (95% CI: 0.80, 1.11) in subjects with TPS ≥20% NSCLC. The median PFS was 6.2 months for pembrolizumab and 6.6 months for chemotherapy. Results from the final analysis were similar to those from the second interim analysis.

TPS ≥1% NSCLC

PFS was comparable for pembrolizumab and chemotherapy, with an HR of 1.07 (95% CI: 0.94, 1.21) in subjects with TPS ≥1% NSCLC. The median PFS was 5.4 months for pembrolizumab and 6.5 months for chemotherapy. Results from the final analysis were similar to those from the second interim analysis.

Objective Response Rate Based on BICR Assessment per RECIST 1.1

A summary of confirmed BOR based on BICR assessment in subjects with TPS ≥50%, ≥20%, and ≥1% NSCLC is presented in the following tables:

Table 17: Summary of best overall response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS ≥ 50%) - cutoff date 26-Feb-2018

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	299		300	
Complete Response (CR)	2	0.7	1	0.3
Partial Response (PR)	116	38.8	95	31.7
Overall Response (CR + PR)	**118**	**39.5**	**96**	**32.0**
Stable Disease (SD)	88	29.4	133	44.3
Disease Control (CR + PR + SD)	**206**	**68.9**	**229**	**76.3**
Progressive Disease (PD)	55	18.4	26	8.7
Not Evaluable (NE)	5	1.7	3	1.0
No Assessment	33	11.0	42	14.0

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization)
No Assessment: no post-baseline assessment available for response evaluation
(Database Cutoff Date: 26FEB2018).

Source: [P042V01MK3475: adam-adsl; adrs]

Table 18: Analysis of objective response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS ≥ 50%) - cutoff date 4-Sep-2018

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. Chemotherapy	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab	299	117	39.1 (33.6,44.9)	7.0 (-0.6,14.6)	0.0353
Chemotherapy	300	96	32.0 (26.8,37.6)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 04SEP2018

Table 19: Summary of best overall response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS ≥ 20%) - cutoff date 26-Feb-2018

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	413		405	
Complete Response (CR)	2	0.5	1	0.2
Partial Response (PR)	136	32.9	116	28.6
Overall Response (CR + PR)	**138**	**33.4**	**117**	**28.9**
Stable Disease (SD)	144	34.9	196	48.4
Disease Control (CR + PR + SD)	**282**	**68.3**	**313**	**77.3**
Progressive Disease (PD)	77	18.6	31	7.7
Not Evaluable (NE)	7	1.7	4	1.0
No Assessment	47	11.4	57	14.1

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization)
No Assessment: no post-baseline assessment available for response evaluation
(Database Cutoff Date: 26FEB2018).

Source: [P042V01MK3475: adam-adsl; adrs]

Table 20: Analysis of objective response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS ≥ 20%) - cutoff date 4-Sep-2018

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. Chemotherapy	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab	413	137	33.2 (28.6,37.9)	4.6 (-1.7,10.9)	0.0744
Chemotherapy	405	117	28.9 (24.5,33.6)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 04SEP2018

Table 21: Summary of best overall response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS ≥ 1%) - cutoff date 26-Feb-2018

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	637		637	
Complete Response (CR)	3	0.5	3	0.5
Partial Response (PR)	171	26.8	166	26.1
Overall Response (CR + PR)	**174**	**27.3**	**169**	**26.5**
Stable Disease (SD)	246	38.6	333	52.3
Disease Control (CR + PR + SD)	**420**	**65.9**	**502**	**78.8**
Progressive Disease (PD)	133	20.9	48	7.5
Not Evaluable (NE)	11	1.7	8	1.3
No Assessment	73	11.5	79	12.4

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization)
No Assessment: no post-baseline assessment available for response evaluation
(Database Cutoff Date: 26FEB2018).

Source: [P042V01MK3475: adam-adsl; adrs]

Table 22: Analysis of objective response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS ≥ 1%) - cutoff date 4-Sep-2018

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. Chemotherapy	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab	637	173	27.2 (23.7,30.8)	0.6 (-4.2,5.4)	0.4060
Chemotherapy	637	169	26.5 (23.1,30.1)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

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

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

Database Cutoff Date: 04SEP2018

Exploratory Efficacy Endpoints

Time to Response and Response Duration Based on BICR Assessment per RECIST 1.1.

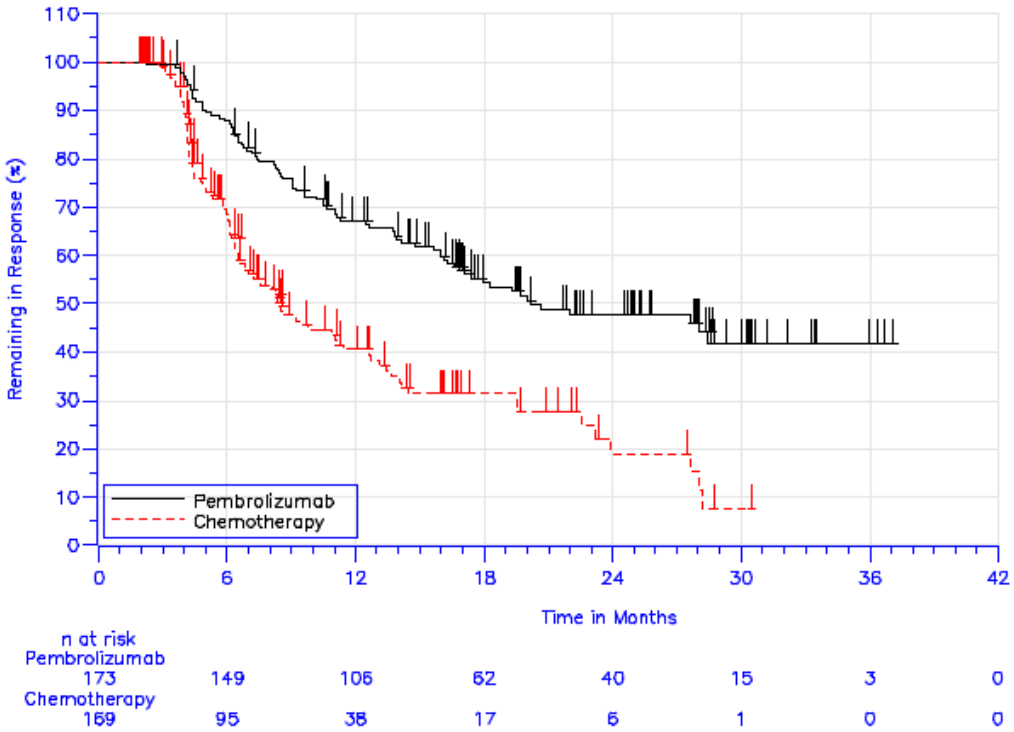


Figure 9: Kaplan-Meier of response duration for subjects with objective response based on BICR assessment per RECIST 1.1 - ITT population with TPS ≥ 1% - cutoff date 4-Sep-2018

Table 23: Summary of time to response and response duration based on RECIST 1.1 per BICR assessment in subjects with confirmed response -ITT population with TPS ≥ 1% - cutoff date 4-Sep-2018

	Pembrolizumab (N=637)	Chemotherapy (N=637)
Number of Subjects with Response[†]	173	169
Time to Response[†] (months)		
Mean (SD)	3.2 (2.3)	3.0 (2.2)
Median (Range)	2.1 (1.0-18.5)	2.1 (1.3-13.9)
Response Duration[‡] (months)		
Median (Range)[§]	20.2 (2.1+ - 37.0+)	8.4 (1.8+ - 30.4+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥ 6 months	149(87.7)	95(68.8)
≥ 12 months	106(67.2)	38(40.5)
≥ 18 months	62(54.3)	17(31.3)
≥ 24 months	40(47.6)	6(18.9)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
[§] "+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 04SEP2018

The DOR and time to response in subjects with TPS ≥20% and ≥50% NSCLC were similar to those for the TPS ≥1% NSCLC population.

Progression-Free Survival Based on Investigator Assessment per RECIST 1.1

The results of the analysis of PFS based on investigator assessment were consistent with the results of the analysis of PFS based on BICR assessment in subjects with TPS ≥50%, ≥20%, and ≥1% NSCLC.

Objective Response Rate Based on Investigator Assessment per RECIST 1.1

The results of the analysis of confirmed ORR based on investigator assessment were consistent with the results of the analysis of ORR based on BICR assessment in subjects with TPS ≥50%, ≥20%, and ≥1% NSCLC.

Progression-Free Survival 2 Based on Investigator Assessment per RECIST 1.1

A total of 240 subjects (37.7%) in the pembrolizumab group and 282 subjects (44.3%) in the chemotherapy group received subsequent anti-cancer therapy upon primary therapy discontinuation.

PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever comes first, was analyzed in subjects with TPS ≥50%, ≥20%, and ≥1% NSCLC.

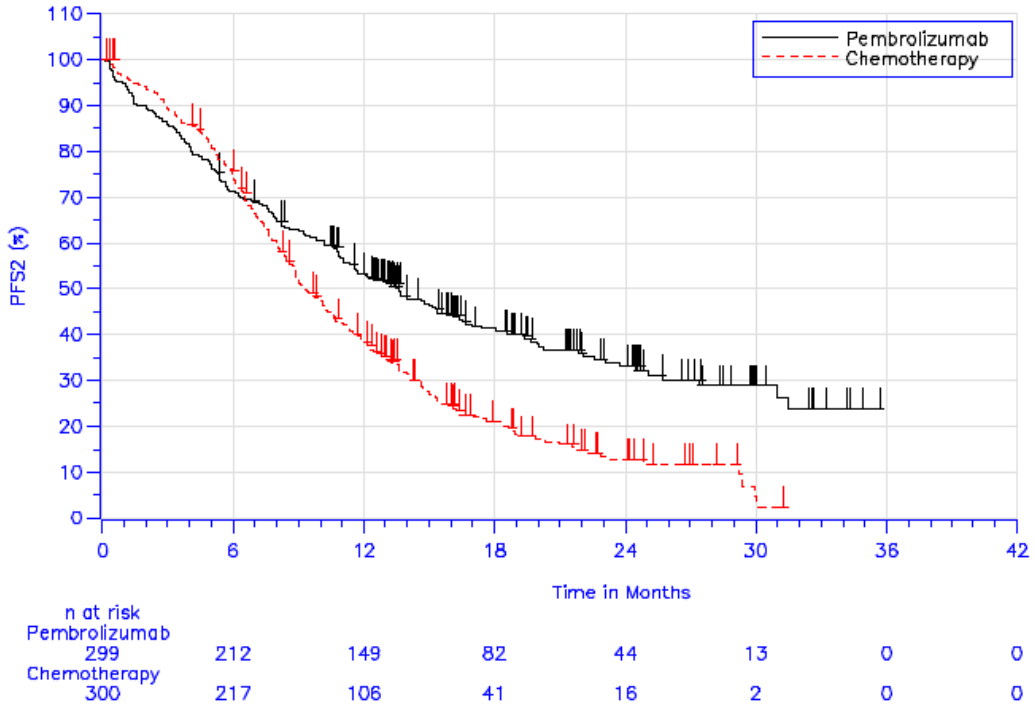


Figure 10: Kaplan-Meier of PFS2 (ITT population with TPS ≥ 50%) - cutoff date 26-Feb-2018

Table 24: Analysis of PFS2 (ITT population with TPS ≥ 50%) - cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS2[†] (Months) (95% CI)	PFS2 Rate at Month 12 in %[†] (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab	299	185 (61.9)	3823.4	4.8	13.6 (11.1, 15.8)	53.3 (47.5, 58.9)	0.63 (0.52, 0.77)	<0.0001
Chemotherapy	300	238 (79.3)	3114.5	7.6	9.3 (8.5, 10.6)	38.4 (32.8, 44.0)	---	---

PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever comes first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
[‡‡] One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

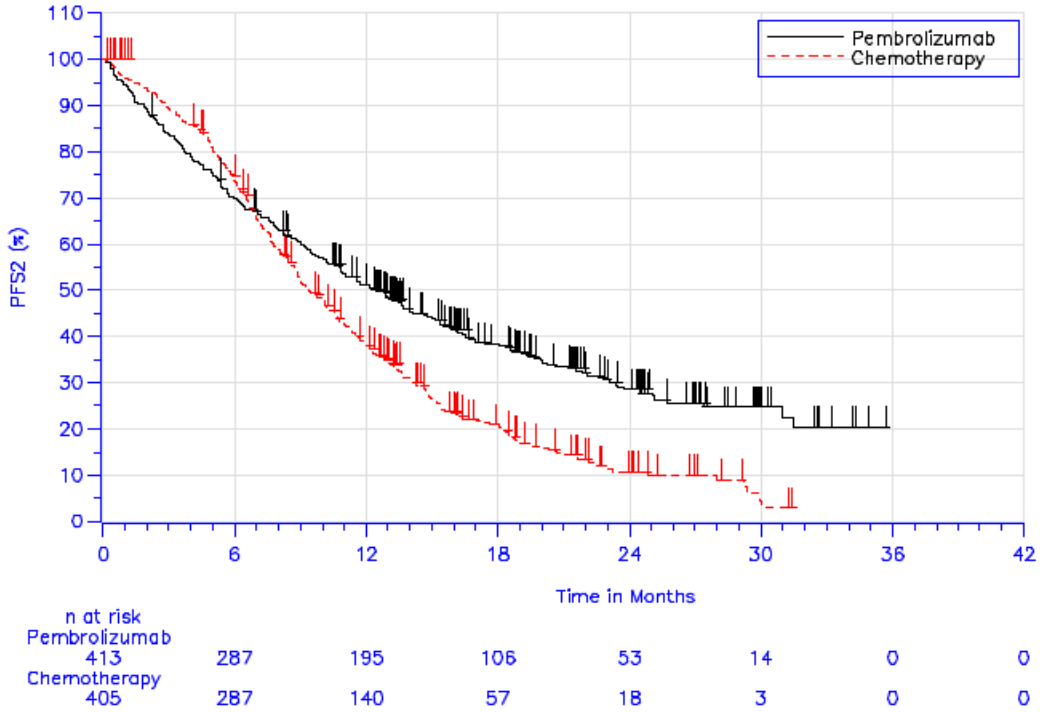


Figure 11: Kaplan-Meier of PFS2 (ITT population with TPS ≥ 20%) - cutoff date 26-Feb-2018

Table 25: Analysis of PFS2 (ITT population with TPS ≥ 20%) - cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS2[†] (Months) (95% CI)	PFS2 Rate at Month 12 in %[†] (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab	413	270 (65.4)	5057.9	5.3	12.5 (10.7, 14.2)	51.2 (46.2, 56.0)	0.66 (0.56, 0.78)	<0.0001
Chemotherapy	405	324 (80.0)	4130.6	7.8	9.4 (8.7, 10.6)	38.1 (33.2, 43.0)	---	---

PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever comes first.

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

[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).

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

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

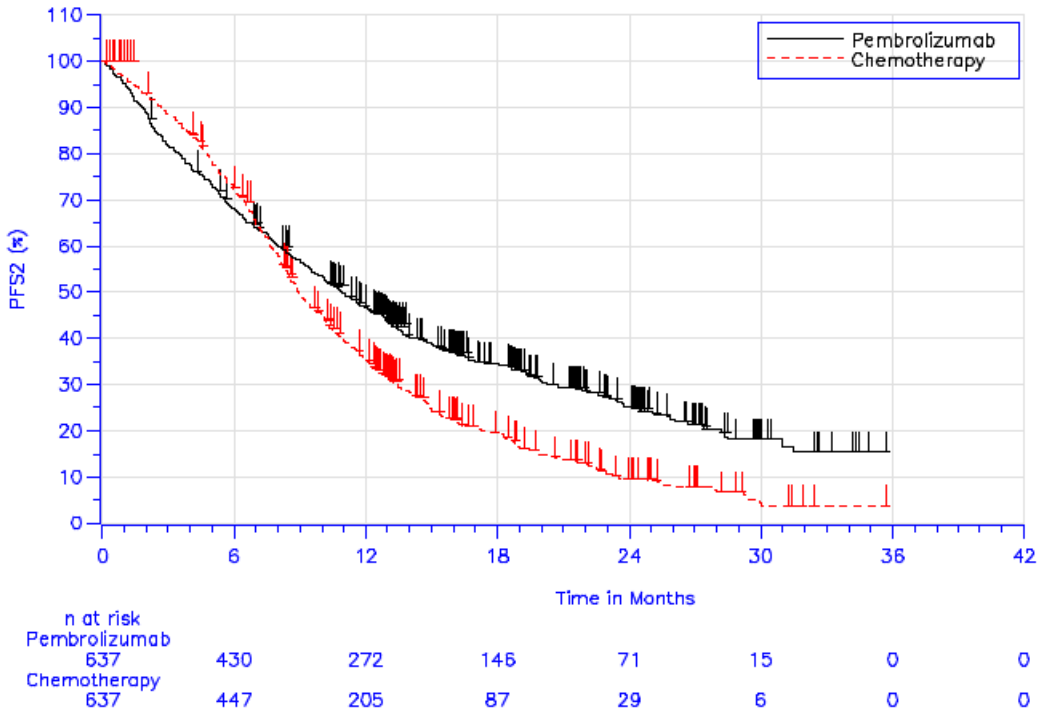


Figure 12: Kaplan-Meier of PFS2 (ITT population with TPS ≥ 1%) - cutoff date 26-Feb-2018

Table 26: Analysis of PFS2 (ITT population with TPS ≥ 1%) - cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS2[†] (Months) (95% CI)	PFS2 Rate at Month 12 in %[†] (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab	637	443 (69.5)	7331.0	6.0	10.9 (9.7, 12.2)	46.8 (42.8, 50.6)	0.74 (0.65, 0.84)	<0.0001
Chemotherapy	637	526 (82.6)	6395.1	8.2	8.9 (8.5, 9.7)	35.4 (31.6, 39.2)	---	---

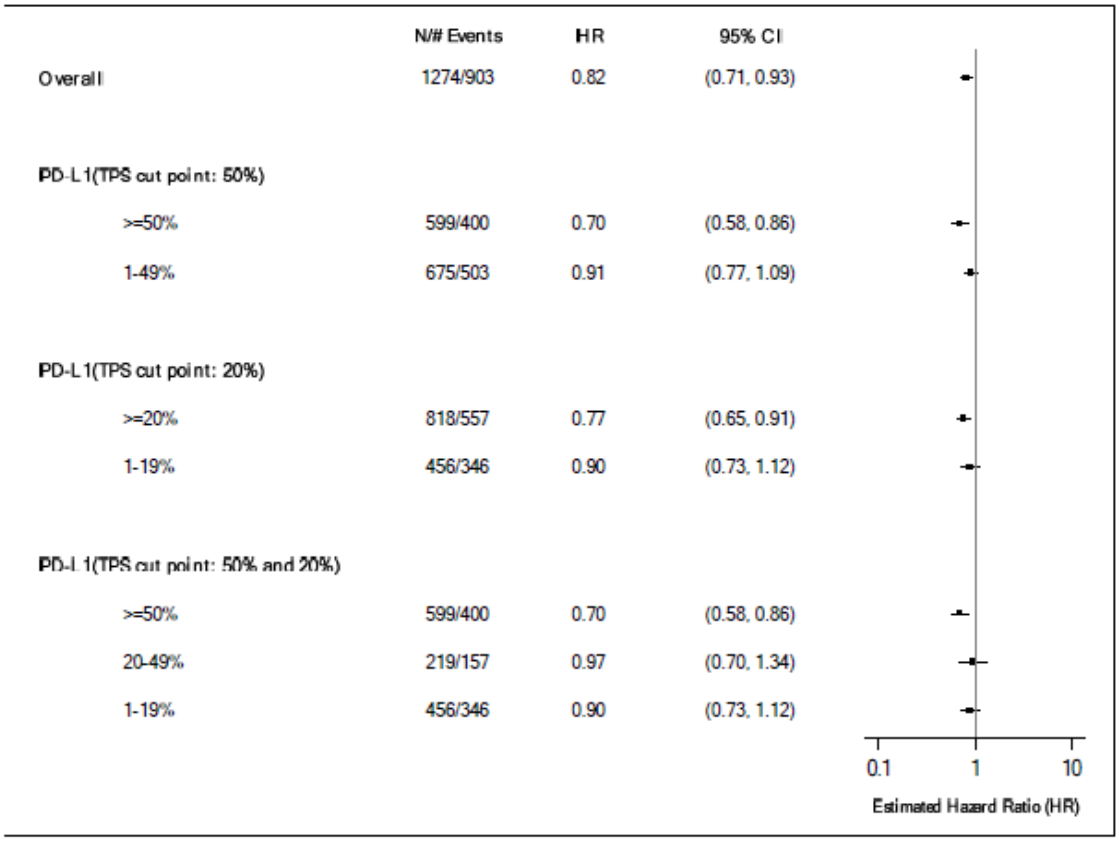
PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever comes first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
[‡‡] One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

At the final analysis, PFS2 HRs were consistent with what was observed at the second interim analysis. A total of 262 subjects (41.1%) in the pembrolizumab group and 294 subjects (46.2%) in the chemotherapy group received subsequent anticancer therapy upon primary therapy discontinuation. Crossover from chemotherapy to pembrolizumab was not part of the study design. At the time of data cut-off, 16 of 637 subjects on chemotherapy continued on treatment. Of the remaining 621 subjects in the chemotherapy group, 134 (21.0%) received a checkpoint inhibitor (pembrolizumab, atezolizumab, avelumab, or nivolumab) as subsequent therapy during survival follow-up.

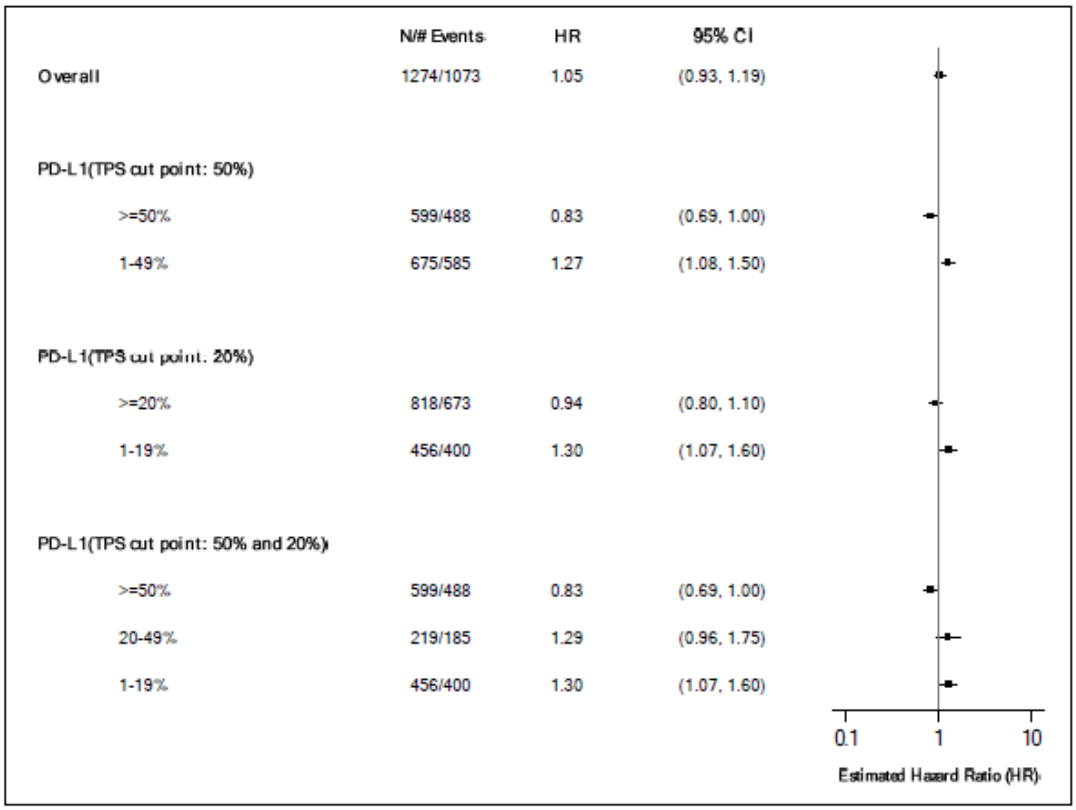
Ancillary analyses

Overall Survival and PFS by PD-L1 score



Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
Database Cutoff Date: 04SEP2018

Figure 13: Forest Plot of OS Hazard Ratio by Subgroup Factor PD-L1 status (ITT Population with TPS≥1%) - cutoff date 04-Sep-2018



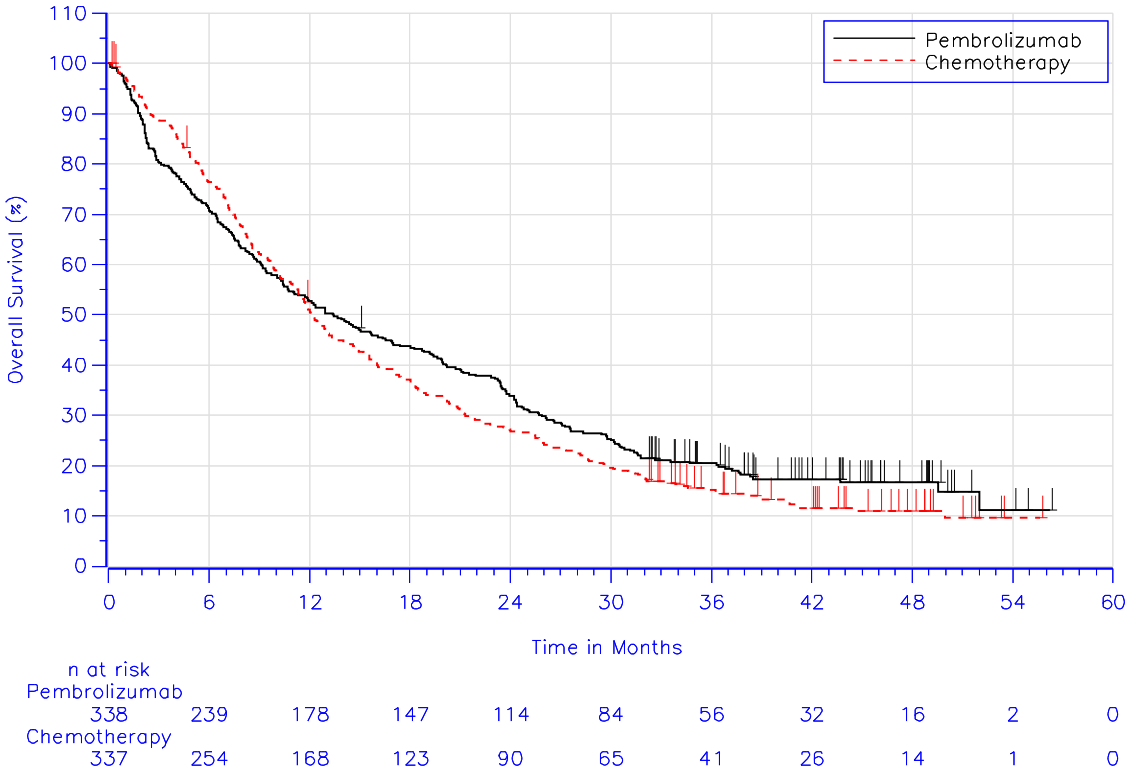
Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
Database Cutoff Date: 04SEP2018

Figure 14: Forest Plot of PFS Hazard Ratio by Subgroup Factor by PD-L1 status BICR Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population with TPS>=1%) - cutoff date 04-Sep-2018

Analysis of Subgroup TPS 1-49%

OS in TPS 1-49%

The exploratory subgroup analysis for TPS 1-49% was prespecified in the protocol; however, formal hypothesis testing was not planned in the SAP for the study.



Database Cutoff Date: 25OCT2019

Figure 15: Kaplan-Meier of Overall survival (ITT population with TPS 1-49%) - cutoff date 25-Oct-2019

Table 27: Analysis of Overall survival (ITT population with TPS 1-49%) - cutoff date 25-Oct-2019

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	338	279 (82.5)	6104.3	4.6	13.4 (10.7, 16.9)	52.7 (47.2, 57.8)	0.90 (0.76, 1.06)	0.0991
Chemotherapy	337	292 (86.6)	5652.1	5.2	12.1 (11.0, 14.0)	50.8 (45.3, 56.0)	---	---

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

‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 25OCT2019

The mortality rates over time in the period before the curves crossed were measured individually for Months 1 to 6 and in combined follow-up thereafter by dividing the number of deaths observed by the sum of the total observation time in each time interval for each treatment.

Table 28: Piecewise hazard rate for overall survival – all subjects (ITT population with TPS= 1-49%)- cutoff date 04-Sep-2018

Month	Pembrolizumab(N=338)		Chemotherapy(N=337)		HR
	Event	Rate	Event	Rate	
1	13	0.039	10	0.030	1.29
2	25	0.080	13	0.041	1.95
3	28	0.099	14	0.046	2.13
4	8	0.030	10	0.034	0.88
5	14	0.054	16	0.057	0.95
6	11	0.045	16	0.061	0.73
7+	115	0.042	160	0.061	0.70
Database Cutoff Date: 26FEB2018					

Source: [P042V01MK3475: adam-adsl; adtte]

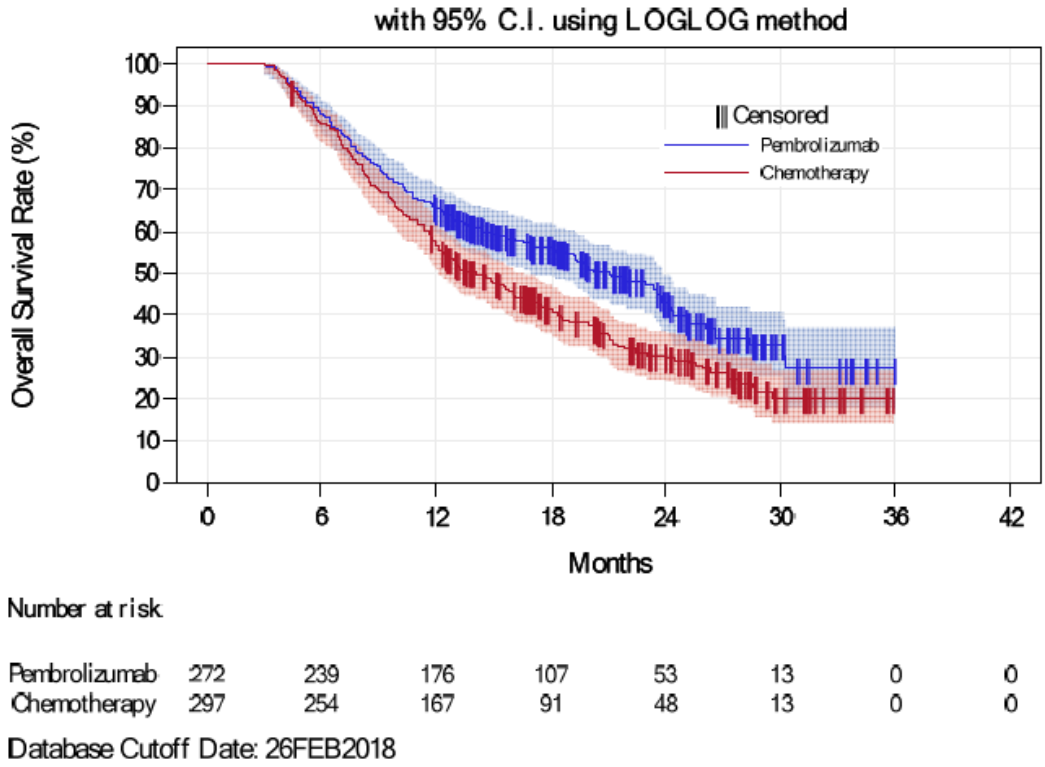


Figure 16: Kaplan-Meier plot of OS landmark analysis for subjects with OS >3 months (ITT population with TPS= 1-49%) - cutoff date 26-Feb-2018

To further explore the risk of early death, a comparison of baseline characteristics considered to be prognostic factors for treatment outcomes were evaluated in the overall TPS 1-49% population. In the pembrolizumab group compared with the chemotherapy group, more subjects had baseline tumour size at/above the ITT population median (49.7% versus 44.8%), ≥3 metastasis sites (54.4% versus 49.0%), and liver metastases at baseline (17.2% versus 13.1%).

Table 29: Subject characteristics (ITT population with TPS =1-49%)- cutoff date 26-Feb-2018

	Pembrolizumab		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	338		337		675	
Gender						
Male	245	(72.5)	242	(71.8)	487	(72.1)
Female	93	(27.5)	95	(28.2)	188	(27.9)
Age (Years)						
< 65	192	(56.8)	187	(55.5)	379	(56.1)
>= 65	146	(43.2)	150	(44.5)	296	(43.9)
Mean	62.7		63.5		63.1	
SD	10.0		9.2		9.6	
Median	64.0		63.0		63.0	
Range	31 to 87		31 to 85		31 to 87	
Race						
American Indian Or Alaska Native	6	(1.8)	2	(0.6)	8	(1.2)
Asian	95	(28.1)	92	(27.3)	187	(27.7)
Black Or African American	10	(3.0)	8	(2.4)	18	(2.7)
Multiple	17	(5.0)	12	(3.6)	29	(4.3)
White	210	(62.1)	223	(66.2)	433	(64.1)
Ethnicity						
Hispanic Or Latino	74	(21.9)	66	(19.6)	140	(20.7)
Not Hispanic Or Latino	263	(77.8)	269	(79.8)	532	(78.8)
Not Reported	1	(0.3)	2	(0.6)	3	(0.4)
Age Group (Years)						
< 65	192	(56.8)	187	(55.5)	379	(56.1)
65 - 74	107	(31.7)	108	(32.0)	215	(31.9)
75 - 84	37	(10.9)	40	(11.9)	77	(11.4)
>= 85	2	(0.6)	2	(0.6)	4	(0.6)
ECOG						
0	102	(30.2)	101	(30.0)	203	(30.1)
1	236	(69.8)	236	(70.0)	472	(69.9)
Cancer Stage at Screening						
IIIA	8	(2.4)	8	(2.4)	16	(2.4)

	Pembrolizumab		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
IIIB	41	(12.1)	41	(12.2)	82	(12.1)
IV	289	(85.5)	288	(85.5)	577	(85.5)
Disease Status						
Metastatic	289	(85.5)	288	(85.5)	577	(85.5)
Advanced	49	(14.5)	49	(14.5)	98	(14.5)
Geographic Region of Enrolling Site						
East Asia	93	(27.5)	91	(27.0)	184	(27.3)
Non-East Asia	245	(72.5)	246	(73.0)	491	(72.7)
Geographic Region of Enrolling Site						
East Asia	93	(27.5)	91	(27.0)	184	(27.3)
EU	78	(23.1)	71	(21.1)	149	(22.1)
Latin America	83	(24.6)	70	(20.8)	153	(22.7)
Other	84	(24.9)	105	(31.2)	189	(28.0)
Histology						
Squamous	136	(40.2)	135	(40.1)	271	(40.1)
Non-Squamous	202	(59.8)	202	(59.9)	404	(59.9)
Smoking Status						
Current	68	(20.1)	87	(25.8)	155	(23.0)
Former	192	(56.8)	177	(52.5)	369	(54.7)
Never	78	(23.1)	73	(21.7)	151	(22.4)
Baseline Weight (kg)						
Subjects with data	338		337		675	
Mean	68.1		67.6		67.9	
SD	14.0		13.9		13.9	
Median	67		68		68	
Range	34 to 119		37 to 121		34 to 121	
Prior Adjuvant Therapy						
Yes	10	(3.0)	8	(2.4)	18	(2.7)
No	328	(97.0)	329	(97.6)	657	(97.3)
Prior Neo-adjuvant Therapy						
Yes	2	(0.6)	2	(0.6)	4	(0.6)

	Pembrolizumab		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
No	336	(99.4)	335	(99.4)	671	(99.4)
Prior Radiation Therapy						
Yes	35	(10.4)	42	(12.5)	77	(11.4)
No	303	(89.6)	295	(87.5)	598	(88.6)
Brain Metastasis Status at Baseline						
Y	16	(4.7)	20	(5.9)	36	(5.3)
N	322	(95.3)	317	(94.1)	639	(94.7)
Liver Metastasis Status at Baseline						
Y	58	(17.2)	44	(13.1)	102	(15.1)
Missing	280	(82.8)	293	(86.9)	573	(84.9)
Baseline Tumor Size (mm)						
Subjects with data	336		336		672	
Mean	106.1		106.9		106.5	
SD	57.3		62.2		59.8	
Median	99		94		96	
Range	16 to 357		10 to 339		10 to 357	
Baseline Tumor Size >= vs < Median of Entire ITT Population						
At/Above Median	168	(49.7)	151	(44.8)	319	(47.3)
Below Median	168	(49.7)	185	(54.9)	353	(52.3)
Missing	2	(0.6)	1	(0.3)	3	(0.4)
Number of metastasis sites						
>=3	184	(54.4)	165	(49.0)	349	(51.7)
<3	150	(44.4)	172	(51.0)	322	(47.7)
Missing	4	(1.2)	0	(0.0)	4	(0.6)
Number of lesions						
Subjects with data	338		337		675	
Mean	5.1		5.0		5.0	
SD	2.5		2.7		2.6	
Median	5		4		5	
Range	1 to 14		1 to 20		1 to 20	
For disease status, Advanced = Stage IIIA and IIIB, Metastatic = Stage IV. Database Cutoff Date: 26FEB2018						

Source: [P042V01MK3475: adam-adsl]

The baseline risk factors for mortality among patients who died or were censored in the first 3 months were compared with those known to have survived for at least 3 months.

In subjects who died or were censored before 3 months versus after 3 months, a higher proportion of patients had liver metastasis at baseline (25.5% versus 13.2%), baseline tumour size at/above the ITT population median (73.6% versus 42.4%), ≥3 sites of metastasis (67.9% versus 48.7%), a higher mean number of lesions (5.8 versus 4.9) and a higher proportion of subjects with ECOG PS of 1 (80.2% versus 68.0%).

A stratified multivariate Cox regression analysis of OS with stepwise variable selection was carried out including the baseline characteristics identified above as well as other factors known to be of prognostic interest in NSCLC. Baseline tumour size, number of metastasis sites, and liver metastasis status at baseline were confirmed as risk factors for early mortality, with p-values based on the Wald test of <0.0001, 0.0001, and 0.0001, respectively.

Table 30: Multivariate Cox regression analysis for overall survival (ITT population with TPS= 1-49%)- cutoff date 26-Feb-2018

Covariate	Hazard Ratio‡ (95% CI)‡	p-Value‡
Treatment		
Pembrolizumab vs. Chemotherapy (reference)	0.83 (0.69, 1.01)	0.0310
Baseline Tumor Size		
< Median vs. >= Median (reference)	0.55 (0.45, 0.67)	<.0001
Number of metastasis sites		
<3 vs. >=3 (reference)	0.69 (0.56, 0.84)	0.0001
Liver Metastasis Status at Baseline		
N vs. Y (reference)	0.62 (0.48, 0.80)	0.0001
‡ Based on multivariate cox regression model with treatment, baseline tumor size, number of metastasis sites and liver metastasis status at baseline as the covariates stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). One-sided p-value based on type III Wald test.		
Database Cutoff Date: 26FEB2018		

Source: [P042V01MK3475: adam-adsl; adtte]

When adjusted by baseline tumour size, the number of metastasis sites, and liver metastasis status at baseline, the OS HR in favour of pembrolizumab in the TPS 1-49% subgroup improved from 0.92 to 0.83.

In addition, the MAH also proposed an alternative approach to further investigate the findings from the post hoc analysis, evaluating whether the early part of the survival curve in the TPS 1-49% subgroup was driven by subjects with poor prognosis, including high tumour burden. Evaluation of baseline factors with prognostic and predictive associations based on the totality of survival data was considered more appropriate for identifying patients at high risk (denoted as Control>Treatment) as well as those who may benefit from the experimental therapy (denoted as Treatment>Control).

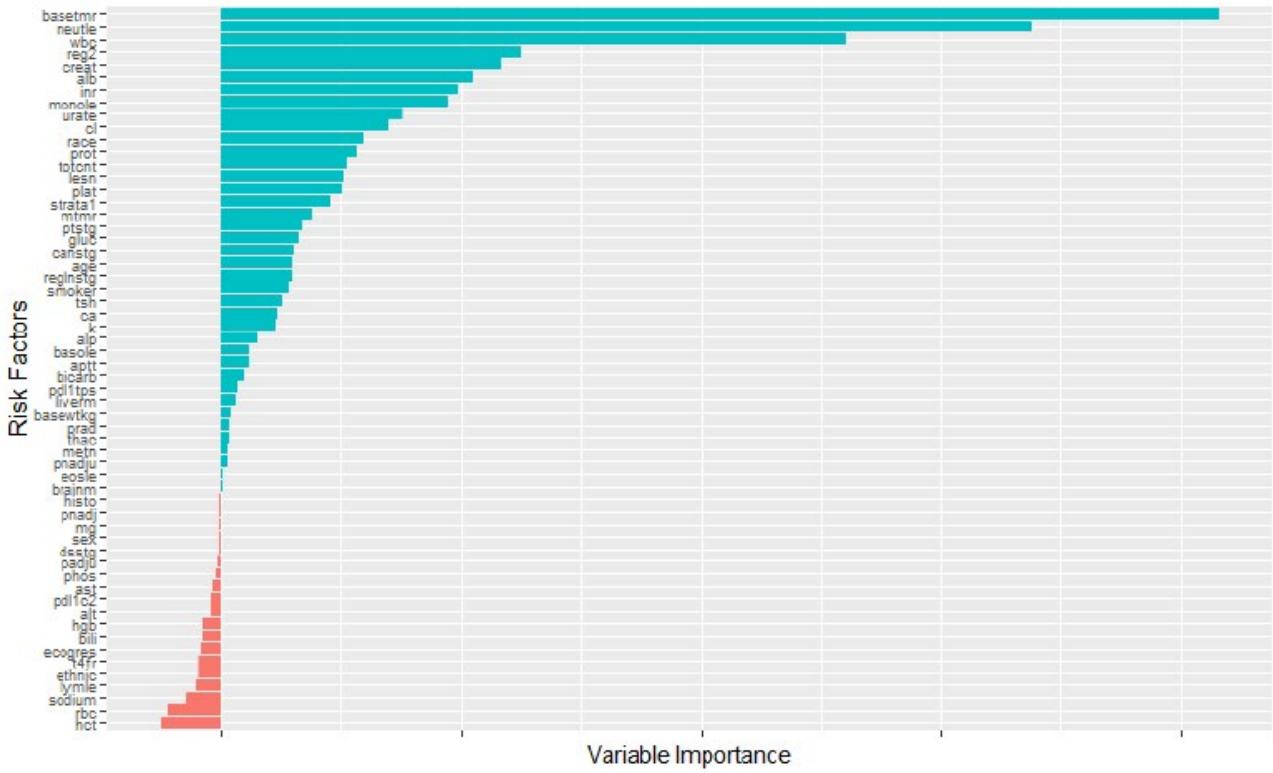


Figure 17: Permutation-based importance ranking of predictive factors

Based on the predictive risk factor ranking, the baseline target tumour sum of longest diameters (SLD) was identified as the most important predictive factor for treatment benefit. A data driven cut-off of 149 mm was estimated based on a classification tree using only baseline tumour SLD as the risk factor. For

subjects with baseline tumour SLD =149 mm vs SLD >149 mm, the overall survival comparison is summarized below:

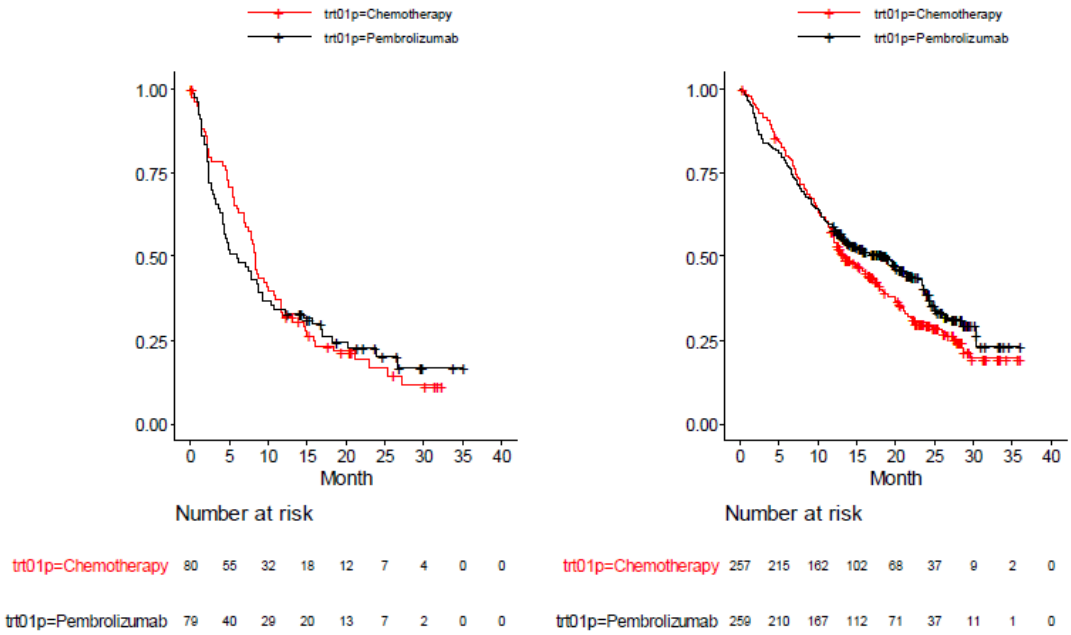


Figure 18: Kaplan-Meier of overall survival in subjects with baseline target tumour sum of longest diameters (SLD)> 149 mm (left) versus ≤149 mm (right) based on 10-fold cross validation

Table 31: Analysis of overall survival by baseline tumour size (ITT population with TPS= 1-49%)- cutoff date 26-Feb-2018

Overall	Pembrolizumab			Chemotherapy			Pembrolizumab vs. Chemotherapy
	N	Number (%) of Events		N	Number (%) of Events		Hazard Ratio (95% CI)†‡
	338	214	(63.3)	337	239	(70.9)	0.92 (0.77, 1.11)
Baseline Tumour Size							
≤ 149 mm	269	153	(56.9)	255	171	(67.1)	0.88 (0.7, 1.09)
> 149 mm	69	61	(88.4)	82	68	(82.9)	1.16 (0.8, 1.68)

† Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS ≥ 50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
‡ Hazard ratio and 95% CI for the identified subgroups were estimated using 10-fold cross-validation.
Database Cutoff Date: 26FEB2018

PFS in TPS 1-49%

PFS analysis and KM plot based on BICR assessment per RECIST 1.1 for the ITT Population with TPS=1-49% are provided below.

Table 32: Analysis of PFS based on BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS =1-49%- cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	338	286 (84.6)	2247.8	12.7	4.2 (4.1, 5.2)	19.2 (15.0, 23.8)	1.32 (1.12, 1.56)	0.9994
Chemotherapy	337	273 (81.0)	2668.3	10.2	6.8 (6.3, 8.1)	25.8 (20.9, 31.0)	---	---

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 geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

At the data cut-off 04-Sep-2018, PFS in TPS 1-49% was HR 1.27 (95%CI 1.08, 1.50).

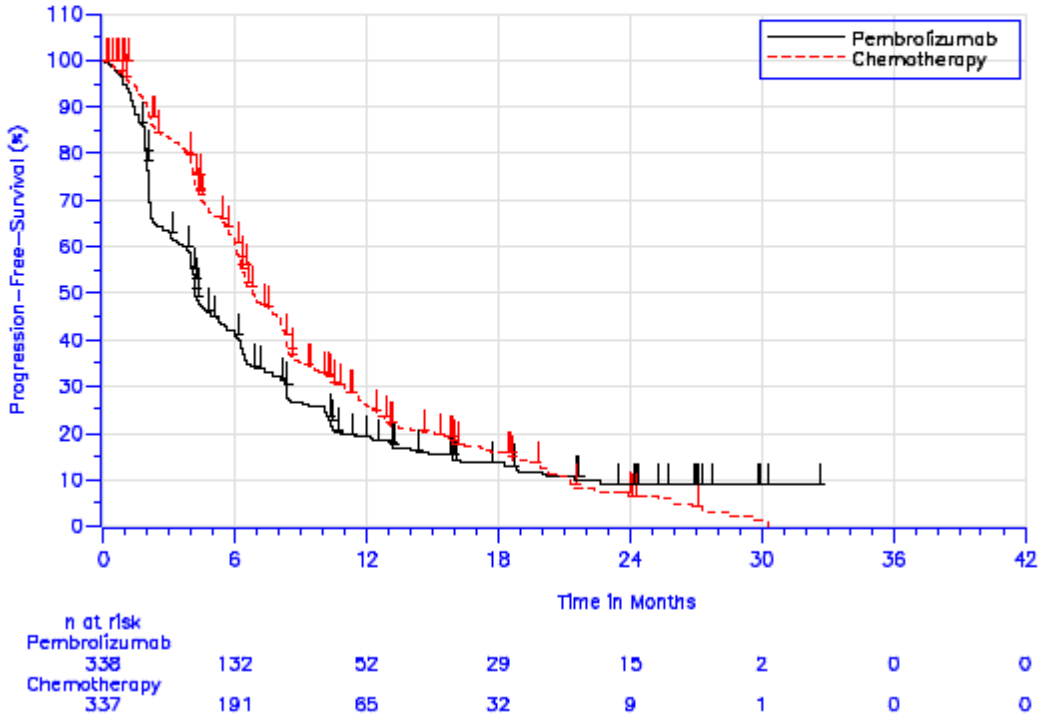


Figure 19: Kaplan-Meier of PFS based on BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS =1-49%- cutoff date 26-Feb-2018

ORR in TPS 1-49%

The summary of best overall response and the ORR analysis for the TPS 1-49% subgroup in KEYNOTE-042 are provided below.

Table 33: Summary of best overall response based on BICR assessment per RECIST 1.1 with confirmation (ITT population with TPS =1-49%)- cutoff date 26-Feb-2018

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	338		337	
Complete Response (CR)	1	0.3	2	0.6
Partial Response (PR)	55	16.3	71	21.1
Overall Response (CR + PR)	**56**	**16.6**	**73**	**21.7**
Stable Disease (SD)	158	46.7	200	59.3
Disease Control (CR + PR + SD)	**214**	**63.3**	**273**	**81.0**
Progressive Disease (PD)	78	23.1	22	6.5
Not Evaluable (NE)	6	1.8	5	1.5
No Assessment	40	11.8	37	11.0

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization)
No Assessment: no post-baseline assessment available for response evaluation
(Database Cutoff Date: 26FEB2018).

Source: [P042V01MK3475: adam-adsl; adrs]

Table 34: Analysis of objective response with confirmation based on BICR assessment per RECIST 1.1 (ITT population with TPS =1-49%)- cutoff date 26-Feb-2018

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. Chemotherapy	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab	338	56	16.6 (12.8,21.0)	-5.2 (-11.1,0.8)	0.9560
Chemotherapy	337	73	21.7 (17.4,26.4)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

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

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adrs]

Time to response and duration of response in TPS 1-49%

Table 35: Summary of time to response and response duration based on RECIST 1.1 per BICR assessment in subjects with confirmed response (ITT population with TPS =1-49%) - cutoff date 4-Sep-2018

	Pembrolizumab (N=338)	Chemotherapy (N=337)
Number of Subjects with Response[†]	56	73
Time to Response[†] (months)		
Mean (SD)	3.3 (1.9)	2.9 (2.1)
Median (Range)	2.1 (1.9-10.2)	2.1 (1.4-13.5)
Response Duration[‡] (months)		
Median (Range)[§]	17.4 (2.2 - 37.0+)	8.1 (1.9+ - 28.2)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥ 6 months	47(83.9)	41(73.9)
≥ 12 months	37(66.1)	14(34.3)
≥ 18 months	21(49.9)	7(27.0)
≥ 24 months	15(44.6)	3(17.3)

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

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

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

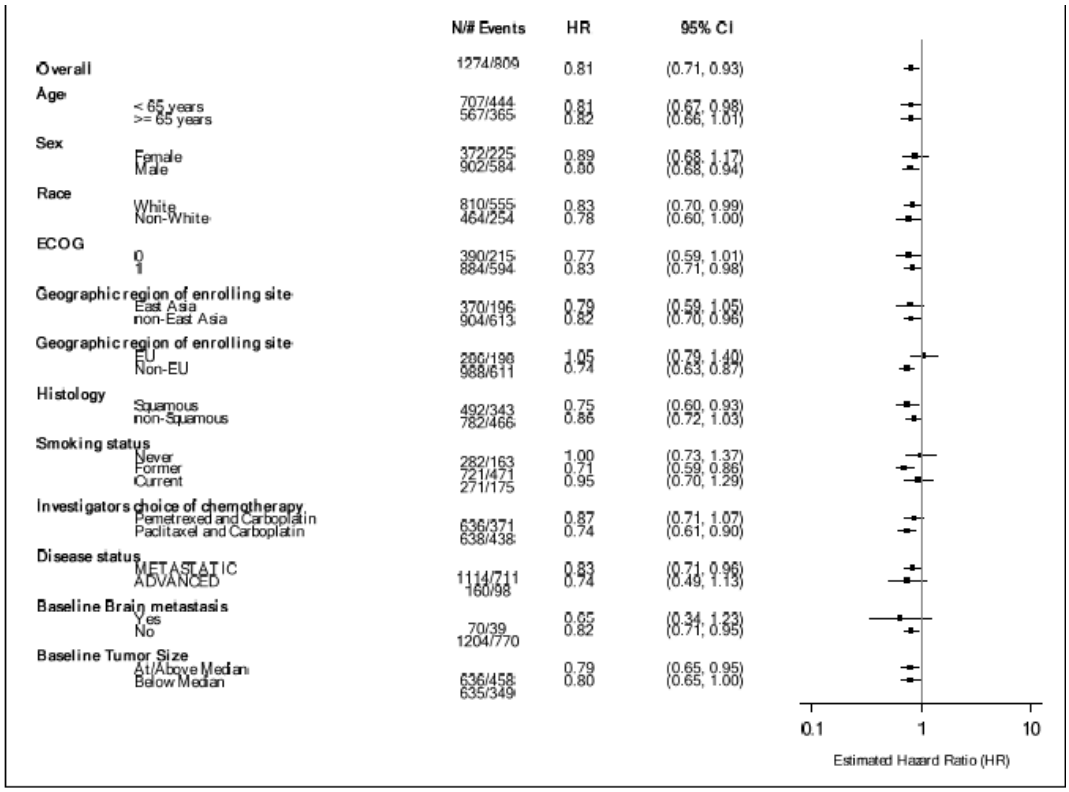
NR = Not Reached.

Database Cutoff Date: 04SEP2018

Non-squamous histology TPS 1-49%

OS and PFS analyses for the subgroup of subjects with non-squamous TPS 1-49% NSCLC are consistent with those of the entire TPS 1-49% subgroup [data not shown].***Analysis of subgroups – ITT population***

Overall Survival by other subgroup factors



Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
For disease status, Advanced = Stage IIIA and IIIB, Metastatic = Stage IV.
Database Cutoff Date: 26FEB2018
Source: [P042V01MK3475: adam-adsl; adtte]

Figure 20: Forest plot of OS hazard ratio by subgroup factor (ITT population with TPS≥1%)- cutoff date 26-Feb-2018

The results of the subgroup analyses for subjects with TPS ≥50% and ≥20% NSCLC were similar to those observed for the entire population (TPS ≥1% NSCLC).

EU Region

While there was reasonable consistency across all analysed subgroups in KEYNOTE-042, an exploratory analysis of the EU subpopulation was undertaken to further examine the treatment effect in this subpopulation, in which the OS HR for the overall ITT population (TPS ≥1% NSCLC) in subjects enrolled in the EU was 1.05 (95% CI: 0.79, 1.40), compared with 0.74 (95% CI: 0.63, 0.87) in non-EU subjects.

A stratified multivariate Cox regression analysis of OS with stepwise variable selection was carried out with baseline tumour size, number of metastasis sites, and liver metastasis status at baseline as covariates.

Table 36: Multivariate Cox regression analysis for overall survival - EU subjects (ITT population with TPS≥1%)- cutoff date 26-Feb-2018

Covariate	Hazard Ratio‡ (95% CI)‡	p-Value‡
Treatment		
Pembrolizumab vs. Chemotherapy (reference)	0.98 (0.74, 1.31)	0.4505
Baseline Tumor Size		
< Median vs. >= Median (reference)	0.47 (0.35, 0.64)	<.0001
Number of metastasis sites		
<3 vs. >=3 (reference)	0.86 (0.63, 1.17)	0.1635
Liver Metastasis Status at Baseline		
N vs. Y (reference)	0.99 (0.68, 1.43)	0.4711

‡ Based on multivariate cox regression model with treatment, baseline tumor size, number of metastasis sites and liver metastasis status at baseline as the covariates stratified by ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous). One-sided p-value based on type III Wald test.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

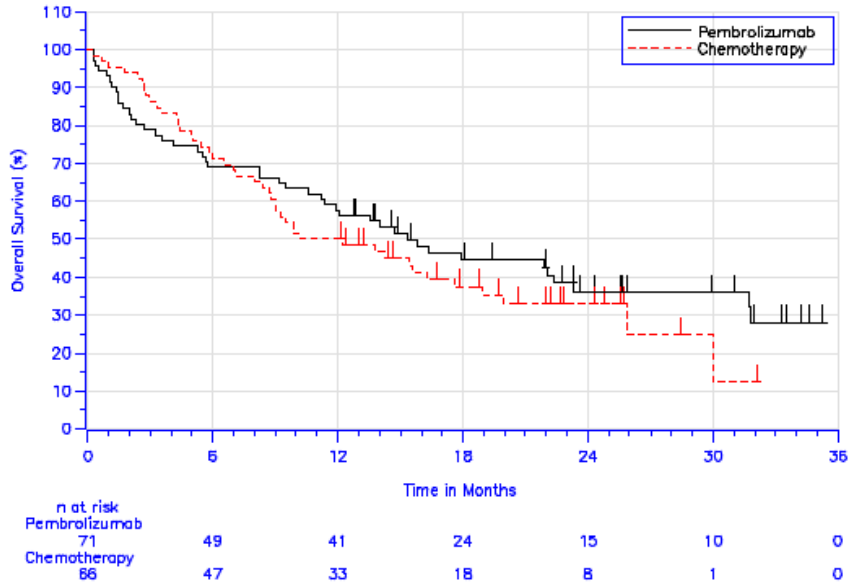
KEYNOTE-042 enrolled 22.4% of study subjects from the EU. OS analyses for EU subjects in the TPS ≥ 50%, ≥20%, and 1-49% subgroups are presented below.

Table 37: Analysis of Overall survival (ITT population with TPS ≥ 50%, EU subjects) - cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	71	44 (62.0)	1041.4	4.2	15.3 (10.6, 23.3)	57.7 (45.4, 68.2)	0.84 (0.55, 1.29)	0.2115
Chemotherapy	66	44 (66.7)	829.1	5.3	11.2 (8.7, 17.6)	50.0 (37.5, 61.3)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]



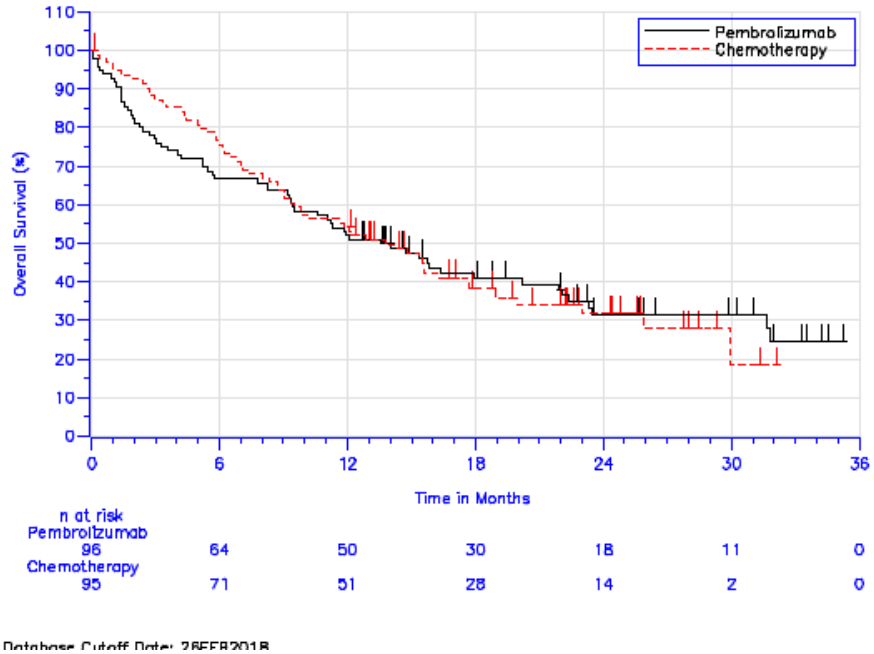
Database Cutoff Date: 26FEB2018

Figure 21: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 50%, EU subjects) - cutoff date 26-Feb-2018

Table 38: Analysis of Overall survival (ITT population with TPS ≥ 20%, EU subjects) - cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	96	63 (65.6)	1310.7	4.8	13.6 (9.4, 20.2)	52.1 (41.7, 61.5)	0.97 (0.67, 1.40)	0.4250
Chemotherapy	95	62 (65.3)	1257.8	4.9	13.8 (9.5, 17.6)	54.3 (43.7, 63.7)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), PD-L Status(TPS>=50% vs. TPS=1-49%) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 26FEB2018



Database Cutoff Date: 26FEB2018

Figure 22: Kaplan-Meier of Overall survival (ITT population with TPS ≥ 20%, EU subjects) - cutoff date 26-Feb-2018

Table 39: Analysis of Overall survival (ITT population with TPS =1-49%, EU subjects) - cutoff date 26-Feb-2018

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	78	62 (79.5)	939.8	6.6	9.6 (6.1, 13.7)	41.0 (30.1, 51.6)	1.26 (0.86, 1.84)	0.8775
Chemotherapy	71	48 (67.6)	1011.1	4.7	12.6 (9.9, 17.4)	52.9 (40.6, 63.7)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 26FEB2018

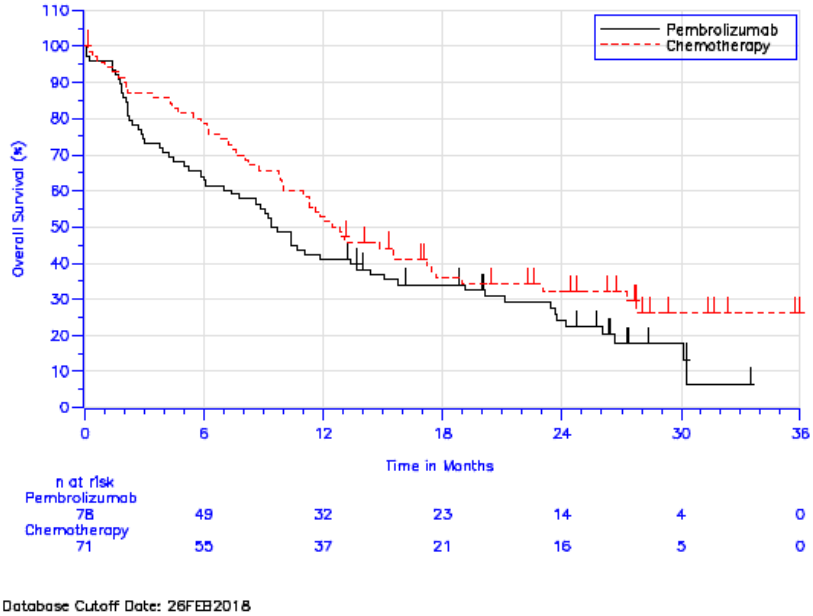
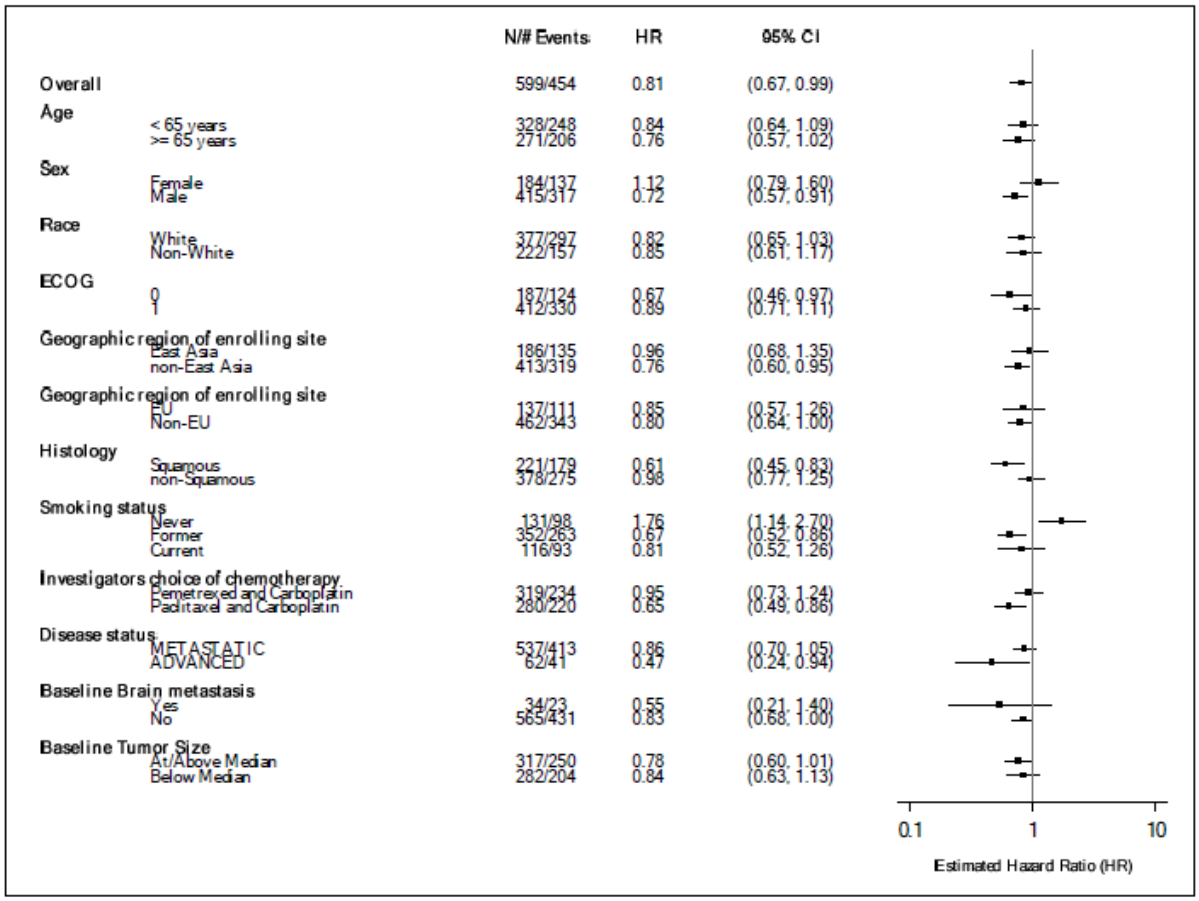


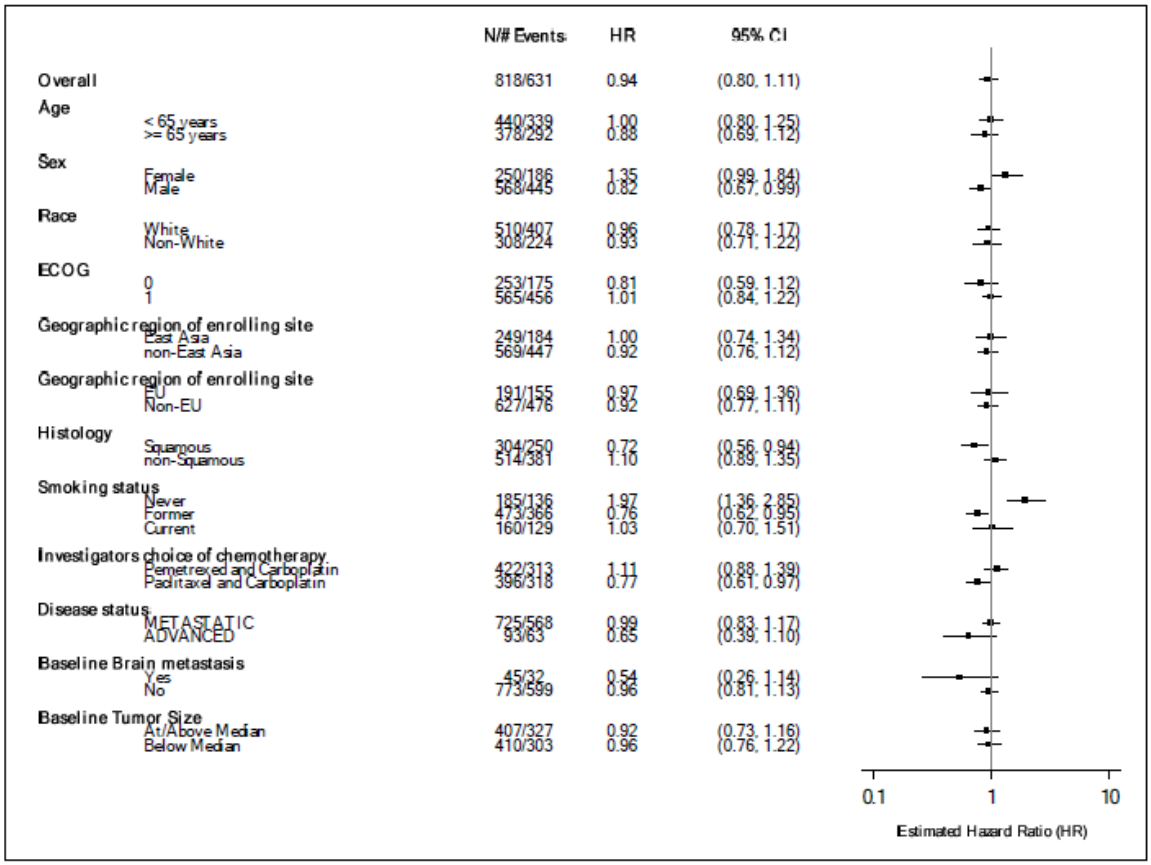
Figure 23: Kaplan-Meier of Overall survival (ITT population with TPS =1-49%, EU subjects) - cutoff date 26-Feb-2018

Progression Free Survival by other subgroup factors



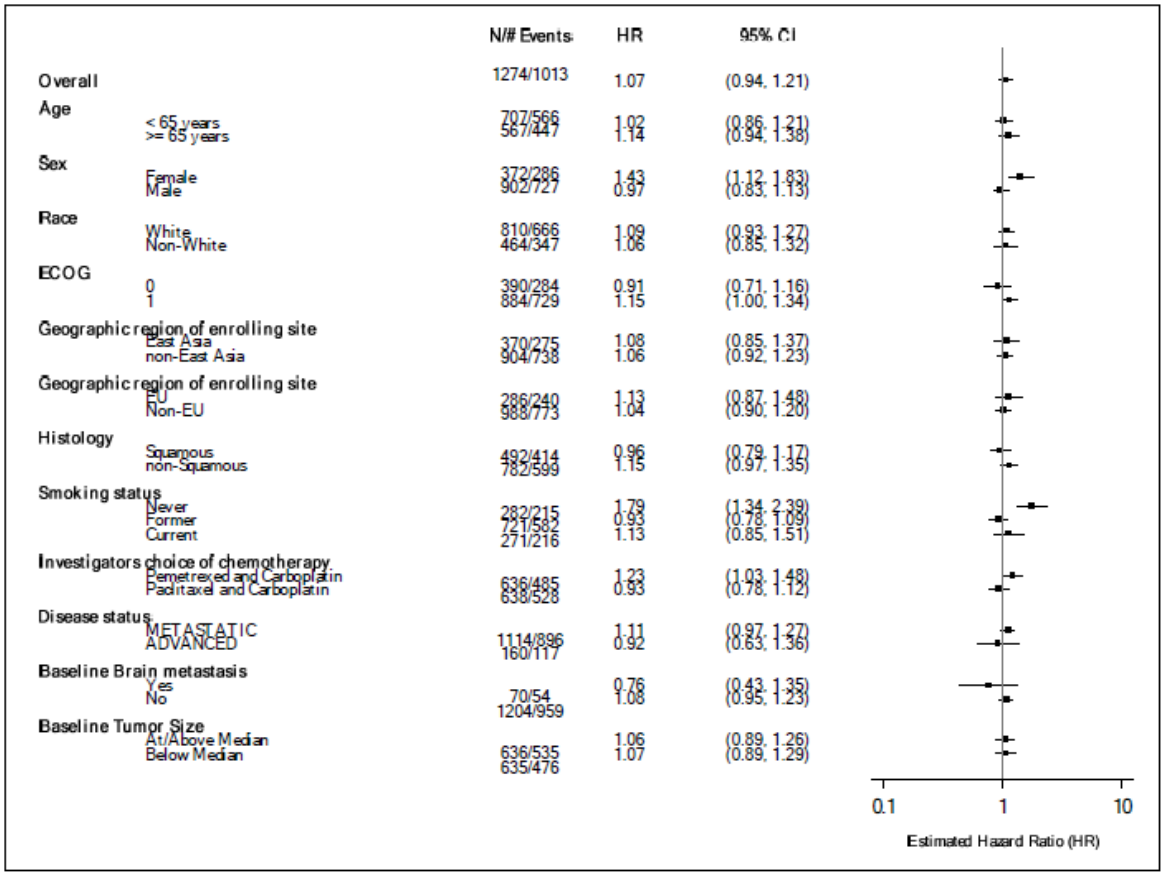
Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
For disease status, Advanced = Stage IIIA and IIIB, Metastatic = Stage IV.|Database Cutoff Date: 26FEB2018
Source: [P042V01MK3475: adam-adsl; adtte]

Figure 24: Forest plot of PFS hazard ratio by subgroup factor BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS≥50%- cutoff date 26-Feb-2018



Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
For disease status, Advanced = Stage IIIA and IIIB, Metastatic = Stage IV.|Database Cutoff Date: 26FEB2018
Source: [P042V01MK3475: adam-adsl; adtte]

Figure 25: Forest plot of PFS hazard ratio by subgroup factor BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS≥20%- cutoff date 26-Feb-2018



Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
For disease status, Advanced = Stage IIIA and IIIB, Metastatic = Stage IV.|Database Cutoff Date: 26FEB2018
Source: [P042V01MK3475: adam-adsl; adtte]

Figure 26: Forest plot of PFS hazard ratio by subgroup factor BICR assessment per RECIST 1.1 (primary censoring rule) - ITT population with TPS≥1%- cutoff date 26-Feb-2018

Summary of main study(ies)

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

Table 40: Summary of Efficacy for trial KEYNOTE-042

Title: 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			
Study identifier	EudraCT 2014-001473-14		
Design	A multicenter, international, randomized, open-label, controlled trial of pembrolizumab monotherapy versus platinum-based chemotherapy		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		21-NOV-2014 / 04-SEP-2018 / 25-OCT-2019 (data cutoff) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab		200 mg IV Q3W until 35 cycles / n= 637 (243 squamous; 394 non-squamous)
	Chemotherapy (squamous)		Carboplatin in combination with paclitaxel for a maximum of 6 cycles / n= 249
	Chemotherapy (non-squamous)		Carboplatin in combination with paclitaxel for a maximum of 6 cycles, followed by optional pemetrexed maintenance / n= 388
Endpoints and definitions	Primary endpoint	OS	Death due to any cause
	Secondary endpoint	PFS, ORR	by RECIST 1.1 as assessed by BICR
	Exploratory endpoint	DOR	by RECIST 1.1 as assessed by BICR
Data cut-off date	04-SEP-2018 (Final Analysis)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Chemotherapy	
	TPS ≥1%			
	Number of subject	637	637	
	OS (Median (months)	16.4	12.1	
	95% CI	14.0, 19.7	11.3, 13.3	
	PFS (Median (months)	5.4	6.5	
	95% CI	--	--	
	ORR (CR+PR,%)	27.3	26.5	
	DOR median (range) months	20.2 (2.1+, 31.2+)	8.3 (1.8+, 28.1)	
	TPS ≥50%			
	Number of subject	299	300	
	OS (Median (months)	20.0	12.2	
	95% CI	15.9, 24.2	10.4, 14.6	

Effect estimate per comparison			Pembrolizumab vs Chemotherapy
	OS (TPS ≥50%)	HR	0.70
		95%-CI	(0.58 – 0.86)
		P-value	0.0003
	OS (TPS ≥20%)	HR	0.77
		95%-CI	(0.65 – 0.91)
		P-value	0.0012
	OS (TPS ≥1%)	HR	0.82
		95%-CI	(0.71, 0.93)
		P-value	0.0013

	OS (TPS 1-49 %)	HR	0.91
		95%-CI	(0.77 – 1.09)
		P-value	0.1624
	PFS (TPS ≥1%)	HR	1.07
		95%-CI	(0.94, 1.21)
Notes	ITT includes patients with TPS ≥ 1%.		

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

In the attempt to define predictors of early death and clinical parameters associated with response to treatment throughout the entire duration of the follow-up, a pooled analysis was presented including the Keynote-024 dataset and subpopulation of TPS≥50% patients of KN-042.

Table 41: Pooled Data (KEYNOTE-024+ KEYNOTE-042) - Interaction Effects between Factors and Treatment Based on Multivariate Cox Regression (Pooled ITT Population - Up to Month 4)

Interaction Effect	Ratio of HR (95% CI)†	Nominal p-value†
Treatment×Liver Metastasis (Reference: Y)	0.65 (0.29, 1.46)	0.29
Treatment×Smoking Status (Reference: Never Smoker)	0.27 (0.10, 0.77)	0.01
Treatment×Ethnicity (Reference: Not Hispanic or Latino)	0.55 (0.20, 1.49)	0.24
Treatment×Prior Radiation (Reference: Y)	2.36 (0.88, 6.33)	0.09
Treatment×Disease Status (Reference: Metastatic)	0.58 (0.10, 3.39)	0.54
Treatment×Sex (Reference: Female)	0.93 (0.41, 2.14)	0.87
Treatment×Age (Reference: <65)	1.08 (0.54, 2.13)	0.83
Treatment×Histology (Reference: Squamous)	0.61 (0.28, 1.33)	0.22
Treatment×Brain Metastasis (Reference: Y)	0.23 (0.05, 1.04)	0.06
Joint Interaction Effect	---	0.06

† Ratio of HR measures the degree of heterogeneity in the treatment effect between two levels in a subgroup, with a ratio 1 indicating constant treatment effect across two levels of a subgroup. This ratio was estimated based on a multivariate cox regression model with the following covariates: treatment, liver metastasis, smoking status, ethnicity, prior radiation status, disease status, sex, age, histology and brain metastasis, and interactions between treatment and each of the above factors. Two-sided nominal p-value is based on Wald test.

‡ Cannot be estimated because there were too few deaths by month 4 in the subgroup.

Database Cutoff Date for KN042: 26FEB2018

Database Cutoff Date for KN024: 10JUL2017

Table 42: Pooled Data (KEYNOTE-024+ KEYNOTE-042) - Interaction Effects between Factors and Treatment Based on Multivariate Cox Regression (Pooled ITT Population – All data)

Interaction Effect	Ratio of HR (95% CI)†	Nominal p-value†
Treatment×Liver Metastasis (Reference: Y)	0.75 (0.48, 1.18)	0.21
Treatment×Smoking Status (Reference: Never Smoker)	0.58 (0.35, 0.97)	0.04
Treatment×Ethnicity (Reference: Not Hispanic or Latino)	0.63 (0.37, 1.09)	0.10
Treatment×Prior Radiation (Reference: Y)	1.72 (1.03, 2.85)	0.04
Treatment×Disease Status (Reference: Metastatic)	0.55 (0.25, 1.21)	0.14
Treatment×Sex (Reference: Female)	0.83 (0.56, 1.25)	0.38
Treatment×Age (Reference: <65)	0.99 (0.70, 1.42)	0.97
Treatment×Histology (Reference: Squamous)	1.12 (0.75, 1.66)	0.59
Treatment×Brain Metastasis (Reference: Y)	0.81 (0.34, 1.93)	0.63
Joint Interaction Effect	---	0.03

† Ratio of HR measures the degree of heterogeneity in the treatment effect between two levels in a subgroup, with a ratio 1 indicating constant treatment effect across two levels of a subgroup. This ratio was estimated based on a multivariate cox regression model with the following covariates: treatment, liver metastasis, smoking status, ethnicity, prior radiation status, disease status, sex, age, histology and brain metastasis, and interactions between treatment and each of the above factors. Two-sided nominal p-value is based on Wald test.

‡ Cannot be estimated because there were too few deaths by month 4 in the subgroup.

Database Cutoff Date for KN042: 26FEB2018

Database Cutoff Date for KN024: 10JUL2017

Considering the statistical significance emerged for the interaction between smoking status and treatment for both the early death time window and the full dataset, further analyses were requested in the form a 3-way interaction study to verify the contribution of other clinical parameters to these results, considering that some factors (i.e. histology and sex) generally present a typical association with the smoking status (i.e. females and non-squamous tumour prevailing within non-smokers) (see Table X).

Table 43: Three-way Interaction Analysis Between Treatment, Smoking Status and Baseline Factors Based on Multivariate Cox Regression (ITT population with TPS ≥50%)

	KN042+KN024 (TPS≥50%)				KN042 (TPS≥50%)		
	Parameter estimate	Standard error	Nominal p-value		Parameter estimate	Standard error	Nominal p-value
Joint 3-way Interaction Effect	---		0.306		---		0.610
Treatment×Smoking Status×Histology (Non-Squamous vs. Squamous)	0.99	0.47	0.034		0.91	0.49	0.063
Treatment×Smoking Status×Liver Metastasis (Y vs N)	0.74	0.42	0.074		0.61	0.47	0.198
Treatment×Smoking Status×Sex (F vs M)	0.28	0.42	0.495		0.25	0.47	0.595
Treatment×Smoking Status×Prior Radiation (N vs Y)	0.40	0.78	0.612		0.46	0.82	0.573
Treatment×Smoking Status×Ethnic (Hispanic or Latino vs. Not Hispanic or Latino)	0.21	0.56	0.712		0.14	0.56	0.800
Treatment×Smoking Status×Age Group (>= 65 vs. <65)	0.13	0.39	0.733		-0.14	0.41	0.733
Treatment×Smoking Status×Disease stage (Metastatic vs. Advanced)	0.14	0.84	0.872		0.16	0.86	0.856
Treatment×Smoking Status×Brain Metastasis (Y vs N)	NA†				NA†		

Parameter estimate, standard error and p-value are based on a multivariate cox regression model with the following covariates: treatment (pembro vs. chemotherapy), smoking status (Non-smoker vs. smoker), histology, liver metastasis status, sex, prior radiation status, ethnicity, age, disease stage, all treatment and baseline factor two-way interactions, and all three-way interactions involving treatment, smoking status and other baseline factors. Two-sided nominal p-value is based on the Wald test.

†There were not enough events in patients with brain metastasis to support the analysis of 3-way interaction.

Database Cutoff Date: 26FEB2018

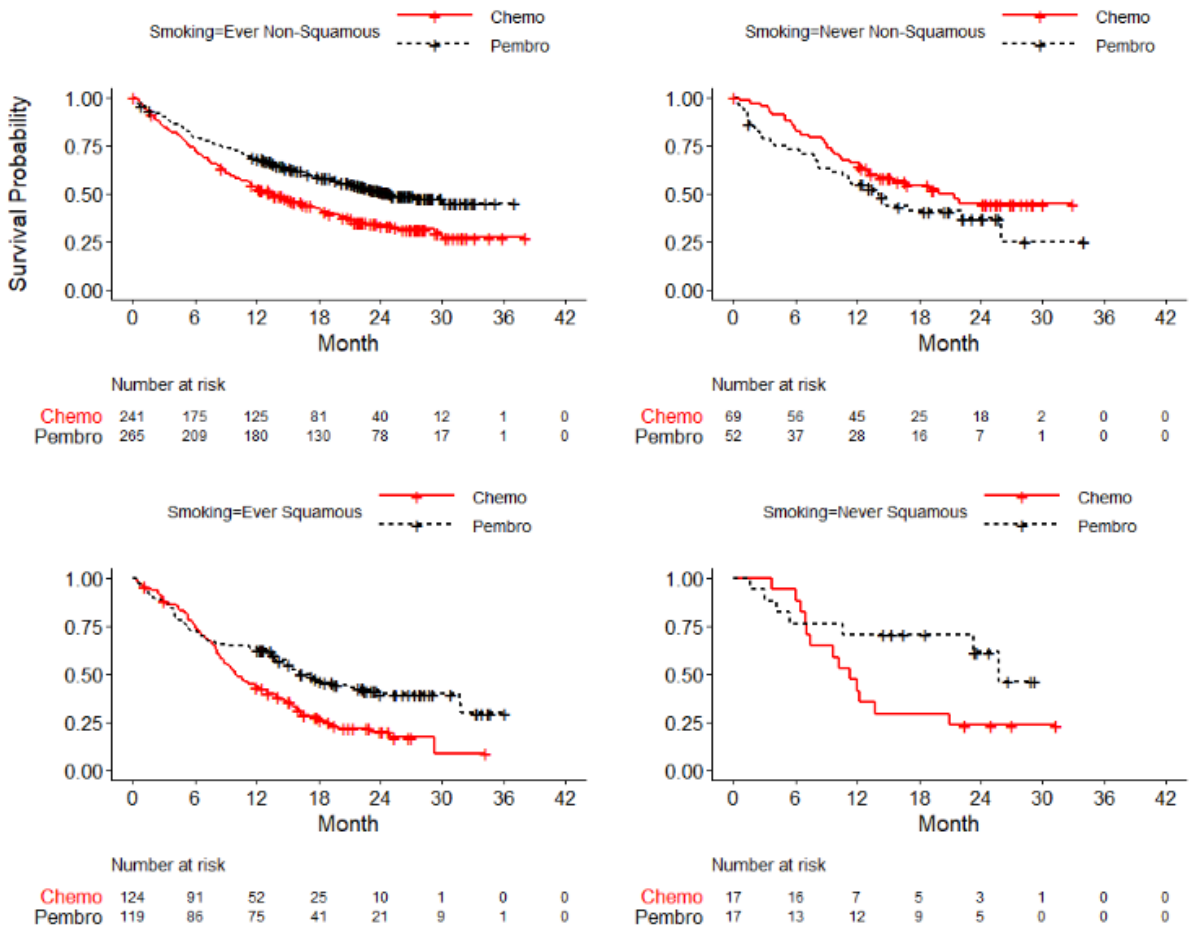


Figure 27: KEYNOTE-024 and KEYNOTE-042 - Kaplan-Meier of Overall Survival by Smoking Status and Histology (Pooled ITT Population with TPS ≥50%)*Clinical studies in special populations*

Patients >75 years of age

The pooled OS subgroup analyses of KEYNOTE-024 and KEYNOTE-042 in the TPS ⩾50% NSCLC population with age >75 years showed that pembrolizumab monotherapy improved OS over chemotherapy in the first line treatment of subjects with a TPS ⩾50% NSCLC and age >75 years.

Table 44: Analysis of Overall survival (pooled ITT population with TPS ≥50% and age>75 years) – Keynote 042 and Keynote 024

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	40	21 (52.5)	627.3	3.3	15.1 (7.9, .)	56.5 (39.7, 70.3)	0.45 (0.25, 0.80)	0.0028
Chemotherapy	38	29 (76.3)	389.8	7.4	7.6 (6.1, 11.1)	33.3 (18.8, 48.6)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS>=50% vs. TPS 1-49%) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date for KN042: 26FEB2018
Database Cutoff Date for KN024: 10JUL2017

Source: [ISE: adam-adsl; adtte]

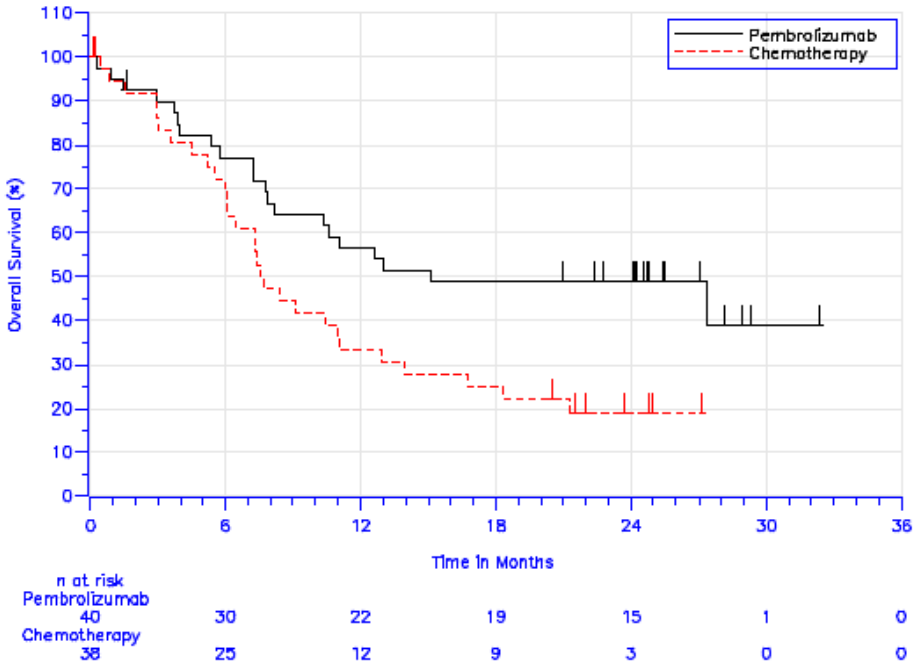


Figure 28: Kaplan-Meier of Overall survival (pooled ITT population with TPS ≥50% and age>75 years) – Keynote 042 and Keynote 024

Supportive study

The MAH presented an updated final OS analysis of KEYNOTE-024 as supportive study.

An additional 14 months of follow-up (data cutoff 10-JUL-2017) were included in the final OS compared to the prior IA2. The KEYNOTE-024 updated OS analysis presented in this submission based on the FA was not subjected to multiplicity control, because the previous analysis of OS and PFS were positive.

At the time of data cut-off, 14.9% of subjects in the pembrolizumab group and 1.3% of subjects in the chemotherapy group were continuing on their randomized study treatment, and 24.4% of subjects in the chemotherapy group remained on treatment with pembrolizumab in the crossover phase of the study. Among the subjects randomized to chemotherapy, 54% crossed over to treatment with pembrolizumab in the crossover phase of the study, as specified within the protocol. In the crossover phase, 45% of these crossover subjects received pembrolizumab for ≥6 months and 21% received pembrolizumab for ≥12 months. Another 8% of subjects in the chemotherapy group received immunotherapy as second-line therapy outside the context of the study.

Table 45: Key efficacy findings of Keynote-024 – ITT population

Endpoint (analysis)	Treatment group	N	Median (95%CI)	HR (95% CI) or Difference ORR (95% CI)	p-value
OS (FA)	Pembrolizumab	154	30.0 (18.3, .)	0.63 (0.47, 0.86)	0.002*
	Chemotherapy	151	14.2 (9.8, 19.0)		
OS (IA2)	Pembrolizumab	154	Not reached (., .)	0.60 (0.41, 0.89)	0.005†
	Chemotherapy	151	Not reached (9.4, .)		
PFS by BICR (IA2)	Pembrolizumab	154	10.3 m (6.7, .)	0.50 (0.37, 0.68)	<0.001†
	Chemotherapy	151	6.0 m (4.2, 6.2)		
ORR by BICR (IA2)	Pembrolizumab	154	44.8% (36.8, 53.0)	16.6% (6.0, 27.0)**	0.0011‡
	Chemotherapy	151	27.8% (20.8, 35.7)		

BICR= blinded independent central radiologist review; CI= confidence interval; FA = final planned analysis (data cutoff: 10-JUL-2017); HR= hazard ratio; IA2= interim analysis 2 (primary alpha-controlled analysis; data cutoff: 09-MAY-2016); m= months; ORR= objective response rate; OS= overall survival; PFS= progression-free survival.

* One-sided p-value based on log-rank test; not formally tested, as statistical significance was established at IA2

† One-sided p-value based on log-rank test

** Difference (95% CI).

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

Additional statistical methods used can be found in the CSR source tables [Ref. 5.3.5.1: P024V02MK3475: 11].

Source: [Ref. 5.3.5.1: P024V01MK3475: 11] [Ref. 5.3.5.1: P024V02MK3475: 11].

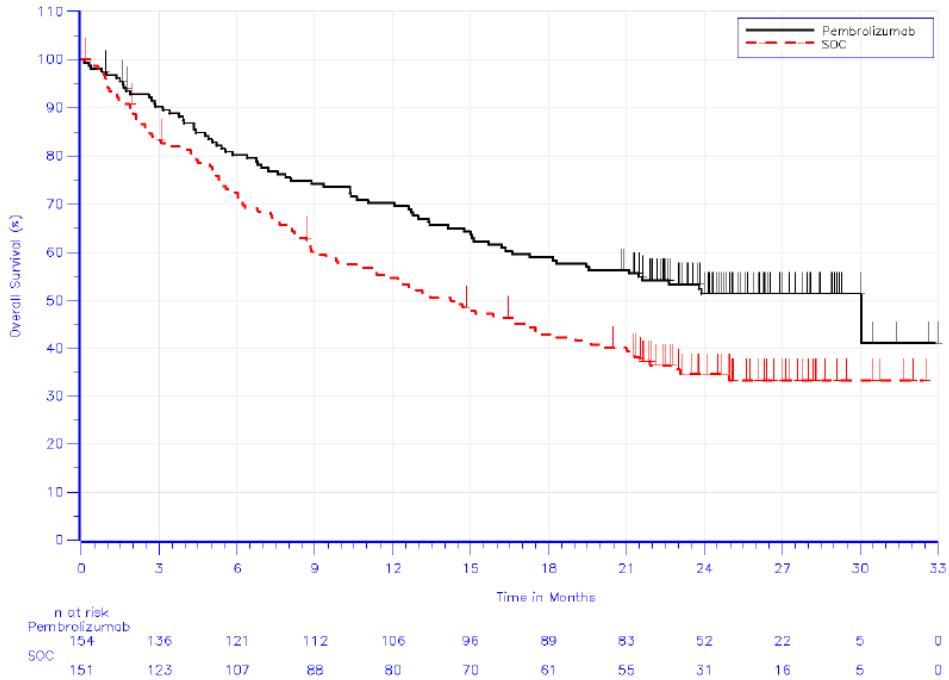


Figure 29: Kaplan-Meier of Overall survival (ITT population with TPS ≥50%) –Keynote 024

The key aspects in terms of study design, subject characteristics (TPS≥50%), and efficacy results of the two studies KEYNOTE-042 and KEYNOTE-024 are summarised below.

Table 46: Key design features of protocols Keynote 042 and Keynote 024

	KEYNOTE-042	KEYNOTE-024
Study Phase	3	3
Sample Size	1274	305
Dose	200 mg Q3W	200 mg Q3W
Prior exposure to platinum therapy	treatment-naive	treatment-naive
***EGFR* or *ALK* genomic tumor aberrations**	no	no
Prior Lines of Therapy	none	none
PD-L1 Status	TPS ≥1%	TPS ≥50%
PD-L1 Assay	Dako	Dako
Randomization	1:1 pembrolizumab vs chemotherapy	1:1 pembrolizumab vs chemotherapy
Enrollment Period	19-DEC-2014 to 06-MAR-2017	05-SEP-2014 to 29-OCT-2015
Source: [Ref. 5.3.5.1: P042V01MK3475: 16.1.1], and [Ref. 5.3.5.1: P024V02MK3475: 16.1.1]		

Table 47: Comparison of subject characteristics in Keynote-042 versus Keynote-024 (ITT population with TPS≥50%)

	KEYNOTE-042		KEYNOTE-024	
	Pembrolizumab	**Chemotherapy**	**Pembrolizumab**	**Chemotherapy**
Sex (male)	68.6%	70.0%	59.7%	62.9%
Age (median, years)	63.0	64.0	64.5	66.0
ECOG PS 1	67.9%	69.7%	64.3%	64.9%
Histology (squamous)	35.8%	38.0%	18.8%	17.2%
Smoking status (never)	21.4%	22.3%	3.2%	12.6%
Region (East Asia)	30.8%	31.3%	13.6%	12.6%
Baseline tumor size (mean, mm)	110.5	115.5	91.4	100.1
Baseline tumor size ≥ population median	51.8%	54.0%	47.4%	50.3%
≥3 sites of metastasis	54.2%	53.7%	55.8%	52.3%
Number of lesions (mean)	5.2	5.4	4.7	5.0
Brain metastases (yes, %)	6.4%	5.0%	11.7%	6.6%
Liver metastases (yes, %)	16.4%	17.0%	13.0%	23.8%

Source: [Table 84] and [Table 85]

Table 48: Comparison of efficacy results across studies in the population with TPS≥50%

Endpoint	KEYNOTE-042*		KEYNOTE-024**	
	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy
OS (median months, 95% CI)	20.0 (95% CI: 15.4, 24.9)	12.2 (95% CI: 10.4, 14.2)	30.0 (18.3, ,)	14.2 (9.8, 19.0)
PFS (median months, 95% CI)	7.1 (95% CI: 5.9, 9.0)	6.4 (95% CI: 6.1, 6.9)	10.3 (6.7, not reached)	6.0 (4.2, 62)
ORR (%, 95% CI)	39.5% (95% CI: 33.9,45.3)	32% (95% CI: 26.8,37.6)	44.8% (36.8, 53.0)	27.8% (20.8, 35.7)
DOR (median months, range)	20.2 (2.1+ to 31.2+)	8.3 (1.8+ to 28.1+)	Not reached (1.9+ - 14.5)	6.3 (2.1+, 12.6+)

Abbreviations: DOR=Duration of response; ORR=Overall response rate; OS=Overall survival; PFS=Progression-free survival; TPS=Tumor proportion score.

Note: KN024 only enrolled subjects with TPS ≥50% NSCLC, whereas KN042 enrolled subjects with TPS ≥1% NSCLC. Only results from subjects with TPS ≥50% NSCLC from KN042 are presented for comparison in this table.

*For KN042, OS and PFS were formally tested; ORR and DOR are nominal results.
**For KN024, results for OS are from the final planned analysis (data cutoff: 10-JUL-2017). Results for PFS, ORR, and DOR are from the second interim analysis when statistical significance was first shown for the primary endpoints of PFS and OS (data cutoff: 09-MAY-2016).

Additional statistical methods used can be found in the CSR source tables [Ref. 5.3.5.1: P024V01MK3475: 11] [Ref. 5.3.5.1: P024V02MK3475: 11] [Ref. 5.3.5.1: P042V01MK3475: 11].

The piecewise hazard ratio analysis was conducted for KEYNOTE-024 and consistently favoured pembrolizumab over chemotherapy starting from months 0 to 2.

Table 49: Piecewise hazard ratio for overall survival in Keynote-024 (ITT population)

Month	Pembrolizumab(N=154)		Chemotherapy(N=151)		HR
	Event	Rate	Event	Rate	
0 to 2	11	0.037	16	0.056	0.66
2 to 4	9	0.033	12	0.048	0.68
4 to 6	10	0.040	13	0.057	0.69
6 to 8	7	0.030	10	0.050	0.60
9+	36	0.022	45	0.039	0.57
Database Cutoff Date: 10JUL2017					

Source: [P024V02MK3475: adam-adsl; adtte]

Since no obvious cut-off was identified for Keynote-024, a 4-month cut-off similar to those used in the TPS ≥50% subgroup of Keynote-042 was used to provide a comparison of all the baseline potential risk factors.

Table 50: Comparison of subject characteristics in Keynote-042 versus Keynote-024 (ITT population with TPS≥50%) – subjects who died or censored before 4 months

	KEYNOTE-042		KEYNOTE-024	
	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy
Sex (male)	74.1%	83.3%	56.5%	71.0%
Age (median, years)	58.5	64.5	65.0	66.0
ECOG PS 1	85.2%	85.7%	78.3%	87.1%
Histology (squamous)	35.2%	33.3%	21.7%	19.4%
Smoking status (never)	27.8%	16.7%	4.3%	3.2%
Region (East Asia)	24.1%	21.4%	8.7%	9.7%
Baseline tumor size (mean, mm)	140.3	148.9	97.7	142.5
Baseline tumor size ≥ population median	68.5%	71.4%	56.5%	74.2%
≥3 sites of metastasis	66.7%	64.3%	65.2%	67.7%
Number of lesions (mean)	5.6	7.0	5.3	5.2
Brain metastases (yes, %)	7.4%	0.0%	21.7%	12.9%
Liver metastases (yes, %)	35.2%	16.7%	13.0%	32.3%

Source: [Table 79] and [Table 82]

Table 51: Interaction effects between factors and treatment in multivariate Cox regression (ITT population)

Interaction Effect	Ratio of HR‡	Two-sided p-value‡
Treatment×Baseline Tumor Size (Reference: >= Median)	1.29	0.44
Treatment×Number of Metastasis Sites (Reference: >=3)	0.74	0.38
Treatment×Liver Metastasis (Reference: Y)	0.69	0.35
Joint Interaction Effect	---	0.52
‡ Based on multivariate cox regression model with treatment, baseline tumor size, number of metastasis sites, liver metastasis, treatment and baseline tumor size interaction, treatment and number of metastasis interaction, and treatment and liver metastasis interaction as the covariates stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). Two-sided p-value based on stratified Wald test.		
Database Cutoff Date: 10JUL2017		

Source: [P024V02MK3475: adam-adsl; adtte]

Similar results were observed for the analysis of OS up to month 4, in which the OS HR (0.67) was consistent with the OS for the entire follow-up period (0.63) and no effects of tumour burden or liver metastasis, nor their interactions with treatment, were observed.

Table 52: Multivariate Cox regression analysis for overall survival (ITT population)

Covariate	Hazard Ratio‡ (95% CI)‡	p-Value‡
Treatment		
Pembrolizumab vs. Chemotherapy (reference)	0.61 (0.45, 0.84)	0.001
Baseline Tumor Size		
< Median vs. >= Median (reference)	0.87 (0.64, 1.20)	0.201
Number of metastasis sites		
<3 vs. >=3 (reference)	0.63 (0.45, 0.88)	0.003
Liver Metastasis Status at Baseline		
N vs. Y (reference)	1.00 (0.68, 1.47)	0.497
‡ Based on multivariate cox regression model with treatment, baseline tumor size and number of metastasis sites, and liver metastasis as the covariates stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), and histology (squamous vs. non-squamous). One-sided p-value based on stratified type III Wald test. Database Cutoff Date: 10JUL2017		

Source: [P024V02MK3475: adam-adsl; adtte]

Table 53: Analysis for overall survival (ITT population, up to 4 months)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 4 in %† (95% CI)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	154	20 (13.0)	569.1	3.5	Not Reached (., .)	86.8 (80.3, 91.3)	0.67 (0.37, 1.18)	0.0808
SOC	151	28 (18.5)	534.3	5.2	Not Reached (., .)	81.2 (74.0, 86.7)	---	---
† From product-limit (Kaplan-Meier) method for censored data. ‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). ‡‡ One-sided p-value based on stratified log-rank test. Database Cutoff Date: 10JUL2017								

Source: [P024V02MK3475: adam-adsl; adtte]

Table 54: Multivariate Cox regression analysis for overall survival (ITT population, up to 4 months)

Covariate	Hazard Ratio‡ (95% CI)‡	p-Value‡
Treatment		
Pembrolizumab vs. Chemotherapy (reference)	0.68 (0.38, 1.22)	0.097
Baseline Tumor Size		
< Median vs. >= Median (reference)	0.58 (0.31, 1.08)	0.043
Number of metastasis sites		
<3 vs. >=3 (reference)	0.62 (0.33, 1.16)	0.067
Liver Metastasis Status at Baseline		
N vs. Y (reference)	0.93 (0.46, 1.85)	0.414
‡ Based on multivariate cox regression model with treatment, baseline tumor size, number of metastasis sites and liver metastasis as the covariates stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). One-sided p-value based on stratified type III Wald test. Database Cutoff Date: 10JUL2017		

Source: [P024V02MK3475: adam-adsl; adtte]

2.4.3. Discussion on clinical efficacy

In the NSCLC indication, pembrolizumab monotherapy is already approved for the first-line treatment of locally advanced or metastatic disease in PD-L1 highly positive patients (≥50% TPS) with no EGFR or ALK positive tumour mutations and in PD-L1 positive patients (≥1% TPS) who have received at least one prior chemotherapy regimen, including approved target therapy for EGFR and ALK aberrations in case of positive tumour mutations. Pembrolizumab in combination with platinum-based chemotherapy and pembrolizumab in combination with carboplatin/(nab)paclitaxel were also recently approved for the treatment of, respectively, non-squamous and squamous NSCLC treatment-naïve patients, regardless of PD-L1 expression.

This application has been submitted to extend the Keytruda indication to the treatment of PD-L1 positive (1% TPS) advanced and metastatic NSCLC in treatment naïve patients.

Design and conduct of clinical studies

KN-042 is a Phase 3 randomised, open-label, clinical study testing the efficacy and safety profile of pembrolizumab against standard of care (i.e. platinum-based doublets) in treatment-naïve advanced or metastatic NSCLC patients, including both squamous and non-squamous histology, who present with

ALK/EGFR negative disease and a level of PD-L1 tumour expression (TPS) ≥1%. The MAH initially submitted data derived from the IA2 with a date cut-off of 26-FEB-2018. During the procedure results were updated based on the planned final analysis (data cut-off of 4-SEP-2018); an additional extended OS analysis was presented, with cut-off date of 25-OCT-2019. In addition, the final OS analysis of KN-024 was submitted, i.e. the pivotal trial based on which pembrolizumab was approved in the first-line setting of NSCLC with TPS≥50%. Although being considered by the MAH supportive to the current application, KN-024 does not provide additional efficacy data on NSCLC patients with a TPS score between 1-49%, which is the population of interest to the sought extension of indication. Nevertheless, an indirect comparison between KN-024 and KN-042 offers important points for discussion in terms of overall clinical performance of pembrolizumab monotherapy in NSCLC patients with TPS≥50%.

The choice of platinum-based doublets as comparator reflects the currently recommended standard-of-care; however, pemetrexed maintenance was optional for patients with non-squamous histology, despite current recommendations which could have led to an underperformance of the chemotherapy arm. In the study, 23.5% of the non-squamous patients who were assigned to the control group and started treatment did not receive pemetrexed maintenance because maintenance was not planned/specified at the time of randomization.

As regards the open-label nature of the clinical trial, it should be acknowledged that the risk of bias was mitigated by the choice of the primary endpoint OS, and the blinded independent review of radiographic imaging based on which the secondary endpoints PFS and ORR were defined.

The calculation of the sample size, which was based on hypotheses formulated within the TPS≥50% population, is deemed adequate.

Histology subtype (squamous vs non-squamous), PD-L1 expression status (based on TPS score of 50% as the cut-point level) were among the randomisation factors (in addition to ECOG PS and geographic region). The allocation to the experimental therapy (pembrolizumab) or the comparator arm was therefore well balanced as regards these clinical variables for a proper statistical analysis. However, while the randomisation was stratified based on a TPS score ≥ 50% or < 50%, the OS analysis by an intermediate cut-off value of ≥20% with a step-down to TPS ≥1% was added with protocol amendment 3. The MAH specified that the intermediate cut-off point of TPS⩾20% was selected based on a B-value plot of data from a different trial, Study KEYNOTE-010. In particular, the cut-off of 20% was chosen because its corresponding relative treatment effect (distance to diagonal line) was relatively similar to that observed at TPS ⩾50% (the maximum distance from the diagonal line).

The study design was amended in several occasions with a change in the target number of events from the initial 354 OS events to 340 (Amendment 03), and finally 398 events (Amendment 06). The supposed HR in the TPS ≥ 50% population changed from 0.70 to 0.65. No sensitivity analysis was planned to handle missing data for the primary efficacy endpoint.

Efficacy data and additional analyses

The study population of the pivotal study KN-042 (1274 patients in total, 637 each in the pembrolizumab and control arm) can be considered overall representative of the population targeted by the sought indication with regard to disease staging (87.4% stage IV, 10.8% stage IIIB and 1.8% stage IIIA) and histology (61.7% non-squamous and 38.6% squamous).

Baseline characteristics as well as demographics appear well balanced between treatment arms in the ITT population (TPS≥1%). Demographics and disease characteristics were also similar between experimental and control groups as stratified by the PD-L1 cut-off levels, with the exception, within both the TPS≥20% ≥50% groups, of a slight difference in tumour sizes above the ITT median between arms (50.7% vs 38.7% and 51.8% vs 40.7% in the pembrolizumab and control, respectively). The prevalence

of the different PDL-1 score within the study population is adequately representative of the distinct categories (35.2% and 36.4% in the pembrolizumab and control arm for TPS 1-19%; 17.9% and 16.5% in pembrolizumab and control group for TPS 20-49%; 46.9% and 47.1% in pembrolizumab and control group for TPS ≥50%), thus rendering the efficacy analysis by TPS numerically appropriate. Nevertheless, a remarkable low number of females is included in the study. Due to the exclusion of patients with EGFR or ALK positive tumour mutations, no data are available for this group of patients. Moreover, data are restricted to patients with good performance status and adequate organ functions.

At the IA2 (cut-off date: 26-Feb-2018), the median duration of follow-up was 13.4 months and 12.2 months for pembrolizumab and chemotherapy. The comparison between pembrolizumab and SoC within the ITT population comprising all patients with a TPS≥1% demonstrated superiority of pembrolizumab vs SoC, with a gain of 4 months in median OS and HR 0.81 (95% CI: 0.71, 0.93; p=0.0018). As expected, the clinical benefit of pembrolizumab over chemotherapy increased by PD-L1 score, with the highest advantage in OS being observed in the TPS ≥ 50% subcategory (a gain of 8 months with HR 0.69;95% CI: 0.56, 0.85; p=0.0003), which slightly decreased in the TPS ≥ 20% group (a gain of around 4 months in OS with HR 0.77;95% CI: 0.64, 0.92; p=0.0020). These results were achieved with an OS maturity of 89.9% at IA2.

During the procedure, the MAH provided results of the final analysis (data cutoff: 04-Sep-2018), with additional 6 months of follow-up compared to IA2. Overall, the final analysis results confirmed previous findings from IA2. Moreover, an extended OS analysis with cutoff date of 25-Oct-2019 was submitted, providing 14 months of additional follow-up from the last reported protocol-specified FA. These newly presented data consolidate the previous analyses showing a long-term benefit of pembrolizumab compared to chemotherapy in terms of OS gain within the ITT population, with the magnitude of the long-term benefit being dependent upon PD-L1 level of expression.

Differently from what had been observed in KN-024, in which the KM curves for OS demonstrated continuous separation from Month 1 favouring pembrolizumab, KN-042 showed an initial advantage of SoC over pembrolizumab with a crossing of OS KM curves at Month 8 that was reported in the ITT population. Importantly, such higher risk of early death is evident also for the TPS ≥ 50% subgroup, with OS KM curves crossing at month 7 (see below risk of early death).

Unlike study KN-024, the analysis of PFS as assessed by BICR in study KN-042 within the TPS ≥ 50% group did not show a statistically significant benefit of pembrolizumab over chemotherapy (HR=0.81, 95% CI 0.67-0.99; p=0.0170 for a tested p-value=0.01455). Although a trend towards a more advantageous overall effect of pembrolizumab vs control can be recognised, the Kaplan-Meier curves of PFS show an early separation in favour of chemotherapy up to Month 6, when the curves cross. The HR was 0.94 (95% CI 0.80-1.11) in TPS ≥20% and 1.07 (95% CI 0.94 -1.21) in TPS ≥1%. Investigator-based analyses were consistent with the independent data review.

Similarly, no statistically significant superiority of pembrolizumab over chemotherapy was demonstrated in ORR (CR+PR, 39.5% vs 32%), while disease control rate (CR+PR+SD) was higher for chemotherapy, regardless of the level of PD-L1 expression, even in the TPS ≥50% subgroup (76.3% vs 68.9%). A progressive decline in ORR was observed according to a reduction in TPS score, so that in the ITT population (TPS ≥1%) an even more marked advantage of SoC vs pembrolizumab was reported in terms of disease control rate (78.8% vs 65.9% in chemotherapy and pembrolizumab, respectively). However, responders to pembrolizumab had a longer response duration compared to the control group (20.2 months vs 8.3 months in median). Data were confirmed by investigator-based analyses.

As regards PFS2, pembrolizumab performed better than chemotherapy in all TPS categories.

Efficacy data in TPS 1-49% NSCLC subgroup

Even though an optimal cut-off was not known when the studies were designed, a relationship between PD-L1 expression level and pembrolizumab activity was known: the principle outlined in several SAs on the need to provide enough evidence in the complementary PD-L1 expression subgroups when it was expected that results in the overall population could be driven by the most responsive subgroup should have been followed.

The MAH provided OS subgroup analysis for TPS 1-49% that was pre-specified in the protocol, although as exploratory, which is considered relevant in the context of this extension of indication from TPS≥50% to TPS≥1% NSCLC patients. The overall effect (OS HR=0.81, 95%IC: 0.71-0.93) in the ITT population (TPS≥1%) seems to be driven by the strong effect observed in the TPS≥50% group (HR=0.69, 95%CI 0.56-0.85). The first part of the OS KM curves for the TPS 1-49% subgroup favoured chemotherapy, and then the curves started to approach one another and crossed around Month 10 (see also discussion on risk of early death).

PFS in TPS 1-49% NSCLC appears clearly in favour of the standard treatment (HR 1.32, 95%CI 1.12, 1.56, median PFS 4.2 vs 6.8 months). Of note, DOR in this subgroup is doubled compared to control, with median DOR: 17.4 vs 8.2 months. Nevertheless, the number of responders was lower in the pembrolizumab group vs. the chemotherapy group with response rates of 16.5% vs 21.3%, respectively.

Overall, no superiority of pembrolizumab over chemotherapy could be detected. The MAH stated that the exploratory subgroup analysis for TPS 1-49% was pre-specified in the protocol but was underpowered and formal hypothesis testing was not planned in the SAP. This is not agreed, since patients with TPS 1-49% contributed to 53% of the study population, and 56% of the total deaths occurred in this group. Therefore, it is considered that the study provided a reliable estimate of treatment effect in the TPS 1-49% population.

Risk of early death

The fact that the survival curves crossed around month 6 in all TPS groups not only poses a methodological concern in using the Cox model for the primary analysis, but also raises doubts on the opportunity to express the treatment effect over time with an overall HR. In light of the statistical hypotheses that underly the study, the MAH was asked to provide the treatment effect before month 6 and after month 6 for all the three TPS groups and provide the additional sensitivity analyses planned to address the issue of the violation of proportional hazards.

The provided HRs were above 1 for both OS and PFS before 6 months, and below 1 after 6 months, across all TPS scores. Restricted mean survival time (RMST) was provided as protocol pre-specified sensitivity analysis in the event of proportional hazard (PH) violation. The RMST is, in fact, suitable even in the absence of PH. According to the RMST analyses, for TPS≥1%, the OS was not statistically different till month 18, with only a modest improvement after 24 months (1.17 months) and 30 months (1.76 months) of follow up. No improvement in PFS was observed. The same considerations apply to the TPS≥20% subgroup where the OS improved by 1.33 months after 24 months and 1.91 months after 30 months of follow up. This sensitivity analysis is not supporting a clinically significant effect of pembrolizumab in the TPS≥1% population. On the contrary, a long-term benefit of pembrolizumab on both PFS and OS can be recognised in the TPS≥50% subgroup with a gain of 2.81 months in OS after 30 months of follow-up. However, no effect was observed up to 6 months of follow-up, and between 12 and 18 months of therapy the OS improvement achieved with pembrolizumab is marginal (data not shown). The first part of the OS KM curves for the TPS 1-49% subgroup favour chemotherapy, and then the curves start to approach one another and cross around Month 10. A piecewise hazard rate analysis revealed a detrimental effect of pembrolizumab vs chemotherapy during the first 3 months of treatment (HR of 1.29, 1.95 and 2.13 at Month 1, 2 and 3 respectively) in this subgroup, with a total of 66 OS events occurring in the experimental arm vs 37 in the control arm. A comparison of the baseline

characteristics between treatment arms showed some slight unbalance in tumour size (under/above ITT median; 49.7% vs 44.8% in pembrolizumab and control, respectively), metastasis sites (≥3 or less than 3; 54.4% vs 49% in pembrolizumab and control, respectively) and liver metastasis (17.2% vs 13.1% in pembrolizumab and control, respectively) that could have favoured chemotherapy in the first 3 months.

The observed crossing of OS KM curves in the TPS≥50% subgroup is relevant for the currently approved indication and a similar piecewise hazard rate analysis was requested for this subgroup. The monthly piecewise hazard rate demonstrated a higher risk in pembrolizumab compared to chemotherapy in the first two months and at month 4, with HR 1.69, 1.94 and 1.84 respectively. Therefore, the MAH has selected the 4-month cutoff for the evaluation of baseline potential risk factors in the TPS ≥50% subgroup which is acceptable. The MAH identified some variables indicative of burden of disease as predictors of early deaths since they were more common in patients who died before 4 months vs after 4 months (baseline tumour size, number of metastasis sites, and liver metastasis status at baseline). Consequently, an adjusted Cox model was run with these factors used as covariates.

The MAH performed additional post-hoc analyses in the ITT population, and in both TPS 1-49% and TPS>=50% groups, in order to identify factors/combination of factors able to explain the early crossing of curves. The max-combo test was also suggested, to take into account the PH violation in detecting differences in survival between subgroups identified by possible combination of factors. The MAH also performed the random forest classification for TPS 1-49% population.

The MAH concluded that in subjects with TPS ≥50% and ≥1% NSCLC, baseline liver metastasis and never smoker status appeared to predict poorer response to pembrolizumab monotherapy in the initial 4 months of treatment, and the observed OS benefit of pembrolizumab monotherapy over chemotherapy was improved by excluding these subjects from the analysis.

A more evident unbalance in tumour sizes above the ITT median was observed between treatments within both the TPS≥20% (50.7% vs 38.7%) and TPS≥50% groups (51.8% vs 40.7% in pembrolizumab and control, respectively).

In the TPS 1-49% subgroup, no definitive factors predictive of early mortality were identified with the proposed in-depth analyses and the Random Forest analysis identifying the tumour burden as the most important predictive factor, corroborating findings of the previous analyses. However, some factors were excluded from these analyses and some indications of interaction between factors and treatment were not adequately explored. Several factors were indicated that seem to be associated to an increased risk of Pembrolizumab compared with chemotherapy, but they were not adequately explored. Furthermore, these analyses are limited due to the exploratory nature, the lack of multiplicity control, and the limited number of events occurring in the first months. Additionally, factors indicated by the CHMP to be associated with an increased risk of early death with pembrolizumab treatment compared with platinum-doublet chemotherapy were included in a multivariate model to further explore treatment interaction for the dataset restricted to early death window and for the full dataset. Contradicting results in terms of potential predictive factors were observed in TPS 1-49% and TPS≥50% subgroups, making any statement on the ITT population of TPS≥1% inconclusive.

Overall, no clear explanation, even from the biological perspective, was provided for the early death observation. The provided data do not to alleviate the CHMP concerns on the higher risk of early death observed with pembrolizumab monotherapy vs SoC in this setting. This is even more relevant for the TPS 1-49% group for which no clear long-term benefit has been observed, making the uncertainty on the short-term outcome not acceptable.

For both the TPS-1-49% and TPS≥50% subgroups, the MAH was also asked to investigate the cause of death for each of the OS events occurring in each arm before the crossing of the K-M OS curves, and, separately, for those occurring in the timeframes in which a higher risk of death for pembrolizumab was

identified based on piecewise hazard rate analyses (e.g. 3 months for the TPS 1-49% subgroup). The main cause of death during both the follow-up period before the K-M OS curve crossing (10.3 months for TPS 1-49% and 6.7 months for TPS≥50%) and the first months of therapy that were unfavourable for pembrolizumab as based on piecewise HRs (3 months for TPS 1-49% and 4 months for TPS≥50%), was malignant progression. More cases of malignant progression were reported in the pembrolizumab arm in the two distinct PD-L1 level of expression subpopulations (TPS≥50%: 34/299 [11.4%] vs 24/300 [8%] before 4 months; TPS 1-49%: 33/338 [9.8%] vs 19/337 [5.6%] before 3 months). Although the benefit/risk balance of pembrolizumab in the TPS ≥50% population is not questioned, the higher number of deaths within 4 months of treatment initiation has been included in sections 4.4 and 5.1 of the SmPC.

An additional analysis was run to compare the baseline characteristics of patients who died/were censored within the first 3 months and those who survived for at least 3 months, in order to identify risk factors for early death. Since the variables identified by the MAH as risk factors for early death were the same for which an unbalance at baseline was observed, a multivariate Cox model using a stepwise selection was performed, by using the baseline characteristics identified above as well as other factors known to be prognostic in NSCLC. The model was applied to the entire follow-up period, and therefore the totality of the events, and resulted in an improvement of the HR from 0.92 to 0.83. In order to better understand how much the higher risk in treatment group in the first 3 months could be explained by this bias, the MAH was asked to limit the multivariate analysis to the first 3 months of follow-up only. The MAH has conducted a data analysis limited to the initial period of treatment when a major risk of fatalities for pembrolizumab was observed. A multivariate analysis was conducted for the first 3 (TPS 1-49%) and 4 months (TPS ≥50% and TPS ≥1%) of follow-up only. Additional analyses were conducted using both the Cox regression model and Random Forest for early death, in order to test several factors for treatment interaction within the early time window as well as the full dataset. However, results were somewhat inconsistent across PD-L1 subgroups not allowing to identify credible predictive factors of high risk of early death or overall response to pembrolizumab. This is even more relevant for the TPS 1-49% in which no clear long-term benefit has been observed, making the uncertainty on the short term outcome not justified.

The analysis performed in subjects with TPS≥50% were requested to be replicated in study KN024 in order to get all the available information. Moreover, for a better understanding of the inconsistency between study KN042 and KN024, the MAH was asked to provide a comparison of the risk factors, especially those found to correlate to risk of early death between the two trials, by treatment group. The between-arm comparison in KEYNOTE-024 of the clinical characteristics of subjects who died/were censored before 4 months revealed an opposite trend in the distribution of factors associated with higher tumour burden including baseline tumour size and liver metastasis (more frequent in the chemotherapy than pembrolizumab group) with respect to the observed frequency of these in KEYNOTE-042 (more frequent in pembrolizumab than chemo). Consistent with this, more patients among those treated with pembrolizumab and who died/were censored before 4 months had liver metastasis at baseline in KEYNOTE-042 (35.2% vs 16.7% in the chemo arm) compared to KEYNOTE-024 (13.0% vs 32.3% in the chemo arm). Although with a less pronounced difference, an unbalance between trials was observed also in tumour burden>median (68.5% vs 56.5% in KEYNOYE-042 vs KEYNOTE-024 respectively in the pembrolizumab group with a similar rate in their respective chemo arms: 71.4% and 74.2%). Moreover, a higher tumour size at baseline characterised patients in the pembrolizumab group of KEYNOTE-042 (140.3 mm in mean) compared to KEYNOYE-024 (97.7 mm in mean), with a similar value in the chemo group of the two trials (148.9 and 142.5 mm). The MAH reported no interaction or influence of these parameters indicative of aggressive disease on OS HR in the individual analysis of KEYNOTE-024 during both, the entire follow-up period and the first 4 months of treatment. However, it is acknowledged that the different distributions of these factors between KEYNOTE-024 and KEYNOTE-042 could potentially explain the difference in outcomes observed between the two studies. The MAH explored factors

identified in subjects with TPS ≥50% NSCLC KN-042 as predictor of higher risk of early death in Pembrolizumab group compared with chemotherapy, also in the study KN-024. In this study the crossing of curves was not observed and therefore the analysis was limited to the first 4 months only for uniformity. Exploration of factors/combination of factors identified in subjects with TPS ≥50% NSCLC from KEYNOTE-042 in KEYNOTE-024 did not demonstrate consistent findings. A possible explanation could be the different histology in the two studies, since in KN-042, 37% of the recruited TPS≥50% population had squamous tumour while in KN-024 was 18%. The individual analysis of KN-024 and KN-042 was somewhat inconclusive, and for some aspects even contradictory. Particularly, the MAH concluded that presence of baseline liver metastasis suggests a poor outcome for pembrolizumab in the first 4 months of treatment; however, the statistical significance related to this parameter in the treatment interaction analysis does not seem to indicate a relevant effect and was not confirmed in the multivariate model applied to all data. The uncertainty of the finding is further reinforced by lack of data reproducibility in KN-024, where results show an even opposite direction for this parameter within the same time window. The interaction between liver metastasis and treatment is absent in the pooled analysis as both limited to the early death time window and the whole dataset. Pooled analyses from Study KN-042 and KN-024 seem to suggest that the never smoker status is predictor of poor outcome on pembrolizumab both in the early time window and in the whole dataset follow-up.

Given the impact of these findings on the currently approved indication of pembrolizumab monotherapy for patients with TPS ≥50%, further exploration of these data testing combination of more factors (i.e. a 3 term interaction factor analysis) was undertaken revealing that among the different clinical parameters included in the model, histology (but not liver metastasis) seems to interact with smoking status and treatment by judging on the basis of a significant p value (0.034) in the pooled population analysis. In particular, the OS K-M curves showed that smokers and never smokers within the non-squamous histology group present with an opposite trend in terms of response to chemotherapy that consequently makes the effect of pembrolizumab more advantageous in the smokers and less advantageous in non-smokers compared to chemotherapy (see sections 4.4 and 5.1 of the SmPC). **Pemetrexed maintenance**

The benefit of pembrolizumab over chemotherapy as expressed by OS HR appears higher when compared against absence than presence of pemetrexed maintenance across all TPS scores. Considering the optimal SoC only, which includes the group receiving pemetrexed maintenance, data (ITT=341 pts assigned to chemotherapy vs 328 to pembrolizumab; OS HR:0.89 [95% CI: 0.73, 1.09], p=0.124) confirm the trend of the primary outcome in the total study population (TPS ⩾1%; ITT=637 pts assigned to chemo vs 637 to pembrolizumab; OS HR:0.81 [95% CI: 0.71, 0.93], p=0.0018). The same consideration can be applied to the TPS⩾50% subpopulation (ITT=166 pts assigned to chemotherapy vs 157 to pembrolizumab; OS HR:0.83 [95% CI: 0.62, 1.12], p=0.1129) when compared with the respective group encompassing all histologies (ITT=300 pts assigned to chemotherapy vs 299 to pembrolizumab; OS HR:0.69 [95% CI: 0.56, 0.85], p=0.0003). Therefore, it can be concluded that Investigator's choice of pemetrexed maintenance did not constitute a bias in data interpretation and analysis (Data not shown).

Subgroup analyses

The efficacy of the experimental treatment in the advanced cancer (stage III) was similar to the one observed in both the metastatic tumour and the overall population. Although limited to 12.6% of the ITT population, the prevalence of patients with "locally advanced" tumour comprising stages IIIA and IIIB is consistent with the expected distribution of disease stages at diagnosis in the "real world". Moreover, there were no unbalances in the number of patients with stage III cancer between treatment arms. For completeness, the MAH specified upon request disease stage in the baseline characteristics of study KN-042 reported in section 5.1 of the SmPC. The prevalence of locally advanced cancer within the TPS ⩾

50% group was 10.4% (62 subjects). Due to the small number of subjects, the efficacy data from this post hoc subgroup analysis should be interpreted with caution, however the efficacy data in locally advanced disease are consistent with results in metastatic cancer patients.

The geographic area was associated with a variable degree of efficacy of pembrolizumab compared to control, with a lower performance in OS being reported for the EU (HR 1.05; 95% CI 0.79-1.40) than non-EU region (HR 0.74; 95% CI 0.63 -0.87). A stratified multivariate COX-regression analysis adjusted by the metastasis number, tumour size and liver metastasis at baseline only slightly modified the outcome (HR for EU-region of 0.98).

The MAH presented results across the different PD-L1 categories as stratified by histology and showed that squamous and non-squamous NSCLC behave similarly in terms of response to pembrolizumab regardless of PD-L1 score. In comparing the KM curves of the control arms, the squamous histology presented with a worse clinical outcome than the non-squamous tumour subtype, and this resulted into an apparent higher advantage of pembrolizumab over chemotherapy for the squamous histology, across all the different TPS categories, albeit differences between histologies were not statistically significant.

The MAH has discussed the negative effect of pembrolizumab in PFS for females and never smokers by comparing the subgroup point estimates of the PFS forest plots with the overall population, together with the OS forest plots of study KEYNOTE-042, to conclude that a dissociation between PFS and OS was observed in both subgroups and similarly to the overall TPS≥1% population. The results of a post-hoc exploratory subgroup analysis indicated a trend towards reduced survival benefit of pembrolizumab compared to chemotherapy, during both the first 4 months and throughout the entire duration of treatment, in patients who were never-smokers. However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn (see section 5.1 of the SmPC).

2.4.4. Conclusions on the clinical efficacy

The increases in the risk of early death, particularly marked in the subgroup of patients expressing PD-L1 1-49% TPS, and the lack of identified clinical indicators for the proper selection of patients do not allow concluding on a benefit of pembrolizumab monotherapy compared to chemotherapy. The MAH during the procedure decided to no longer pursue the extension of indication to include the first-line treatment of locally advanced or metastatic non-small cell lung cancer tumours for patients expressing PD-L1 1-49% TPS, based on data from study KEYNOTE-042. The scope of the Type II variation application is therefore revised to reflect an update of sections 4.4, 4.8 and 5.1 of the SmPC in order to include the data from KEYNOTE-042.

2.5. Clinical safety

Introduction

Safety data in support of the current application were derived from the following datasets:

• KEYNOTE-042 Dataset (N=636): Subjects with previously untreated locally advanced or metastatic NSCLC treated with pembrolizumab who participated in KEYNOTE-042.

• First-line NSCLC Dataset (N=790): Subjects with previously untreated locally advanced or metastatic NSCLC treated with pembrolizumab who participated in KEYNOTE-042 or KEYNOTE-024.

• Reference Safety Dataset (RSD) (N=3830): Subjects 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 lymphoma), KEYNOTE-024 (NSCLC), KEYNOTE-045 and KEYNOTE-052 (urothelial cancer), and

KEYNOTE-087 (classical Hodgkin lymphoma). This dataset represents the established safety profile for pembrolizumab monotherapy based on the currently approved indications in the European Union.

• Cumulative Running Safety Dataset (CSD)(N=5246): Subjects who received at least 1 dose of pembrolizumab in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3 (melanoma, NSCLC); KEYNOTE-002 (original phase, melanoma), KEYNOTE-006 (melanoma), KEYNOTE-010 (NSCLC), KEYNOTE-012 Cohorts B and B2 (head and neck cancer), Cohort C (bladder cancer) and Cohort D (gastric cancer), KEYNOTE-013 Cohort 3 (Hodgkin lymphoma), KEYNOTE-013 Cohort 4A (mediastinal large B-cell lymphoma), KEYNOTE-024 (NSCLC), KEYNOTE-028 (advanced solid tumor), KEYNOTE-042 (NSCLC), KEYNOTE-045 and KEYNOTE-052 (urothelial cancer), KEYNOTE-059 Cohort 1 (gastric cancer), KEYNOTE-087 (classical Hodgkin lymphoma), KEYNOTE-158 (advanced solid tumor), KEYNOTE-164 Cohort A (colorectal carcinoma), and KEYNOTE-170 (primary mediastinal large B-cell lymphoma).

Moreover, the individual analysis of Study KEYNOTE-042 (n=636 vs 615 patients in the pembrolizumab and chemotherapy arm, respectively) was presented, as well as a pooled pembrolizumab (n= 790) versus pooled chemotherapy (n=765) analysis including Studies KEYNOTE-024 and KEYNOTE-042.

Patient exposure

Table 55: Summary of drug exposure (Subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖ (N=636)	First-line NSCLC Dataset for Pembrolizumab†† (N=790)	Reference Safety Dataset for Pembrolizumab¶ (N=3830)	Cumulative Running Safety Dataset for Pembrolizumab§ (N=5246)
Study Days On-Therapy (Months)				
Mean	8.3	8.8	6.7	6.6
Median	5.55	5.78	4.71	4.19
SD	7.78	8.15	6.06	6.31
Range	0.03 to 27.30	0.03 to 32.46	0.03 to 32.46	0.03 to 32.46
Number of Administrations				
Mean	12.5	13.2	11.1	10.9
Median	9.00	9.00	8.00	7.00
SD	10.91	11.40	9.56	9.81
Range	1.00 to 36.00	1.00 to 39.00	1.00 to 59.00	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 Pembrolizumab in KN042.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN042 and KN024.
¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.
§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN024, KN028, KN042, KN045, KN052, KN059 Cohort 1, KN087, KN158, KN164 Cohort A (Colorectal Carcinoma), and KN170.
Pembrolizumab Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Pembrolizumab Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
Pembrolizumab Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Pembrolizumab Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3:27SEP2016, KN087:25SEP2016)
Pembrolizumab Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045:18JAN2017, KN052:09MAR2017)
Pembrolizumab Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Pembrolizumab Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 04AUG2017, KN170: 15AUG2017)
Pembrolizumab Database Cutoff Date for Cervical (KN028: 20FEB2017, KN158: 23AUG2017)

Source: [ISS: adam-adsl; adexsum]

Table 56: Clinical trial exposure to drug by duration (Subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖ (N=636)			First-line NSCLC Dataset for Pembrolizumab†† (N=790)			Reference Safety Dataset for Pembrolizumab¶ (N=3830)			Cumulative Running Safety Dataset for Pembrolizumab§ (N=5246)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	636	(100.0)	(440.7)	790	(100.0)	(580.9)	3,830	(100.0)	(2,123.7)	5,246	(100.0)	(2,892.5)
>=1 m	541	(85.1)	(438.1)	671	(84.9)	(577.8)	3,269	(85.4)	(2,104.7)	4,413	(84.1)	(2,864.7)
>=3 m	413	(64.9)	(418.1)	521	(65.9)	(554.4)	2,314	(60.4)	(1,945.1)	3,086	(58.8)	(2,646.3)
>=6m	302	(47.5)	(377.5)	393	(49.7)	(507.4)	1,640	(42.8)	(1,700.2)	2,166	(41.3)	(2,313.7)

>=12m	187	(29.4)	(295.0)	250	(31.6)	(405.2)	785	(20.5)	(1,079.5)	1,078	(20.5)	(1,527.7)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN042.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN042 and KN024.
† Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.
§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN024, KN028, KN042, KN045, KN052, KN059 Cohort 1, KN087, KN158, KN164 Cohort A (Colorectal Carcinoma), and KN170.
Pembrolizumab Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Pembrolizumab Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
Pembrolizumab Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 21APR2017)
Pembrolizumab Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3:27SEP2016, KN087:25SEP2016)
Pembrolizumab Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045:18JAN2017, KN052:09MAR2017)
Pembrolizumab Database Cutoff Date for Colorectal (KN164-Cohort A: 03AUG2016)
Pembrolizumab Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 04AUG2017, KN170: 15AUG2017)
Pembrolizumab Database Cutoff Date for Cervical (KN028: 20FEB2017, KN158: 23AUG2017)

Source: [ISS: adam-adsl; adexsum]

Adverse events

Overall AEs

KEYNOTE-042

A summary of adverse event at the final analysis cut-off date is presented below:

Table 57: Adverse event summary (ASaT population)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	636		615	
with one or more adverse events	608	(95.6)	605	(98.4)
with no adverse event	28	(4.4)	10	(1.6)
with drug-related† adverse events	405	(63.7)	553	(89.9)
with toxicity grade 3-5 adverse events	326	(51.3)	350	(56.9)
with toxicity grade 3-5 drug-related adverse events	117	(18.4)	253	(41.1)
with serious adverse events	257	(40.4)	187	(30.4)
with serious drug-related adverse events	88	(13.8)	91	(14.8)
who died	68	(10.7)	47	(7.6)
who died due to a drug-related adverse event	13	(2.0)	14	(2.3)
discontinued drug due to an adverse event	130	(20.4)	91	(14.8)
discontinued drug due to a drug-related adverse event	62	(9.7)	59	(9.6)
discontinued drug due to a serious adverse event	104	(16.4)	57	(9.3)
discontinued drug due to a serious drug-related adverse event	42	(6.6)	27	(4.4)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
Database Cutoff Date: 04SEP2018

Table 58: Exposure-adjusted adverse events overall (including multiple occurrences of events) (incidence >0% in one or more treatment groups) (ASaT population)

	Event Count and Rate (Events/100 person-months)†	
	Pembrolizumab	Chemotherapy
Number of subjects exposed	636	615
Total exposure‡ person-months	5862.28	3752.71
Total events (rate)	4875 (83.16)	6392 (170.33)

Table 59: Exposure-adjusted Grade 3-5 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)[†]	
	Pembrolizumab	Chemotherapy
Number of subjects exposed	636	615
Total exposure[‡] person-months	5862.28	3752.71
Total events (rate)	615 (10.49)	820 (21.85)

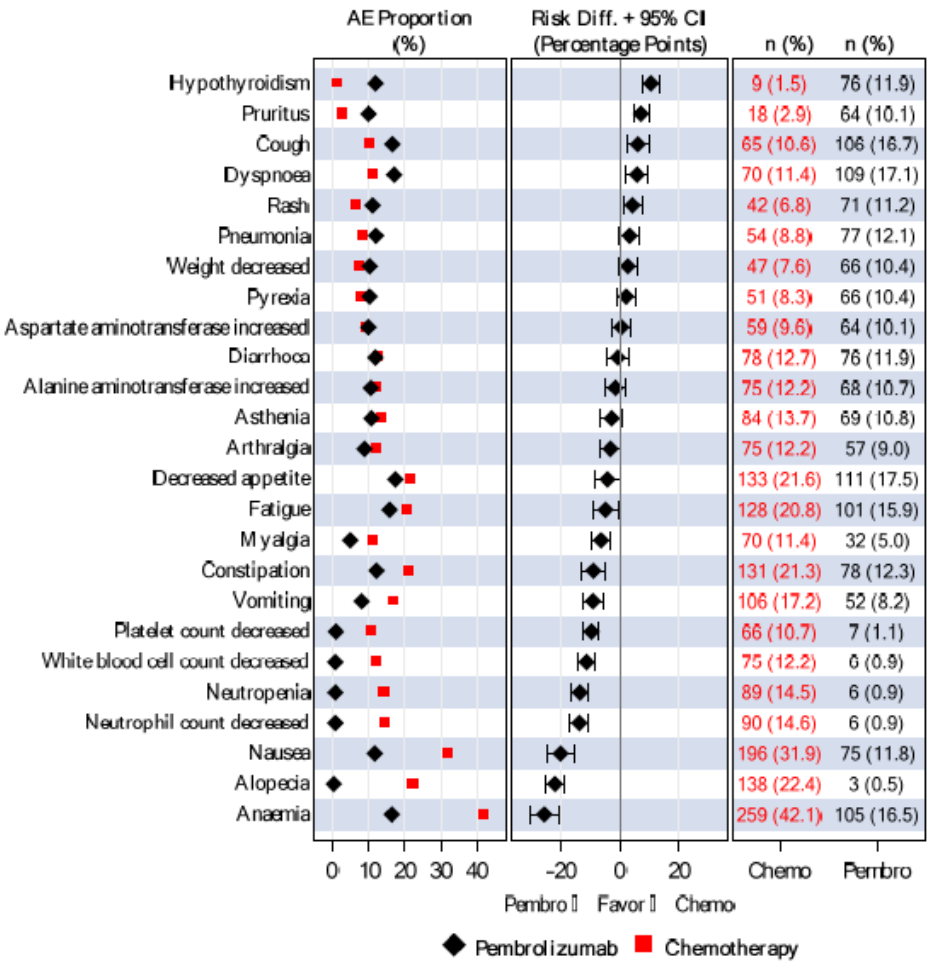
Table 60: Exposure-adjusted serious adverse events (including multiple occurrences of events) (incidence >0% in one or more treatment groups) (ASaT population)

	Event Count and Rate (Events/100 person-months)[†]	
	Pembrolizumab	Chemotherapy
Number of subjects exposed	636	615
Total exposure[‡] person-months	5862.28	3752.71
Total events (rate)	406 (6.93)	302 (8.05)

Table 61: Exposure-adjusted adverse events leading to drug discontinuation (including multiple occurrences of events) (incidence >0% in one or more treatment groups) (ASaT population)

	Event Count and Rate (Events/100 person-months)[†]	
	Pembrolizumab	Chemotherapy
Number of subjects exposed	636	615
Total exposure[‡] person-months	5862.28	3752.71
Total events (rate)	132 (2.25)	103 (2.74)

Plot for adverse events according to the final analysis cut-off date is presented below:



Database Cutoff Date: 04SEP2018

Figure 30: Rainfall plot for adverse event by preferred term (≥10% incidence) – Pembrolizumab (N=636) vs. Chemotherapy (N=615)

Comparison across Pembrolizumab datasets

Table 62: Adverse event summary (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	610	(95.9)	761	(96.3)	3,720	(97.1)	5,086	(97.0)
with no adverse event	26	(4.1)	29	(3.7)	110	(2.9)	160	(3.0)
with drug-related† adverse events	399	(62.7)	517	(65.4)	2,751	(71.8)	3,636	(69.3)
with toxicity grade 3-5 adverse events	318	(50.0)	413	(52.3)	1,802	(47.0)	2,567	(48.9)
with toxicity grade 3-5 drug-related adverse events	113	(17.8)	161	(20.4)	577	(15.1)	812	(15.5)
with non-serious adverse events	575	(90.4)	722	(91.4)	3,647	(95.2)	4,961	(94.6)
with serious adverse events	259	(40.7)	338	(42.8)	1,450	(37.9)	2,044	(39.0)
with serious drug-related adverse events	87	(13.7)	122	(15.4)	403	(10.5)	563	(10.7)
with dose modification‡ due to an adverse event	297	(46.7)	374	(47.3)	1,256	(32.8)	1,797	(34.3)
who died	70	(11.0)	82	(10.4)	157	(4.1)	277	(5.3)
who died due to a drug-related adverse event	13	(2.0)	15	(1.9)	17	(0.4)	32	(0.6)
discontinued drug due to an adverse event	122	(19.2)	148	(18.7)	452	(11.8)	651	(12.4)
discontinued drug due to a drug-related adverse event	57	(9.0)	78	(9.9)	224	(5.8)	311	(5.9)
discontinued drug due to a serious adverse event	102	(16.0)	120	(15.2)	338	(8.8)	502	(9.6)
discontinued drug due to a serious drug-related adverse event	39	(6.1)	52	(6.6)	149	(3.9)	211	(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.

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN042.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN042 and KN024.

¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.

§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN024, KN028, KN042, KN045, KN052, KN059 Cohort 1, KN087, KN158, KN164 Cohort A (Colorectal Carcinoma), and KN170.

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

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

Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

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

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

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

Pembrolizumab Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045:18JAN2017, KN052:09MAR2017)

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

Pembrolizumab Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 04AUG2017, KN170: 15AUG2017)

Pembrolizumab Database Cutoff Date for Cervical (KN028: 20FEB2017, KN158: 23AUG2017)

Source: [ISS: adam-adsl; adae]

Table 63: Subjects with adverse events (Incidence ≥10% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	610	(95.9)	761	(96.3)	3,720	(97.1)	5,086	(97.0)
with no adverse events	26	(4.1)	29	(3.7)	110	(2.9)	160	(3.0)
Decreased appetite	110	(17.3)	144	(18.2)	822	(21.5)	1,109	(21.1)
Dyspnoea	105	(16.5)	146	(18.5)	688	(18.0)	914	(17.4)
Fatigue	101	(15.9)	139	(17.6)	1,320	(34.5)	1,679	(32.0)
Anaemia	99	(15.6)	123	(15.6)	508	(13.3)	782	(14.9)
Cough	99	(15.6)	129	(16.3)	804	(21.0)	1,028	(19.6)
Constipation	77	(12.1)	112	(14.2)	695	(18.1)	914	(17.4)
Hypothyroidism	77	(12.1)	93	(11.8)	346	(9.0)	502	(9.6)
Pneumonia	76	(11.9)	81	(10.3)	180	(4.7)	284	(5.4)
Diarrhoea	74	(11.6)	116	(14.7)	838	(21.9)	1,047	(20.0)
Nausea	74	(11.6)	107	(13.5)	884	(23.1)	1,124	(21.4)
Rash	69	(10.8)	97	(12.3)	643	(16.8)	790	(15.1)
Asthenia	67	(10.5)	79	(10.0)	470	(12.3)	615	(11.7)
Pyrexia	65	(10.2)	94	(11.9)	531	(13.9)	732	(14.0)
Alanine aminotransferase increased	64	(10.1)	82	(10.4)	239	(6.2)	348	(6.6)
Weight decreased	64	(10.1)	78	(9.9)	308	(8.0)	464	(8.8)
Back pain	62	(9.7)	86	(10.9)	477	(12.5)	623	(11.9)
Pruritus	62	(9.7)	92	(11.6)	764	(19.9)	912	(17.4)
Arthralgia	56	(8.8)	85	(10.8)	628	(16.4)	764	(14.6)
Vomiting	51	(8.0)	68	(8.6)	533	(13.9)	707	(13.5)
Headache	45	(7.1)	56	(7.1)	468	(12.2)	578	(11.0)
Oedema peripheral	31	(4.9)	50	(6.3)	402	(10.5)	533	(10.2)

Drug-Related Adverse Events

KEYNOTE-042

Table 64: Subjects with drug-related adverse events (Incidence ≥10% in one or more treatment groups) by decreasing incidence (ASaT population)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	636		615	
with one or more adverse events	399	(62.7)	553	(89.9)
with no adverse events	237	(37.3)	62	(10.1)
Hypothyroidism	69	(10.8)	2	(0.3)
Fatigue	50	(7.9)	102	(16.6)
Decreased appetite	40	(6.3)	109	(17.7)
Anaemia	35	(5.5)	229	(37.2)
Nausea	31	(4.9)	184	(29.9)
Vomiting	15	(2.4)	97	(15.8)
Constipation	8	(1.3)	68	(11.1)
Neutropenia	5	(0.8)	88	(14.3)
White blood cell count decreased	3	(0.5)	71	(11.5)
Alopecia	2	(0.3)	136	(22.1)
Neutrophil count decreased	2	(0.3)	86	(14.0)
Platelet count decreased	2	(0.3)	64	(10.4)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

Comparison across Pembrolizumab datasets

Table 65: Subjects with drug-related adverse events (Incidence ≥5% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	399	(62.7)	517	(65.4)	2,751	(71.8)	3,636	(69.3)
with no adverse events	237	(37.3)	273	(34.6)	1,079	(28.2)	1,610	(30.7)
Hypothyroidism	69	(10.8)	82	(10.4)	309	(8.1)	441	(8.4)
Fatigue	50	(7.9)	72	(9.1)	826	(21.6)	1,002	(19.1)
Pruritus	46	(7.2)	64	(8.1)	608	(15.9)	715	(13.6)
Rash	46	(7.2)	62	(7.8)	485	(12.7)	587	(11.2)
Alanine aminotransferase increased	45	(7.1)	56	(7.1)	132	(3.4)	199	(3.8)
Pneumonitis	43	(6.8)	54	(6.8)	121	(3.2)	175	(3.3)
Aspartate aminotransferase increased	41	(6.4)	49	(6.2)	127	(3.3)	199	(3.8)
Decreased appetite	40	(6.3)	55	(7.0)	337	(8.8)	430	(8.2)
Hyperthyroidism	37	(5.8)	47	(5.9)	116	(3.0)	177	(3.4)
Anaemia	35	(5.5)	43	(5.4)	122	(3.2)	190	(3.6)
Diarrhoea	34	(5.3)	59	(7.5)	445	(11.6)	526	(10.0)
Nausea	31	(4.9)	46	(5.8)	395	(10.3)	481	(9.2)
Arthralgia	27	(4.2)	41	(5.2)	324	(8.5)	399	(7.6)
Asthenia	27	(4.2)	32	(4.1)	260	(6.8)	314	(6.0)

Grade 3-5 Adverse Events

KEYNOTE-042

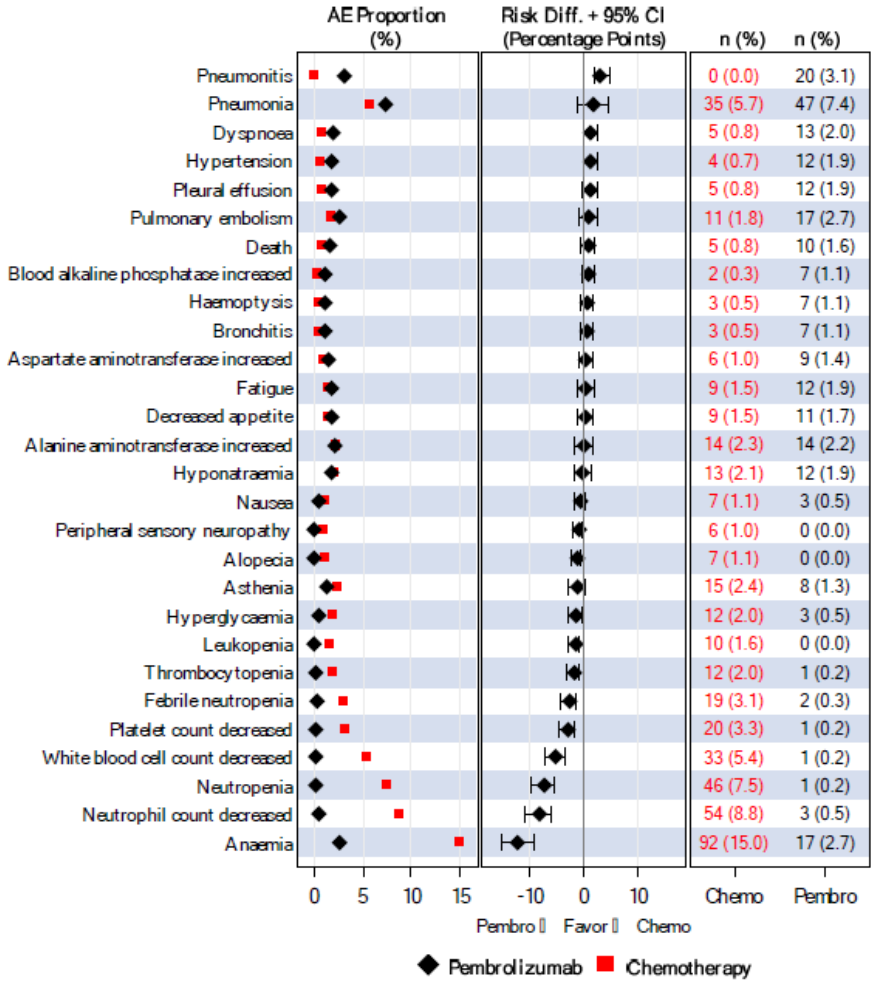


Figure 31: Rainfall plot for grade 3-5 adverse event by preferred term (≥1% incidence) – Pembrolizumab (N=636) vs. Chemotherapy (N=615)

Comparison across Pembrolizumab datasets

Table 66: 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 treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	318	(50.0)	413	(52.3)	1,802	(47.0)	2,567	(48.9)
with no adverse events	318	(50.0)	377	(47.7)	2,028	(53.0)	2,679	(51.1)
Pneumonia	47	(7.4)	51	(6.5)	102	(2.7)	164	(3.1)
Pneumonitis	20	(3.1)	25	(3.2)	49	(1.3)	75	(1.4)
Anaemia	17	(2.7)	26	(3.3)	159	(4.2)	250	(4.8)
Pulmonary embolism	17	(2.7)	21	(2.7)	58	(1.5)	88	(1.7)
Alanine aminotransferase increased	14	(2.2)	17	(2.2)	38	(1.0)	65	(1.2)
Dyspnoea	13	(2.0)	16	(2.0)	95	(2.5)	134	(2.6)
Fatigue	12	(1.9)	15	(1.9)	103	(2.7)	143	(2.7)

Table 67: Exposure-adjusted Grade 3-5 adverse events (including multiple occurrences of events) (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	Event Count and Rate (Events/100 person-months)†			
	KN042 Dataset for Pembrolizumab‖	First-line NSCLC Dataset for Pembrolizumab††	Reference Safety Dataset for Pembrolizumab¶	Cumulative Running Safety Dataset for Pembrolizumab§
Number of subjects exposed	636	790	3830	5246
Total exposure‡ person-months	5862.28	7674.18	26483.35	35298.86
Total events (rate)	615 (10.49)	833 (10.85)	3913 (14.78)	5635 (15.96)
Pneumonia	52 (0.9)	57 (0.7)	112 (0.4)	182 (0.5)
Pneumonitis	20 (0.3)	25 (0.3)	50 (0.2)	76 (0.2)
Anaemia	19 (0.3)	31 (0.4)	188 (0.7)	292 (0.8)
Pulmonary embolism	17 (0.3)	21 (0.3)	61 (0.2)	91 (0.3)
Alanine aminotransferase increased	16 (0.3)	19 (0.2)	38 (0.1)	67 (0.2)

Grade 3 to 5 Drug-Related Adverse Events

KEYNOTE-042

Table 68: Subjects with drug-related grade 3-5 adverse events by decreasing incidence (Incidence ≥1% in one or more treatment groups) (ASaT population)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	636		615	
with one or more adverse events	113	(17.8)	252	(41.0)
with no adverse events	523	(82.2)	363	(59.0)
Pneumonitis	20	(3.1)	0	(0.0)
Alanine aminotransferase increased	9	(1.4)	5	(0.8)
Decreased appetite	5	(0.8)	9	(1.5)
Anaemia	4	(0.6)	80	(13.0)
Asthenia	3	(0.5)	10	(1.6)
Fatigue	3	(0.5)	8	(1.3)
Hyponatraemia	1	(0.2)	6	(1.0)
Neutropenia	1	(0.2)	46	(7.5)
Pneumonia	1	(0.2)	15	(2.4)
Thrombocytopenia	1	(0.2)	10	(1.6)
Alopecia	0	(0.0)	7	(1.1)
Febrile neutropenia	0	(0.0)	17	(2.8)
Leukopenia	0	(0.0)	10	(1.6)
Nausea	0	(0.0)	7	(1.1)
Neutrophil count decreased	0	(0.0)	54	(8.8)
Peripheral sensory neuropathy	0	(0.0)	6	(1.0)
Platelet count decreased	0	(0.0)	20	(3.3)
White blood cell count decreased	0	(0.0)	32	(5.2)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

Comparison across Pembrolizumab datasets

Table 69: Subjects with drug-related grade 3-5 adverse events (Incidence ≥0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‡		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	113	(17.8)	161	(20.4)	577	(15.1)	812	(15.5)
with no adverse events	523	(82.2)	629	(79.6)	3,253	(84.9)	4,434	(84.5)
Pneumonitis	20	(3.1)	25	(3.2)	45	(1.2)	70	(1.3)
Alanine aminotransferase increased	9	(1.4)	10	(1.3)	20	(0.5)	37	(0.7)
Decreased appetite	5	(0.8)	5	(0.6)	11	(0.3)	18	(0.3)
Diarrhoea	5	(0.8)	11	(1.4)	40	(1.0)	49	(0.9)
Anaemia	4	(0.6)	6	(0.8)	18	(0.5)	31	(0.6)
Aspartate aminotransferase increased	4	(0.6)	6	(0.8)	21	(0.5)	34	(0.6)
Autoimmune hepatitis	4	(0.6)	4	(0.5)	9	(0.2)	13	(0.2)
Pericardial effusion	4	(0.6)	4	(0.5)	4	(0.1)	8	(0.2)
Pleural effusion	4	(0.6)	4	(0.5)	2	(0.1)	7	(0.1)
Rash maculo-papular	4	(0.6)	5	(0.6)	9	(0.2)	16	(0.3)
Asthenia	3	(0.5)	4	(0.5)	17	(0.4)	22	(0.4)
Colitis	3	(0.5)	6	(0.8)	41	(1.1)	48	(0.9)
Fatigue	3	(0.5)	6	(0.8)	45	(1.2)	61	(1.2)
Pulmonary embolism	3	(0.5)	4	(0.5)	3	(0.1)	6	(0.1)
Rash	3	(0.5)	5	(0.6)	12	(0.3)	19	(0.4)
Abdominal pain upper	2	(0.3)	2	(0.3)	0	(0.0)	3	(0.1)
Adrenal insufficiency	2	(0.3)	2	(0.3)	9	(0.2)	12	(0.2)
Blood alkaline phosphatase increased	2	(0.3)	2	(0.3)	9	(0.2)	13	(0.2)
Cardiac failure acute	2	(0.3)	2	(0.3)	0	(0.0)	2	(0.0)
Dyspnoea	2	(0.3)	3	(0.4)	17	(0.4)	21	(0.4)
Gamma-glutamyltransferase increased	2	(0.3)	3	(0.4)	9	(0.2)	12	(0.2)
Hepatic function abnormal	2	(0.3)	2	(0.3)	1	(0.0)	5	(0.1)
Hyperkalaemia	2	(0.3)	2	(0.3)	1	(0.0)	3	(0.1)
Hypophysitis	2	(0.3)	3	(0.4)	7	(0.2)	9	(0.2)
Interstitial lung disease	2	(0.3)	2	(0.3)	4	(0.1)	6	(0.1)
Pruritus	2	(0.3)	2	(0.3)	4	(0.1)	6	(0.1)
Weight decreased	2	(0.3)	2	(0.3)	4	(0.1)	7	(0.1)
Acute kidney injury	1	(0.2)	1	(0.1)	4	(0.1)	7	(0.1)
Anaphylactic reaction	1	(0.2)	1	(0.1)	1	(0.0)	2	(0.0)
Blood calcium increased	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Blood creatine phosphokinase increased	1	(0.2)	1	(0.1)	4	(0.1)	5	(0.1)
Blood potassium increased	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Bronchitis	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Bronchitis chronic	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)

Adverse drug reactions ADRs

For pembrolizumab monotherapy, the following studies have been included in the pooled dataset: KEYNOTE-048, KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase), KEYNOTE-006, KEYNOTE-010, KEYNOTE-012 HNSCC, KEYNOTE-013 Cohort 3, KEYNOTE-024, KEYNOTE-040, KEYNOTE-042, KEYNOTE-045, KEYNOTE-052, KEYNOTE-054, KEYNOTE-055, and KEYNOTE-087.

Table 70: Adverse Reactions in Patients Treated with Pembrolizumab Monotherapy

		Monotherapy (N=5884)	
		All % (n)	Gr 3-5 n
Infections and infestations			
Common	pneumonia	5.8% (343)	209
Blood and lymphatic system disorders			
Very common	anaemia	13.9% (819)	234
Common	thrombocytopenia	1.5% (89)	17
Common	lymphopenia	1.1% (65)	16
Uncommon	neutropenia	0.8% (48)	15

Uncommon	leukopenia	0.8% (45)	7
Uncommon	eosinophilia	0.7% (39)	0
Rare	immune thrombocytopenic purpura	0.05% (3)	3
Rare	haemolytic anaemia	0.02% (1)	1
Rare	pure red cell aplasia[#]	(0)	0
Immune system disorders			
Common	infusion reactions[a]	2.3% (134)	13
Uncommon	sarcoidosis	0.2% (10)	0
Not known	solid organ transplant rejection*	(0)	0
Endocrine disorders			
Very common	hypothyroidism[b]	11.0% (645)	8
Common	hyperthyroidism	4.1% (244)	7
Uncommon	hypophysitis[c]	0.6% (36)	20
Uncommon	thyroiditis[d]	0.95% (56)	1
Uncommon	adrenal insufficiency	0.7% (41)	18
Metabolism and nutrition disorders			
Very common	decreased appetite	19.0% (1117)	72
Common	hyponatraemia	5.8% (339)	151
Common	hypokalaemia	4.6% (271)	59
Common	hypocalcaemia	1.9% (112)	10
Uncommon	type 1 diabetes mellitus[e]	0.3% (20)	19
Psychiatric disorders			
Common	insomnia	7.1% (417)	7
Nervous system disorders			
Very common	headache	11.9% (703)	18
Common	dizziness	7.2% (424)	11
Common	neuropathy peripheral	1.9% (112)	2
Common	lethargy	1.2% (71)	2
Common	dysgeusia	2.5% (149)	1
Uncommon	epilepsy	0.2% (11)	7
Rare	guillain-barre syndrome[f]	0.07% (4)	2
Rare	myasthenic syndrome[g]	0.05% (3)	1
Rare	meningitis (aseptic)[h]	0.05% (3)	3
Rare	encephalitis	0.03% (2)	2
Eye disorders			
Common	dry eye	1.6% (94)	0
Uncommon	uveitis[i]	0.3% (20)	2
Rare	Vogt-Koyanagi-Harada syndrome[#]	(0)	0
Cardiac disorders			
Uncommon	pericardial effusion	0.9% (51)	25
Uncommon	pericarditis	0.1% (8)	4
Rare	myocarditis[j]	0.08% (5)	5
Vascular disorders			
Common	hypertension	4.9% (288)	99
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	16.6% (976)	130
Very common	cough	19.0% (1118)	9
Common	pneumonitis[k]	4.3% (253)	91
Gastrointestinal disorders			
Very common	diarrhoea	20.2% (1186)	78
Very common	abdominal pain[l]	12.3% (726)	55
Very common	nausea	20.4% (1198)	49
Very common	vomiting	12.3% (721)	42
Very common	constipation	16.7% (983)	24
Common	colitism	1.8% (107)	65
Common	dry mouth	4.8% (280)	1
Uncommon	pancreatitis[n]	0.3% (16)	9
Rare	small intestinal perforation	0.03% (2)	1
Hepatobiliary disorders			
Uncommon	hepatitis[o]	0.8% (50)	39
Skin and subcutaneous tissue disorders			
Very common	rash[p]	19.5% (1149)	2
Very common	pruritus[q]	18.3% (1075)	1
Common	severe skin reactions[r]	1.5% (89)	66
Common	erythema	2.8% (165)	2
Common	dry skin	5.1% (299)	1
Common	vitiligos	4.2% (245)	0
Common	eczema	1.5% (91)	0
Common	alopecia	1.4% (84)	0
Common	dermatitis acneiform	1.2% (72)	0

Uncommon	lichenoid keratosis[t]	0.4% (25)	9
Uncommon	psoriasis	0.6% (34)	4
Uncommon	dermatitis	0.9% (55)	1
Uncommon	papule	0.5% (27)	1
Uncommon	hair colour changes	0.3% (20)	0
Rare	stevens-johnson syndrome	0.05% (3)	2
Rare	erythema nodosum	0.05% (3)	0
Rare	toxic epidermal necrolysis[#]	(0)	0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[u]	18.7% (1102)	96
Very common	arthralgia	14.3% (839)	38
Common	pain in extremity	6.6% (386)	18
Common	myositis[v]	7.5% (443)	16
Common	arthritis[w]	2.2% (132)	9
Uncommon	tenosynovitis[x]	0.5% (30)	1
Renal and urinary disorders			
Uncommon	nephritis[y]	0.4% (22)	15
General disorders and administration site conditions			
Very common	fatigue	31.8% (1870)	143
Very common	asthenia	11.2% (657)	58
Very common	oedema[z]	11.5% (678)	42
Very common	pyrexia	12.4% (729)	28
Common	influenza like illness	3.7% (219)	1
Common	chills	4.1% (244)	0
Investigations			
Common	aspartate aminotransferase increased	6.5% (380)	64
Common	alanine aminotransferase increased	6.5% (384)	59
Common	hypercalcaemia	3.1% (184)	52
Common	blood alkaline phosphatase increased	4.0% (237)	47
Common	blood bilirubin increased	2.1% (126)	23
Common	blood creatinine increased	4.2% (250)	11
Uncommon	amylase increased	0.3% (17)	8

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

[*] Adverse reaction frequencies presented may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

[#] The "rule of 3" has been applied in calculation.

a. infusion reactions (anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, infusion related reaction)
b. hypothyroidism (hypothyroidism, myxoedema, primary hypothyroidism)
c. hypophysitis (hypophysitis, hypopituitarism)
d. thyroiditis (autoimmune thyroiditis, thyroid disorder, thyroiditis)
e. type 1 diabetes mellitus (diabetic ketoacidosis, type 1 diabetes mellitus)
f. guillain-barre syndrome (axonal neuropathy, demyelinating polyneuropathy, guillain-barre syndrome)
g. myasthenic syndrome (myasthenia gravis, myasthenic syndrome)
h. meningitis (aseptic) (meningitis, meningitis noninfective)
i. uveitis (iridocyclitis, iritis, uveitis)
j. myocarditis (autoimmune myocarditis, myocarditis)
k. pneumonitis (interstitial lung disease, organising pneumonia, pneumonitis)
l. abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper)
m. colitis (autoimmune colitis, colitis, colitis microscopic, enterocolitis)
n. pancreatitis (autoimmune pancreatitis, pancreatitis, pancreatitis acute)
o. hepatitis (autoimmune hepatitis, drug-induced liver injury, hepatitis, hepatitis acute, immune-mediated hepatitis)
p. rash (genital rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular)
q. pruritus (pruritus, pruritus generalised, pruritus genital, urticaria, urticaria papular)
r. severe skin reactions (dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, pemphigus, pruritus, pruritus generalised, pruritus genital, rash, rash erythematous, rash generalised, rash maculo-papular, rash pruritic, rash pustular, skin necrosis, stevens-johnson syndrome, toxic skin eruption)
s. vitiligo (hypopigmentation of eyelid, skin depigmentation, skin hypopigmentation, vitiligo)
t. lichenoid keratosis (lichen planus, lichen sclerosus, lichenoid keratosis)
u. musculoskeletal pain (back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, torticollis)
v. myositis (myalgia, myopathy, myositis, polymyalgia rheumatica, rhabdomyolysis)
w. arthritis (arthritis, joint effusion, joint swelling, polyarthritis)
x. tenosynovitis (synovitis, tendon pain, tendonitis, tenosynovitis)
y. nephritis (acute kidney injury, autoimmune nephritis, glomerulonephritis membranous, nephritis, nephrotic syndrome, renal failure, tubulointerstitial nephritis)
z. oedema (eyelid oedema, face oedema, fluid overload, fluid retention, generalised oedema, lip oedema, localised oedema, oedema, oedema peripheral, periorbital oedema)

Serious adverse event/deaths/other significant events

Overall SAEs

KEYNOTE-042

Table 71: Subjects with serious adverse events by decreasing incidence (Incidence ≥1% in one or more treatment groups) (ASaT population)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	636		615	
with one or more adverse events	259	(40.7)	187	(30.4)
with no adverse events	377	(59.3)	428	(69.6)
Pneumonia	47	(7.4)	32	(5.2)
Pneumonitis	25	(3.9)	1	(0.2)
Pulmonary embolism	15	(2.4)	11	(1.8)
Pleural effusion	14	(2.2)	5	(0.8)
Death	10	(1.6)	5	(0.8)
Dyspnoea	8	(1.3)	2	(0.3)
Bronchitis	7	(1.1)	2	(0.3)
Haemoptysis	7	(1.1)	1	(0.2)
Anaemia	3	(0.5)	17	(2.8)
Febrile neutropenia	1	(0.2)	15	(2.4)
Neutropenia	0	(0.0)	6	(1.0)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
SAE is monitored until 90 days after last dose.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

Comparison across Pembrolizumab datasets

Table 72: 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 treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	259	(40.7)	338	(42.8)	1,450	(37.9)	2,044	(39.0)
with no adverse events	377	(59.3)	452	(57.2)	2,380	(62.1)	3,202	(61.0)
Pneumonia	47	(7.4)	51	(6.5)	114	(3.0)	176	(3.4)
Pneumonitis	25	(3.9)	33	(4.2)	69	(1.8)	100	(1.9)
Pulmonary embolism	15	(2.4)	17	(2.2)	48	(1.3)	75	(1.4)
Pleural effusion	14	(2.2)	20	(2.5)	56	(1.5)	88	(1.7)
Death	10	(1.6)	10	(1.3)	19	(0.5)	38	(0.7)
Dyspnoea	8	(1.3)	8	(1.0)	57	(1.5)	76	(1.4)
Bronchitis	7	(1.1)	8	(1.0)	13	(0.3)	22	(0.4)
Haemoptysis	7	(1.1)	9	(1.1)	14	(0.4)	22	(0.4)
Colitis	5	(0.8)	7	(0.9)	41	(1.1)	51	(1.0)
Diarrhoea	4	(0.6)	7	(0.9)	37	(1.0)	49	(0.9)
Pyrexia	4	(0.6)	6	(0.8)	51	(1.3)	66	(1.3)
Acute kidney injury	3	(0.5)	3	(0.4)	41	(1.1)	52	(1.0)
Anaemia	3	(0.5)	5	(0.6)	48	(1.3)	68	(1.3)

Table 73: Exposure-adjusted serious adverse events (including multiple occurrences of events) (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	Event Count and Rate (Events/100 person-months)[†]			
	KN042 Dataset for Pembrolizumab[‖]	First-line NSCLC Dataset for Pembrolizumab[††]	Reference Safety Dataset for Pembrolizumab[¶]	Cumulative Running Safety Dataset for Pembrolizumab[§]
Number of subjects exposed	636	790	3830	5246
Total exposure[‡] person-months	5862.28	7674.18	26483.35	35298.86
Total events (rate)	406 (6.93)	556 (7.25)	2624 (9.91)	3637 (10.30)
Pneumonia	51 (0.9)	56 (0.7)	123 (0.5)	191 (0.5)
Pneumonitis	26 (0.4)	34 (0.4)	75 (0.3)	108 (0.3)
Pleural effusion	16 (0.3)	22 (0.3)	65 (0.2)	99 (0.3)
Pulmonary embolism	15 (0.3)	17 (0.2)	51 (0.2)	78 (0.2)
Death	10 (0.2)	10 (0.1)	19 (0.1)	38 (0.1)
Dyspnoea	9 (0.2)	9 (0.1)	60 (0.2)	80 (0.2)
Haemoptysis	8 (0.1)	10 (0.1)	15 (0.1)	24 (0.1)
Bronchitis	7 (0.1)	8 (0.1)	13 (0.0)	22 (0.1)
Interstitial lung disease	6 (0.1)	6 (0.1)	5 (0.0)	13 (0.0)
Pericardial effusion	6 (0.1)	7 (0.1)	19 (0.1)	28 (0.1)
Colitis	5 (0.1)	7 (0.1)	43 (0.2)	55 (0.2)
Autoimmune hepatitis	4 (0.1)	4 (0.1)	9 (0.0)	13 (0.0)

Drug-related SAEs

KEYNOTE-042

Table 74: Subjects with drug-related serious adverse events by decreasing incidence (Incidence ≥0% in one or more treatment groups) (ASaT population)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	636		615	
with one or more adverse events	87	(13.7)	90	(14.6)
with no adverse events	549	(86.3)	525	(85.4)
Pneumonitis	25	(3.9)	0	(0.0)
Pleural effusion	6	(0.9)	0	(0.0)
Autoimmune hepatitis	4	(0.6)	0	(0.0)
Colitis	4	(0.6)	0	(0.0)
Interstitial lung disease	4	(0.6)	1	(0.2)
Pericardial effusion	4	(0.6)	0	(0.0)

Comparison across Pembrolizumab datasets

Table 75: Subjects with drug-related serious adverse events up to 90 days of last dose (Incidence ≥0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab[‖]		First-line NSCLC Dataset for Pembrolizumab[††]		Reference Safety Dataset for Pembrolizumab[¶]		Cumulative Running Safety Dataset for Pembrolizumab[§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	87	(13.7)	122	(15.4)	403	(10.5)	563	(10.7)
with no adverse events	549	(86.3)	668	(84.6)	3,427	(89.5)	4,683	(89.3)
Pneumonitis	25	(3.9)	33	(4.2)	65	(1.7)	95	(1.8)
Pleural effusion	6	(0.9)	6	(0.8)	3	(0.1)	12	(0.2)
Autoimmune hepatitis	4	(0.6)	4	(0.5)	9	(0.2)	13	(0.2)
Colitis	4	(0.6)	6	(0.8)	34	(0.9)	41	(0.8)
Interstitial lung disease	4	(0.6)	4	(0.5)	5	(0.1)	11	(0.2)
Pericardial effusion	4	(0.6)	4	(0.5)	4	(0.1)	8	(0.2)

Deaths

KEYNOTE-042

Table 76: Subjects with adverse events resulting in death by decreasing incidence (Incidence ≥0% in one or more treatment groups) (ASaT population)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	636		615	
with one or more adverse events	70	(11.0)	46	(7.5)
with no adverse events	566	(89.0)	569	(92.5)
Death	10	(1.6)	5	(0.8)
Pneumonia	8	(1.3)	7	(1.1)
Pulmonary embolism	6	(0.9)	5	(0.8)
Pulmonary haemorrhage	4	(0.6)	2	(0.3)
Respiratory failure	3	(0.5)	3	(0.5)
Cardiac arrest	2	(0.3)	0	(0.0)
Cardio-respiratory arrest	2	(0.3)	1	(0.2)
Gastric ulcer haemorrhage	2	(0.3)	0	(0.0)
Sepsis	2	(0.3)	0	(0.0)
Septic shock	2	(0.3)	1	(0.2)
Accidental death	1	(0.2)	0	(0.0)
Acute respiratory failure	1	(0.2)	0	(0.0)
Brain injury	1	(0.2)	0	(0.0)
Cardiac failure	1	(0.2)	1	(0.2)
Cardiac failure acute	1	(0.2)	0	(0.0)
Cerebrovascular accident	1	(0.2)	1	(0.2)
Chronic obstructive pulmonary disease	1	(0.2)	0	(0.0)
Coma	1	(0.2)	0	(0.0)
Diverticulitis	1	(0.2)	0	(0.0)
Embolism	1	(0.2)	0	(0.0)
Encephalopathy	1	(0.2)	0	(0.0)
Febrile neutropenia	1	(0.2)	0	(0.0)
Haemoptysis	1	(0.2)	1	(0.2)
Hypercalcaemia of malignancy	1	(0.2)	0	(0.0)
Hypovolaemic shock	1	(0.2)	0	(0.0)
Ileus	1	(0.2)	0	(0.0)
Intestinal ischaemia	1	(0.2)	0	(0.0)
Ischaemic stroke	1	(0.2)	0	(0.0)
Klebsiella infection	1	(0.2)	0	(0.0)
Lung infection	1	(0.2)	0	(0.0)
Malignant neoplasm progression	1	(0.2)	0	(0.0)
Myocardial infarction	1	(0.2)	0	(0.0)
Peripheral artery occlusion	1	(0.2)	0	(0.0)
Pleural effusion	1	(0.2)	1	(0.2)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Pneumonitis	1	(0.2)	0	(0.0)
Pulmonary artery thrombosis	1	(0.2)	0	(0.0)
Pulmonary sepsis	1	(0.2)	2	(0.3)
Sudden death	1	(0.2)	0	(0.0)
Tumour embolism	1	(0.2)	0	(0.0)
Abdominal sepsis	0	(0.0)	1	(0.2)
Acute coronary syndrome	0	(0.0)	1	(0.2)
Biliary sepsis	0	(0.0)	1	(0.2)
Cardiopulmonary failure	0	(0.0)	1	(0.2)
Cerebral infarction	0	(0.0)	1	(0.2)
Completed suicide	0	(0.0)	1	(0.2)
Dyspnoea	0	(0.0)	1	(0.2)
Infection	0	(0.0)	1	(0.2)
Ketoacidosis	0	(0.0)	1	(0.2)
Neutropenic sepsis	0	(0.0)	1	(0.2)
Pancytopenia	0	(0.0)	1	(0.2)
Pulmonary oedema	0	(0.0)	2	(0.3)
Respiratory distress	0	(0.0)	1	(0.2)
Sinus tachycardia	0	(0.0)	1	(0.2)
Sudden cardiac death	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

At the final analysis, the incidence of deaths due to AEs was 10.7% (68) in the pembrolizumab group and 7.6% (47) in the chemotherapy group. The incidences of deaths due to drug-related AEs were similar in the 2 treatment groups (pembrolizumab: 2.0%; chemotherapy: 2.3%).

Comparison across Pembrolizumab datasets

Table 77: Subjects with adverse events resulting in death up to 90 days of last dose (Incidence ≥0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	70	(11.0)	82	(10.4)	157	(4.1)	277	(5.3)
with no adverse events	566	(89.0)	708	(89.6)	3,673	(95.9)	4,969	(94.7)
Death	10	(1.6)	10	(1.3)	19	(0.5)	38	(0.7)
Pneumonia	8	(1.3)	9	(1.1)	16	(0.4)	27	(0.5)
Pulmonary embolism	6	(0.9)	6	(0.8)	3	(0.1)	12	(0.2)
Pulmonary haemorrhage	4	(0.6)	4	(0.5)	1	(0.0)	5	(0.1)
Respiratory failure	3	(0.5)	4	(0.5)	8	(0.2)	14	(0.3)
Cardiac arrest	2	(0.3)	4	(0.5)	4	(0.1)	9	(0.2)
Cardio-respiratory arrest	2	(0.3)	2	(0.3)	1	(0.0)	3	(0.1)
Gastric ulcer haemorrhage	2	(0.3)	2	(0.3)	0	(0.0)	2	(0.0)
Sepsis	2	(0.3)	2	(0.3)	3	(0.1)	7	(0.1)
Septic shock	2	(0.3)	2	(0.3)	5	(0.1)	8	(0.2)
Accidental death	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Acute respiratory failure	1	(0.2)	2	(0.3)	2	(0.1)	4	(0.1)
Brain injury	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Cardiac failure	1	(0.2)	1	(0.1)	2	(0.1)	3	(0.1)
Cardiac failure acute	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Cerebrovascular accident	1	(0.2)	1	(0.1)	3	(0.1)	4	(0.1)
Chronic obstructive pulmonary disease	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Coma	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Diverticulitis	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Embolism	1	(0.2)	1	(0.1)	3	(0.1)	4	(0.1)
Encephalopathy	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Febrile neutropenia	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Haemoptysis	1	(0.2)	1	(0.1)	1	(0.0)	2	(0.0)
Hypercalcaemia of malignancy	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Hypovolaemic shock	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Ileus	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Intestinal ischaemia	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Ischaemic stroke	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Klebsiella infection	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Lung infection	1	(0.2)	1	(0.1)	1	(0.0)	2	(0.0)
Malignant neoplasm progression	1	(0.2)	1	(0.1)	1	(0.0)	2	(0.0)
Myocardial infarction	1	(0.2)	1	(0.1)	2	(0.1)	4	(0.1)
Peripheral artery occlusion	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)
Pleural effusion	1	(0.2)	1	(0.1)	0	(0.0)	3	(0.1)
Pneumonitis	1	(0.2)	2	(0.3)	5	(0.1)	6	(0.1)
Pulmonary artery thrombosis	1	(0.2)	1	(0.1)	0	(0.0)	1	(0.0)

Table 78: Exposure-adjusted adverse events leading to death (Incidence ≥0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	Event Count and Rate (Events/100 person-months)†			
	KN042 Dataset for Pembrolizumab‖	First-line NSCLC Dataset for Pembrolizumab††	Reference Safety Dataset for Pembrolizumab¶	Cumulative Running Safety Dataset for Pembrolizumab§
Number of subjects exposed	636	790	3830	5246
Total exposure‡ person-months	5862.28	7674.18	26483.35	35298.86
Total events (rate)	70 (1.19)	83 (1.08)	162 (0.61)	284 (0.80)
Death	10 (0.2)	10 (0.1)	19 (0.1)	38 (0.1)
Pneumonia	8 (0.1)	9 (0.1)	16 (0.1)	27 (0.1)
Pulmonary embolism	6 (0.1)	6 (0.1)	3 (0.0)	12 (0.0)
Pulmonary haemorrhage	4 (0.1)	4 (0.1)	1 (0.0)	5 (0.0)
Respiratory failure	3 (0.1)	4 (0.1)	8 (0.0)	14 (0.0)
Cardiac arrest	2 (0.0)	4 (0.1)	4 (0.0)	9 (0.0)
Cardio-respiratory arrest	2 (0.0)	2 (0.0)	1 (0.0)	3 (0.0)

Adverse events of special interests (AEOSIs)

Table 79: Adverse event summary for AEOSI (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab‖		First-line NSCLC Dataset for Pembrolizumab††		Reference Safety Dataset for Pembrolizumab¶		Cumulative Running Safety Dataset for Pembrolizumab§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	177	(27.8)	228	(28.9)	857	(22.4)	1,192	(22.7)
with no adverse event	459	(72.2)	562	(71.1)	2,973	(77.6)	4,054	(77.3)
with drug-related† adverse events	163	(25.6)	205	(25.9)	744	(19.4)	1,035	(19.7)
with toxicity grade 3-5 adverse events	51	(8.0)	71	(9.0)	229	(6.0)	316	(6.0)
with toxicity grade 3-5 drug-related adverse events	48	(7.5)	64	(8.1)	196	(5.1)	275	(5.2)
with non-serious adverse events	137	(21.5)	175	(22.2)	698	(18.2)	974	(18.6)
with serious adverse events	53	(8.3)	72	(9.1)	227	(5.9)	307	(5.9)
with serious drug-related adverse events	51	(8.0)	68	(8.6)	199	(5.2)	273	(5.2)
with dose modification‡ due to an adverse event	85	(13.4)	109	(13.8)	312	(8.1)	436	(8.3)
who died	1	(0.2)	2	(0.3)	7	(0.2)	8	(0.2)
who died due to a drug-related adverse event	1	(0.2)	2	(0.3)	7	(0.2)	8	(0.2)
discontinued drug due to an adverse event	32	(5.0)	43	(5.4)	129	(3.4)	172	(3.3)
discontinued drug due to a drug-related adverse event	32	(5.0)	43	(5.4)	127	(3.3)	170	(3.2)
discontinued drug due to a serious adverse event	24	(3.8)	30	(3.8)	99	(2.6)	132	(2.5)
discontinued drug due to a serious drug-related adverse event	24	(3.8)	30	(3.8)	97	(2.5)	130	(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 Pembrolizumab in KN042.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN042 and KN024.

¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.

§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), Cohort C (Bladder Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN013 Cohort 4A (MLBCL), KN024, KN028, KN042, KN045, KN052, KN059 Cohort 1, KN087, KN158, KN164 Cohort A (Colorectal Carcinoma), and KN170.

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

Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

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

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

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

Pembrolizumab Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045:18JAN2017, KN052:09MAR2017)

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

Pembrolizumab Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013-Cohort 4A: 04AUG2017, KN170: 15AUG2017)

Pembrolizumab Database Cutoff Date for Cervical (KN028: 20FEB2017, KN158: 23AUG2017)

Source: [ISS: adam-adsl; adae]

Table 80: Subjects with adverse events of special interest by maximum toxicity grade (Incidence ≥0% in one or more treatment groups) (subjects in ASaT population treated with pembrolizumab)

	KN042 Dataset for Pembrolizumab[‖]		First-line NSCLC Dataset for Pembrolizumab[††]		Reference Safety Dataset for Pembrolizumab[¶]		Cumulative Running Safety Dataset for Pembrolizumab[§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	636		790		3,830		5,246	
with one or more adverse events	177	(27.8)	228	(28.9)	857	(22.4)	1,192	(22.7)
Grade 1	35	(5.5)	45	(5.7)	215	(5.6)	292	(5.6)
Grade 2	91	(14.3)	112	(14.2)	413	(10.8)	584	(11.1)
Grade 3	43	(6.8)	59	(7.5)	199	(5.2)	275	(5.2)
Grade 4	7	(1.1)	10	(1.3)	23	(0.6)	33	(0.6)
Grade 5	1	(0.2)	2	(0.3)	7	(0.2)	8	(0.2)
with no adverse events	459	(72.2)	562	(71.1)	2,973	(77.6)	4,054	(77.3)
Hypothyroidism	**77**	**(12.1)**	**93**	**(11.8)**	**347**	**(9.1)**	**503**	**(9.6)**
Grade 1	15	(2.4)	20	(2.5)	89	(2.3)	127	(2.4)
Grade 2	61	(9.6)	72	(9.1)	254	(6.6)	368	(7.0)
Grade 3	1	(0.2)	1	(0.1)	4	(0.1)	8	(0.2)
Pneumonitis	**53**	**(8.3)**	**65**	**(8.2)**	**142**	**(3.7)**	**211**	**(4.0)**
Grade 1	8	(1.3)	11	(1.4)	33	(0.9)	45	(0.9)
Grade 2	23	(3.6)	27	(3.4)	56	(1.5)	85	(1.6)
Grade 3	17	(2.7)	19	(2.4)	38	(1.0)	59	(1.1)
Grade 4	4	(0.6)	6	(0.8)	9	(0.2)	15	(0.3)
Grade 5	1	(0.2)	2	(0.3)	6	(0.2)	7	(0.1)
Hyperthyroidism	**39**	**(6.1)**	**50**	**(6.3)**	**134**	**(3.5)**	**200**	**(3.8)**
Grade 1	26	(4.1)	34	(4.3)	99	(2.6)	144	(2.7)
Grade 2	12	(1.9)	15	(1.9)	31	(0.8)	51	(1.0)
Grade 3	1	(0.2)	1	(0.1)	4	(0.1)	5	(0.1)
Colitis	**7**	**(1.1)**	**13**	**(1.6)**	**74**	**(1.9)**	**94**	**(1.8)**
Grade 1	1	(0.2)	2	(0.3)	10	(0.3)	14	(0.3)
Grade 2	2	(0.3)	4	(0.5)	16	(0.4)	22	(0.4)
Grade 3	4	(0.6)	7	(0.9)	45	(1.2)	55	(1.0)
Grade 4	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.1)
Hepatitis	**9**	**(1.4)**	**10**	**(1.3)**	**24**	**(0.6)**	**36**	**(0.7)**
Grade 1	1	(0.2)	1	(0.1)	1	(0.0)	2	(0.0)
Grade 2	1	(0.2)	1	(0.1)	4	(0.1)	6	(0.1)
Grade 3	5	(0.8)	6	(0.8)	17	(0.4)	24	(0.5)
Grade 4	2	(0.3)	2	(0.3)	2	(0.1)	4	(0.1)

Laboratory findings

In the KEYNOTE-042 Dataset, the most frequently reported (incidence >30%) laboratory abnormalities with a clinically meaningful worsening in CTCAE grade (all grades) in subjects treated with pembrolizumab were increased glucose (51.8%), decreased haemoglobin (43.1%), decreased albumin (33.3%), increased ALT (32.9%), increased AST (31.4%), and decreased sodium (30.6%). There were no important differences from the Reference Safety Dataset in the incidence of laboratory abnormalities.

Nearly all changes from baseline in laboratory abnormalities in KEYNOTE-042 were CTCAE Grade 1 or 2.

Grade 3 to 4 laboratory abnormalities occurred much more frequently in subjects treated with chemotherapy compared with pembrolizumab. Grade 3 to 4 laboratory abnormality occurred in >9% of subjects treated with pembrolizumab, whereas abnormalities in several parameters were observed in >10% of subjects treated with chemotherapy. Furthermore, the most common Grade 3 to 4 laboratory abnormalities in the pembrolizumab group occurred with similar or lower frequencies compared with those in the chemotherapy group. The most common Grade 3 to 4 laboratory abnormalities in both treatment groups were as follows:

• For pembrolizumab (>4%): decreased sodium (8.7%), decreased lymphocytes (7.3%), ALT increased (4.8%), increased glucose (4.7%), decreased phosphate (4.7%), and decreased haemoglobin (4.4%).

• For chemotherapy (>4%): decreased haemoglobin (19.1%), decreased neutrophils (18.1%), decreased leukocytes (13.0%), decreased lymphocytes (12.7%), decreased platelets (9.3%), decreased sodium (8.4%), increased glucose (5.1%), and decreased phosphate (4.3%).

Safety in special populations

Age

Table 81: Adverse event summary by age category (<65, 65-74, 75-84, ≥85 years) (subjects in ASaT population treated with pembrolizumab)

	First-line NSCLC Dataset for Pembrolizumab‖								Reference Safety Dataset for Pembrolizumab¶							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	435		267		79		9		2,056		1,164		522		88	
with one or more adverse events	418	(96.1)	257	(96.3)	77	(97.5)	9	(100.0)	1,997	(97.1)	1,127	(96.8)	509	(97.5)	87	(98.9)
with no adverse event	17	(3.9)	10	(3.7)	2	(2.5)	0	(0.0)	59	(2.9)	37	(3.2)	13	(2.5)	1	(1.1)
with drug-related† adverse events	290	(66.7)	175	(65.5)	46	(58.2)	6	(66.7)	1,475	(71.7)	832	(71.5)	379	(72.6)	65	(73.9)
with toxicity grade 3-5 adverse events	208	(47.8)	148	(55.4)	52	(65.8)	5	(55.6)	880	(42.8)	584	(50.2)	284	(54.4)	54	(61.4)
with toxicity grade 3-5 drug-related adverse events	70	(16.1)	64	(24.0)	23	(29.1)	4	(44.4)	271	(13.2)	197	(16.9)	94	(18.0)	15	(17.0)
with non-serious adverse events	402	(92.4)	241	(90.3)	70	(88.6)	9	(100.0)	1,963	(95.5)	1,099	(94.4)	500	(95.8)	85	(96.6)
with serious adverse events	176	(40.5)	116	(43.4)	42	(53.2)	4	(44.4)	688	(33.5)	482	(41.4)	238	(45.6)	42	(47.7)
with serious drug-related adverse events	58	(13.3)	45	(16.9)	16	(20.3)	3	(33.3)	191	(9.3)	136	(11.7)	67	(12.8)	9	(10.2)
with dose modification‡ due to an adverse event	194	(44.6)	134	(50.2)	41	(51.9)	5	(55.6)	602	(29.3)	418	(35.9)	208	(39.8)	28	(31.8)
who died	40	(9.2)	28	(10.5)	12	(15.2)	2	(22.2)	61	(3.0)	58	(5.0)	30	(5.7)	8	(9.1)
who died due to a drug-related adverse event	8	(1.8)	5	(1.9)	2	(2.5)	0	(0.0)	7	(0.3)	6	(0.5)	3	(0.6)	1	(1.1)
discontinued drug due to an adverse event	70	(16.1)	53	(19.9)	23	(29.1)	2	(22.2)	205	(10.0)	150	(12.9)	89	(17.0)	8	(9.1)
discontinued drug due to a drug-related adverse event	33	(7.6)	33	(12.4)	10	(12.7)	2	(22.2)	92	(4.5)	81	(7.0)	48	(9.2)	3	(3.4)
discontinued drug due to a serious adverse event	58	(13.3)	40	(15.0)	20	(25.3)	2	(22.2)	154	(7.5)	110	(9.5)	68	(13.0)	6	(6.8)
discontinued drug due to a serious drug-related adverse event	23	(5.3)	20	(7.5)	7	(8.9)	2	(22.2)	63	(3.1)	53	(4.6)	32	(6.1)	1	(1.1)

† 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 Pembrolizumab in KN042 and KN024.
¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.
Pembrolizumab Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Pembrolizumab Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Pembrolizumab Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Table 82: Adverse event summary for elderly subjects by age category (subjects in ASaT population treated with pembrolizumab)

	First-line NSCLC Dataset for Pembrolizumab‖								Reference Safety Dataset for Pembrolizumab¶							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	435	(100.0)	267	(100.0)	79	(100.0)	9	(100.0)	2056	(100.0)	1164	(100.0)	522	(100.0)	88	(100.0)
with one or more adverse events	75	(17.2)	53	(19.9)	20	(25.3)	3	(33.3)	1997	(97.1)	1127	(96.8)	509	(97.5)	87	(98.9)
who died	6	(1.4)	4	(1.5)	1	(1.3)	1	(11.1)	61	(3.0)	58	(5.0)	30	(5.7)	8	(9.1)
with serious adverse events	35	(8.0)	29	(10.9)	14	(17.7)	1	(11.1)	688	(33.5)	482	(41.4)	238	(45.6)	42	(47.7)
discontinued‡ due to an adverse event	12	(2.8)	10	(3.7)	4	(5.1)	0	(0.0)	205	(10.0)	150	(12.9)	89	(17.0)	8	(9.1)
CNS (confusion/extrapyramidal)	8	(1.8)	3	(1.1)	3	(3.8)	2	(22.2)	175	(8.5)	112	(9.6)	40	(7.7)	16	(18.2)
AE related to falling	7	(1.6)	11	(4.1)	0	(0.0)	0	(0.0)	151	(7.3)	118	(10.1)	59	(11.3)	17	(19.3)
CV events	16	(3.7)	14	(5.2)	6	(7.6)	1	(11.1)	381	(18.5)	272	(23.4)	123	(23.6)	20	(22.7)
Cerebrovascular events	4	(0.9)	2	(0.7)	1	(1.3)	0	(0.0)	37	(1.8)	26	(2.2)	13	(2.5)	3	(3.4)
Infections	35	(8.0)	24	(9.0)	9	(11.4)	1	(11.1)	868	(42.2)	531	(45.6)	233	(44.6)	37	(42.0)

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN042 and KN024.
¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.
Pembrolizumab Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015).
Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018).
Pembrolizumab Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Pembrolizumab Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: analysis-adsl; adae]

Sex

Table 83: Adverse event summary by gender (male, female) (subjects in ASaT population treated with pembrolizumab)

	First-line NSCLC Dataset for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab¶			
	M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	541		249		2,366		1,464	
with one or more adverse events	519	(95.9)	242	(97.2)	2,297	(97.1)	1,423	(97.2)
with no adverse event	22	(4.1)	7	(2.8)	69	(2.9)	41	(2.8)
with drug-related† adverse events	353	(65.2)	164	(65.9)	1,713	(72.4)	1,038	(70.9)
with toxicity grade 3-5 adverse events	272	(50.3)	141	(56.6)	1,124	(47.5)	678	(46.3)
with toxicity grade 3-5 drug-related adverse events	108	(20.0)	53	(21.3)	379	(16.0)	198	(13.5)
with non-serious adverse events	494	(91.3)	228	(91.6)	2,257	(95.4)	1,390	(94.9)
with serious adverse events	228	(42.1)	110	(44.2)	924	(39.1)	526	(35.9)
with serious drug-related adverse events	83	(15.3)	39	(15.7)	269	(11.4)	134	(9.2)
with dose modification‡ due to an adverse event	259	(47.9)	115	(46.2)	776	(32.8)	480	(32.8)
who died	60	(11.1)	22	(8.8)	106	(4.5)	51	(3.5)
who died due to a drug-related adverse event	9	(1.7)	6	(2.4)	13	(0.5)	4	(0.3)
discontinued drug due to an adverse event	105	(19.4)	43	(17.3)	284	(12.0)	168	(11.5)
discontinued drug due to a drug-related adverse event	57	(10.5)	21	(8.4)	152	(6.4)	72	(4.9)
discontinued drug due to a serious adverse event	82	(15.2)	38	(15.3)	216	(9.1)	122	(8.3)
discontinued drug due to a serious drug-related adverse event	36	(6.7)	16	(6.4)	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 Pembrolizumab in KN042 and KN024.

¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.

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

Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

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

Pembrolizumab Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

ECOG

Table 84: Adverse event summary by ECOG status category (0, 1) (subjects in ASaT population treated with pembrolizumab)

	First-line NSCLC Dataset for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab¶			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	248		541		1,811		1,851	
with one or more adverse events	240	(96.8)	521	(96.3)	1,770	(97.7)	1,789	(96.7)
with no adverse event	8	(3.2)	20	(3.7)	41	(2.3)	62	(3.3)
with drug-related† adverse events	164	(66.1)	353	(65.2)	1,400	(77.3)	1,261	(68.1)
with toxicity grade 3-5 adverse events	120	(48.4)	293	(54.2)	743	(41.0)	960	(51.9)
with toxicity grade 3-5 drug-related adverse events	57	(23.0)	104	(19.2)	263	(14.5)	285	(15.4)
with non-serious adverse events	234	(94.4)	488	(90.2)	1,750	(96.6)	1,741	(94.1)
with serious adverse events	101	(40.7)	237	(43.8)	587	(32.4)	780	(42.1)
with serious drug-related adverse events	44	(17.7)	78	(14.4)	193	(10.7)	192	(10.4)
with dose modification‡ due to an adverse event	108	(43.5)	266	(49.2)	537	(29.7)	659	(35.6)
who died	20	(8.1)	62	(11.5)	50	(2.8)	95	(5.1)
who died due to a drug-related adverse event	5	(2.0)	10	(1.8)	7	(0.4)	10	(0.5)
discontinued drug due to an adverse event	38	(15.3)	110	(20.3)	182	(10.0)	244	(13.2)
discontinued drug due to a drug-related adverse event	23	(9.3)	55	(10.2)	105	(5.8)	106	(5.7)
discontinued drug due to a serious adverse event	32	(12.9)	88	(16.3)	128	(7.1)	190	(10.3)
discontinued drug due to a serious drug-related adverse event	17	(6.9)	35	(6.5)	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 Pembrolizumab in KN042 and KN024.
¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.
Pembrolizumab Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)
Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Pembrolizumab Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Pembrolizumab Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Race

Table 85: Adverse event summary by race (white, non-white) (subjects in ASaT population treated with pembrolizumab)

	First-line NSCLC Dataset for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab¶			
	White		Non-White		White		Non-White	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	522		266		3,325		461	
with one or more adverse events	506	(96.9)	253	(95.1)	3,237	(97.4)	441	(95.7)
with no adverse event	16	(3.1)	13	(4.9)	88	(2.6)	20	(4.3)
with drug-related† adverse events	319	(61.1)	196	(73.7)	2,420	(72.8)	300	(65.1)
with toxicity grade 3-5 adverse events	288	(55.2)	125	(47.0)	1,571	(47.2)	209	(45.3)
with toxicity grade 3-5 drug-related adverse events	102	(19.5)	59	(22.2)	505	(15.2)	66	(14.3)
with non-serious adverse events	475	(91.0)	245	(92.1)	3,176	(95.5)	431	(93.5)
with serious adverse events	231	(44.3)	107	(40.2)	1,266	(38.1)	172	(37.3)
with serious drug-related adverse events	66	(12.6)	56	(21.1)	344	(10.3)	55	(11.9)
with dose modification‡ due to an adverse event	261	(50.0)	113	(42.5)	1,090	(32.8)	150	(32.5)
who died	64	(12.3)	18	(6.8)	130	(3.9)	26	(5.6)
who died due to a drug-related adverse event	10	(1.9)	5	(1.9)	11	(0.3)	6	(1.3)
discontinued drug due to an adverse event	102	(19.5)	46	(17.3)	399	(12.0)	51	(11.1)
discontinued drug due to a drug-related adverse event	45	(8.6)	33	(12.4)	198	(6.0)	24	(5.2)
discontinued drug due to a serious adverse event	83	(15.9)	37	(13.9)	299	(9.0)	38	(8.2)
discontinued drug due to a serious drug-related adverse event	28	(5.4)	24	(9.0)	130	(3	18	(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.

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

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN042 and KN024.

¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.

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

Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

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

Pembrolizumab Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Region

Table 86: Adverse event summary by region (EU, ex-EU) (subjects in ASaT population treated with pembrolizumab)

	First-line NSCLC Dataset for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab¶			
	EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	228		562		1,384		2,446	
with one or more adverse events	222	(97.4)	539	(95.9)	1,334	(96.4)	2,386	(97.5)
with no adverse event	6	(2.6)	23	(4.1)	50	(3.6)	60	(2.5)
with drug-related† adverse events	127	(55.7)	390	(69.4)	946	(68.4)	1,805	(73.8)
with toxicity grade 3-5 adverse events	119	(52.2)	294	(52.3)	644	(46.5)	1,158	(47.3)
with toxicity grade 3-5 drug-related adverse events	37	(16.2)	124	(22.1)	213	(15.4)	364	(14.9)
with non-serious adverse events	210	(92.1)	512	(91.1)	1,295	(93.6)	2,352	(96.2)
with serious adverse events	106	(46.5)	232	(41.3)	550	(39.7)	900	(36.8)
with serious drug-related adverse events	26	(11.4)	96	(17.1)	163	(11.8)	240	(9.8)
with dose modification‡ due to an adverse event	102	(44.7)	272	(48.4)	454	(32.8)	802	(32.8)
who died	28	(12.3)	54	(9.6)	68	(4.9)	89	(3.6)
who died due to a drug-related adverse event	2	(0.9)	13	(2.3)	6	(0.4)	11	(0.4)
discontinued drug due to an adverse event	43	(18.9)	105	(18.7)	160	(11.6)	292	(11.9)
discontinued drug due to a drug-related adverse event	17	(7.5)	61	(10.9)	84	(6.1)	140	(5.7)
discontinued drug due to a serious adverse event	34	(14.9)	86	(15.3)	127	(9.2)	211	(8.6)
discontinued drug due to a serious drug-related adverse event	9	(3.9)	43	(7.7)	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 Pembrolizumab in KN042 and KN024.

¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052, and KN087.

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

Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

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

Pembrolizumab Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

No interaction studies have been submitted as part of this application.

Discontinuation due to adverse events

Table 87: Exposure-adjusted adverse events leading to drug discontinuation (including multiple occurrence of events) (Incidence ≥0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	Event Count and Rate (Events/100 person-months)[†]			
	KN042 Dataset for Pembrolizumab[‖]	First-line NSCLC Dataset for Pembrolizumab[††]	Reference Safety Dataset for Pembrolizumab[¶]	Cumulative Running Safety Dataset for Pembrolizumab[§]
Number of subjects exposed	636	790	3830	5246
Total exposure[‡] person-months	5862.28	7674.18	26483.35	35298.86
Total events (rate)	132 (2.25)	159 (2.07)	490 (1.85)	706 (2.00)
Pneumonitis	19 (0.3)	27 (0.4)	57 (0.2)	80 (0.2)
Death	10 (0.2)	10 (0.1)	11 (0.0)	25 (0.1)
Pneumonia	9 (0.2)	10 (0.1)	10 (0.0)	20 (0.1)
Alanine aminotransferase increased	6 (0.1)	8 (0.1)	4 (0.0)	15 (0.0)

Table 88: Exposure-adjusted adverse events leading to dose modification (including multiple occurrence of events) (Incidence ≥0% in one or more treatment groups) by decreasing frequency of preferred term (subjects in ASaT population treated with pembrolizumab)

	Event Count and Rate (Events/100 person-months)[†]			
	KN042 Dataset for Pembrolizumab[‖]	First-line NSCLC Dataset for Pembrolizumab[††]	Reference Safety Dataset for Pembrolizumab[¶]	Cumulative Running Safety Dataset for Pembrolizumab[§]
Number of subjects exposed	636	790	3830	5246
Total exposure[‡] person-months	5862.28	7674.18	26483.35	35298.86
Total events (rate)	537 (9.16)	693 (9.03)	2099 (7.93)	3049 (8.64)
Pneumonitis	39 (0.7)	49 (0.6)	101 (0.4)	150 (0.4)
Pneumonia	28 (0.5)	30 (0.4)	46 (0.2)	83 (0.2)
Alanine aminotransferase increased	22 (0.4)	27 (0.4)	53 (0.2)	88 (0.2)
Hypothyroidism	18 (0.3)	20 (0.3)	25 (0.1)	44 (0.1)
Aspartate aminotransferase increased	16 (0.3)	20 (0.3)	50 (0.2)	80 (0.2)
Rash	14 (0.2)	16 (0.2)	31 (0.1)	47 (0.1)
Diarrhoea	13 (0.2)	27 (0.4)	97 (0.4)	114 (0.3)
Asthenia	11 (0.2)	12 (0.2)	16 (0.1)	29 (0.1)
Dyspnoea	11 (0.2)	16 (0.2)	46 (0.2)	64 (0.2)
Death	10 (0.2)	10 (0.1)	11 (0.0)	25 (0.1)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 03-Sept-2018 through 03-Sep-2019.

2.5.1. Discussion on clinical safety

The MAH presented a comparison of the safety profile of pembrolizumab vs chemotherapy as first-line treatment of NSCLC through an individual analysis of Study KN-042 (ASaT population: 636 and 615 patients in the pembrolizumab and control arm) as well as a pooled database incorporating KN-042 and KN-024 (ASaT population: 790 and 765 patients in the pembrolizumab and control arm). The safety data derived from the clinical experience with pembrolizumab in the first-line setting of NSCLC was compared to the Reference Dataset (RDS; N=3830) and cumulative Database (CDS; N=5246), mainly including trials of pembrolizumab in the second-line therapy of distinct clinical indications.

The duration of exposure was longer for pembrolizumab compared with chemotherapy (mean 253.3 vs 156.6 days and median number of administrations 9 vs. 6, respectively). A total of 302 (47.5%) subjects in the pembrolizumab group and 143 (23.3%) subjects in the chemotherapy group received treatment

for ≥ 6 months. As expected for the 1L NSCLC setting the mean exposure to pembrolizumab in KN042 was also longer compared with the RSD (8.3 months vs 6.7 months, respectively) as were the proportions of subjects exposed to pembrolizumab for ≥12 months (29.4% vs 20.5%).

Pembrolizumab treatment favorably compares with chemotherapy in terms of drug-related AEs (62.7% vs 89.9%), Grade≥3 AEs (50% vs 57.1%), drug-related Grade≥3 AEs (17.8% vs 41%), serious drug-related AEs (13.7 vs 14.6%). Similarly, pembrolizumab treatment favorably compares with chemotherapy in relation to treatment discontinuation due to drug-related AEs (19.2% vs 14.5%) and treatment discontinuation due to SAEs (16% vs 9.3%) and drug-related SAEs (6.1% vs 4.2%). The longer exposure of patients to pembrolizumab rather than chemotherapy (9 vs. 6 administrations in median) accounts for an even more favourable safety profile of pembrolizumab following adjustment by exposure time (overall AEs rate of 83.16 vs 170.33 events/100 person-months). Similarly, exposure-adjusted grade 3-5 AEs (10.49 vs 21.85 events/100 person-months) and SAEs (6.93 vs 8.05 events/100 person-months) occurred at a lower frequency in the pembrolizumab than control arm, while a similar incidence of AEs leading to discontinuation was found between treatments (2.25 vs 2.74 events/100 person-months).

As expected on the basis of the disease specific setting and prior experience with pembrolizumab, endocrine (hypothyroidism), skin (rash) and respiratory disorders (dyspnoea, cough and pneumonia) were the most commonly reported AEs in the experimental arm of KN-042 (>10% incidence), while gastrointestinal (vomiting, constipation and nausea) and blood disturbances (myelosuppression) were the prevailing AEs in the chemotherapy group (all of them with an incidence >10%). The incidence of overall AEs in the KN-042 pembrolizumab dataset was comparable to the RDS and CDS; however, pneumonia occurred more frequently in the pivotal trial than previously reported (11.9% incidence vs 4.7% and 5.4% in the RDS and CDS, respectively) likely due to the underlying disease of the study population.

Drug-related AEs were more commonly reported in the chemotherapy (89.9%) than pembrolizumab (62.7%) group.

Overall analysis of Grade 3 to 5 AEs was in favour of the pembrolizumab group; Grade 3 to 5 AEs were reported in 50.0% of subjects in the pembrolizumab group and 57.1% in the chemotherapy group. Analysis of exposure-adjusted event rates of Grade 3 to 5 AEs showed that the rate for pembrolizumab group was half of the rate for the chemotherapy group (10.49 vs 21.85 events/100 person-months) and the median time to first Grade 3 to 5 AE was longer in the pembrolizumab group than in the chemotherapy group (49.4 weeks vs 17.0 weeks). These numerical differences in Grade 3-5 AEs appeared to be mainly driven by the higher proportion of haematological toxicities in the chemotherapy group.

Among the Grade 3-5 AEs, pneumonitis was the main event that was causally-related to pembrolizumab in study KN-042 (3.1% vs 0% in the control), followed by drug-related ALT increase (1.4% vs 0.8%); both of them presented with a higher frequency than in the prior datasets (1.2% and 1.3% for pneumonitis in the RDS and CDS; 0.5% and 0.7% for ALT increase in the RDS and CDS) as also confirmed by the exposure-adjustment analysis. Similar considerations apply to the analysis of SAEs, for which pneumonia was reported in 7.4% of patients receiving pembrolizumab vs 5.2% assigned to chemotherapy (no cases of pneumonia were considered drug-related), and pneumonitis in 3.9% of the experimental arm (all cases considered drug-related) vs 0.2% in the control. The incidence of pneumonitis as drug-related SAE was higher in KN-042 (3.9%) compared to the RDS (1.8%) and CDS (1.7%); this is likely due to the specific NSCLC-disease setting. The MAH provided further analyses on immune-related pneumonitis, and consequently updated the SmPC to present incidence rates of pneumonitis for all patients, for patients with NSCLC and for subjects with and without prior thoracic irradiation in the pooled monotherapy population.

Additionally, numerically higher rates for Grade 3 to 5 cardiac disorders were notable with 4.4% for pembrolizumab in KN-042 vs. 2.8% in the Reference Safety Dataset; (Exposure adjusted rates for cardiac disorders were 0.6 events/100 person-months in the pembrolizumab group of KN-042 compared to 0.3 in the chemotherapy group of KN-042). Rates of drug-related grade 3-5 cardiac disorders were 1.4% vs. 0.2%, respectively. Of note are the high incidences of serious cardiac disorder events in the pembrolizumab arm of KN-042. Serious cardiac disorders were also slightly higher compared to the RSD. In the analysis of SAEs by SOC 4.2% of subjects experienced a cardiac disorder in the KN-042 Dataset for pembrolizumab compared to 3.1% of subjects in the RSD. The higher rate of events in the KEYNOTE-042 pembrolizumab group was driven by increases in the frequency of Grade 3 to 5 AEs and SAEs of cardiac arrest, cardiac failure/cardiac failure acute, myocardial infarction, and, more notably, pericardial effusion and cardiac tamponade as compared with chemotherapy and the RSD. However, interpretation of these data is difficult. It is acknowledged that the observed differences may be partially related to the longer exposure to pembrolizumab in the 1L NSCLC setting and that underlying disease progression and pre-existing conditions are confounding factors to assess the clear contribution of pembrolizumab to the manifestation of the events. Moreover, small events numbers further hamper drawing definitive conclusions. However, cardiac toxicity will need persistent attention with further evolving safety data.

A higher rate of deaths due to AEs in the KN-042 was observed with pembrolizumab arm (11%) compared to chemotherapy (7.5%). The overall incidence of deaths due to AEs in this trial was even higher compared with the Reference Safety Dataset (4.1%), and with Study KN-024 (7.8%). The cause of death was most frequently unknown (10/70 patients, 1.6%), followed bypneumonia (1.3%), pulmonary embolism (0.9%), pulmonary haemorrhage (0.6%) and respiratory failure (0.5%). The findings of a higher rate of deaths compared to Study KN-024, together with the observation of the higher risk of early deaths reported in Study KN-042 (but not in Study KN-024) raises concerns. A review of AEs resulting in death for each arm, ordered by the time from randomization and the type of event did not raise concerns. They were mainly respiratory and cardiovascular causes, the majority of them being not considered causally related to the study drug by the Investigator.

While the number of subjects who died due to an AE was generally similar between the pembrolizumab and chemotherapy groups for subjects with TPS ≥50%, more subjects died due to an AE in the pembrolizumab group compared with the chemotherapy group for TPS 1-49% group. This is driven by the higher percentage of subjects with PD as the best overall response. Across all subgroups a large proportion of patients had "no assessment", probably related to an early death with no subsequent imaging assessment for response. Overall, these data indicate that the higher rates of death due to an AE in this study might be rather associated with the lack of efficacy in the low PD-L1 expression subgroup than to an increased toxicity of pembrolizumab monotherapy.

No major differences emerged in the analysis of safety in special populations that showed a similar profile across patient subgroups by either intrinsic or extrinsic factors, between KN-042 and the reference datasets.

The proportion of subjects who experienced AEs generally increased with increasing age for all AE categories for both pembrolizumab and chemotherapy and no major concerns emerged regarding the tolerability of pembrolizumab monotherapy in elderly NSCLC patients (although the limitations of the still small patient numbers in the age group beyond 75 years have be taken into account).

In terms of AEs leading to drug discontinuation, the exposure-adjusted analysis indicates a similar profile of pembrolizumab between study KN-042 and the reference datasets.

Finally, AEOSIs in KN-042 occurred at a similar frequency than previously reported with the exception of hypothyroidism (12.1% vs 9.1% in RSD and 9.6% in CSD), pneumonitis (8.3% vs 3.7% in RSD and 4% in CSD) and hyperthyroidism (6.1% vs 3.5% in RSD and 3.8% in CSD) which could be attributable

to both the longer treatment in KN-042 than the reference datasets as well as NSCLC disease-specific setting. Of note, the majority of these events were of Grade 1-2. As discussed above, the higher incidence of pneumonitis and the relative figures have been included in the SmPC. The analysis of hypothyroidism and hyperthyroidism events was comparable in NSCLC and non-NSCLC populations, therefore the SmPC has not been updated.

2.5.2. Conclusions on clinical safety

The safety profile of pembrolizumab monotherapy that emerges from KN-042 is overall consistent with the prior clinical experience. Of note, the comparison with chemotherapy revealed a more favourable outcome achieved with pembrolizumab in NSCLC patients. Further analyses indicated that the higher rates of death due to an AE in this study might be rather associated with the lack of efficacy in the low PD-L1 expression subgroup than to an increased toxicity of pembrolizumab monotherapy.

A somewhat worse toxicity profile is notable for pembrolizumab in the 1L NSCLC indication compared to the reference safety dataset, which might be partly attributable to a slightly longer exposure of pembrolizumab and the underlying disease.

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 28.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 28.0 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

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

Pharmacovigilance plan

Table III.3.1: On-Going and Planned Additional Pharmacovigilance Activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities					
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT.	Important potential 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) -Important potential risk (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	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 Non-squamous Non-small Cell Lung Cancer Subjects (KN189)	To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy and to evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using OS.	-Important identified risks (Immune-related adverse reactions) -Important potential risk (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Jun 2021

Risk minimisation measures

Table V.3.1: Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures
	Important Identified Risks: Immune-Related Adverse Reactions

Table V.3.1: Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.
	Additional risk minimisation measures: Patient educational materials
	Important Potential Risks
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted

2.7. Update of the Product information

Sections 4.4, 4.8 and 5.1 of the SmPC have been updated to reflect the results from study KEYNOTE-042; an international, randomized, open-label Phase 3 study investigating KEYTRUDA monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC. Particularly, a new warning with regard to a higher number of deaths within 4 months of treatment initiation of Keytruda monotherapy compared to chemotherapy has been added to the product information.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups..

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

With the current application, the MAH was initially seeking an extension of indication for pembrolizumab monotherapy in the first-line treatment of squamous and non-squamous metastatic and locally advanced NSCLC with a positive PD-L1 score (TPS ≥1%) and negative for EGFR and ALK gene mutations.

3.1.2. Available therapies and unmet medical need

Current guidelines recommend the use of pembrolizumab monotherapy for the treatment of non-small cell lung cancer (NSCLC), i.e. the prevailing histological subtype (85%-90%) of all lung malignancies, as follows:

- First-line treatment of patients with metastatic NSCLC in patients whose tumours have high PD-L1 expression [Tumour Proportion Score (TPS) ≥ 50%] with no EGFR or ALK positive tumour aberrations
- Advanced or metastatic NSCLC in patients whose tumours express PD-L1 (TPS ≥1%) and who have received prior platinum-based therapy, and if the tumours express EGFR or ALK genomic tumour aberrations should have disease progression on approved therapy before receiving Keytruda.

Moreover, Keytruda is currently authorised as add-on therapy to pemetrexed and platinum chemotherapy as first-line option for patients with metastatic non-squamous NSCLC, irrespective of the PD-L1 level of expression. However, the combined therapy was proven to hold higher toxicity than chemotherapy alone, particularly in elderly patients. This could represent an important limitation to the use of this therapeutic scheme on the basis of patient tolerability, particularly for those with a TPS < 50% for whom chemotherapy would be the only licensed therapy. The same applies to squamous NSCLC, for which pembrolizumab in combination with carboplatin/(nab)paclitaxel has been approved in first-line. The treatment of NSCLC remains a high unmet medical need.

3.1.3. Main clinical studies

KEYNOTE-042 is the pivotal trial supporting this application. It is a Phase 3, randomized, open-label, controlled clinical study of pembrolizumab versus platinum-based chemotherapy in treatment-naïve advanced or metastatic NSCLC patients, including both squamous and non-squamous histology, who present with ALK/EGFR negative disease and a positive PD-L1 score (TPS ≥1%). The MAH submitted results from the second interim analysis (IA2; date cutoff: 26-Feb-2018). During the procedure, the planned Final Analysis (FA; date cutoff: 04-Sep-2018) was also provided, and an additional extended follow-up served for an updated analysis of OS (cutoff date: 25-Oct-2019).

3.2. Favourable effects

In the final analysis, pembrolizumab demonstrated superiority over chemotherapy in the ITT population (TPS≥1%), with a gain in 4 months in OS and HR 0.82 (95% CI: 0.71, 0.93; p=0.0013; 12-month and 18-month OS rates of 57.8% versus 50.7% and 49.7% versus 37.5%, respectively).

Within the TPS ≥50% group, OS was in favour of pembrolizumab with a gain of 8 months in median OS (HR= 0.70;95% CI: 0.58, 0.86; p=0.0003).

Superiority of pembrolizumab over chemotherapy was also demonstrated in the TPS ≥ 20% subgroup with a gain of around 5 months in median OS (HR 0.77;95% CI: 0.65, 0.91; p=0.0012).

3.3. Uncertainties and limitations about favourable effects

Within the subgroup of patients of main interest to the current application (TPS 1-49% group), no benefit of pembrolizumab compared to chemotherapy was demonstrated in terms of OS (HR 0.91, 95% CI: 0.77-1.09; p=n.s). HR of PFS in TPS 1-49% NSCLC was 1.27 favouring chemotherapy.

The number of responders was lower in the pembrolizumab group vs. the chemotherapy group in TPS 1-49% NSCLC with response rates of 16.5% vs 21.3%.

Within the ITT population (TPS ≥1%) as well as in all subgroup analyses (TPS ≥20% and TPS ≥50%) the OS K-M curves crossed at around month 6, showing a more favourable outcome in the control arm during the first months from treatment initiation while an increased risk of early deaths emerged in the subgroup of patients exposed to pembrolizumab. Inconsistent results were achieved in terms of predictive factors for early death across PD-L1 categories. Sections 4.4 and 5.1 of the SmPC have been updated to reflect that a higher number of deaths within 4 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy for the already approved indication of pembrolizumab in NSCLC patients with TPS ≥50%.

3.4. Unfavourable effects

As expected on the basis of the disease specific setting and prior experience with pembrolizumab, endocrine (hypothyroidism), skin (rash) and respiratory disorders (dyspnoea, cough and pneumonia) were the most commonly reported AEs with Keytruda (>10% incidence), while gastrointestinal (vomiting, constipation and nausea) and blood disturbances (myelosuppression) were the prevailing AEs in the chemotherapy group (>10% incidence).

A higher rate of deaths due to AEs in the KN-042 was observed with pembrolizumab arm (11%) compared to chemotherapy (7.5%). The overall incidence of deaths due to AEs in this trial was even higher compared with the Reference Safety Dataset (4.1%), and with Study KN-024 (7.8%). The higher rates of death due to an AE in this study might be rather associated with the lack of efficacy in the low PD-L1 expression subgroup than to an increased toxicity of pembrolizumab monotherapy.

Pembrolizumab showed a more favourable safety profile than chemotherapy following adjustment by exposure time. Overall AEs rate was 83.16 vs 170.33 events/100 person-months and grade 3-5 AE rate of 10.49 vs 21.85 events/100 person-months for pembrolizumab versus chemotherapy respectively. SAEs were 6.93 (pembrolizumab) vs 8.05 events/100 person-months (chemotherapy) while a similar incidence of AEs leading to discontinuation was found between treatments (2.25 vs 2.74 events/100 person-months).

3.5. Uncertainties and limitations about unfavourable effects

The incidence of overall AEs in the KN-042 pembrolizumab dataset was comparable to the reference dataset and cumulative dataset; however, pneumonia occurred more frequently in the pivotal trial than previously reported (11.9% incidence vs 4.7% and 5.4% in the RDS and CDS, respectively) likely due to the underlying disease of the study population. The slight increase of pneumonitis in the NSCLC compared with the non-NSCLC population and the RDS may be attributed to the higher frequency of patients in the NSCLC population who received prior thoracic radiation (15.8%) compared with the non-NSCLC population (2.8%) and the RSD (8.0%).

Rates of severe and serious cardiac events for pembrolizumab in 1L NSCLC appeared to be increased compared to chemotherapy and compared to the RSD. The higher rate of events in the KEYNOTE-042 pembrolizumab group was driven by increases in the frequency of Grade 3 to 5 AEs and SAEs of cardiac

arrest, cardiac failure/cardiac failure acute, myocardial infarction, and, more notably, pericardial effusion and cardiac tamponade as compared with chemotherapy and the RSD.

However, interpretation of these data is difficult due to the longer exposure to pembrolizumab in the 1L NSCLC setting, underlying disease progression and comorbidities and the small event numerosity. Cardiac toxicity will need persistent attention with further evolving safety data (routine pharmacovigilance).

3.6. Effects Table

Table 89: Effects Table for pembrolizumab monotherapy versus platinum based chemotherapy in treatment-naïve advanced or metastatic NSCLC patients, including both squamous and non-squamous histology, who present with ALK/EGFR negative disease and a positive PD-L1 score (TPS ≥1%) (KEYNOTE-042) (data cut-off: 04-Sep-2018)

Effect	Short description	Unit	Pembrolizumab 200 mg QW3	chemotherapy	Uncertainties / Strength of evidence	Ref
Favourable Effects						
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	16.4 (14.0, 19.7)	12.1 (11.3, 13.3)	Efficacy not demonstrated for the TPS 1-49% subgroup (target population of the current extension of indication) OS in TPS 1-49%: median OS 13.4 (10.7, 16.9) vs 12.1 (11.0, 14.0) months; HR 0.90 (0.76, 1.06)	CSR
PFS	survival without progression from randomization to PD or death whichever occurred first BIRC per RECIST 1.1	median months (95% CI)	5.4 (4.3, 6.2)	6.6 (6.3, 7.3)	PFS not reaching statistical significance PFS in TPS 1-49%: median PFS 4.2 (4.1, 5.2) vs 6.8 (6.3, 8.1) months; HR 1.27 (95%CI 1.08, 1.50)	CSR
ORR	Confirmed CR + PR BIRC per RECIST 1.1	%	27.2%	26.5%	Disease control trended towards a more favourable effect of chemotherapy (76.3% vs 68.9% in the TPS ⩾ 50% category) ORR in TPS 1-49%: 16.6% vs 21.7%	CSR
Unfavourable Effects						
Tolerability	Drug-related AEs	%	63.7	89.9	The rate of overall AEs in the pembrolizumab group was comparable to the reference datasets	CSR
	Grade 3-5 AEs	%	51.3	56.9		
	Drug-related G 3-5 AEs	%	18.4	41.1		
	SAEs	%	40.4	30.4		
	Death due to AEs	%	10.7	7.6		
	Discontinuation due to AEs	%	20.4	14.8		
	Discontinuation due to SAEs	%	16.4	9.3		
Selected AEOSIs	Pneumonitis	%	8.2	0.5	An increased incidence of pneumonitis was reported compared with the reference datasets	CSR
	Hypothyroidism	%	11.9	1.5		

Abbreviations: OS: overall survival; PFS: progression free survival; ORR: overall response rate; AEOSI: Adverse events of special interest

Notes: the ITT population of KN-042 study is TPS≥1%. Results are from final analysis.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study KN-042 showed that the clinical benefit of immunotherapy over chemotherapy within the ITT population (TPS ≥1%) is mainly derived from the subgroup of patients with PD-L1 highly expressing tumours (TPS ≥50%), for whom pembrolizumab is already licensed. Extension of the clinical indication to include the complementary population with PD-L1 score 1-49% is not currently supported by a demonstrated clinical benefit of pembrolizumab compared to chemotherapy in this subcategory of patients, on the basis of a non-significant advantage in OS of pembrolizumab over chemotherapy, lack of beneficial effect on PFS and superiority of chemotherapy over pembrolizumab in ORR.

Moreover, contradicting results in terms of potential predictive factors for response to treatment were observed in the TPS 1-49% and TPS≥50% group, not allowing any claim on the ITT population of TPS≥1%. The presented data are not considered conclusive and do not alleviate the CHMP concerns on the higher risk of early death in the ITT population of TPS≥1%. This is more relevant for the TPS 1-49%, that represents a relevant portion of the ITT population (53% and 54% of the study population and total deaths, respectively). Considering the absence of a clear long-term benefit in this group, the uncertainty on the short-term outcome cannot be overcome.

The safety profile of pembrolizumab monotherapy that emerges from KN-042 is consistent with the prior clinical experience. Of note, the comparison with chemotherapy revealed a more favourable outcome achieved with pembrolizumab in NSCLC patients. However, patient subgroups at increased risk of early deaths with pembrolizumab compared to SOC have not been fully characterized so far despite several analyses. In the absence of clinical indicators able to select patients with TPS 1-49%, for treatment appropriately, the acceptability of the uncertainties related to the higher risk of early death might be envisaged only in subjects not suitable for chemotherapy or pembrolizumab combination (the latter recently approved in the first line setting of both squamous and non-squamous histology). However, this was not the target population enrolled in KN-042.

3.7.2. Balance of benefits and risks

At the present stage, taking into account the observed increases in the risk of early death, particularly marked in the subgroup of patients with PD-L1 expression TPS 1-49%, and due the lack of identified clinical indicators for the proper selection of patients, the current extension of indication is considered not approvable.

3.8. Conclusions

The overall B/R of Keytruda monotherapy is considered negative for patients with a PD-L1 TPS 1-49%. During the procedure, the MAH has decided to no longer pursue the extension of the indication and to only update the PI with relevant safety and efficacy information from study KN-042.

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 II

Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect the results from study KEYNOTE-042; an international, randomized, open-label Phase 3 study investigating KEYTRUDA monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC. An updated RMP version 28.0 was submitted as part of the application. In addition, the MAH revised the due date for the submission of Annex II study P361 to Q4 2020.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect the results from study KEYNOTE-042; an international, randomized, open-label Phase 3 study investigating KEYTRUDA monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC. An updated RMP version 28.0 was submitted as part of the application. In addition, the MAH revised the due date for the submission of Annex II study P361 to Q4 2020.

Summary

Please refer to the Scientific Discussion Keytruda-H-C-3820/II/0057.