15 December 2016
EMA/16441/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0011

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 Event of Special Interest
ALB	Albumin
ALK	Anaplastic Lymphoma Kinase
AMT	amount
ASaT	All Subject as Treated
AUC	Area under the concentration versus time curve
BIL	Bilirubin
BICR	Blinded Independent Central Radiologist
BSLD	Baseline Tumor burden
CL	Clearance
CMAX	Peak serum concentration
CMT	Compartment
CONC	Concentration
CNS	Central Nervous System
CR	Complete Response
CRA	Commercial Ready Assay
CV	Percent coefficient of variation = [standard deviation/mean] x 100
CWRES	Conditional weighted residuals
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eDMC	external Data Monitoring Committee
DF	Degree of freedom
DV	Dependent variable (observed concentration)
EGFR	Epidermal Growth Factor Receptor
FAS	Full Analysis Set
FO	First order estimation method of NONMEM
FOCE	First order conditional estimation method of NONMEM
H	Hour
HR	Hazard Ratio
IA2	Second Interim Analysis
IHC	Immunohistochemistry
IPI	ipilimumab
IPRED	Individual predicted concentration
irAE	Immune-related Adverse Event
irRC	Immune-related Response Criteria
ITT	Intention To Treat
IV	intravenous
Kg	kilogram
L	Liter
MDV	Missing concentration (dependent variable)
µg	Microgram
mg	Milligram
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
NM-TRAN	NONMEM translator
NONMEM	Nonlinear mixed-effects modeling software
NSCLC	Non Small Cell Lung Cancer

OFV	Objective function value
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetic
Pop PK	Population Pharmacokinetic
PRED	Population predicted concentration
PS	Performance Status
PL	Package Leaflet
PR	Partial Response
PRO	Patient Reported Outcome
Q	Inter-compartmental flow rate
Q3W	every 3 weeks
QoL	Quality of Life
RECIST 1.1	Response Evaluation Criteria on Solid Tumors Version 1.1
RSE	Percent relative standard error = [standard error/population mean estimate] x 100
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	Standard of Care
t1/2	Terminal elimination half-life
WRES	Weighted residuals
WT	Body weight
ω^2	Variance of the interindividual variability
σ^2	Variance of the residual variability

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 Limited submitted to the European Medicines Agency on 26 July 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment of previously untreated patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) whose tumors express PD-L1; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are proposed to be updated. The Package Leaflet is updated in accordance. An updated RMP version 4.0 was provided as part of the application.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0059/2014 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0059/2014 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

Scientific advice on the design of the pivotal study P024 has been obtained from the CHMP (EMEA/H/SAH/023/1/2014/II).

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	26 July 2016
Start of procedure	13 August 2016
CHMP Rapporteur Assessment Report	7 October 2016
CHMP Co-Rapporteur Assessment Report	5 October 2016
PRAC Rapporteur Assessment Report	13 October 2016
PRAC members comments	19 October 2016
Updated PRAC Rapporteur Assessment Report	20 October 2016
PRAC Outcome	27 October 2016
CHMP members comments	31 October 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2016
Request for supplementary information (RSI)	10 November 2016
Submission of responses	15 November 2016
PRAC Rapporteur Assessment Report	30 November 2016
CHMP Rapporteur Assessment Report	30 November 2016
CHMP members comments	1 December 2016
PRAC members comments	N/A
Updated CHMP Rapporteur Assessment Report	7 December 2016
Updated PRAC Rapporteur Assessment Report	7 December 2016
Opinion	15 December 2016
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Keytruda in comparison with existing therapies (Appendix 1)	15 December 2016

2. Scientific discussion

2.1. Introduction

Keytruda (pembrolizumab, MK-3475) is a humanized monoclonal antibody acting as immune checkpoint inhibitor through the block of the interaction between the programmed death-1 (PD-1) receptor and its ligands PD-L1 and PDL2. As a consequence, the functional activity of the target lymphocytes is enhanced to facilitate immune-mediated anti-tumour activity.

Lung cancer has been among the most common cancers in the world for several decades. The 2012 worldwide estimates of cancer incidence and mortality by GLOBOCAN, indicate a total of 1.8 million new lung cancer cases and 1.6 million lung cancer related deaths, accounting for 13.0% of all cancer cases (except non-melanoma skin cancers) and 19.4% of all cancer deaths (except non-melanoma skin cancers). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601

and 583,100, respectively). In 2013, the estimated number of lung cancer related deaths is 159,480 in the United States (Siegel et al 2013) and 269,610 in the European Union (Malvezzi et al, 2013).

The two most prevalent sub-types of lung cancer are small cell lung cancer and NSCLC. Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma (Brambilla et al, 2014 and Schrump DS et al NSCLC; Principles and Practice of Oncology. 9th Edition. 2011). Recently, histology has emerged as a predictive factor for pemetrexed efficacy (Scagliotti G. et al 2011) and a determinant of toxicity with bevacizumab for patients with advanced NSCLC (Johnson DH. et al, 2004).

For the majority of patients, NSCLC is diagnosed at an advanced stage with an overall poor prognosis. The overall survival (OS) for metastatic NSCLC is dismal with 5-year survival of <5% (Lindsey A. et al, 2016).

In addition, over the past decade molecular subsets based on the presence of driver mutations have been identified. In particular, epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements were the first molecular alterations shown to confer sensitivity to specific targeted therapies.

According to the ESMO Clinical Practice Guidelines for metastatic NSCLC (Novello S. et al, 2016), in the absence of driver mutations first-line platinum-based doublet chemotherapy (four with a maximum of six cycles) is recommended in patients with good performance status, based on the observed prolonged survival and improved quality of life (QoL). A comparable efficacy has been observed with several regimens including cisplatin and carboplatin combinations with gemcitabine, paclitaxel and docetaxel (Schiller JH. et al, 2002). The addition of bevacizumab to platinum-based backbone regimen improved OS in non-squamous NSCLC patients with ECOG PS 0-1 (Sandler A. et al, 2006). Therefore, the combination of bevacizumab and platinum-based chemotherapy should be considered in eligible non-squamous NSCLC.

In case of epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements, approved target therapy agents are available.

The efficacy of maintenance treatment, either as maintained use of an agent included in first-line treatment ("*continuation maintenance"*) or as introduction of a new agent after 4 cycles of platinum-based chemotherapy (*"switch maintenance"*) has been investigated in various trials. Improvement in efficacy has been reported with pemetrexed (both continuation and switch maintenance, only in non-squamous histology) and erlotinib (switch maintenance in patients with stable disease after first-line chemotherapy).

The prognosis for patients who failed first line therapies is dismal. A poor response rate was reported from single agent docetaxel, pemetrexed, or erlotinib (4.0% - 17.9%), with the median progression free survival (PFS) of 1.5 to 4.2 months and the overall survival (OS) ranging from 5.4 to 14.8 months. A small but statistically significant improvement over docetaxel single agent was registered with the addition of ramucirumab, a monoclonal antibody specifically binding VEGF Receptor 2, that has been recently approved in combination with docetaxel as a second-line therapy for advanced NSCLC patients. The combination of docetaxel plus ramucirumab showed a small but statistically significant improvement in terms of PFS (HR 0.76, median PFS 4.5 vs. 3.0 months) and OS (HR 0.86, median OS 10.5 vs. 9.1 months).

Nintedanib, a multi kinase inhibitor, in combination with docetaxel has been also approved for the second-line treatment of NSCLC patients with adenocarcinoma, based on the demonstration of a statistically significant improvement in PFS and OS compared to docetaxel single agent (PFS: HR 0.84, median PFS 4.2 vs. 2.8 months in the follow-up analysis of the primary endpoint, OS: HR 0.83, median 12.6 vs. 10.3 months).

Nivolumab, a different antibody directed against PD-1, is approved for the treatment of locally advanced or metastatic squamous and non-squamous NSCLC after prior chemotherapy.

Additional therapeutic options able to prolong survival and to improve quality of life are still needed for the treatment of advanced NSCLC.

In the European Union (EU) Keytruda received a marketing authorisation (MA) on 17 July 2015 as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, and was approved on 29 July 2016 for the treatment of previously treated PD-L1 positive NSCLC patients.

The current application is a type II variation to extend the indication for the treatment of advanced PD-L1 positive Non-Small Cell Lung Carcinoma (NSCLC) also including patients previously untreated, based on results from the study KEYNOTE-024 "*A Randomized Open-Label Phase III Trial of Pembrolizumab versus (vs.) Platinum based Chemotherapy in First-Line (1L) Subjects with Programmed Cell Death 1 Ligand 1 (PD-L1) Strong Metastatic NSCLC*".

The MAH applied for the following change of indication:

"KEYTRUDA is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 ~~and who have received at least one prior chemotherapy regimen~~. Patients with EGFR or ALK positive tumour mutations should ~~also~~ have received *prior therapy* ~~approved therapy for these mutations prior to~~ *before* receiving KEYTRUDA."

Based on the CHMP request to restrict the pembrolizumab indication in the treatment of first-line NSCLC to PD-L1 strong tumour (TPS≥50%), the MAH proposed to update the wording of the indication as follows:

"*KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.*

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received ~~approved~~ targeted therapy ~~for these mutations prior to~~ before receiving KEYTRUDA."

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
3475-P024V01 [Ref. 5.3.5.1: P024 V01MK3475]	III	Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, and United States	A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer	Randomized, open-label, parallel, active-controlled trial	Pembrolizumab 200 mg IV Q3W Pemetrexed 500 mg/m^2 IV Q3W on Day 1 for 4 to 6 cycles (permitted for non-squamous histologies only) Optional pemetrexed maintenance of 500 mg/m^2 IV Q3W (permitted for non-squamous histologies only) after completion of some platinum based treatment combination course. Carboplatin AUC 5 to 6 IV Q3W on Day 1 for 4 to 6 cycles Cisplatin 75 mg/m^2 IV Q3W on Day 1 for 4 to 6 cycles Gemcitabine 1250 mg/m^2 IV at Days 1 and 8 Q3W for 4-6 cycles Paclitaxel 200 mg/m^2 IV Q3W for 4 to 6 cycles	Male and female subjects ≥18 years of age on the day of consent with PD-L1 strong metastatic non-small cell lung cancer	As of 09-May-2016 Pembrolizumab (154 subjects treated) Pemetrexed and carboplatin followed by optional pemetrexed, (66 subjects treated with pemetrexed and carboplatin; 28 of these 66 subjects also received pemetrexed maintenance) Pemetrexed and cisplatin followed by optional pemetrexed, (36 subjects treated with pemetrexed and cisplatin; 18 of these 36 subjects also received pemetrexed maintenance) Gemcitabine and cisplatin, (4 subjects treated) Gemcitabine and carboplatin, (5 subjects treated) Paclitaxel and carboplatin followed by optional pemetrexed maintenance, (12 subjects treated with paclitaxel and carboplatin, 0 of these 12 subjects received pemetrexed maintenance)

2.3.2. Pharmacokinetics

KEYNOTE-024 is the first study providing a substantial amount of pharmacokinetic data on the 200 mg Q3W fixed dose regimen in NSCLC patients.

Pharmacokinetics in target populations

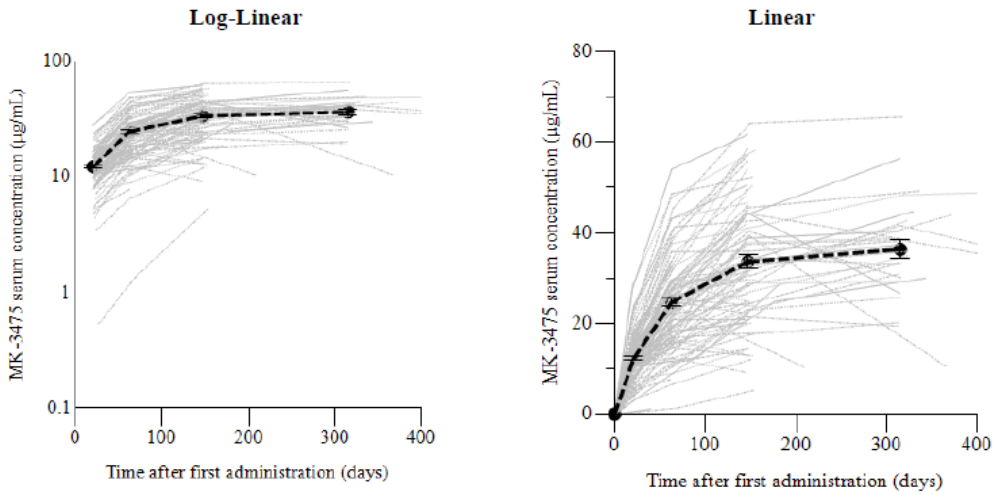
Pre-dose (trough) samples were taken from 150 patients at cycle 1, 2, 4, 8 and every 8 cycles thereafter, plus at 1, 3 and 6 months after last dose of pembrolizumab (at the same time as blood collection for anti-pembrolizumab antibodies). Post-dose samples were taken at cycle 1: within 30 minutes after end of infusion, and one sample between 72 and 168 hr post-infusion. Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in NSCLC subjects from P024 are presented in the table below:

Table 1: Descriptive statistics of pembrolizumab trough (pre-dose) and post-dose concentrations at 200 mg/kg Q3W in protocol P024

Protocol P024 200 mg Q3W				Ctrough				
Rel. Time	TAFD (day)	Cycle	N	GM (%CV)	AM (SD)	Min	Median	Max
					(µg/mL)			
Pre-Dose	0	1 (Week 0)	150	n.a.	0 (0)	0.00	0.00	0.00
	21	2 (Week 3)	132	11.1 (54)	12.3 (5)	0.535	12.2	28.5
	63	4 (Week 9)	105	22.5 (52)	24.7 (10)	1.35	24.5	54.0
	147	8 (Week 21)	82	30.6 (50)	33.6 (13)	5.26	32.7	64.1
	315	16 (Week 45)	28	34.4 (37)	36.3 (11)	10.5	36.7	65.5
					Post-Dose			
Post-Dose	0.02	1 (week 0)	147	67.5 (23)	69.3 (16)	36.6	66.8	132
72-168HR	5	1 (week 0)	140	26.8 (31)	28.0 (9)	13.4	26.4	60.1

Rel. Time = Relative time to dosing; GM = Geometric Mean; CV%: Geometric Coefficient of Variation; n.a.: not applicable;
TAFD = Nominal time after first dose; Postdose samples are drawn within 30 min after infusion;
Results reported for time points with N >= 3

The individual and arithmetic mean observed pembrolizumab trough concentrations from these same subjects are presented in the figure below:



Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE.

Figure 1: Individual and arithmetic mean (SE) pembrolizumab trough concentrations vs time at 200 mg Q3W in protocol P024

2.3.3. Pharmacodynamics

Mechanism of action

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

Primary and secondary pharmacology

Immunogenicity

An **Immunogenicity Analysis** has been performed to evaluate immunogenicity status of subjects with Melanoma (P001, P002, P006), NSCLC (P001, P010, P024) and HNSCC (P012, P055).

In the immunogenicity assessment, 2873 subjects were included (1535 Melanoma subjects, 1237 NSCLC subjects and 101 HNSCC subjects). The overall immunogenicity incidence was defined as the proportion of treatment emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

The samples were assayed for anti-pembrolizumab antibodies presence, using a validated electrochemiluminescense (ECL) immunoassay. During the course of the study, measurement of the ADA samples was transferred from Intertek to another Vendor (PPD).

As part of the assay transfer, the ADA screening assay was further optimized to increase the DTL. Part of the samples was analysed at Intertek, and part of the samples was analysed at PPD. All the samples were analysed using the same type of assay. For the evaluation of each individual ADA sample, the DTL of the corresponding assay has been used. The DTL for the ADA assay executed at Intertek is 25 µg/mL, the DTL for the ADA screening assay executed at PPD is 124 µg/mL.

In the current database, 12824 samples from 3182 subjects were available. All samples were tested in the ADA screening assay, 7932 samples were tested at Intertek (P001, P002, P006, P010 and P012), and 5053 samples were tested at PPD (P001, P006, P010, P012, P024 and P055), including 161 samples reanalysed at

PPD because of non-reportable or missing results from Intertek. From one sample the quantity was not sufficient (QNS), and eight samples were non-reportable (NRR). In total, 12815 samples had reportable results from the screening assay.

A summary of subject immunogenicity results is reported in the table below.

Table 2: Summary of subject immunogenicity results (pooled analysis of P001, P002, P006, P010, P012, P024 and P055)

Pooled analysis (P001, P002, P006, P010, P012, P024, P055) Stratified by treatment				
Immunogenicity status	All treatments	Treatment		
		2 mg/kg	10 mg/kg	200 mg
Assessable subjects[a]	2873	706	1982	185
Inconclusive subjects[b]	1584	136	1448	0
Evaluable subjects[c]	**1289**	**570**	**534**	**185**
Negative[d]	1251 (97.1%)	555 (97.4%)	519 (97.2%)	177 (95.7%)
Non-Treatment emergent positive[d]	12 (0.9%)	7 (1.2%)	4 (0.7%)	1 (0.5%)
Treatment emergent Positive[d]	26 (2.0%)	8 (1.4%)	11 (2.1%)	7 (3.8%)

Pooled analysis (P001, P002, P006, P010, P012, P024, P055) Stratified by Treatment and Indication							
Immunogenicity status	2 mg/kg		10 mg/kg			200 mg	
	Melanoma	NSCLC	Melanoma	NSCLC	HNSCC	NSCLC	HNSCC
Assessable subjects[a]	345	361	1190	736	56	**140**	45
Inconclusive subjects[b]	124	12	977	432	39	0	0
Evaluable subjects[c]	**221**	**349**	**213**	**304**	**17**	**140**	**45**
Negative[d]	219 (99.1%)	336 (96.3%)	208 (97.7%)	295 (97.0%)	16 (94.1%)	134 (95.7%)	43 (95.6%)
Non-Treatment emergent positive[d]	2 (0.9%)[g]	5 (1.4%)	2 (0.9%)	1 (0.3%)	1 (5.9%)	0	1 (2.2%)
Treatment emergent Positive[d]	0	8 (2.3%)	3 (1.4%)	8 (2.6%)	0	6 (4.3%)	1 (2.2%)

Pooled analysis (P001, P002, P006, P010, P012, P024, P055) Stratified by Indication			
Immunogenicity status	Melanoma	NSCLC	HNSCC
Assessable subjects[a]	1535	1237	101
Inconclusive subjects[b]	1101	444	39
Evaluable subjects[c]	**434**	**793**	**62**
Negative[d]	427 (98.4%)	765 (96.5%)	59 (95.2%)
Non-Treatment emergent positive[d]	4 (0.9%)	6 (0.8%)	2 (3.2%)
Treatment emergent Positive[d]	3 (0.7%)	22 (2.8%)	1 (1.6%)

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

2.3.4. PK/PD modelling

Pharmacokinetics of Pembrolizumab in First-line NSCLC on Protocol 024

The definitive population PK model was developed by a pooled analysis of concentration data from P001 (all data related to doses of 1 mg/kg and higher), P002 and P006. Based on this population PK analysis, the pembrolizumab PK profile is typical for a therapeutic mAb, with a low systemic clearance (0.2 L/day) and a low volume of distribution (7 L) at steady state, that is predicted to be achieved after approximately 19 weeks (for the dosing regimen of 2 mg/kg Q3W). Elimination half-life (t1/2) is 25 days. For this updated population PK evaluation, the data from studies P010 and P024 were added to the initial dataset and the parameters from the existing population PK model were re-estimated to obtain posthoc parameters for all the individuals included in this pooled dataset.

The final analysis data set comprised 16800 pembrolizumab concentrations from 2993 subjects. The number of subjects and PK observations by dose in the pooled analysis datasets are provided in the table below.

Table 3: Numbers of subjects and observations by dose and dosing regimen in the pooled analysis dataset (P001, P002, P006, P010, P024)

Protocol	N of subjects	[%] of subjects	N of PK observations	[%] of PK-observations
P001	1221	40.8	6538	38.9
P002	419	14	1910	11.4
P006	548	18.3	3785	22.5
P010	653	21.8	3953	23.5
P024	152	5.08	614	3.65

Pembrolizumab serum concentrations determined to be below the limit of quantification (BLQ) were excluded from the analysis and effects of outliers (defined as data with |CWRES|>6 or |IWRES|>6) on parameter estimates and uncertainty were assessed re-running the final model after reintroduction of the outlying data.

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

In addition to body weight, the existing popPK model contained several more covariate relationships, which were established through a stepwise covariate search.

For continuous covariates was used the generic form similar to the relationships for body weight. Following are reported the distributive statistics of continuous covariates included in the dataset.

Table 4: Summary of continuous covariate included in the analysis dataset

Covariate	Min		Median		Mean		Max		N		Missing	
	PA	P24	PA	P24	PA	P24	PA	P24	PA	P24	PA	P24
WT (kg)	35.7	38	75	69.7	77.2	68.9	210	110	2841	152	0 (0.0%)	0 (0.0%)
AGE (yr)	15	33	62	64	61	63.9	94	90	2841	152	0 (0.0%)	0 (0.0%)
ALP (IUL)	18	47	85	116	107	144	1680	465	2801	152	40 (1.4%)	0 (0.0%)
AST (IUL)	5	9	21	20	24.6	21.8	197	75	2801	152	40 (1.4%)	0 (0.0%)
ALT (IUL)	3	6	18.6	18	22.8	20.8	321	62	2804	152	37(1.3%)	0 (0.0%)
ALB (g/L)	15	23	40	38	39.6	38	59	53	2788	150	53 (1.9%)	2 (1.3%)
BIL (uml/L)	1	2	8	7.78	8.92	8.02	87.2	18.1	2805	152	36 (1.3%)	0 (0.0%)
IGG (g/L)	1.7	N.E	10.1	N.E	10.5	N.E	38	N.E	1023	N.E	1818 (64.0%)	N.E
BSLD (mm)	10	14	84.6	82	110	90.3	895	322	2589	149	252 (8.9%)	3 (2.0%)
EGFR ($mL/min/1.73m^2$)	25.4	35.9	88.7	93.5	91.1	99.2	403	246	2815	152	26 (0.9%)	0 (0.0%)
LMPCT ($10^9/L$)	0.14	0.5	1.34	1.6	1.46	1.71	9.4	9	880	131	1961(69.0%)	21 (13.8%)

PA stands for previous analysis for P1P2P6P10 and P24 denotes P024. NE stands for not evaluated

Descriptive statistics of categorical covariates in the analysis dataset are reported below.

Table 5: Summary of categorical covariates included in the analysis dataset

Covariates	N		Missing	
	PA	P24	PA	P24
Gender			0 (0.0%)	0 (0.0%)
Male	1691 (59.5%)	90 (59.2%)		
Female	1150(40.5%)	62 (40.8%)		
Race			20(0.7%)	2 (1.3%)
White	2518 (88.6%)	124 (81.6%)		
Black	49 (1.72%)	2 (1.32%)		
Asian	229 (8.06%)	24 (15.8%)		
Others	25 (0.88%)			
Coadministered drugs (Use of Glucocorticoids)			0 (0.0%)	0 (0.0%)
No	2429 (85.5 %)	134 (88.2%)		
Yes	412 (14.5%)	18 (11.8%)		
Cancer type			22(0.8%)	0 (0.0%)
Melanoma	1612 (56.7%)	0		
Non-Small Cell Lung Cancer (NSCLC)	1207 (42.5%)	152 (100%)		
Baseline ECOG Performance			5 (0.2%)	0 (0.0%)
0 Asymptomatic	1480 (52.1%)	53 (34.9%)		
1 Symptomatic	1356 (47.7%)	98 (64.5%)		
Line of NSCLC therapy			29 (1.0%)	0 (0.0%)
0 non-NSCLC (Melanoma)	1612 (56.7%)	0		
1 first line NSCLC	109 (3.84%)	152 (100%)		
2 second line NSCLC	1091(38.4%)	0		

PA stands for previous analysis from P1P2P6P10 and P24 denotes for Protocol 24. N.E means not evaluated. One subject has BECOGN=2 (0.658%), but was not considered as a separate category in the covariate model due to insufficient subject in the category, rather this subject was pooled with the subjects with ECOG=1.

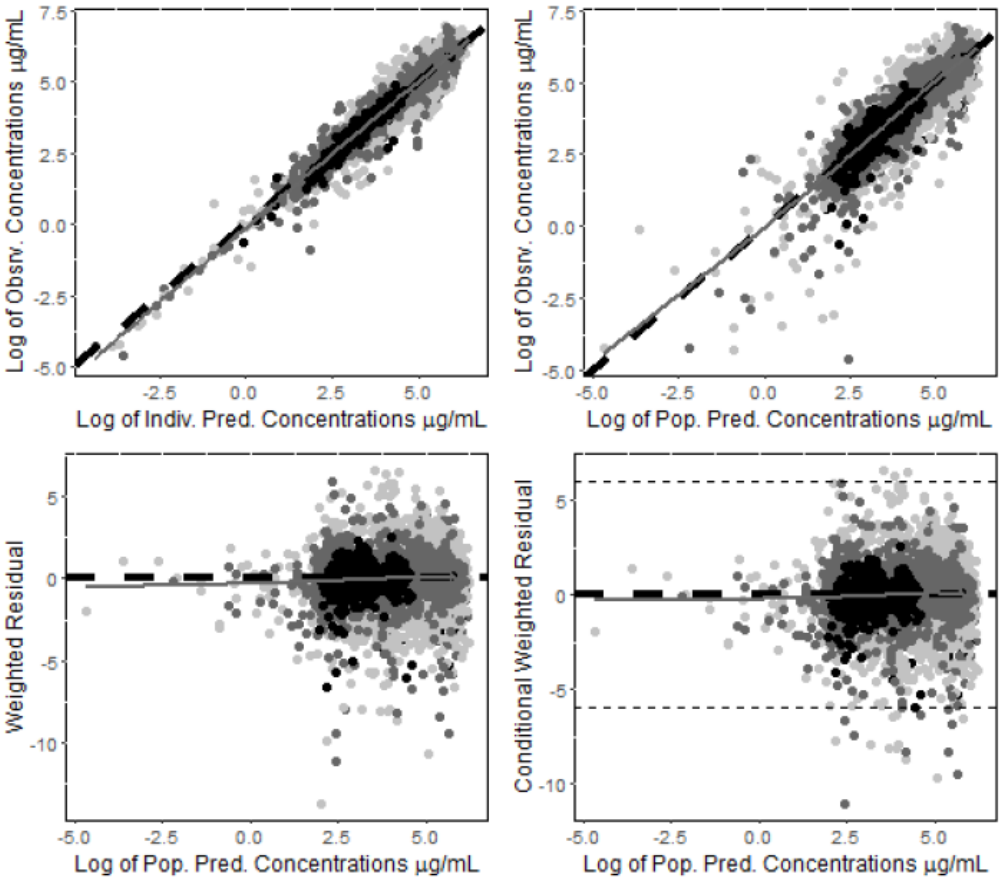
The first-line NSCLC population from Protocol 024 was generally similar to the melanoma and second-line NSCLC population in terms of continuous and categorical covariate distributions. Average body weight was somewhat lower in first-line NSCLC patients, and baseline ALP was somewhat higher, proportion of patients with ECOG=1 was larger.

No formal covariate evaluation was planned, previously established covariate relationships were re-estimated (see table below).

Table 6: Covariates included in definitive pop PK model

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

The stepwise covariate analysis identified a statistically significant effect of the line of NSCLC therapy covariate on both CL and Vc. As the estimates of the effects for first-line NSCLC and second-line NSCLC relative to melanoma were similar, this covariate has been converted into an indication indicator (NSCLC versus melanoma). Since for both CL and Vc, the pooling of the two NSCLC subgroups did result in a minor (non-significant at $P<0.001$) change in OFV, the model was subsequently simplified to have cancer type as a covariate on CL and Vc. Goodness of fit plots of the final model are reported below.



Black dots are 1st line NSCLC individual data, Dark gray dots are 2nd line NSCLC individual data, Grey dots are individual data for other indications, solid lines are smooth lines. In the two plots of the first row, bold dashed lines are lines of identity, whilst in the two plots of the second row dashed lines represent zero line.

Figure 2: Goodness of fit plots of the popPK model using integrated dataset

The value of the ETA shrinkage of the individual empirical Bayes estimates on CL and Q parameters is 13.2%. The shrinkage of the volume parameters is 27.7%. The correlation between ETA1 and ETA2 is 0.30.

Comparison of parameter estimates of the final model using the integrated dataset (i.e. P001, P002, P006, P010 and P024) and the dataset used in previous pop PK model (Pooled Protocol 001, 002 and 006 Dataset) is shown in the table below.

Table 7: Comparison of popPK parameters of pembrolizumab from the definitive model vs updated model including first-line NSCLC subjects

	Definitive Population PK Model N=2188 [Ref. 5.3.5.3: 04DDV3]			Update Model N=2993		
Parts and Studies included in the analysis	**Melanoma/NSCLC**; A, A1, A2, B1, B2, B3, C, D, F1, F2 and F3 from P001, P002, P006			**Melanoma/NSCLC**; A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from KN001, KN002, KN006, KN010, KN024		
Data cut-off date	P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014			P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014 P010V01; 30-September-2015 **P024V01**; 09-May- 2016		
Parameter	**Value**	**%RSE**	**%CV[a]**	**Value**	**%RSE**	**%CV[a]**
CL (L/day)	0.22	2.14	37.9	0.229	1.67	36.8
Vc (L)	3.48	0.891	20.6	3.52	0.938	20.0
Q (L/day)	0.795	4.01	37.9	0.769	3.08	36.8
Vp (L)	4.06	2.01	20.6	3.96	1.72	20.0
α for CL and Q	0.595	7.95		0.595	6.12	
α for Vc and Vpc	0.489	6.05		0.51	4.86	
Albumin on CL	-0.907	8.39		-0.902	6.78	
eGFR on CL	0.135	23.2		0.132	18.9	
GENDER on CL	-0.152	11.6		-0.151	8.81	
Cancer Type (NSCLC vs Mel +other) on CL	0.145	17		0.0745	22.4	
Baseline ECOG on CL	-0.0739	22.7		-0.0666	22.1	
Baseline tumor size on CL	0.0872	12.2		0.102	9.37	
Prior IPI treatment on CL	0.139	18.5		NE	NE	
Albumin on Vc	-0.208	22.7		-0.224	17.6	
GENDER Vc	-0.134	9.33		-0.129	8.06	
Prior IPI treatment on Vc	0.0735	23.5		NE	NE	
Cancer Type (NSCLC vs Mel +other) on Vc	NE	NE		-0.0532	19	
Residual error	-0.272	1.87		-0.261	1.81	

[a] %CV of residual error is related to estimate of between-subject variability on this parameter

Presented population parameter estimates exclude effects of covariates; therefore apply to a hypothetical typical patient with average characteristics. CL: clearance; Vc: central volume of distribution; Q: intercompartmental clearance; Vp: peripheral volume of distribution; %RSE: relative standard error (%); 95% CI: 95% confidence interval of parameter estimate based on bootstrap results; %CV: coefficient of variation of between-subject distributions of parameters; NE: not evaluated.

Peer Reviewed per SOP QP2-005.

Visual predictive checks were carried out to check the ability of the model to describe the new data from P024; those were stratified by dose. 1000 simulated datasets were generated using the final model. The VPC for trough sample concentrations of the 200mg Q3W dosing group is reported below.

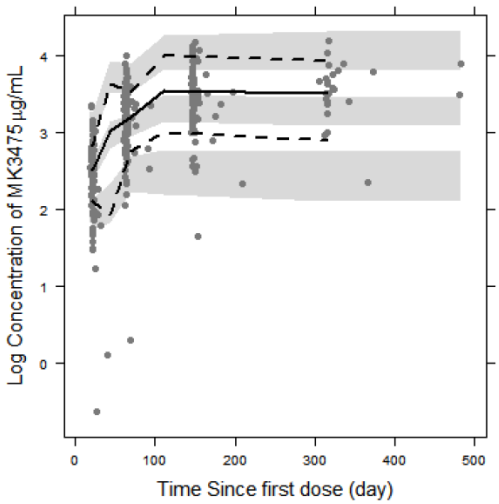


Figure 3: Visual predictive check for 200 mg Q3W dosing group trough concentrations for P024

The small underprediction observed, especially at later time points, is similar to that observed in previous population PK analyses. The MAH performed a dedicated evaluation to assess potential origins of this apparent bias in the model predictions. The results of this evaluation indicated that the apparent on-study increases in concentration at time points long after treatment initiation are mostly attributable to informative censoring patterns in the data. After accounting for the association between clearance and dropout, the adjusted visual predictive checks adequately reflected the available data.

The Visual Predictive Check (VPC) for peak sample concentrations of the 200mg Q3W dosing group is reported below.

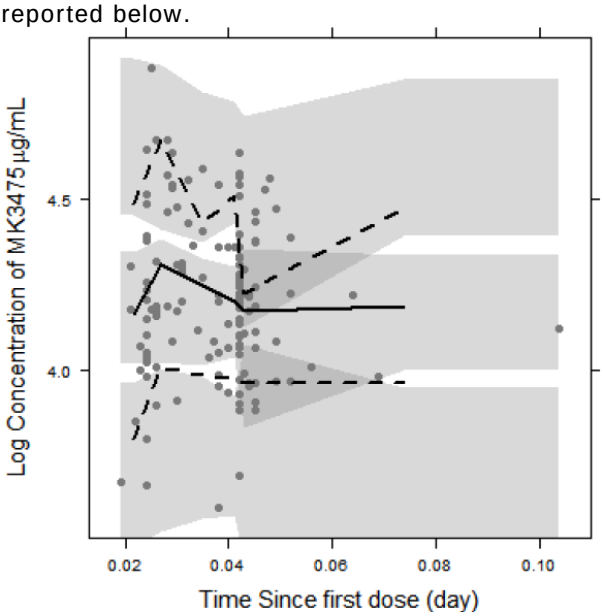
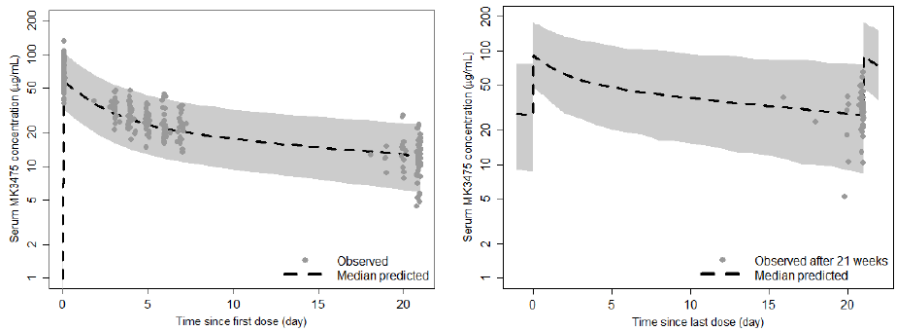


Figure 4: Visual predictive check for 200 mg Q3W dosing group peak concentrations for P024

Given the limited peak concentrations and time points collected in 200mg Q3W comparing to other dosing groups, VPC shows that the peak concentrations of the 200mg Q3W are less well described by the model.

The existing population PK model, developed on data obtained with weight-based dose regimens, provided predictions of the concentration observations with this fixed dose regimen, indicating that the PK of pembrolizumab are consistent across fixed and weight-based dose regimens.

Pembrolizumab serum concentrations for the first line NSCLC subjects treated with 200 mg Q3W, together with a predicted concentration range (median and 90% prediction interval) from the definitive population PK model are depicted in the figure below.



Left panel: after first dose; right panel: at steady state (after 21 weeks). Dots are individual data from first-line NSCLC patients; Solid line is median prediction from the model for a regimen of 200 mg Q3W and the shaded area represents the 90% prediction interval. The right panel mainly shows predicted concentration ranges at steady state of repeated dosing at 200 mg Q3W together with the observations obtained after 21 weeks.

Figure 5: Consistency of observed concentrations in first line NSCLC subjects with predictions based on definitive popPK model: pembrolizumab concentration-time profiles during the 1st dose (left panel) or at steady state (right panel) of 200 mg Q3W

Based on a simulation of 5000 typical subjects with median body weight, predicted pembrolizumab descriptive statistics, at the following dose regimens 2 mg/kg Q3W, 10 mg/kg Q2W or Q3W, and 200 mg Q3W were computed. The tables below report PK parameters for each dose regimen.

Table 8: Median (90% prediction interval) exposure parameters of pembrolizumab at steady state of regimens of 2 mg/kg Q3W, 200 mg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W

Exposure parameter	Pembrolizumab dose regimen			
	2 mg/kg Q3W	200 mg Q3W	10 mg/kg Q3W	10 mg/kg Q2W
C_{max} (µg/mL)	64.2 (46.3; 91.8)	85.6 (60.3; 122)	320 (231; 457)	388 (273; 587)
C_{trough} (µg/mL)	21.0 (9.07; 42.7)	28.0 (11.6; 57.2)	105 (45.6; 213)	173 (84.8; 346)
AUCss, 6-week (µg·day/mL)	1316 (732; 2354)	1751(955; 3136)	6600(3678; 11711)	9765 (5528; 17762)

C_{max}: maximum concentration at end of infusion; C_{trough}: concentration at the end of the dosing interval; AUCss,6-week: area under the concentration time curve over 6 weeks.
Summary statistics based on simulations of N=5000 typical subjects (with median weight) per dose regimen.

Below are reported the summaries of descriptive statistics for posthoc estimates of CL, Vc as well as derived parameters for first-line NSCLC, second-line NSCLC and melanoma populations.

Table 9: Comparisons of descriptive statistics of individual PK parameters (CL, Vc) and derived parameters (t1/2, Vdss, time to steady state) between 1st line NSCLC, 2nd line NSCLC and melanoma patients

	1L NSCLC				2L NSCLC				Melanoma			
	N	Mean	Median	SD	N	Mean	Median	SD	N	Mean	Median	SD
CL (L/day)	261	0.239	0.221	0.0881	1091	0.234	0.213	0.0969	1612	0.234	0.202	0.126
Vc (L)	261	3.13	3.12	0.576	1091	3.09	3.04	0.661	1612	3.49	3.45	0.799
Half life (days)	261	24.4	23.8	6.87	1091	25	24.4	7.26	1612	28	27.8	9.1
Vdss (L)	261	7	6.97	1.14	1091	6.94	6.82	1.33	1612	7.61	7.51	1.6
Time to steady state (days)	261	122	119	34.3	1091	125	122	36.3	1612	140	139	45.5

A comparison among patient with NSCLC or melanoma receiving the following regimen, 200 mg Q3W, 2 mg/kg Q3W, 10 mg/kg Q2W or 10 mg/kg Q3W, is reported below.

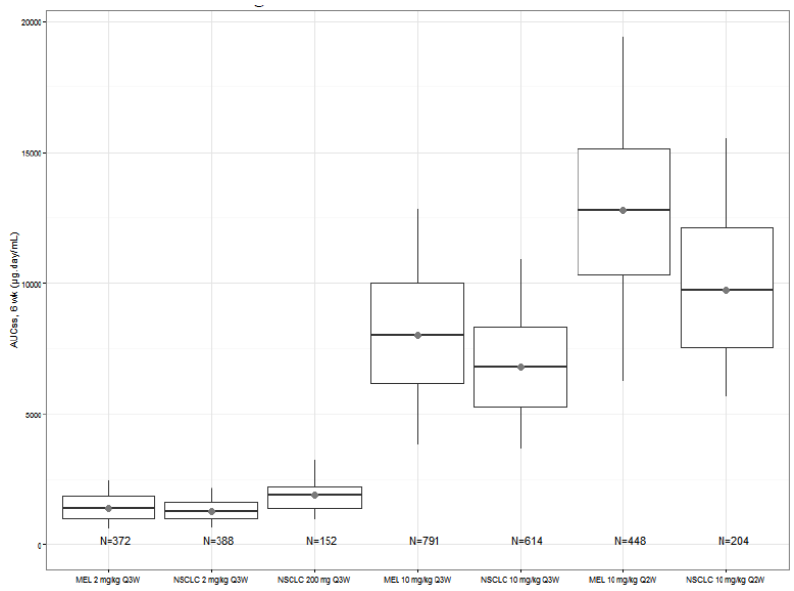


Figure 6: pembrolizumab exposure across indications at clinically tested dose regimens

The exposure data for 200 mg Q3W from KEYNOTE-024 lie between the exposures from the cumulative clinical experience at 2 and 10 mg/kg and is similar to exposures from historical 2 mg/kg dose data.

With the expanded dataset, the additional effect of cancer type on central volume of distribution was identified, which was not present in the definitive population PK model as established for pembrolizumab. As the effect size was small, this covariate effect has been judged clinically unimportant by the MAH.

The predicted median concentration-time profiles over the initial 24 weeks of pembrolizumab for the four dosing regimens evaluated across pembrolizumab program are presented in the figure below. The 200 mg Q3W regimen exhibits a very similar accumulation pattern as seen with 2 mg/kg Q3W. There is only limited overlap in individual exposures between 200 mg Q3W and 10 mg/kg Q2W or Q3W, which can be expected with the large difference between these two doses.

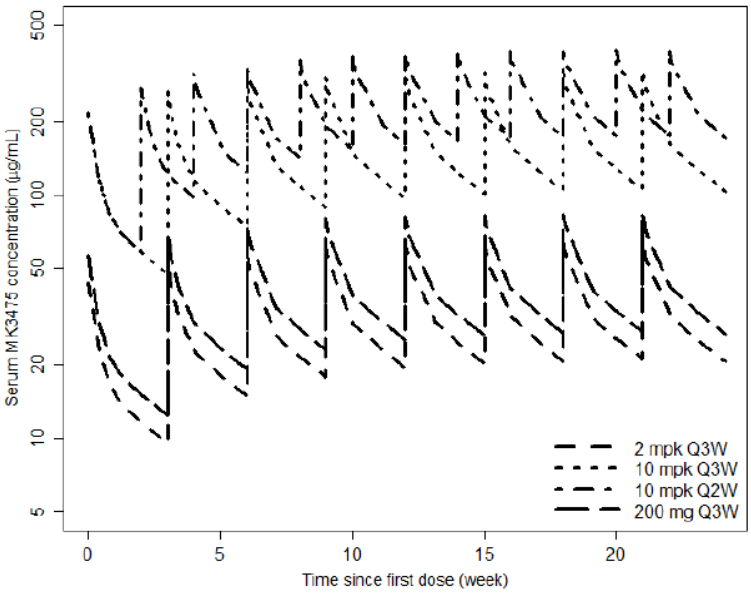


Figure 7: Predicted pembrolizumab concentration-time profiles showing exposure at 200 mg Q3W, 2 mg/kg and 10 mg/kg Q3W, and 10 mg/kg Q2W

Exposure-response analysis for efficacy

The MAH performed an **ER analysis** in order to assess the relationship between exposure to pembrolizumab in serum (i.e. AUC over 6 weeks at steady state; AUCss-6weeks) and the anti-tumor response measured as the sum of the longest dimension (SLD) of the tumour lesions in first-line NSCLC (including subjects treated in adjuvant and neo-adjuvant settings). A flat concentration-efficacy relationship was demonstrated for NSCLC with the Modelling & Simulation Report "Model-based analysis of the relationship between pembrolizumab exposure and efficacy in patients with non-small-cell lung carcinoma (NSCLC) in PN001 and PN010". As results of covariate research it was found that that PD-L1 expression status was significantly associated with the estimated rate of tumour size decline; subject age and EGFR mutation status were predictive of higher rates of tumour growth.

In support of this submission, an exploratory analysis of tumour size change was conducted with all available data in treatment-naïve subjects with NSCLC to verify whether new data from subjects receiving the 200 mg fixed dose alters prior exposure-response assessments from the body weight-based dosing.

All data preparation and presentation was performed using SAS Version 9 and R version 3.0.1 (R-project, www.r-project.org) were used for post-processing.

The dataset consist of patients receiving MK-347 as first line therapy for NSCLC, a subset of patients from P001, P010 and from P024. A total of 278 patients were allocated to receive MK-3475 as 1L/adjuvant/neo-adjuvant therapy for NSCLC. Of these patients, 263 were treated with MK-3475 and 247 had both a baseline tumour measurement and available PK data. The table below reports the number of patients with available PK data:

Table 10: Number of patients in tumour size modelling (FAS) dataset with available PK data, categorised by treatment (dose + schedule) and cohort (protocol 1 N=85/ Protocol 10 N=13/ Protocol 24 N=149)

Treatment	P1				P10	P24
	Part C	Part F1	Part F2	Part F3		
2 mpk Q3W	0	4	0	0	6	N/A
10 mpk Q2W	0	39	0	0	N/A	N/A
10 mpk Q3W	0	42	0	0	7	N/A
200 mg Q3W	N/A	N/A	N/A	N/A	N/A	149

The total of 1122 SLD observations were taken from the 247 patients with at least one observable baseline measurement and available PK data. Of these 247 patients, 131 had a tumour size measurement within the 26-30 week (28 +/- 2 week) window. Of these 131 subjects, 102 had a PD-L1 tumour proportion score (TPS) ≥50%, 20 subjects were PD-L1 TPS 1-49%), 4 subjects were PDL1 TPS <1%, and 5 were classified as PD-L1 unknown.

Percentage change from baseline tumour size categorized by PDL-L1 expression status is reported below.

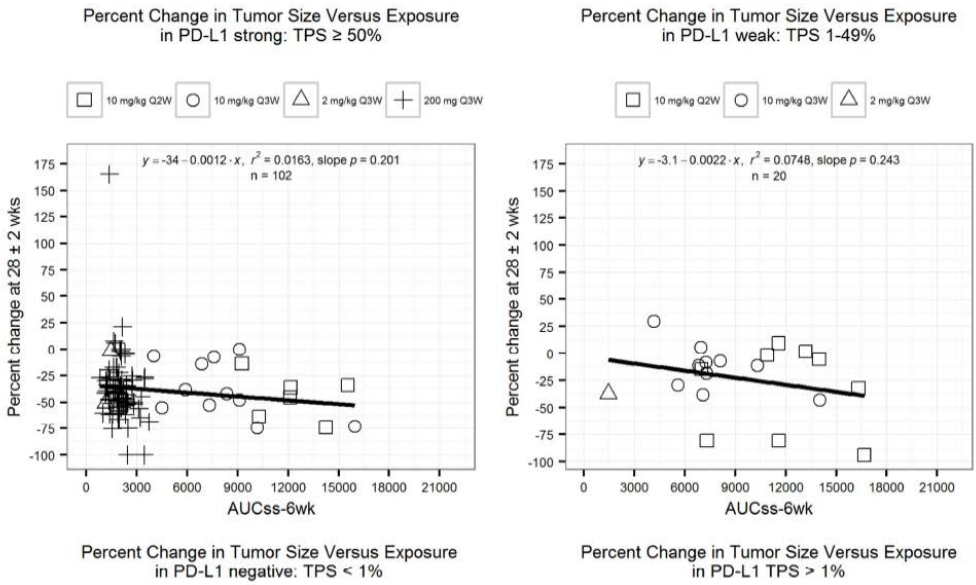
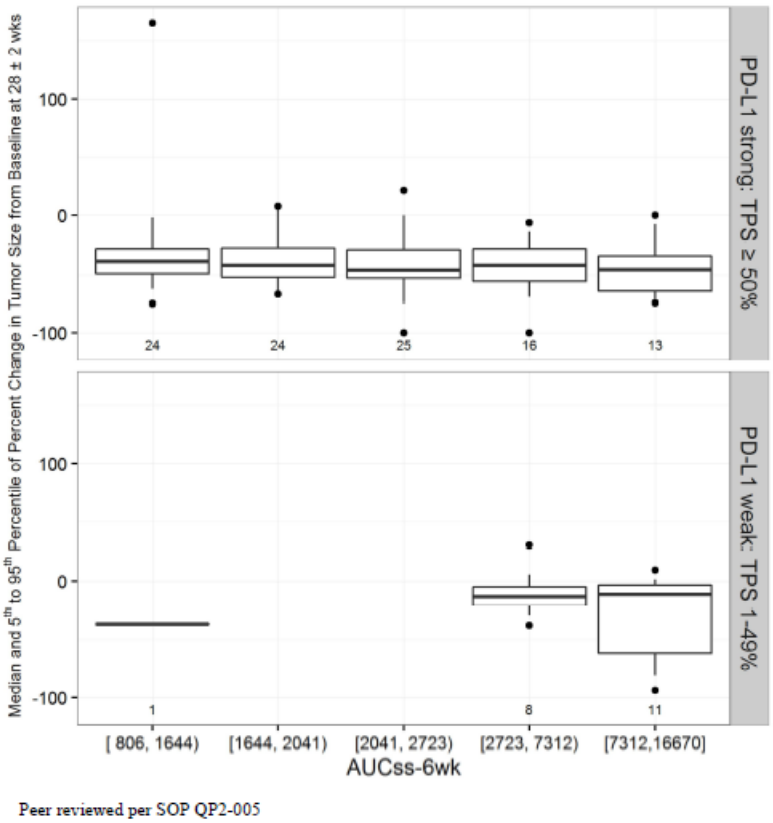


Figure 8: Percent change from baseline tumour size at week 28 vs. $AUC_{ss\text{-}6weeks}$ stratified by PD-L1 status

Distribution of Individual percent change from baseline tumour size categorized by PDL-L1 expression status is reported below.



Top: PD-L1 TPS≥ 50%, bottom: PD-L1 TPS 1-49%. The sample size per group is provided below each box-whisker plot. The boxes indicate variability with the 25th and 75th percentile. The ends of the whiskers correspond to the 5th and 95th percentiles of the observed data.

Figure 9: Distribution of individual percent change from baseline tumour size responses at week 28 by $AUC_{ss\text{-}6weeks}$ quintiles categorised by PD-L1 expression status

Data suggest that PDL1 status is a strong predictor of response.

Exposure-response analysis for safety

A prior exposure-adverse event (AE) analysis was conducted by pooling across all subjects included in KEYNOTE-001,-002, -006 and -010, encompassing both melanoma and NSCLC indications. The potential for exposure-dependent immune-related AEs is not expected to be substantially influenced by indication, thus supporting a cross-indication pooled analysis.

The primary focus of this analysis was evaluation of potential relationship between pembrolizumab exposure (AUC6wks) and the occurrence of AEs of special interest (AEOSIs). Additionally the analysis investigated covariates related to study design and disease severity as possible predictors for the AE response. More specifically, the following covariates were explored and tested during the analysis: duration of treatment, dosing regimen, randomization status, indication, baseline tumor size, ECOG performance status, body weight, sex, EGFR status and PD-L1 status. Only data from pembrolizumab treatment arms of P001, P002, P006, P010 and P024 studies were included in the analysis.

The following baseline covariates were included in the analysis datasets: duration of treatment, dosing regimen, randomization status, indication, baseline tumor size, ECOG performance status, body weight, sex, EGFR status and PD-L1 status. The categorical covariates were coded in the dataset as follows:

Dosing regimen (QW: Q2W=2, Q3W=3)

Randomization status (RAND: randomized=1, non-randomized=0)

Indication (CLDIAGN: Melanoma=1, NSCLC=2)

ECOG status (BECOGN: 0 or 1)

Sex (SEX: Male=1, Female=2)

EGFR status (EGFR: 1=mutated, 0=not mutated)

PD-L1 status (PDL1: 1=PD-L1-positive, 0=PD-L1-negative)

Exposure at steady-state (AUCss) was calculated from the individual post hoc parameter estimates from the population PK model by the ratio of total dose administered in one dosing interval and the individual clearance parameter. Because the population PK clearance estimates are based on the complete time course of individual concentration data, these AUCss values are representative of the average steady-state exposure in an individual patient throughout the treatment. To account for differences in dosing frequency, AUC6wks was calculated as AUCssx2 or AUCssx3 for the Q3W or Q2W dosing regimen, respectively.

The possibility of an exposure-response (ER) relationship was investigated by means of a logistic regression describing the frequency of AEs. The potential ER relationship characterization was further refined through logistic regression models of the relationship between an independent variable (here: AUC6wks or exposure) and a categorical dependent variable (here: the absence or presence of an AE).

Data from 2965 patients (received at least one dose of pembrolizumab) were available for this exposure-safety analysis. In total, 81 patients were excluded due to missing exposure information. Of the resulting 2884 patients, 1191 belong to study P001, 340 to study P002, 548 to study P006, 653 to study P010 and 152 to study P024. No correlated covariates were included in the model.

The potential presence of an exposure response relationship was investigated by means of bar plots of AE frequency vs bins of AUC_{6wks} for different covariates. The factors that could influence the AE response can be divided into several categories 1) exposure related (AUC_{6wks}, dosing regimen); 2) study design related (treatment duration, randomization status), 3) disease related (indication, baseline tumour size, ECOG performance, EGFR status, PD-L1 status) and 4) demographic (sex, body weight).

When administered a fixed 200 mg dose regimen, a flat relationship between incidence of AEOSI across body weight (38-110 kg) in first-line NSCLC was observed, the number of subject with AEOSI ranged from 28.9% to 31.6%, suggesting the weight did not influence the AEOSI incidence.

Instead, there is evidence for a correlation between exposure and treatment duration; in the higher exposure group, a higher percentage of patients had treatment duration above the median (i.e. longer treatment duration). The figure below reports the treatment duration versus AUC:

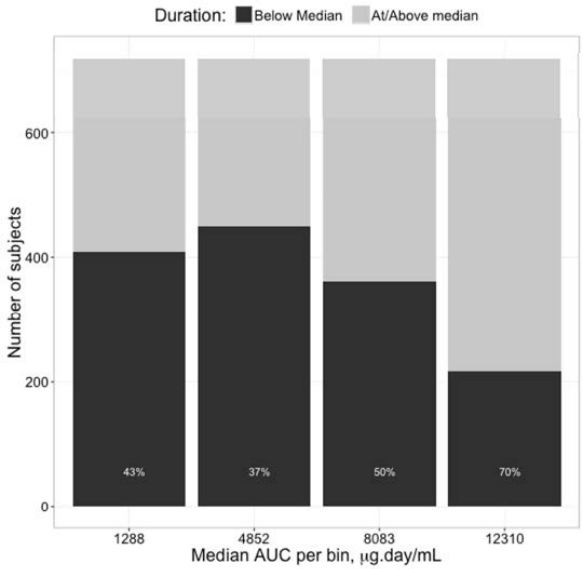
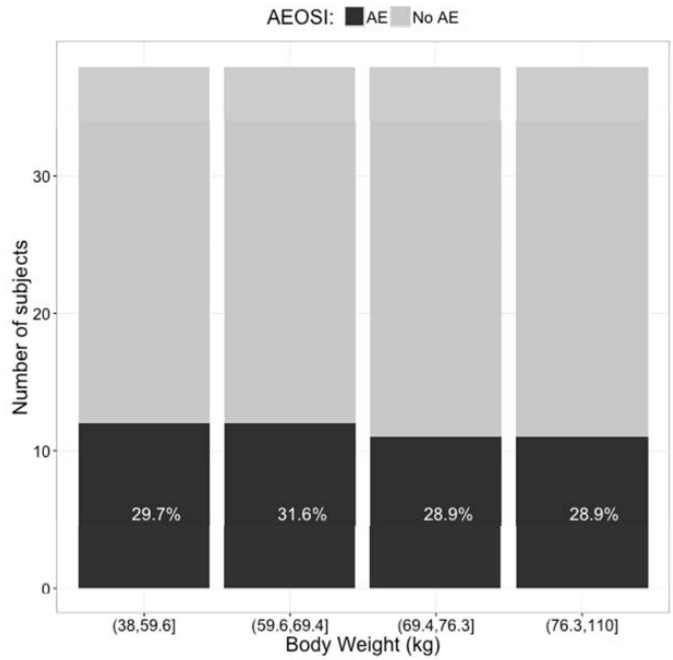


Figure 10: Summary of treatment duration vs AUC in full dataset

During visual inspection of the exploratory plots as well as stepwise covariate model building, the following covariates were investigated: duration of treatment, dosing regimen, randomization status, indication, baseline tumour size, ECOG performance status, body weight, sex, EGFR status and PD-L1 status. A specific component of the covariate analysis was to assess the importance of time (duration of treatment) for the occurrence of AEOSI. The results of the stepwise covariate analysis (first forward addition) revealed the duration of treatment as the main covariate that was statistically significant on intercept, indicating that patients with longer treatment duration have somewhat higher probability to experience an AEOSI. Following inclusion of this covariate, no other covariate relationships were found to meet the criterion for inclusion in the model.

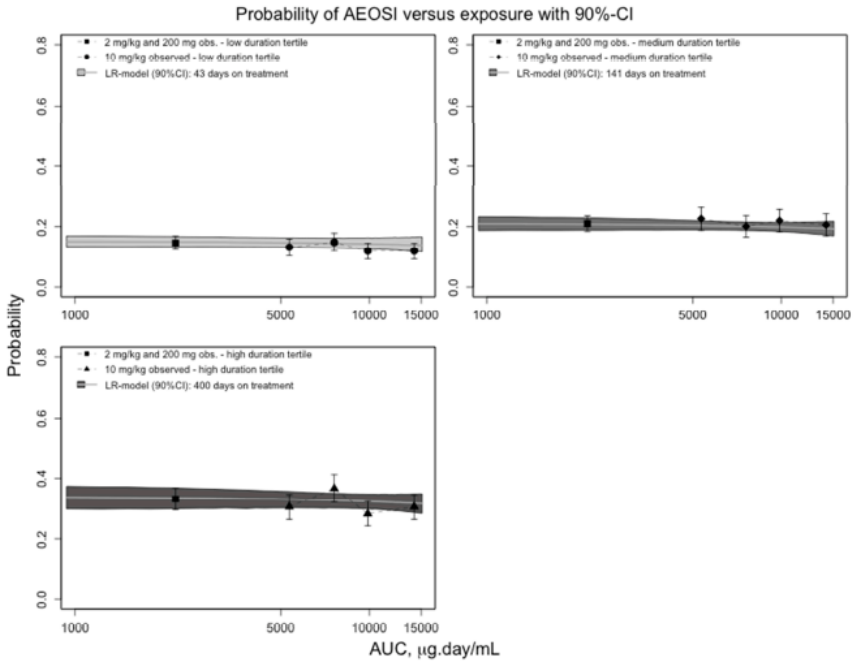
Whereas a weight-based dose generally produces higher systemic exposures in subjects with heavier body weight, the trend is reversed with the fixed dose, ie, lower body weight subjects tend to have higher exposures on a fixed 200 mg dose. To address the safety risk profile for lighter body weight subjects receiving the 200 mg fixed dose, an exploration of the relationship between AEOSI and body weight was conducted. The figure below demonstrates a flat relationship between incidence of AEOSI across body weight in first-line NSCLC, suggesting the lower weight subjects are not put at additional risk for AEOSI when administered a fixed 200 mg dose regimen.



Each body weight bins consisted approximately of 38 subjects

Figure 11: **Summary of incidence of AEOSI across body weight for 200 mg Q3W**

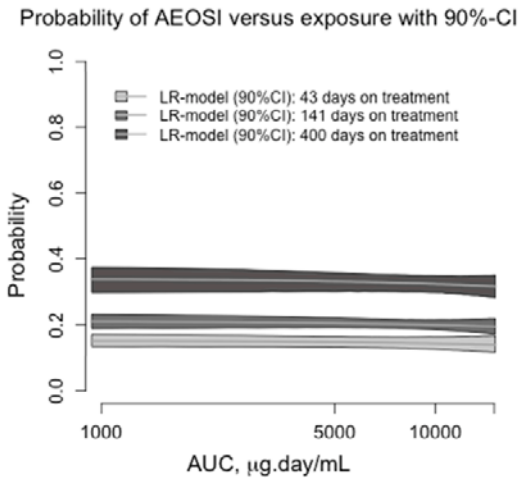
As part of the qualification process, a VPC was performed by simulating 10000 subjects. The VPC for the final model including a non-significant exposure to pembrolizumab and incidence of AEOSI is displayed below



Solid symbols connected by thin dotted lines represent observed AE incidence per bin of individual AUC (one bin for 2 mg/kg and 200 mg and four equally sized bins for 10 mg/kg) and treatment duration values. Each panel represents a tertile in the distribution of treatment duration. Solid line represents model estimated probability representing the median of treatment duration in each tertile. Shaded area represents the 90% confidence interval for that prediction. Model predictions extend to the 5% and 95% quantiles of the AUC estimates in the dataset. Error bars on the observed data represent ± 1 standard deviation.

Figure 12: VPC of the final developed logistic regression model to investigate the relationship between pembrolizumab exposure and incidence of AEOSI

The simulated probability of experiencing an AEOSI in function of exposure, using the final model, is shown below.



The median (95% CI) simulated probability of experiencing an AE of the AEOSI group during 141 days of treatment (median treatment duration in dataset) for an exposure equal to the median AUC6wks for 2 mg/kg Q3W, 200 mg Q3W, 10 mg/kg Q3W or 10 mg/kg Q2W was 0.21 (0.19, 0.23), 0.21 (0.19, 0.23), 0.20 (0.19, 0.21) and 0.20 (0.18, 0.21), respectively. Thus, simulations indicate AEOSI occurrence to remain similar with increasing exposure.

Figure 13: Simulated probability of experiencing an AE for the AEOSI group in function of exposure and duration of treatment with associated 90% CI's

Data support a flat relationship between incidence of AEOSI across body weight in first line therapy.

2.3.5. Discussion on clinical pharmacology

The SmPC of pembrolizumab reported that near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the median Cmin at 18 weeks was approximately 24 mcg/mL at a dose of 2 mg/kg every 3 weeks. **Data from study P024** show that the median Ctrough (pre-dose) concentration at week 21 is 32.7 mcg/mL at a dose of 200 mg every 3 weeks. As expected, a slight difference in the pk parameters has been observed. This is in line with previous predictions of a 30% higher exposure than after 2 mg/kg Q3W.

All the PK data collected during the study P024 were included in the previous population PK, called definitive population PK, and the parameters from the existing **population PK model** were re-estimated to obtain posthoc parameters for all the individuals included in this pooled dataset.

However the conditional number, one of the evaluation model parameter used, is outside the range generally accepted. The conditional number of the final model is 34.6 while the degree of collinearity between the parameter estimates is acceptable for a conditional number ≤20. Moreover the ETA shrinkage values are quite high, very close to the upper boundary of the generally accepted range (The shrinkage of the volume parameters is 27.7%). According to the MAH these shrinkage values could be due to limited information in the dataset to inform the individual estimation of these parameters.

In order to verify the ability of the model to describe the new data, visual predictive checks were performed. The VPC for Ctrough concentrations in 200mg Q3W shows that the model tends to underpredict plasma concentrations: both median line and 95th percentile of observations are at higher concentrations values compared to the 90% CI of predictions. The VPC for peak concentrations in 200mg Q3W are poorly described by the model. The MAH performed a dedicated evaluation in order to assess potential origins of the model underprediction observed in the VPC (Report 04FYYY).

Mainly the addition of time-dependency in pembrolizumab CL in the population PK model and the impact of censoring (dropout) on the performance of pembrolizumab population PK diagnostic results were explored

as causes of the underprediction. Results showed that apparent on-study increases in concentration at time points long after treatment initiation are mostly attributable to informative censoring patterns. However due to the limitations of the analysis the potential for a small, true biologic time-dependency in pembrolizumab CL cannot be ruled out even though this time dependency is not clinically relevant and has no meaningful impact on assessment of intrinsic/extrinsic factor effects or exposure-response relationships. Based on this investigation, the static model is considered the definitive PK model used to interpret sparse concentration data collected in pembrolizumab trials to inform intrinsic and extrinsic factor effects and exposure-response characterizations.

The predicted statistics for C_{max} at 2 mg/kg Q3W and 200 mg Q3W dose regimen were 64.2 µg/mL and 85.6 µg/mL respectively. The predicted statistics for steady state exposure parameters, both C_{trough} and $AUC_{ss, 6\text{-week}}$, confirmed the finding of the study P024, PK exposure parameters after 200 mg Q3W are slightly higher compared to 2 mg/kg Q3W.

A comparison of the derived PK parameters was done also by first line (1L) NSCLC, second line (2L) NCSLC and Melanoma patients. The estimated CL is slightly lower for patients with melanoma, resulting in a slightly higher Vd, t1/2 and time to steady state. Thus the line of therapy did not affect PK parameters in NSCLC, but there was a difference in VD and CL between Melanoma and NCSLC patients in line with the results of the covariate selection procedure indicating the additional effect of cancer type (NSCLC vs melanoma) on Volume of distribution. Therefore in the Clinical study report the MAH refers to the final model as the model having cancer type as covariate on CL and Vc. Overall, the model is considered adequate for the purpose of this variation.

A flat concentration-efficacy relationship was previously demonstrated for NSCLC with the Modelling & Simulation Report “Model-based analysis of the relationship between pembrolizumab (MK-3475) exposure and efficacy in patients with non-small-cell lung carcinoma (NSCLC) in PN001 and PN010”.

The **ER analysis** was performed in order to investigate the relationship between exposure to pembrolizumab in serum (i.e. AUCss-6weeks) and the anti-tumour response in first-line (1L) NSCLC. The number of subjects with TPS<50% is very low, so it is not possible to draw any firm conclusion about this subgroup of patients. For patients with TPS ≥50%, data indicate that the tumour response is not correlated to the AUCss-6wk.

However, in the majority of patients (i.e. in all patients < 100 kg BW) the resulting exposure relative to body weight after a 200 mg flat dose is higher than 2 mg/kg (up to 4 mg/kg in a 50 kg patient). In contrast, heavier patients (> 100 kg body weight) receive a relative dose which is lower than after 2 mg/kg. However, considering the limited number of patients with weight ≥100 kg (5 patients), no sound conclusion can be drawn based on available data.

The MAH justifies the slightly higher incidence of **anti-drug antibody** (ADA) against pembrolizumab in NSCLC relative to the melanoma indication as the results of the ongoing optimization of the immunogenicity assay framework, the majority of the NSCLC data were analysed with the most recent assay at PPD which has a higher tolerance level for the presence of pembrolizumab. However, analysing immunogenicity results stratified by treatment and indication, it can be observed that the higher incidence of ADA in NSCLC has been recorded also in 2mg/kg and 10 mg/kg groups. Thus data suggests a slightly higher incidence of ADA in NSCLC. Overall, the incidence is low and any consequence on pembrolizumab exposure is unlikely.

The modelling and simulation approach is being applied also to investigate **exposure-response relationships for safety**.

The Exposure-Adverse event analysis revealed that the flat dose do not increase the probability to have a AEOSI compared to the weight adjusted dosage. The duration of treatment was found to correlate with the occurrence of AEOSI.

2.3.6. Conclusions on clinical pharmacology

Data from study P024 show that the median C_{trough} concentration at steady state were slightly higher after dose of 200 mg Q3W (C_{trough} at week 21 was 32.7 mcg/mL) compared to 2 mg/kg Q3W (C_{min} at 18 weeks was approximately 24 mcg/mL).
All the PK data collected during the study P024 were included in the previous population PK - "Model-based analysis of the relationship between pembrolizumab exposure and efficacy in patients with non-small-cell lung carcinoma (NSCLC) in PN001 and PN010".
Overall, the model is adequate for the purpose of this variation. Results show that the line of therapy did not affect PK parameters in NSCLC, but there was a difference in VD and CL between Melanoma and NCSLC patients. The duration of treatment was found to correlate with the occurrence of AEOSI.

2.4. Clinical efficacy

To support the Keytruda extension of indication as first line treatment in NSCLC, the second interim analysis (IA2) of the multicenter, international, open label study KEYNOTE-024 (P024), in which untreated patients were randomized to receive pembrolizumab 200 mg (fixed dose) or Investigator choice of pre-specified SOC (Standard of Care) platinum based chemotherapies, was submitted by the MAH. Based on these results (data cut-off date 9 May 2016), the trial was stopped per external Data Monitoring Committee (eDMC)'s recommendation and pembrolizumab was offered to remaining subjects on the SOC arm.

Study ID / centres / locations	**Study design**	**Treatment**	**No of pts planned / random / treated**	**Demographics**	**Primary endpoint**	**Secondary endpoints**
KEYNOTE-024 P024 149 centers activated in 16 countries: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherland, New Zealand, Spain, United Kingdom, United States	Randomized (1:1), multicenter, open-label, controlled trial of IV pembrolizumab monotherapy vs the choice of multiple standard of care (SOC) platinum based chemotherapies in subjects previously untreated for their Stage IV, PD-L1 strong NSCLC.	**<u>Pembrolizumab</u>** 200 mg IV Q3W **<u>Investigator's choice SOC</u>** Pemetrexed 500 mg/m^2 + carboplatin AUC 5 to 6 mg/mL/min IV Q3W Day 1 (4-6 cycles) followed by optional pemetrexed 500 mg/m^2 (maintenance) Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m2 IV Q3W Day 1 (4-6 cycles) followed by optional pemetrexed 500 mg/m^2 (maintenance) Gemcitabine 1250 mg/m^2 IV Days 1 and 8 + cisplatin 75 mg/m^2 Q3W Day 1 (4-6 cycles) Gemcitabine 1250 mg/m^2 IV Days 1 and 8 + carboplatin AUC 5 to 6 mg/mL/min IV Q3W Day 1 (4-6 cycles) Paclitaxel 200 mg/m^2 + carboplatin AUC 5 to 6 mg/mL/min Q3W Day 1 (4 to 6 cycles) followed by optional pemetrexed 500 mg/m^2 (maintenance)	150/154/154 150/151/150 66 pts treated 36 pts treated 11 pts treated 20 pts treated 17 pts treated	Sex: 92M/62F Median age (min/max): 64.5 years (33-90) Sex: 95M/56F Median age (min/max): 66 years (38-85)	**PFS**	**<u>OS</u>** **<u>ORR</u>** (RECIST 1.1) by BICR

2.4.1. Dose response study

The pivotal study P024 is the first trial with pembrolizumab administered as 200 mg fixed dose. The choice of this dose was based on modelling and simulations performed using the population PK model of pembrolizumab. Results showed that the 200 mg Q3W fixed dose provide exposures consistent with those obtained with the 2 mg/kg dose Q3W, maintaining individual subject exposures in the range established in melanoma to be associated with maximal efficacy response and safety.

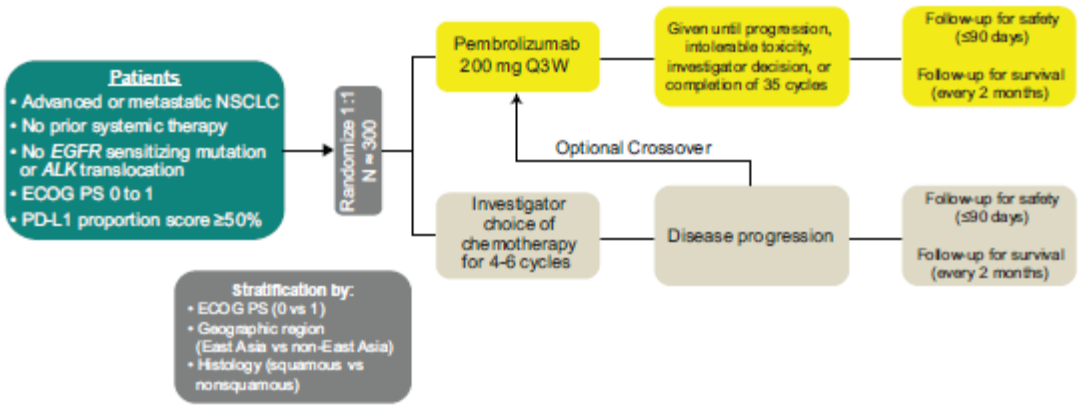
In support of this submission, an exploratory analysis of tumour size change was conducted with all available data in treatment-naïve subjects with NSCLC to verify whether new data from subjects receiving the 200 mg fixed dose alters prior exposure-response assessments from the body weight-based dosing. All three major components of prior exposure-efficacy analyses (ie, the exploratory plots, exposure slope estimates from the model, and covariate-normalized simulations) were consistently in agreement.

The rationale and results supporting the switch in the clinical development from a weight-based dose of 2 mg/kg to a 200 mg fixed dose of pembrolizumab administered every 3 weeks (Q3W) are discussed in Section on PK/PD modelling.

2.4.2. Main study

A Randomized Open-Label Phase III Trial of Pembrolizumab versus (vs.) Platinum based Chemotherapy in First-Line (1L) Subjects with Programmed Cell Death 1 Ligand 1 (PD-L1) Strong Metastatic NSCLC

Study design



Methods

Study participants

Main inclusion criteria

- Histologically or cytologically confirmed diagnosis of NSCLC, Stage IV, with no EGFR sensitizing (activating) mutation or ALK translocation, and not prior systemic chemotherapy treatment for metastatic NSCLC.
- Measurable disease based on RECIST 1.1, as determined by the site.
- Age ≥18 years
- Life expectancy ≥3 months
- ECOG Performance Status of 0 or 1
- Provided formalin fixed tumour tissue sample from a biopsy of a tumour lesion either at the time of or after the diagnosis of metastatic disease had been made AND from a site not previously

irradiated, to assess for PD-L1 status. The tissue sample was to be received by the central vendor prior to randomization. Fine needle aspirates, endobronchial ultrasound, or cell blocks were not acceptable. Needle or excisional biopsies, or resected tissue was required.

- Investigators were to be able to produce the source documentation of the EGFR mutation and ALK translocation status in all subjects with non-squamous histologies AND for subjects in whom testing was clinically recommended. If either an EGFR sensitizing mutation or ALK translocation was detected, additional information regarding the mutation status of the other molecule was not required. If unable to test for these molecular changes, formalin fixed paraffin embedded tumour tissue of any age were to be submitted to a central laboratory designated by the Sponsor for such testing. Subjects with non-squamous histologies were not randomized until the EGFR mutation status and/or ALK translocation status was available in source documentation at the site. For subjects enrolled who were known to have a tumour of predominantly squamous histology, molecular testing for EGFR and ALK translocation was not required.
- PD-L1 strong tumour (TPS≥50%) as determined by IHC at a central laboratory.

Main exclusion criteria

- Systemic therapy for the treatment of their stage IV NSCLC. Completion of 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 metastatic disease.
- Current or previous participation in a study of an investigational agent, with study therapy received or investigation device used within 4 weeks of the first dose of treatment.
- Tumor specimen not evaluable for PD-L1 expression by the central laboratory. If an additional tumour specimen was submitted AND evaluable for PD-L1 expression, the subject was eligible to participate if PD-L1 expression was assessed as “strong” by the central laboratory.
- Systemic steroid therapy <3 days prior to the first dose of trial treatment or any other form of immunosuppressive medication (corticosteroid use on study for management of ECIs, as pre-medication for the control chemotherapies, and/or a premedication for IV contrast allergies/reactions were allowed). Subjects who were receiving daily steroid replacement therapy served as an exception to this rule.
- Requirement of any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).
- Prior systemic cytotoxic chemotherapy, biological therapy, OR major surgery within 3 weeks of the first dose of trial treatment; thoracic radiation therapy of >30 Gy received within 6 months of the first dose of trial treatment.
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects whose brain metastases have been treated were allowed to participate provided they showed radiographic stability. In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment had to be returned to baseline or resolved.
- Active autoimmune disease that had required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
- Allogenic tissue/solid organ transplant.
- Administration of live vaccine within 30 days prior to the first administration of study medication

Treatments

- Pembrolizumab 200 mg administered as a 30 minute (-5, +10) IV infusion Q3W.
- SOC chemotherapies:
    - Pemetrexed 500 mg/m^2 Q3W and carboplatin AUC 5 to 6 mg/mL/min Q3W on Day 1, for 4

to 6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (for non-squamous histologies only)

- Pemetrexed 500 mg/m^2 Q3W and cisplatin 75 mg/m^2 Q3W on Day 1, for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (for non-squamous histologies only)
- Gemcitabine 1250 mg/m^2 at Days 1 and 8 and cisplatin 75 mg/m^2 Q3W on Day 1 for 4 to 6 cycles
- Gemcitabine 1250 mg/m^2 at Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min Q3W on Day 1 for 4 to 6 cycles
- Paclitaxel 200 mg/m^2 Q3W and carboplatin AUC 5 to 6 mg/mL/min Q3W on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance for non-squamous histologies only)

The specific platinum doublet (including whether pemetrexed maintenance was offered for those subjects with non-squamous histologies) as well as the dose (for example, AUC 5 OR 6 mg/mL/min for carboplatin) to be administered was identified prior to randomization.

Subjects continued with the assigned study treatment until RECIST 1.1-defined progression of disease as determined by BICR review, unacceptable toxicity, intercurrent illness that prevented further administration of treatment, Investigator's decision to withdraw the subject, subject withdrew consent, pregnancy of the subject, non-compliance with trial treatment or procedure requirements, administrative reasons, or the subject had received 35 trial treatments of pembrolizumab. Treatment could have been continued despite RECIST 1.1 defined progression if the subject was clinically stable and considered to be deriving clinical benefit by the Investigator.

Pembrolizumab-treated subjects who attained a confirmed complete response (CR) could consider stopping trial treatment. These subjects, as well as those subjects assigned to the pembrolizumab arm who stopped trial therapy after 35 trial treatments for reasons other than disease progression or intolerability, were eligible for re-treatment with pembrolizumab in the Second Course Phase after they experienced radiographic disease progression at the discretion of the Investigator.

Objectives

The study primary objective was to compare the PFS, per RECIST 1.1 based on blinded independent central radiologists' review (BICR), of pembrolizumab to SOC chemotherapies in subjects with PD-L1 strong, previously untreated metastatic NSCLC.

The secondary objectives included the comparison of OS, ORR (RECIST 1.1 by BICR) and safety/tolerability in pembrolizumab and SOC groups.

Other exploratory objectives were to compare pembrolizumab and SOC chemotherapies in terms of PFS and ORR per irRC, PFS per RECIST 1.1 by Investigator in the next line of therapy (PFS2, second progression free survival), response duration per RECIST 1.1 by BICR and per irRC, and to evaluate patient-reported treatment effects at pre-specified time points while on treatment and post-discontinuation (EQ-5D-3L; EORTC QLQ-C30 and LC13), Quality adjusted Time without Symptoms or Toxicity (Q-TWiST) and genomic signature that predict for response in pembrolizumab treated patients.

Comparison of the time to progression while on the control arm to the time to progression following crossover to pembrolizumab was included as an exploratory objective in the Statistical Analysis Plan (SAP), but this analysis was not conducted.

Outcomes/endpoints

The primary efficacy endpoint was PFS, defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first.

As secondary endpoints, OS and ORR per RECIST 1.1 by BICR were evaluated.

OS was defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis were censored at the date of the last follow-up.

ORR was defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR), based upon blinded independent central radiologists' review per RECIST 1.1.

Among the planned exploratory endpoints, results have been submitted for:

- Time to response, defined as the time from randomization to the first assessment of CR or PR.
- Response duration, defined as the time from the first CR/PR to documented PD.

Only confirmed CR/PRs were included in the analysis for time to response and response duration. Subjects who did not have PD were censored at the time of the last disease response assessment.

- PRO at pre-specified time points while on treatment (every cycle for the first three cycles and every third cycle, 9 weeks, thereafter until PD) and post-discontinuation (at Treatment Discontinuation Visit and 30-day Safety Follow-up Visit) as measured by changes from baseline in all domains and single items of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (C30) and Lung Cancer 13 (LC13), with particular emphasis on EORTC QLQ-C30 QoL domain, chest pain, cough, and dyspnoea.

Sample size

The study was event-driven and planned to randomize approximately 300 subjects with 1:1 ratio into the pembrolizumab arm and the SOC arm. One analysis of ORR, one analysis of PFS and two analyses of OS (one interim at the time of PFS analysis, and one final) were planned. The overall type I error rate for this study was strictly controlled at 2.5% (one-sided). The sample size calculation was based on PFS with the following assumptions: 1) PFS follows an exponential distribution with a median of 5.5 months in the control arm, 2) hazard ratio between pembrolizumab and control is 0.55, 3) enrollment period of 14 months and at least 6 months PFS follow-up after enrollment completion, and 4) a dropout rate of 10% per year.

The first planned analysis (the ORR analysis) had to be conducted after first 191 subjects had a minimum of 6 months of follow up. This analysis had ~95% power to detect a 30% difference in ORR (e.g., 32% in SOC vs. 62% in pembrolizumab) at alpha=0.5%. In case this analysis resulted not significant, 0.5% of the 2.5% alpha had to be spent at the subsequent PFS and OS analyses to strictly control the overall type I error rate of the study [See below Section on Statistical Methods].

The planned PFS analysis had to be conducted after approximately 175 PFS events were observed between the pembrolizumab arm and control. If there were less than 110 OS events at the time, the analysis could have been delayed for up to 2 months or when the target OS number was reached, whichever occurred first. With ~175 PFS events, the study had ~98% [97%] power to detect a hazard ratio 0.55 at alpha = 2.5%[2%] (one-sided) at the PFS analysis, respectively, depending on the alpha spent at the ORR analysis. With ~110 OS events at the interim OS analysis, the study had ~60% power to demonstrate a numerically positive OS effect when the true hazard ratio is 0.7 assuming that half of the subjects in the control arm crossed over to pembrolizumab at the time of analysis.

The final OS analysis had to be conducted after approximately 170 deaths had occurred between the pembrolizumab arm and control. The final OS analysis was expected to occur 14 months after enrolment completion. With 170 deaths at final OS analysis, the study had ~75% power to observe a hazard ratio < 1 assuming that ~70% of the subjects in the control arm crossed over to pembrolizumab. The calculation was based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 13 months in the control arm, 2) hazard ratio between pembrolizumab and control is 0.7, 3) an enrolment period of 14 months and 14-15 months follow-up after enrolment completion, and 4) a dropout rate of 0.005 per month. With two planned OS analyses, i.e., ~110 OS events at final PFS analysis and ~170 OS events at final OS analysis, the study had approximately 60%[57%] power to detect a hazard ratio of 0.7 with the overall alpha controlled at 2.5%[2.0%] (one-sided).

Randomisation

Patients were centrally assigned randomly in a 1:1 ratio to pembrolizumab and SOC, using an interactive voice response system/integrated web response system (IVRS/IWRS). Randomization was to be stratified by geographic region (East Asia vs. non-East Asia), ECOG status (0 vs. 1) and histology (squamous vs. non-squamous).

Blinding (masking)

N/A

Statistical methods

The analysis of the primary and secondary efficacy endpoints is based on the intention-to-treat (ITT) population. The overall type I error rate for this study is strictly controlled at 2.5% (one-sided). One analysis of ORR, one analysis of PFS and two analyses of OS (one interim at the time of PFS analysis, and one final) were planned. The ORR analysis was planned when the first 191 randomized subjects had a minimum of 6 months of follow up, and was to be tested at the 0.5% (one-sided) alpha level. PFS was to be tested only once at the planned PFS analysis after ~175 PFS events were observed, and was to be tested at the 2.5% (one-sided) level if ORR testing was positive or at the 2.0% (one-sided) level if ORR testing was negative. OS was to be tested only if PFS was positive and at the same level, but proportional to the number of events at its interim analysis relative to the target final analysis number of events. A Hwang-Shih-DeCani alpha-spending function with the gamma parameter -0.4 and beta-spending function with gamma -35 was constructed to implement group sequential boundaries.

Table 11: Analysis Strategy for the key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary			
PFS (RECIST 1.1) by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based
Secondary			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based
ORR (RECIST 1.1) by BICR	Stratified Miettinen & Nurminen method	ITT	Subjects with missing data were considered non-responders

BICR = blinded independent central radiologist; ITT = intention-to-treat;
ORR = objective response rate; OS = overall survival; PFS = progression-free survival;
RECIST 1.1 = Response Evaluation Criteria on Solid Tumors Version 1.1

Progression Free Survival (PFS)

The non-parametric Kaplan-Meier method is used to estimate the PFS curve in each treatment group. The treatment difference in PFS is assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling is used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate is reported. The same stratification factors used for randomization (East Asia vs non-East Asia, ECOG PS 0 vs 1, and squamous histology vs. non-squamous) are applied to both the stratified log-rank test and the stratified Cox model.

Sensitivity analyses, with a different set of censoring rules, are performed for comparison of PFS based on

investigator's assessment. Sensitivity analysis 1 is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. Sensitivity analysis 2 is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in the following table.

Table 12: Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation 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

Overall Survival (OS)

The Kaplan-Meier method is used to estimate the survival curves. The treatment difference in survival is assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling is used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate are reported. The same stratification factors used for randomization are applied to both the stratified log-rank test and the stratified Cox model. Since subjects in the control arm were expected to discontinue from the study earlier compared to subjects in the pembrolizumab arm because of earlier onset of PD, with a possibility to switch to the pembrolizumab treatment after the confirmed progressive disease, it was planned to use the Rank Preserving Structural Failure Time (RPSFT) model to adjust for the effect of crossover on OS. To further account for the possible confounding effect, it was also planned to conduct a sensitivity analysis of OS censoring subjects at the time of initiation of new therapy and an additional analysis that treats initiation of new therapy as a time-dependent binary covariate.

For both PFS and OS, subgroup analyses, to determine whether the treatment effect is consistent across various subgroups, are conducted on the following classification variables: Age category (≤65, >65 years); Sex (female, male); Race (white, non-white); ECOG status (0, 1); Geographic region of enrolling site (East Asia, non-East Asia); Histology (squamous, non-squamous); Smoking status (never, former, current); Brain metastasis status (baseline brain metastasis, no baseline brain metastasis); Investigators' choice of standard of care chemotherapy.

Objective Response Rate (ORR)

The Stratified Miettinen and Nurminen's method (weighted with sample size) is used for comparison of the objective response rates between the treatment groups. A 95% confidence interval for the difference in response rates between the pembrolizumab arm and the control as well as the p-value is provided. The same stratification factors used for randomization are applied to the analysis. Sensitivity analyses are performed for comparison of ORR based on investigator's assessment.

Exploratory endpoints

Time to response/Duration of response

Response duration is summarized descriptively using Kaplan-Meier medians. Response rate at specific time points (for example, 6 months etc.) based on Kaplan-Meier method are summarized. Only the combined subset of subjects who show a confirmed complete or partial response are included in this analysis. For subjects who cross over to pembrolizumab after disease progression on the control arm, time to progression while on the control arm was planned to be compared to the time to progression following crossover, where the time to progression following crossover is defined as the time from time of crossover to the earliest documented disease progression.

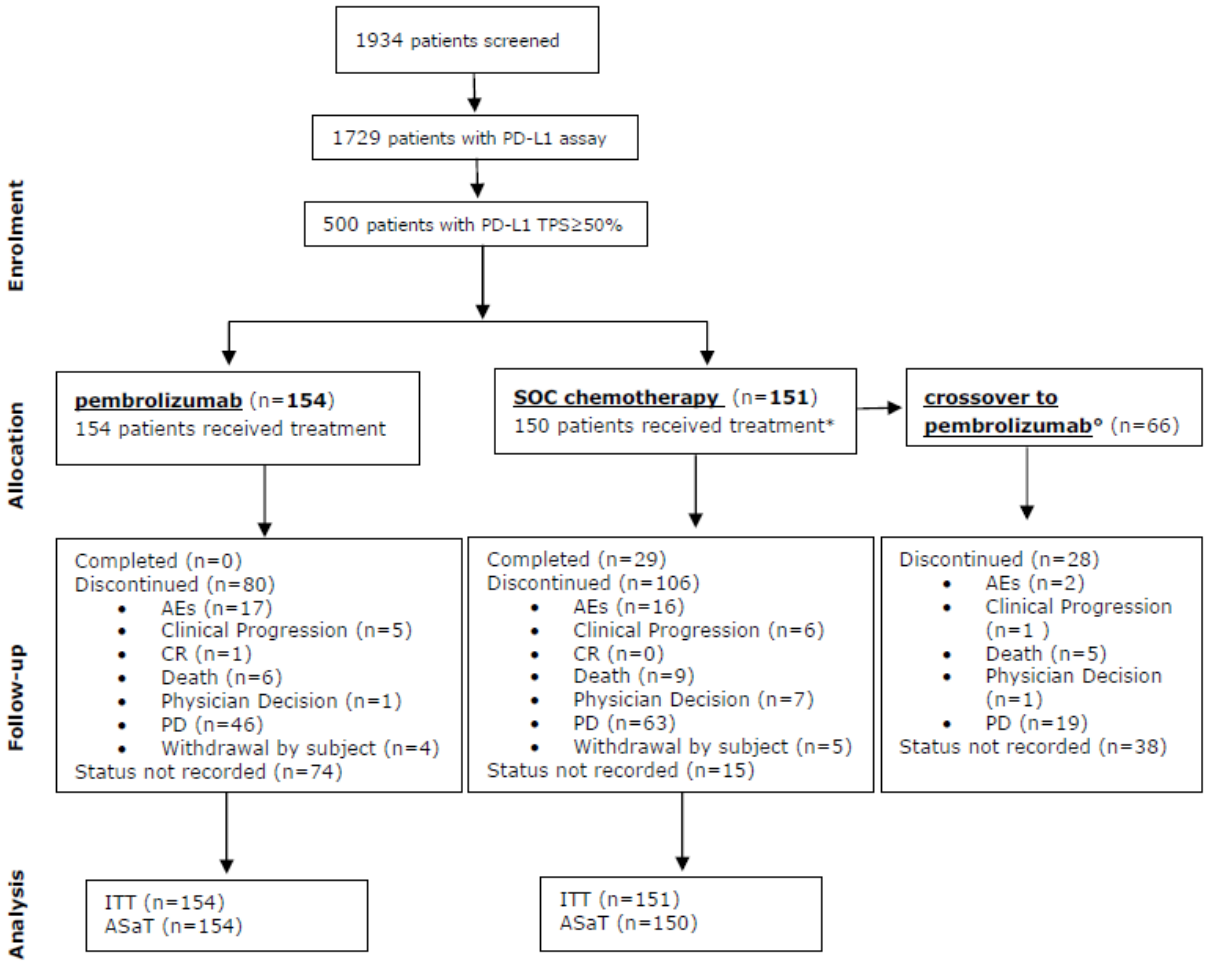
Patient Reported Outcomes (PROs)

The key PRO endpoints are the mean score changes from baseline to week 15 as measured by the EORTC QLQ-C30 and the Time to deterioration (TTD) in the composite endpoint of cough (LC13-Q1), chest pain (LC13-Q10) and dyspnoea (LC13-Q3-5). Although no formal hypothesis is formulated, the nominal p-value is provided for treatment comparisons of pembrolizumab vs. SOC for PRO endpoints. No multiplicity adjustment is performed. Longitudinal and descriptive data analysis are used to evaluate patient-reported outcomes (PROs). Several approaches are considered to address the issue of informative missing data.

Supportive PRO endpoints are the mean score changes, and the number and proportions of deterioration/stable/improvement from baseline to week 15 specifically related to: (1) EORTC QLQ-C30 global health status/quality of life scale (the number and proportions of deterioration/stable/improvement only); (2) Each EORTC QLQ-C30 functional subscale: physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning; (3) Each EORTC QLQ-C30 symptom subscale score: Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea; (4) Each EORTCQLQ-LC13 item: pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis (mean score changes from baseline only); (5)The EORTC QLQ-LC13 dyspnoea multi-item sub-scale (mean score changes from baseline only).

Results

Participant flow



*the reason for not dosing patient #245137 was not provided; °Subjects on the SOC arm were considered for crossover to pembrolizumab after documented, progressive disease per RECIST 1.1 guidelines (based on centrally reviewed assessment). Crossover was optional ; ITT: Intention to treat; ASaT: All Subject as Treated.

Among 500 patients screened as PD-L1 TPS≥50%, only 305 have been enrolled. Most of the PD-L1 strongly positive screen failure patients (39%) were not randomized because the evaluation of PD-L1 status was performed in tissue specimens not permitted by the protocol, or the tissue sample was obtained from irradiated lesions, or prior to the diagnosis of metastatic disease or prior to administration of systemic therapy. The provided information reassures on the correctness of patients selection.

Recruitment

Overall, 350 PD-L1 positive (TPS ≥50%) patients were enrolled in 142 out of the 149 activated sites in 16 countries. The first patient was randomized on 19 September 2014 and the last subject was assigned treatment on 29 October 2015. The highest enrolling country was the US with a total of 42 subjects and the top recruiter site was in Spain (14 patients).

Conduct of the study

A total of 5 protocol amendments to the original protocol (dated 27 March 2014), including global and country-specific changes, were implemented during the study.

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

Protocol Amendment	Most relevant changes
#01 (16 October 2014)	Input from the regulatory authorities on entry criteria: - Abstinence acceptable if established and preferred contraception method. - Exclusion of subjects with active tuberculosis. - Removal of KRAS testing. - Subject eligibility based on site assessment rather than central review of the screening CT images. - Total administration of pembrolizumab was changed from 2 years to 35 cycles, and the second course phase was limited to 1 year.
#02 (7 November 2014)	Country specific (Germany): requirement of a tuberculosis test at screening in order to comply with regulatory guidance.
#03 (28 January 2016)	Addition of an interim efficacy analysis (ORR) for an external DMC review.
#04 (12 February 2016)	Country specific (Germany)
#05 (24 March 2016)	Country specific (Germany)

Protocol deviations

For this trial, a major protocol deviation was defined as any protocol deviation which could significantly/adversely impact the completeness, accuracy, and/or reliability of the trial data or that could significantly/adversely affect a subject's rights, safety, or well-being. Major deviations were defined based on subject protections described in the protocol and included protocol specific deviations based on the trial design, critical procedures, trial data, and the planned analyses of trial data. The medical monitoring process included review of all major deviations documented as of 06-Jun-2016 (n=285).

Table 13: Summary of most pertinent protocol deviations

Deviation Category
Inclusion Criteria
#1 – Stag IIIB
#5 – ECOG performance status 2
#10 – Tumors were not PD-L1 TPS≥50%
Exclusion Criteria
#7 – Radiotherapy to thorax >30 Gy
#10 – Lupus erythematodes disseminatus
ECOG = Eastern Cooperative Oncology Group; Gy = gray; PD-L1 = programmed cell death 1 ligand 1. Source: [16.2.2]

Baseline data

The majority of enrolled patients were male (61.3%), White (82.3%), non-Hispanic (92.5%), and non-East Asian (86.9%). Most of them had Stage IV adenocarcinoma (69.5%) NSCLC without prior neo-adjuvant (98.7%) or adjuvant (97%) chemotherapy. An ECOG 1 at baseline was registered in the 64.6% of subjects.

Table 14: Subject Characteristics

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		151	
Gender				
Male	92	(59.7)	95	(62.9)
Female	62	(40.3)	56	(37.1)
Age (Years)				
< 65	77	(50.0)	64	(42.4)
>= 65	77	(50.0)	87	(57.6)
Mean	63.9		64.6	
SD	10.1		9.5	
Median	64.5		66.0	
Range	33 to 90		38 to 85	
Race				
American Indian Or Alaska Native	0	(0.0)	1	(0.7)
Asian	25	(16.2)	21	(13.9)
Black Or African American	2	(1.3)	2	(1.3)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.7)
White	125	(81.2)	126	(83.4)
Missing	2	(1.3)	0	(0.0)
Ethnicity				
Hispanic Or Latino	1	(0.6)	5	(3.3)
Not Hispanic Or Latino	147	(95.5)	135	(89.4)
Not Reported	4	(2.6)	6	(4.0)
Unknown	2	(1.3)	5	(3.3)
ECOG				
0	54	(35.1)	53	(35.1)
1	99	(64.3)	98	(64.9)
2	1	(0.6)	0	(0.0)
Cancer Stage at Screening				
IIIB	1	(0.6)	1	(0.7)
IV	153	(99.4)	150	(99.3)
Geographic Region of Enrolling Site				
Non-East Asia	133	(86.4)	132	(87.4)
East Asia	21	(13.6)	19	(12.6)
Histology				
ADENOCARCINOMA	104	(67.5)	108	(71.5)
ADENOSQUAMOUS	2	(1.3)	2	(1.3)
LARGE CELL CARCINOMA	2	(1.3)	2	(1.3)
NON-SQUAMOUS CELL CARCINOMA	5	(3.2)	7	(4.6)
POORLY DIFFERENTIATED	9	(5.8)	3	(2.0)
SARCOMATOID	3	(1.9)	2	(1.3)
SQUAMOUS CELL CARCINOMA	29	(18.8)	26	(17.2)
POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA	0	(0.0)	1	(0.7)
Smoking Status				
Current	34	(22.1)	31	(20.5)
Former	115	(74.7)	101	(66.9)
Never	5	(3.2)	19	(12.6)
Brain Metastasis Status at Baseline				
Y	18	(11.7)	10	(6.6)
N	136	(88.3)	141	(93.4)
Baseline Tumor Size (mm)				
Subjects with data	151		150	
Mean	90.9		99.8	
SD	53.4		63.4	
Median	82		84	
Range	14 to 322		14 to 369	
Baseline Weight (kg)				
Subjects with data	154		151	
Mean	68.8		72.7	
SD	13.7		17.2	
Median	69		70	
Range	38 to 110		39 to 132	
Prior Adjuvant Therapy				
Yes	6	(3.9)	3	(2.0)
No	148	(96.1)	148	(98.0)
Prior Neo-adjuvant Therapy				
Yes	3	(1.9)	1	(0.7)
No	151	(98.1)	150	(99.3)

(Database Cutoff Date: 09MAY2016).

Numbers analysed

The ITT population, including all randomized subjects (305 patients), served as the primary population for both primary and secondary efficacy endpoints.

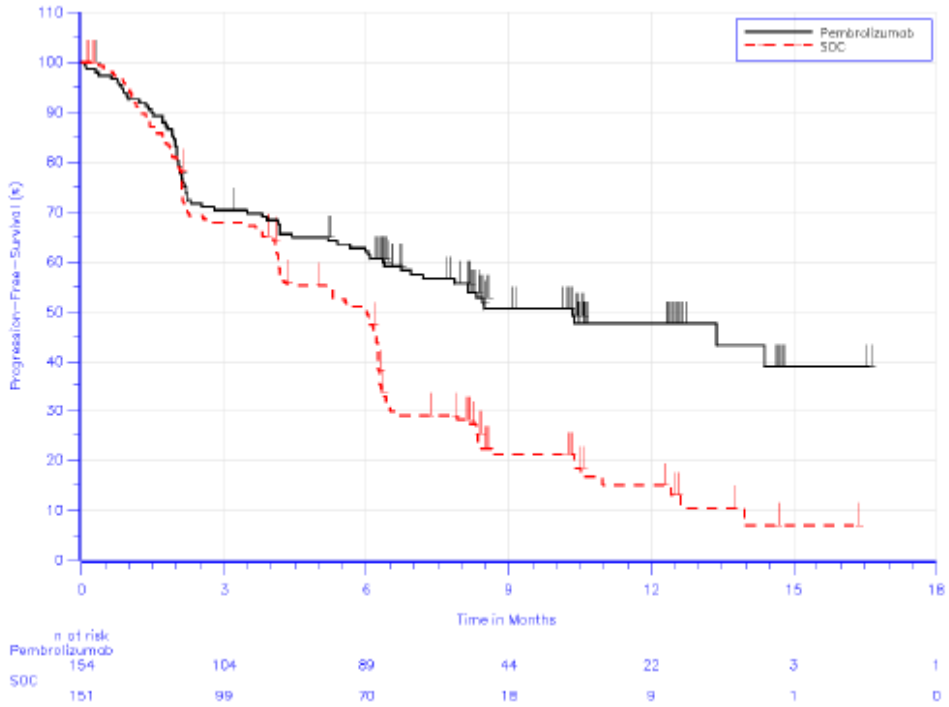
For the analysis of pre-specified exploratory PRO endpoints, a specific Full Analysis Set (FAS) population, that consisted of all randomized subjects who received at least one dose of study medication and completed at least one PRO instrument (299 patients), was considered.

The All Subject as Treated (AsaT) population, defined as all randomized subjects who received at least one dose of study treatment (304 patients) was used for the analysis of safety data.

Outcomes and estimation

The data cut-off date for the submitted analysis (IA2) was on 9 May 2016, with a median duration of follow-up of 11 months (range 6.3 to 19.7 months).

Progression Free Survival (primary endpoint)



Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	154	73 (47.4)	1000.2	7.3	10.3 (6.7, .)	62.1 (53.8, 69.4)	---	---
SOC	151	116 (76.8)	785.6	14.8	6.0 (4.2, 6.2)	50.3 (41.9, 58.2)	0.50 (0.37, 0.68)	<0.001

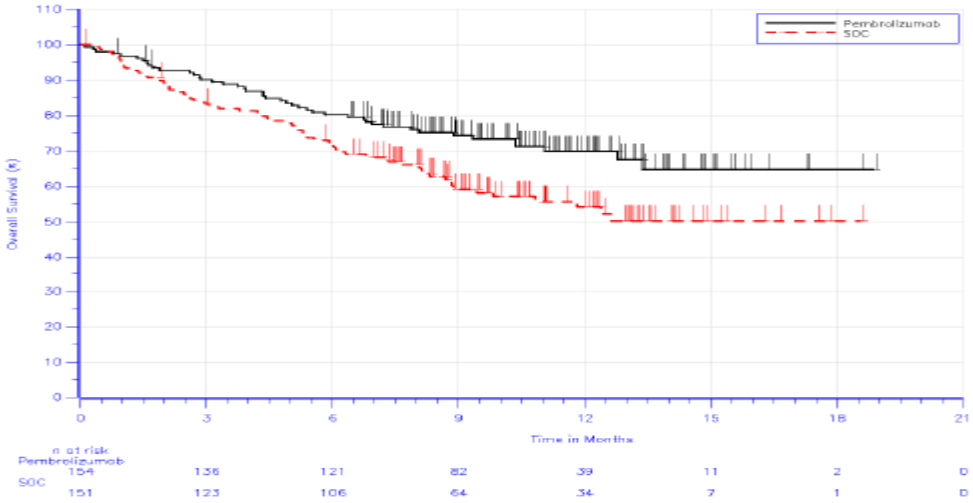
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on log-rank test.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adtte]

Figure 14: Kaplan-Meier of PFS based on BICR assessment per RECIST 1.1 (Primary Censoring Rule) ITT Population

The 12-month PFS rates are 47% and 15% for pembrolizumab and SOC, respectively.

Overall Survival (secondary endpoint)



Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	154	44 (28.6)	1402.0	3.1	Not Reached (. , .)	80.2 (72.9, 85.7)	---	---
SOC	151	64 (42.4)	1227.5	5.2	Not Reached (9.4, .)	72.4 (64.5, 78.9)	0.60 (0.41, 0.89)	0.005

† 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 log-rank test.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adtte]

Figure 15: Kaplan-Meier of OS (ITT Population)

The 12-month OS rates are 69.9% and 54.2% for pembrolizumab and SOC, respectively.

Cross-over occurred in 66 out of the 116 patients with PFS events. The median time to crossover (200.5 days) is similar to median PFS observed in the control arm (6 months, 95%CI 4.2, 6.2), with a wide range (54 to 443).

Objective Response Rate (secondary endpoint)

Table 15: Analysis of Objective Response with confirmation based on BICR assessment per RECIST 1.1 (ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. SOC	
				Estimate (95% CI)†	p-Value††
Pembrolizumab	154	69	44.8 (36.8,53.0)	16.6 (6.0,27.0)	0.0011
SOC	151	42	27.8 (20.8,35.7)		

† 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: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adopa]

Table 16: Summary of Best Overall Response with confirmation based on BICR assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Number of Subjects in Population	154		151	
Complete Response (CR)	6	3.9	1	0.7
Partial Response (PR)	63	40.9	41	27.2
Overall Response (CR + PR)	**69**	**44.8**	**42**	**27.8**
Stable Disease (SD)	38	24.7	60	39.7
Disease Control (CR + PR + SD)	**107**	**69.5**	**102**	**67.5**
Progressive Disease (PD)	34	22.1	28	18.5
Not Evaluable (NE)	4	2.6	6	4.0
No Assessment	9	5.8	15	9.9

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
(Database Cutoff Date: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adopa]

Time to Response and Response Duration (exploratory endpoint)

Table 17: Summary of Time to Response and Response Duration in subject with Objective Response based on BICR assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab (N=154)	SOC (N=151)
Number of Subjects with Response[†]	69	42
Time to Response[†] (months)		
Mean (SD)	3.0 (1.4)	3.2 (2.2)
Median (Range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
Response Duration[‡] (months)		
Median (Range)[§]	Not reached (1.9+ - 14.5+)	6.3 (2.1+ - 12.6+)
Number of Subjects with Response ≥ 2 months(%)[‡]	68(100.0)	42(100.0)
Number of Subjects with Response ≥ 4 months(%)[‡]	59(93.6)	33(89.3)
Number of Subjects with Response ≥ 6 months(%)[‡]	43(88.0)	16(59.4)
Number of Subjects with Response ≥ 9 months(%)[‡]	15(81.9)	4(36.2)

[†] Analysis on time to response and response duration are based on Subjects with a best overall response as confirmed complete response or partial response only.
[‡] From product-limit (Kaplan-Meier) method for censored data.
[§] "+" indicates the response duration is censored.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adtte]

Patient Reported Outcome (exploratory endpoint)

Compliance rates for EORTC QLQ-C30 and EORTC QLQ-LC13 at baseline were above 90% in the two treatment arms and close to 80% at week 15, with a slightly lower rate in the SOC than in the pembrolizumab arm. As expected, completion rates continued to decrease at each time point.

EORTC QLQ-C30 score change from baseline to week 15

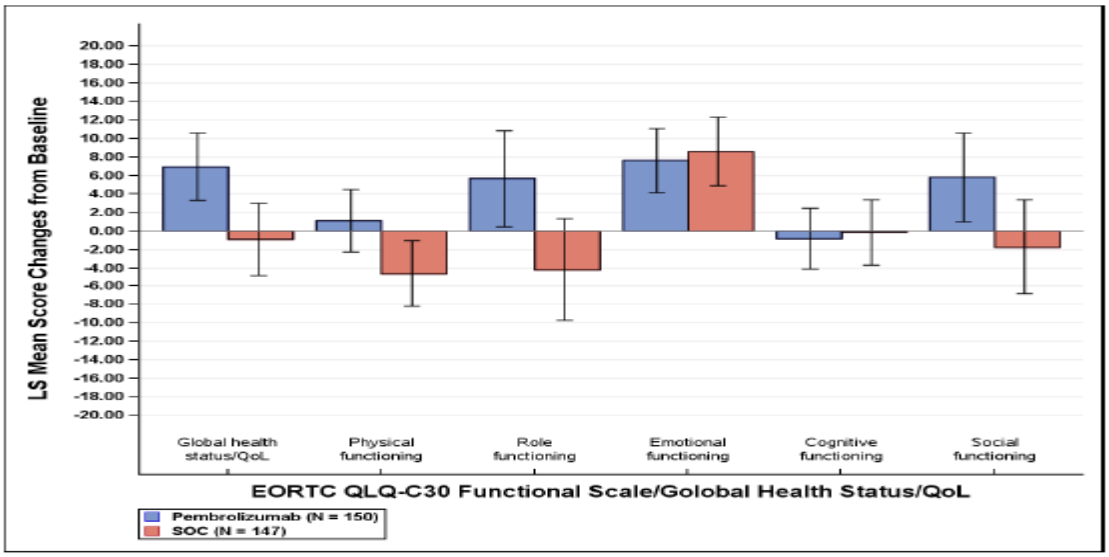
Table 18: Analysis of Change from baseline in EORTC QLQ-C30 Global health status/QoL at week 15 (FAS Population)

	Baseline		Week 15		Change from Baseline at Week 15		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]	
Pembrolizumab	145	62.24 (22.267)	109	70.95 (21.234)	150	6.94 (3.29, 10.58)	
SOC	137	59.85 (22.306)	92	63.68 (20.546)	147	-0.88 (-4.78, 3.02)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. SOC						7.82 (2.85, 12.79)	0.002

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) as covariates.
For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff: 09MAY2016

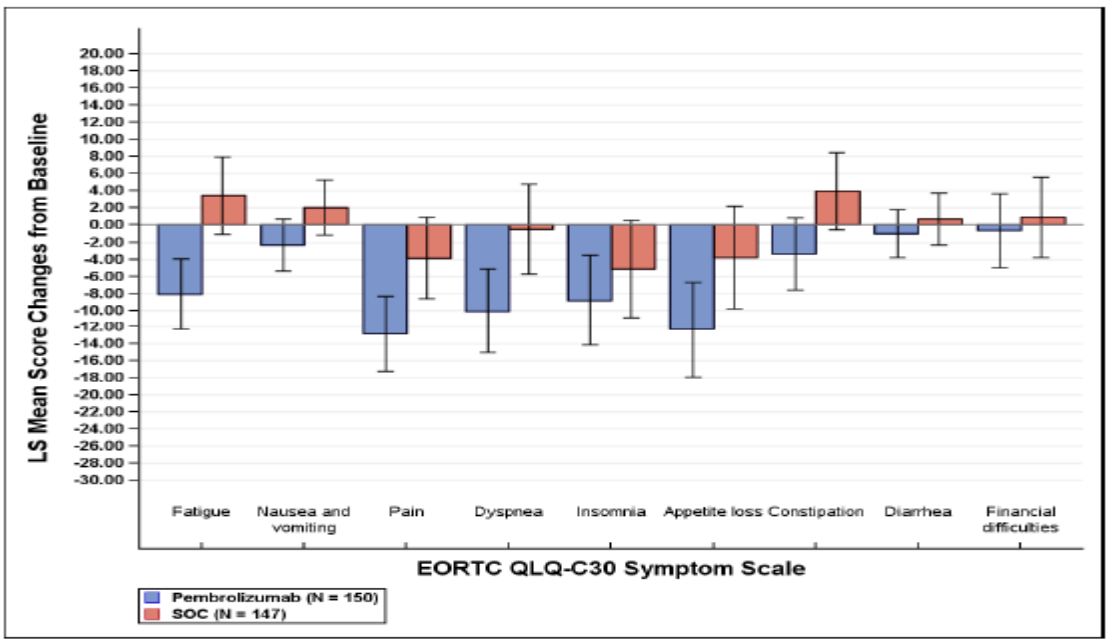
Source: [P024V01MK3475: analysis-adplda]

The longitudinal score changes from baseline to week 15 in EORTC QLQ-C30 global health status/QoL and functioning scales and symptom scales are reported in the following tbles:



*For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function. N is the number of subjects in the analysis population in each treatment group.
(Database Cutoff: 09MAY2016)
Source: [P024V01MK3475: analysis-adplda]

Figure 16: Change from baseline for EORTC QLQ-C30 functional scale/ global health status/QoL at week 15* - LS Mean Change and 95%CI (FAS Population)



*For symptoms scales, a higher score denotes worse symptoms. N is the number of subjects in the analysis population in each treatment group.
(Database Cutoff: 09MAY2016)
Source: [P024V01MK3475: analysis-adplda]

Figure 17: Change from baseline for EORTC QLQ-C30 symptom scale at week 15* - LS Mean Change and 95%CI (FAS Population)

The association of disease progression with subsequent score changes for global health status/QoL was also explored. Among subjects *without* disease progression, there was a greater improvement in global health status/QoL score from baseline to Week 15 for pembrolizumab compared to SOC whereas among subjects

with disease progression, there was less worsening in health status/QoL score from baseline to Week 15 for pembrolizumab than for SOC (see Table below).

Table 19: Analysis of Change from Baseline of EORTC QLQ-C30 Global health status / Quality of Life at Week 15 by Progressive Disease (PD) Status FAS Population

Treatment	Without PD LS Mean (95% CI)‡	With PD LS Mean (95% CI)‡	Difference by PD Status LS Mean (95% CI)‡
Pembrolizumab	9.09 (5.33, 12.86)	-3.52 (-10.49, 3.44)	-12.62 (-19.78, -5.46)
SOC	0.68 (-3.37, 4.72)	-9.97 (-15.78, -4.16)	-10.65 (-15.89, -5.40)

‡ Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) , PD status and PD status by treatment arm as covariates.
LS Mean: Least square mean; CI: Confidence interval.
Database Cutoff: 09MAY2016

Source: [P024V01MK3475: analysis-adplda]

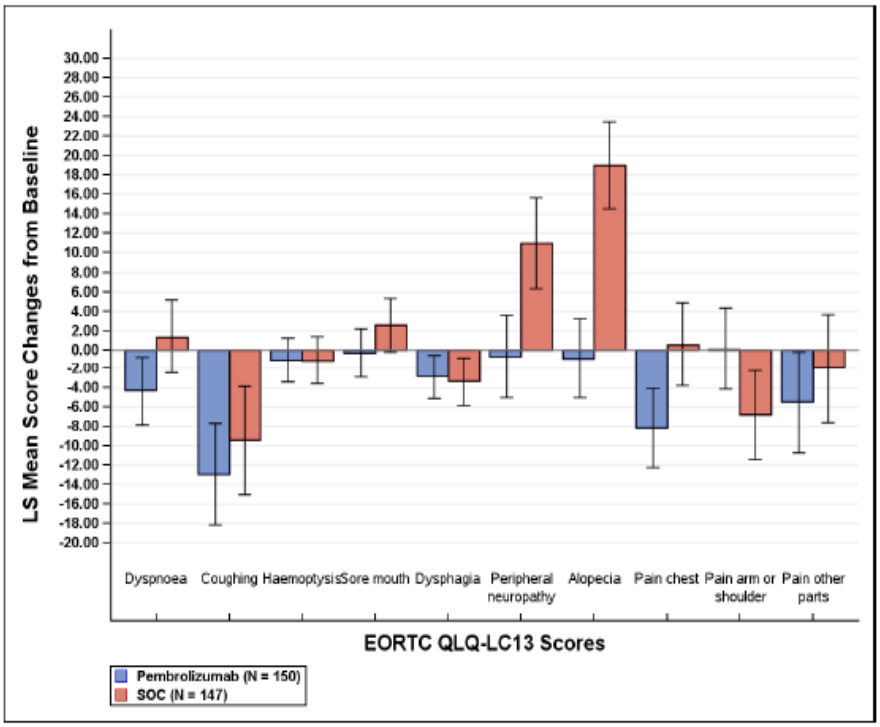
Time to Deterioration Analysis of EORTC QLQ-LC13 composite endpoint (cough, chest pain and dyspnea)

Table 20: Time to True Deterioration for Cough (LC13-Q1), Chest Pain (LC13-Q10) and Dyspnea (LC13-Q5) FAS Population

Treatment	N	Deterioration (Events) %	Pembrolizumab vs. SOC	
			Hazard Ratio† (95% CI)†	p-Value‡
Pembrolizumab	151	46 (30.5)	---	---
SOC	148	58 (39.2)	0.66 (0.44, 0.97)	0.029

True deterioration is defined as the time to first onset of 10 or more decrease from baseline with confirmation under right-censoring rule (the last observation).
† Based on Cox regression model with treatment as a covariate stratified by 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 log-rank test.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adttd]



*For symptoms scales, a higher score denotes worse symptoms. N is the number of subjects in the analysis population in each treatment group.
(Database Cutoff: 09MAY2016)
Source: [P024V01MK3475: analysis-adplda]

Figure 18: Change from baseline for EORTC QLQ-LC13 Scores at week 15* - LS Mean Change and 95%CI (FAS Population)

With few exceptions, changes from baseline to Week 15 in EORTC functioning and symptom domains were numerically superior for pembrolizumab arms compared to SOC and several, including fatigue, peripheral neuropathy, alopecia, and chest pain, were nominally significant (i.e., 95% CI did not overlap).

Ancillary analyses

PFS sensitivity analyses

Sensitivity analysis 1 is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment (see Table 12 for further details).

Table 21: Analysis of Progression-Free Survival based on BICR Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab	154	73 (47.4)	1000.2	7.3	10.3 (6.7, .)	62.1 (53.8, 69.4)	0.52 (0.38, 0.69)	<0.001
SOC	151	113 (74.8)	787.5	14.3	6.0 (4.2, 6.2)	51.5 (43.0, 59.3)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
[‡‡] One-sided p-value based on log-rank test.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adtte]

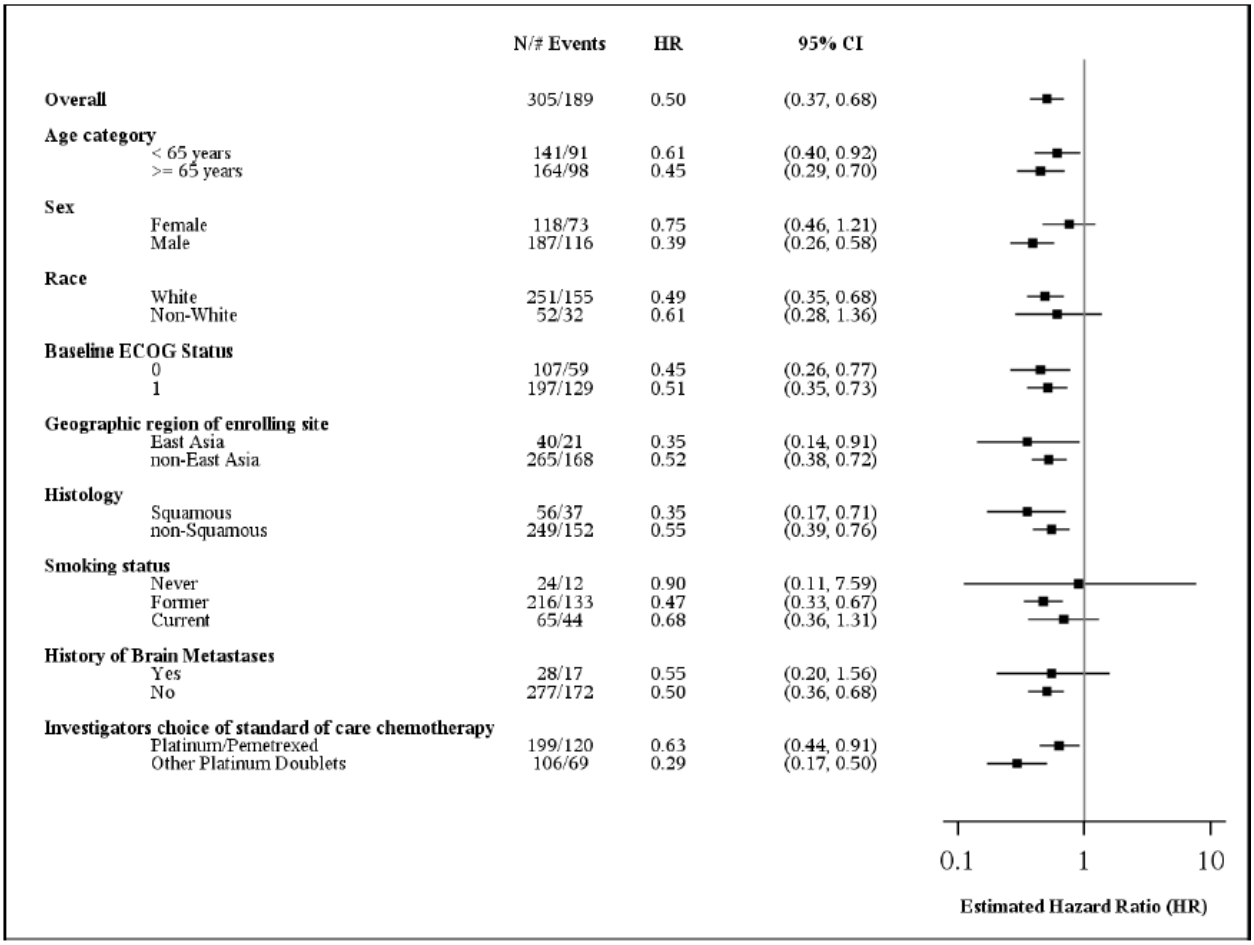
Table 22: Analysis of Progression-Free Survival based on BICR assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembrolizumab	154	89 (57.8)	985.5	9.0	7.2 (5.8, 10.3)	57.5 (49.3, 64.9)	0.49 (0.37, 0.64)	<0.001
SOC	151	143 (94.7)	779.7	18.3	4.9 (4.1, 6.1)	44.7 (36.6, 52.4)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
[‡‡] One-sided p-value based on log-rank test.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adtte]

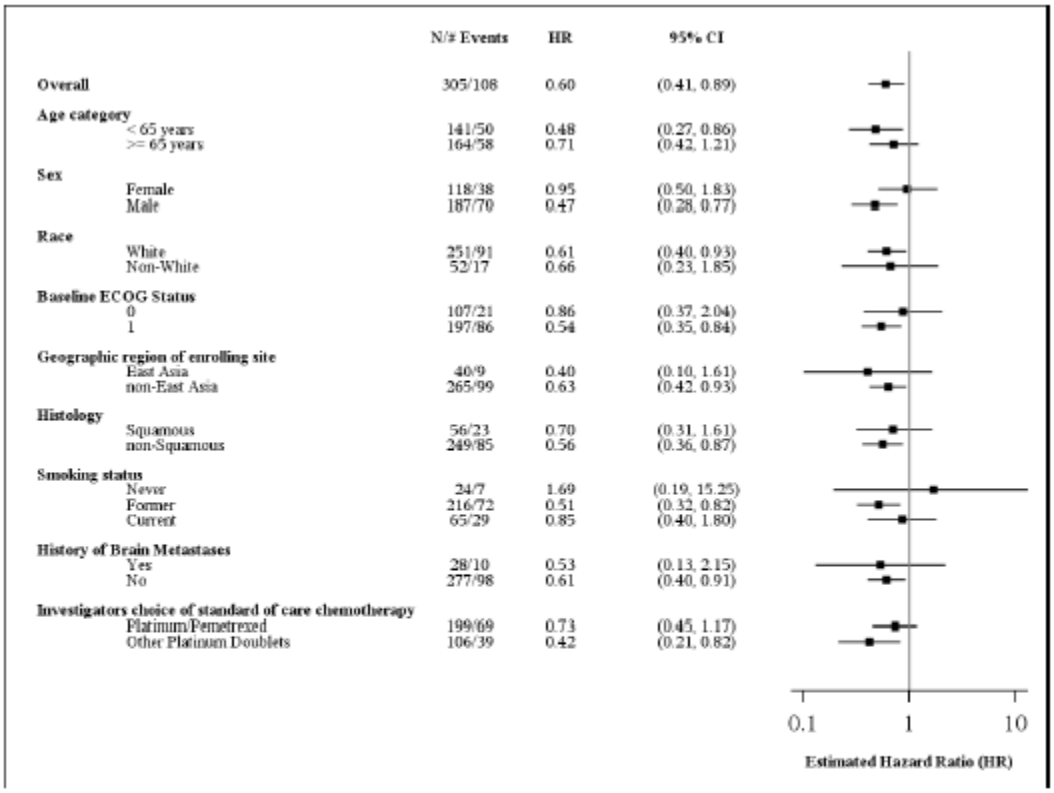
PFS subgroup analysis



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).
(Database Cutoff Date: 09MAY2016).

Figure 19: Forest Plot of PFS Hazard Ratio by subgroup factor BICR assessment (Primary Censoring Rule)

OS subgroup analysis



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).
(Database Cutoff Date: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adtte]

Figure 20: Forest Plot of OS Hazard Ratio by subgroup factor

Table 23: Analysis of Overall Survival - Only Never Smoked ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	5	1 (20.0)	40.3	2.5	Not Reached (8.0, .)	100.0 (100.0, 100.0)	1.69 (0.19, 15.25)	0.682
SOC	19	6 (31.6)	193.1	3.1	Not Reached (8.9, .)	84.2 (58.7, 94.6)	---	---

† 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) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on log-rank test.
(Database Cutoff Date: 09MAY2016)

Source: [P024V01MK3475: analysis-adsl; adtte]

Summary of main study

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

Table 24: Summary of Efficacy for trial KEYNOTE-024

Title: A Randomized Open-Label Phase III Trial of Pembrolizumab versus (vs.) Platinum based Chemotherapy in First-Line (1L) Subjects with Programmed Cell Death 1 Ligand 1 (PD-L1) Strong Metastatic NSCLC

Study identifier	EudraCT number: 2014-000323-25		
Design	Multicenter, international, randomized, open-label, controlled trial of IV pembrolizumab monotherapy vs the choice of multiple SOC platinum based chemotherapies in previously untreated Stage IV, PD-L1 strong positive NSCLC.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	not applicable not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	pembrolizumab	200 mg IV Q3W 154 subjects treated	
	SOC	Pemetrexed 500 mg/m^2 Q3W + carboplatin AUC 5 to 6 mg/mL/min Q3W on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (non-squamous histologies only) 66 subjects treated (28 also received pemetrexed maintenance)	
		Pemetrexed 500 mg/m^2 Q3W + cisplatin 75 mg/m^2 Q3W on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (for non-squamous histologies only) 36 subjects treated (18 also received pemetrexed maintenance)	
		Gemcitabine 1250 mg/m^2 at Days 1 and 8 + cisplatin 75 mg/m^2 Q3W on Day 1 for 4 to 6 cycles 11 subjects treated	
		Gemcitabine 1250 mg/m^2 at Days 1 and 8 + carboplatin AUC 5 to 6 mg/mL/min Q3W on Day 1 for 4 to 6 cycles 20 subjects treated	
		Paclitaxel 200 mg/m^2 Q3W + carboplatin AUC 5 to 6 mg/mL/min Q3W on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for non-squamous histologies only) 17 subjects treated (none received pemetrexed maintenance)	
Endpoints and definitions	Primary endpoint	PFS	time from randomization to documented progressive disease per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first
	Secondary endpoint	OS	time from randomization to death due to any cause
	Secondary endpoint	ORR	proportion of patients in the analysis population with a CR or PR, based on BICR review per RECIST 1.1
	Exploratory endpoint	Time to response	time from randomization to the first assessment of CR or PR in the ITT population based on BICR assessment per RECIST 1.1
	Exploratory endpoint	Response duration	time from the first CR/PR to documented PD in the ITT population based on BICR assessment per RECIST 1.1
Database lock	03 June 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and effect estimate per comparison	Treatment group	Pembrolizumab 200 mg	Platinum-based SOC
	Number of subject	154	151
	Primary endpoint		

	PFS (BICR RECIST 1.1) N. with events (%)	73 (47.4)	116 (76.8)
	Median PFS months (95% CI)	10.3 (6.7,..)	6.0 (4.2, 6.2)
	Hazard Ratio Pembrolizumab vs SOC (95% CI)	0.50 (0.37, 0.68)	
	p-value (one sided log-rank test)	<0.001	
	Secondary endpoints		
	OS N. with events n (%)	44 (28.6)	64 (42.4)
	Median OS months (95% CI)	Not reached (..,..)	Not reached (9.4,..)
	Hazard Ratio Pembrolizumab vs SOC (95% CI)	0.60 (0.41, 0.89)	
	p-value (one sided log-rank test)	0.005	
	ORR (BICR-RECIST 1.1) (95% CI)	44.8 (36.8, 53.0)	27.8 (20.8, 35.7)
	Difference % vs SOC (95% CI)	16.6 (6.0, 27.0)	
	p-value (one sided)	0.0011	
	Exploratory endpoints		
	Number of subjects with response	69	42
	Time to response Median (months) range	2.2 (1.4, 8.2)	2.2 (1.8, 12.2)
	Response duration Median (months) range	Not reached (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

2.4.3. Discussion on clinical efficacy

In the NSCLC therapeutic scenario, pembrolizumab already plays its role being approved for the treatment of locally advanced or metastatic disease in PD-L1 positive patients who have received at least one prior chemotherapy regimen, including approved target therapy for EGFR and ALK aberrations in case of positive tumour mutations.

This application has been submitted to extend the Keytruda indication to the treatment of PD-L1 positive (TPS≥50%) metastatic NSCLC in patients previously untreated.

Design and conduct of clinical studies

To support the pembrolizumab efficacy in the first line NSCLC setting, the MAH submitted results from one single, phase III, randomized, pivotal study (KEYNOTE-024), comparing pembrolizumab to a SOC platinum-based doublet that was selected by the investigator at the time of randomization among 5 different options (pemetrexed 500 mg/m^2 plus carboplatin AUC 5 to 6 mg/mL/min or cisplatin 75 mg/m^2 day 1, for 4 to 6 cycles followed by optional maintenance pemetrexed, in non-squamous histologies only; gemcitabine 1250 mg/m^2 days 1 and 8 plus carboplatin AUC 5 to 6 mg/mL/min or cisplatin 75 mg/m^2 day 1, for 4 to 6 cycles; paclitaxel 200 mg/m^2 plus carboplatin AUC 5 to 6 mg/mL/min day 1, for 4 to 6 cycles, followed by optional maintenance pemetrexed only in non-squamous histologies). Platinum-based chemotherapy regimen is still the standard of care for the first line treatment of NSCLC not harbouring EGFR activating mutations and ALK translocations, with no major differences in efficacy across combination. The control arm is therefore considered adequate.

A fixed dose regimen of pembrolizumab 200 mg has been first administered in this study, based on

modelling and simulations showing consistent exposure compared to that obtained with weight-based pembrolizumab dose (2 mg/kg). This flat dose is currently being used for the whole pembrolizumab clinical development, including several different indications in solid and haematological malignancies.

The primary efficacy endpoint was PFS, with OS, ORR per RECIST 1.1 by BICR, and safety as secondary endpoints. Time to response, Response Duration and PROs were also included as exploratory endpoints.

The study had 97% power to detect a hazard ratio 0.55 at alpha = 2.5% (one-sided) at the PFS analysis. An interim ORR analysis (IA1) was planned with alpha strictly controlled. With ~110 OS events at the time of the final PFS analysis, an interim OS analysis (IA2) was planned with ~60% power to demonstrate a numerically positive OS effect when the true hazard ratio is 0.7 assuming that half of the subjects in the control arm crossed over to pembrolizumab at the time of analysis. All the provided assumptions are comprehensive and adequate for a proper determination of the study sample size. The statistical methods are overall adequate. A more compelling overall type I error rate (strictly < 2.5% one-sided) to meet the statistical requirements for proper design of a One Pivotal Study could have been used. However, this limitation should be put in the right perspective considering the target magnitude of benefit and the reported clinical results.

Overall, eligibility criteria clearly define the target population. Among 500 patients screened as PD-L1 TPS≥50%, only 305 have been enrolled. Most of the PD-L1 strongly positive screen failure patients (39%) were not randomized due to issues related to the tissue samples used for the evaluation of PD-L1 status. Baseline characteristics were overall well balanced, apart from smoking status ("never-smokers": 12.6% vs. 3.2% in SOC and pembrolizumab, respectively), and brain metastases (6.6% vs 11.7% in SOC and pembrolizumab, respectively).

Patients with ECOG performance status score ⩾ 2 were excluded from KEYNOTE-024 similarly to what has been done in studies supporting approval of the other indications (see sections 4.2, 4.4 and 5.1 of the SmPC).

Efficacy data and additional analyses

Results of the IA2, on which basis the eDMC recommended to stop the study, have been provided.

At the provided cut-off date (9 May 2016), the median duration of follow-up was 11 months (6.3-19.7 months). A clinically significant improvement was reported with pembrolizumab compared to SOC in terms of PFS (10.3 vs 6.0 months, HR: 0.50, p<0.001), with 6-month and 12-month PFS rates of 62.1% vs 50.3% and 47% vs 15%, respectively. Although 44% of patients in the control group crossed over to pembrolizumab, a considerable advantage was observed in OS (HR: 0.60, p=0.005; 12-month OS rate: 69.9% vs 54.2%). The median OS was not reached in either arm possibly due to significant rate of crossover. The CHMP considered that available OS data should be included in the SmPC, taking into account the median follow-up of almost 12 months (near to what expected with standard treatment in the target population) and the rate of OS events already observed in the control arm (42.4%). Results from an OS analysis, based on 170 death events, will be available approximately in June 2018.

The applicant is recommended to provide further information on patients who crossed over from SOC arm to pembrolizumab together with the submission of the final report of KEYNOTE-024 expected approximately in June 2018.

Pembrolizumab was superior also in terms of confirmed ORR (44.8% vs 27.8%). Interestingly, no differences in the median time to response were observed, with early onset (2.2. months, i.e. the first planned tumour assessment) in both arms. A DoR of at least 9 months was reported in more than 80% of the responders in the pembrolizumab arm vs 36.2% in the SOC arm. Provided sensitivity and subgroup analyses support the primary results, with the exception of finding in the subgroup of female patients where a reduced effect in terms of both PFS (HR: 0.75, 95%CI: 0.46-1.21) and OS (HR: 0.95, 95%CI:0.50-1.83) was

observed. However, based on available data the observed effect could be a chance finding due to small numbers. In addition, a smaller benefit was observed with pembrolizumab in never smokers NSCLC patients however, due to the small number of patients, no definitive conclusions can be drawn from these data. This information has been reflected in section 5.1 of the SmPC.

The key PRO endpoints are the mean score changes from baseline to week 15 as measured by the EORTC QLQ-C30 and the Time to deterioration (TTD) in the composite endpoint of cough (LC13-Q1), chest pain (LC13-Q10) and dyspnoea (LC13-Q3-5). No formal hypothesis was formulated. The 15 week time point was selected to minimize loss of data due to death or disease progression. This is acknowledged. However, the relatively short time-frame covered by the submitted results from this exploratory analysis provide limited information on the short term effect.

2.4.4. Conclusions on the clinical efficacy

Based on provided data, the efficacy of pembrolizumab in the treatment of PD-L1 strongly positive previously untreated NSCLC patients is considered demonstrated.

2.5. Clinical safety

Introduction

The known pembrolizumab safety profile, to date evaluated in 2,799 patients, including 1,567 with advanced melanoma and 1,232 with advanced NSCLC, is mainly associated with immune-related adverse reactions and characterized by general (fatigue), gastrointestinal (diarrhoea and nausea), skin (rash and pruritus) and musculoskeletal (arthralgia) disorders. The majority of adverse reactions reported were of Grade 1 or 2 severity and the most serious were immune-related adverse reactions and severe infusion-related reactions.

The primary safety analyses in the pivotal study KEYNOTE-024 has been conducted in the All Subject as Treated (AsaT) population including all randomized patients who received at least one dose of study treatment. Adverse events (AEs) observed in the 66 patients who received pembrolizumab as part of the in study crossover (cut-off date 9 May 2016) were not submitted by the MAH.

Patient exposure

In study KEYNOTE-024, the median exposure to treatment was 214.00 days (mean 205.73, SD 144.93) for patients who received pembrolizumab compared to 106.00 days (mean 120.83, SD 105.94) for those in the SOC arm. The breakdown of chemotherapy regimens administered in the SOC arm by histology is shown in the table below.

Actual Study Medication	Non-squamous N (%)	Squamous N (%)	Total N (%)
Gemcitabine and carboplatin	5 (3.33)	15 (10)	20 (13.33)
Gemcitabine and cisplatin	4 (2.67)	7 (4.67)	11 (7.33)
Paclitaxel and carboplatin without pemetrexed maintenance	12 (8.00)	5 (3.33)	17 (11.33)
Pemetrexed and carboplatin with pemetrexed maintenance	28 (18.67)	0 (0)	28 (18.67)
Pemetrexed and carboplatin without pemetrexed maintenance	38 (25.33)	0 (0)	38 (25.33)
Pemetrexed and cisplatin with pemetrexed maintenance	18 (12.00)	0 (0)	18 (12.00)
Pemetrexed and cisplatin without pemetrexed maintenance	18 (12.00)	0 (0)	18 (12.00)
Total	123 (82.00)	27 (18.00)	150 (100.00)
N = number Frequency missing = 1			

Source: [P024V01MK3475: analysis-adsl]

The most common chemotherapy regimen was pemetrexed in combination with carboplatin received by 66

patients (44%). The majority of non-squamous NSCLC patients were administered a pemetrexed containing doublet (102 patients, 83%), and 46 of them (37%) received pemetrexed maintenance.

Overall, 87 subjects in the pembrolizumab arm compared to 29 subjects in the SOC arm received treatment for ≥6 months, and the treatment was administered ≥12 months respectively in 23 and 5 patients (see Table below).

Table 25: Exposure by Duration (AsaT Population)

Duration of Exposure	Pembrolizumab (N=154)		SOC (N=150)	
	n	Subject Years	n	Subject Years
> 0 m	154	86.7	150	49.6
≥ 1 m	130	86.2	119	48.9
≥ 3 m	108	82.8	84	43.1
≥ 6 m	87	74.5	29	23.9
≥ 12 m	23	27.3	5	5.7

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date +1.
(Database Cutoff Date: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl] [P024V01MK3475: tabulations-explus]

Adverse events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. The analysis of safety results followed a tiered approach. The tiers differ with respect to the analyses that will be performed. Tier 2 parameters were assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 safety parameters. There are no Tier 1 safety analyses in this study. No p-values would be provided for safety comparison.

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

The following Table displays an overview of the numbers and percentages of subjects in the AsaT population who had AEs up to 30 days and SAEs up to 90 days after the last dose of study medication:

Table 26: Adverse Events Summary (ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	148	(96.1)	145	(96.7)
with no adverse event	6	(3.9)	5	(3.3)
with drug-related† adverse events	113	(73.4)	135	(90.0)
with toxicity grade 3-5 adverse events	82	(53.2)	109	(72.7)
with toxicity grade 3-5 drug-related adverse events	41	(26.6)	80	(53.3)
with serious adverse events	68	(44.2)	66	(44.0)
with serious drug-related adverse events	33	(21.4)	31	(20.7)
who died	9	(5.8)	7	(4.7)
who died due to a drug-related adverse event	1	(0.6)	3	(2.0)
discontinued‡ due to an adverse event	14	(9.1)	21	(14.0)
discontinued due to a drug-related adverse event	11	(7.1)	16	(10.7)
discontinued due to a serious adverse event	13	(8.4)	11	(7.3)
discontinued due to a serious drug-related adverse event	10	(6.5)	7	(4.7)

†Determined by the investigator to be related to the drug.
‡Study medication withdrawn.
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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Adverse Events (AEs)

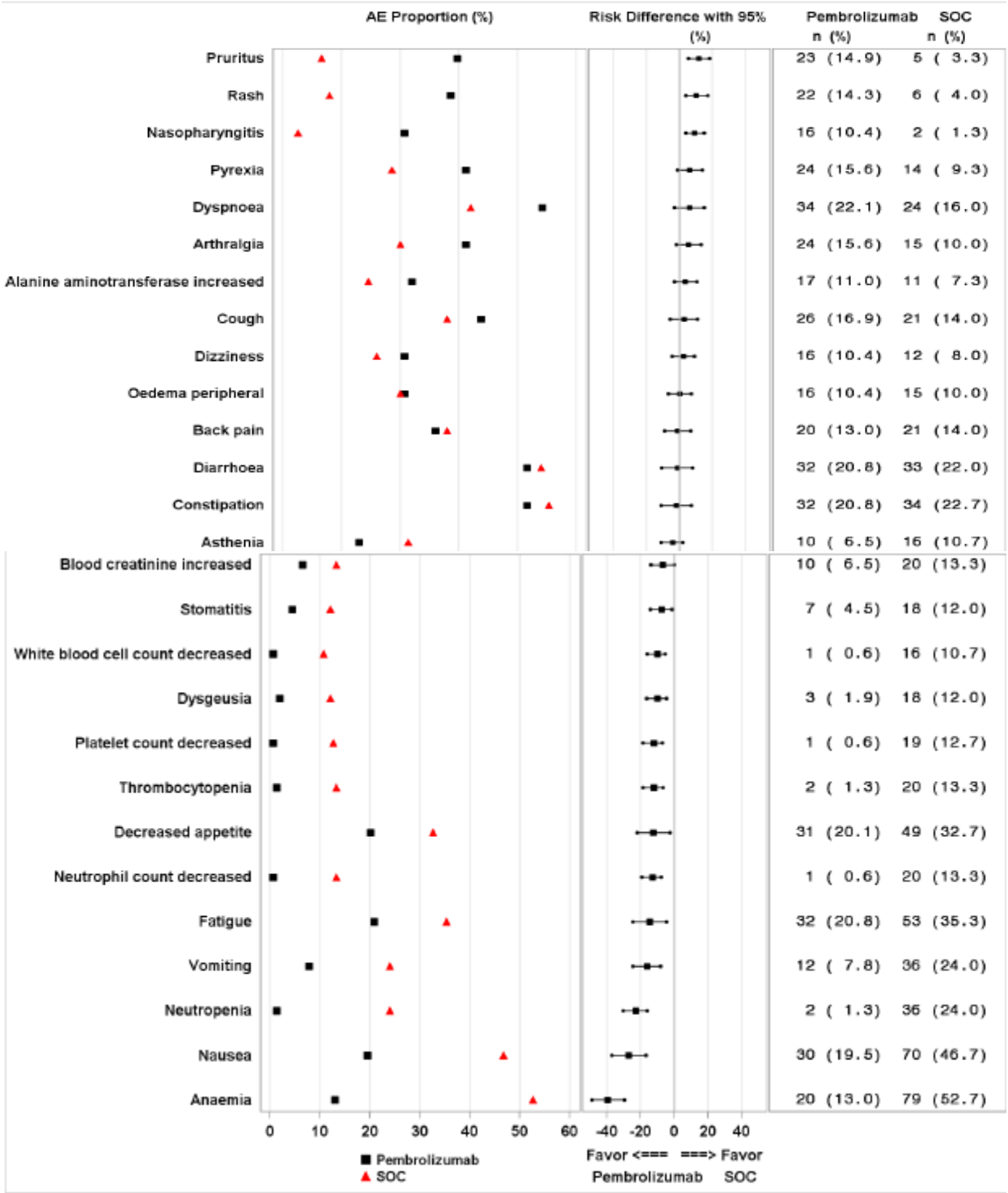
Table 27: Subjects With Adverse Events by Decreasing Incidence (Incidence ≥10% in One or More Treatment Groups) - ASaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	148	(96.1)	145	(96.7)	293	(96.4)
with no adverse events	6	(3.9)	5	(3.3)	11	(3.6)
Nausea	30	(19.5)	70	(46.7)	100	(32.9)
Anaemia	20	(13.0)	79	(52.7)	99	(32.6)
Fatigue	32	(20.8)	53	(35.3)	85	(28.0)
Decreased appetite	31	(20.1)	49	(32.7)	80	(26.3)
Constipation	32	(20.8)	34	(22.7)	66	(21.7)
Diarrhoea	32	(20.8)	33	(22.0)	65	(21.4)
Dyspnoea	34	(22.1)	24	(16.0)	58	(19.1)
Vomiting	12	(7.8)	36	(24.0)	48	(15.8)
Cough	26	(16.9)	21	(14.0)	47	(15.5)
Back pain	20	(13.0)	21	(14.0)	41	(13.5)
Arthralgia	24	(15.6)	15	(10.0)	39	(12.8)
Neutropenia	2	(1.3)	36	(24.0)	38	(12.5)
Pyrexia	24	(15.6)	14	(9.3)	38	(12.5)
Oedema peripheral	16	(10.4)	15	(10.0)	31	(10.2)
Blood creatinine increased	10	(6.5)	20	(13.3)	30	(9.9)
Alanine aminotransferase increased	17	(11.0)	11	(7.3)	28	(9.2)
Dizziness	16	(10.4)	12	(8.0)	28	(9.2)
Pruritus	23	(14.9)	5	(3.3)	28	(9.2)
Rash	22	(14.3)	6	(4.0)	28	(9.2)
Asthenia	10	(6.5)	16	(10.7)	26	(8.6)
Stomatitis	7	(4.5)	18	(12.0)	25	(8.2)
Thrombocytopenia	2	(1.3)	20	(13.3)	22	(7.2)
Dysgeusia	3	(1.9)	18	(12.0)	21	(6.9)
Neutrophil count decreased	1	(0.6)	20	(13.3)	21	(6.9)
Platelet count decreased	1	(0.6)	19	(12.7)	20	(6.6)
Nasopharyngitis	16	(10.4)	2	(1.3)	18	(5.9)
White blood cell count decreased	1	(0.6)	16	(10.7)	17	(5.6)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

A comparison between treatments of specific AEs with incidence ≥10% is reported in the following figure.



(Database Cutoff Date: 09MAY2016 | Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]).

Figure 21: Between-treatment comparisons in AEs, Selected AEs (≥10% incidence) and sorted by Risk Difference - pembrolizumab (154) vs SOC (150)

Grade 3-5 AEs

Table 28: Subjects With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥1% in One or More Treatment Groups) ASaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	82	(53.2)	109	(72.7)	191	(62.8)
with no adverse events	72	(46.8)	41	(27.3)	113	(37.2)
Anaemia	7	(4.5)	35	(23.3)	42	(13.8)
Neutropenia	0	(0.0)	21	(14.0)	21	(6.9)
Pneumonia	3	(1.9)	11	(7.3)	14	(4.6)
Hyponatraemia	5	(3.2)	7	(4.7)	12	(3.9)
Pleural effusion	6	(3.9)	4	(2.7)	10	(3.3)
Diarrhoea	6	(3.9)	3	(2.0)	9	(3.0)
Fatigue	2	(1.3)	7	(4.7)	9	(3.0)
Platelet count decreased	0	(0.0)	9	(6.0)	9	(3.0)
Thrombocytopenia	0	(0.0)	9	(6.0)	9	(3.0)
Pulmonary embolism	4	(2.6)	4	(2.7)	8	(2.6)
Back pain	2	(1.3)	5	(3.3)	7	(2.3)
Chronic obstructive pulmonary disease	6	(3.9)	1	(0.7)	7	(2.3)
Decreased appetite	2	(1.3)	5	(3.3)	7	(2.3)
Dyspnoea	3	(1.9)	4	(2.7)	7	(2.3)
Neutrophil count decreased	0	(0.0)	6	(4.0)	6	(2.0)
Asthenia	1	(0.6)	4	(2.7)	5	(1.6)
Hyperglycaemia	4	(2.6)	1	(0.7)	5	(1.6)
Hypoalbuminaemia	2	(1.3)	3	(2.0)	5	(1.6)
Lower respiratory tract infection	2	(1.3)	3	(2.0)	5	(1.6)
Lung infection	3	(1.9)	2	(1.3)	5	(1.6)
Pneumonitis	4	(2.6)	1	(0.7)	5	(1.6)
Hypokalaemia	2	(1.3)	2	(1.3)	4	(1.3)
Hypophosphataemia	0	(0.0)	4	(2.7)	4	(1.3)
Lymphocyte count decreased	1	(0.6)	3	(2.0)	4	(1.3)
Nausea	0	(0.0)	4	(2.7)	4	(1.3)
Vomiting	1	(0.6)	3	(2.0)	4	(1.3)
Atrial fibrillation	0	(0.0)	3	(2.0)	3	(1.0)
Cardiac failure	1	(0.6)	2	(1.3)	3	(1.0)
Febrile neutropenia	0	(0.0)	3	(2.0)	3	(1.0)
Hypertension	2	(1.3)	1	(0.7)	3	(1.0)
Neutropenic sepsis	1	(0.6)	2	(1.3)	3	(1.0)
Pancytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Pericardial effusion	2	(1.3)	1	(0.7)	3	(1.0)
Respiratory tract infection	2	(1.3)	1	(0.7)	3	(1.0)
Urinary tract infection	1	(0.6)	2	(1.3)	3	(1.0)
White blood cell count decreased	0	(0.0)	3	(2.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Alanine aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Aspartate aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Bone pain	0	(0.0)	2	(1.3)	2	(0.7)
Cancer pain	0	(0.0)	2	(1.3)	2	(0.7)
Chest pain	0	(0.0)	2	(1.3)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Dehydration	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Dysphagia	0	(0.0)	2	(1.3)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Hypercalcaemia	0	(0.0)	2	(1.3)	2	(0.7)
Hyperkalaemia	2	(1.3)	0	(0.0)	2	(0.7)
Leukocytosis	0	(0.0)	2	(1.3)	2	(0.7)
Leukopenia	0	(0.0)	2	(1.3)	2	(0.7)
Pelvic pain	2	(1.3)	0	(0.0)	2	(0.7)
Pulmonary oedema	0	(0.0)	2	(1.3)	2	(0.7)
Pulmonary sepsis	0	(0.0)	2	(1.3)	2	(0.7)
Rash	2	(1.3)	0	(0.0)	2	(0.7)
Stomatitis	0	(0.0)	2	(1.3)	2	(0.7)
Syncope	0	(0.0)	2	(1.3)	2	(0.7)
Transaminases increased	2	(1.3)	0	(0.0)	2	(0.7)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Drug-related AEs

The following table shows the number and percentage of subjects with AEs (incidence ≥10%) considered by the Investigator to be "possibly", "probably", or "definitely" related to the study treatment:

Table 29: Subjects With Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥10% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	113	(73.4)	135	(90.0)	248	(81.6)
with no adverse events	41	(26.6)	15	(10.0)	56	(18.4)
Nausea	15	(9.7)	65	(43.3)	80	(26.3)
Anaemia	8	(5.2)	66	(44.0)	74	(24.3)
Fatigue	16	(10.4)	43	(28.7)	59	(19.4)
Decreased appetite	14	(9.1)	39	(26.0)	53	(17.4)
Diarrhoea	22	(14.3)	20	(13.3)	42	(13.8)
Neutropenia	1	(0.6)	34	(22.7)	35	(11.5)
Vomiting	4	(2.6)	30	(20.0)	34	(11.2)
Pyrexia	16	(10.4)	8	(5.3)	24	(7.9)
Constipation	6	(3.9)	17	(11.3)	23	(7.6)
Stomatitis	4	(2.6)	18	(12.0)	22	(7.2)
Neutrophil count decreased	0	(0.0)	20	(13.3)	20	(6.6)
Blood creatinine increased	3	(1.9)	15	(10.0)	18	(5.9)
Platelet count decreased	0	(0.0)	18	(12.0)	18	(5.9)
Thrombocytopenia	0	(0.0)	17	(11.3)	17	(5.6)
White blood cell count decreased	1	(0.6)	16	(10.7)	17	(5.6)
Dysgeusia	1	(0.6)	15	(10.0)	16	(5.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Drug-Related Adverse Events (Incidence >1% in One or More Treatment Groups) in patients treated with pembrolizumab across studies KN001, KN002, KN006, KN010 and KN024 are shown by decreasing frequency in the following table.

Table 30: Subjects with Drug-Related AEs (Incidence > 1% in One or More Treatment Groups) - Studies KN024, KN001, KN002, KN006, and KN010 by Decreasing Frequency of Preferred Term (ASaT Population)

	KN024		Established safety dataset Lung indication[a]		Reference safety dataset[b]		Cumulative running safety dataset[c]	
	n	%	n	%	n	%	n	%
Subjects in population	154		1,232		2,799		2,953	
with ≥1 AEs	113	(73.4)	821	(66.6)	2,062	(73.7)	2,175	(73.7)
with no AEs	41	(26.6)	411	(33.4)	737	(26.3)	778	(26.3)
Diarrhoea	22	(14.3)	93	(7.5)	343	(12.3)	365	(12.4)
Fatigue	16	(10.4)	199	(16.2)	678	(24.2)	694	(23.5)
Pyrexia	16	(10.4)	49	(4.0)	126	(4.5)	142	(4.8)
Nausea	15	(9.7)	109	(8.8)	304	(10.9)	319	(10.8)
Decreased appetite	14	(9.1)	135	(11.0)	255	(9.1)	269	(9.1)
Arthralgia	13	(8.4)	81	(6.6)	281	(10.0)	294	(10.0)
Hypothyroidism	12	(7.8)	88	(7.1)	213	(7.6)	225	(7.6)
Pruritus	12	(7.8)	116	(9.4)	467	(16.7)	479	(16.2)
Hyperthyroidism	11	(7.1)	35	(2.8)	82	(2.9)	93	(3.1)
Rash	11	(7.1)	123	(10.0)	386	(13.8)	397	(13.4)
Alanine aminotransferase increased	10	(6.5)	37	(3.0)	97	(3.5)	107	(3.6)
Anaemia	8	(5.2)	45	(3.7)	94	(3.4)	102	(3.5)
Aspartate aminotransferase increased	8	(5.2)	33	(2.7)	94	(3.4)	102	(3.5)
Dry skin	8	(5.2)	37	(3.0)	90	(3.2)	98	(3.3)
Pneumonitis	8	(5.2)	47	(3.8)	80	(2.9)	88	(3.0)

Constipation	6	(3.9)	34	(2.8)	90	(3.2)	96	(3.3)
Asthenia	5	(3.2)	70	(5.7)	218	(7.8)	223	(7.6)
Blood thyroid stimulating hormone increased	5	(3.2)	14	(1.1)	29	(1.0)	34	(1.2)
Cough	5	(3.2)	24	(1.9)	112	(4.0)	117	(4.0)
Hyponatraemia	5	(3.2)	8	(0.6)	17	(0.6)	22	(0.7)
Rash macculo-papular	5	(3.2)	17	(1.4)	76	(2.7)	81	(2.7)
Weight decreased	5	(3.2)	34	(2.8)	60	(2.1)	65	(2.2)
Abdominal pain	4	(2.6)	13	(1.1)	65	(2.3)	69	(2.3)
Blood thyroid stimulating hormone decreased	4	(2.6)	6	(0.5)	18	(0.6)	22	(0.7)
Dyspnoea	4	(2.6)	43	(3.5)	109	(3.9)	113	(3.8)
Oedema peripheral	4	(2.6)	18	(1.5)	54	(1.9)	58	(2.0)
Stomatitis	4	(2.6)	29	(2.4)	33	(1.2)	37	(1.3)
Vomiting	4	(2.6)	40	(3.2)	107	(3.8)	111	(3.8)
Blood creatinine increased	3	(1.9)	17	(1.4)	35	(1.3)	38	(1.3)
Chills	3	(1.9)	16	(1.3)	78	(2.8)	81	(2.7)
Eosinophilia	3	(1.9)	2	(0.2)	14	(0.5)	17	(0.6)
Erythema	3	(1.9)	6	(0.5)	46	(1.6)	49	(1.7)
Gamma-glutamyltransferase increased	3	(1.9)	6	(0.5)	18	(0.6)	21	(0.7)
Hyperkalaemia	3	(1.9)	5	(0.4)	7	(0.3)	10	(0.3)
Hypoalbuminaemia	3	(1.9)	7	(0.6)	11	(0.4)	14	(0.5)
Infusion related reaction	3	(1.9)	15	(1.2)	27	(1.0)	30	(1.0)
Myalgia	3	(1.9)	36	(2.9)	146	(5.2)	149	(5.0)
Night sweats	3	(1.9)	5	(0.4)	35	(1.3)	38	(1.3)
Pruritus generalized	3	(1.9)	3	(0.2)	19	(0.7)	22	(0.7)
Thyroiditis	3	(1.9)	2	(0.2)	11	(0.4)	14	(0.5)
Transaminase increased	3	(1.9)	4	(0.3)	7	(0.3)	10	(0.3)
Abdominal distension	2	(1.3)	4	(0.3)	18	(0.6)	20	(0.7)
Arthritis	2	(1.3)	10	(0.8)	26	(0.9)	28	(0.9)
Back pain	2	(1.3)	15	(1.2)	47	(1.7)	49	(1.7)
Colitis	2	(1.3)	10	(0.8)	37	(1.3)	39	(1.3)
Diabetes mellitus	2	(1.3)	1	(0.1)	3	(0.1)	5	(0.2)
Dizziness	2	(1.3)	16	(1.3)	46	(1.6)	48	(1.6)
Dyspepsia	2	(1.3)	2	(0.2)	9	(0.3)	11	(0.4)
Dysuria	2	(1.3)	2	(0.2)	4	(0.1)	6	(0.2)
Hepatic enzyme increased	2	(1.3)	0	(0.0)	2	(0.1)	4	(0.1)
Hiccups	2	(1.3)	3	(0.2)	4	(0.1)	6	(0.2)
Hyperglycaemia	2	(1.3)	4	(0.3)	15	(0.5)	17	(0.6)
Lower respiratory tract infection	2	(1.3)	1	(0.1)	1	(0.0)	3	(0.1)
Lymphopenia	2	(1.3)	6	(0.5)	14	(0.5)	16	(0.5)
Neuropathy peripheral	2	(1.3)	8	(0.6)	26	(0.9)	28	(0.9)
Oedema	2	(1.3)	5	(0.4)	12	(0.4)	14	(0.5)
Paraeshesia	2	(1.3)	10	(0.8)	24	(0.9)	26	(0.9)
Psoriasis	2	(1.3)	6	(0.5)	12	(0.4)	14	(0.5)
Rash pruritic	2	(1.3)	8	(0.6)	26	(0.9)	28	(0.9)
Skin exfoliation	2	(1.3)	0	(0.0)	4	(0.1)	6	(0.2)
Urticaria	2	(1.3)	1	(0.1)	8	(0.3)	10	(0.3)
Eczema	1	(0.6)	5	(0.4)	30	(1.1)	31	(1.0)
Headache	1	(0.6)	24	(1.9)	111	(4.0)	112	(3.8)
Influenza like illness	1	(0.6)	13	(1.1)	46	(1.6)	47	(1.6)
Musculoskeletal pain	1	(0.6)	15	(1.2)	31	(1.1)	32	(1.1)

Table made by the Assessor. [a] Includes all subjects who received at least one pembrolizumab dose in KN001 Part C, F1, F2, F3 and KN010; [b] Includes all subjects who received at least one pembrolizumab dose in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, and KN010; [c] Includes all subjects who received at least one pembrolizumab dose in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, and KN024.

Drug-related Grade 3-5 AEs

The Table below shows the number of subjects with drug-related Grade 3 to 5 AEs (incidence ≥1% in one or more treatment groups).

Table 31: Subjects with Grade 3-5 Drug-related AEs by decreasing incidence (Incidence ≥1% in one or more treatment groups) - AsaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	41	(26.6)	80	(53.3)	121	(39.8)
with no adverse events	113	(73.4)	70	(46.7)	183	(60.2)
Anaemia	3	(1.9)	29	(19.3)	32	(10.5)
Neutropenia	0	(0.0)	20	(13.3)	20	(6.6)
Platelet count decreased	0	(0.0)	9	(6.0)	9	(3.0)
Diarrhoea	6	(3.9)	2	(1.3)	8	(2.6)
Thrombocytopenia	0	(0.0)	8	(5.3)	8	(2.6)
Fatigue	2	(1.3)	5	(3.3)	7	(2.3)
Neutrophil count decreased	0	(0.0)	6	(4.0)	6	(2.0)
Pneumonitis	4	(2.6)	1	(0.7)	5	(1.6)
Decreased appetite	0	(0.0)	4	(2.7)	4	(1.3)
Hypoalbuminaemia	2	(1.3)	2	(1.3)	4	(1.3)
Asthenia	1	(0.6)	2	(1.3)	3	(1.0)
Febrile neutropenia	0	(0.0)	3	(2.0)	3	(1.0)
Lymphocyte count decreased	0	(0.0)	3	(2.0)	3	(1.0)
Nausea	0	(0.0)	3	(2.0)	3	(1.0)
Pancytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Pneumonia	0	(0.0)	3	(2.0)	3	(1.0)
White blood cell count decreased	0	(0.0)	3	(2.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Aspartate aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Leukopenia	0	(0.0)	2	(1.3)	2	(0.7)
Lower respiratory tract infection	2	(1.3)	0	(0.0)	2	(0.7)
Lung infection	0	(0.0)	2	(1.3)	2	(0.7)
Stomatitis	0	(0.0)	2	(1.3)	2	(0.7)
Transaminases increased	2	(1.3)	0	(0.0)	2	(0.7)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

The incidence of Grade 3-5 Adverse Events in patients treated with pembrolizumab across studies KN001, KN002, KN006, KN010 and KN024 is reported in the Table below.

Table 32: Subjects With Grade 3-5 AEs (Incidence > 1% in One or More Treatment Groups) Studies KN024, KN001, KN002, KN006, and KN010 - By SOC and PT (ASaT Population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	82	(53.2)	568	(46.1)	1,273	(45.5)	1,355	(45.9)
with no adverse events	72	(46.8)	664	(53.9)	1,526	(54.5)	1,598	(54.1)
Blood and lymphatic system disorders	**7**	**(4.5)**	**43**	**(3.5)**	**123**	**(4.4)**	**130**	**(4.4)**
Anaemia	7	(4.5)	27	(2.2)	90	(3.2)	97	(3.3)
Cardiac disorders	**6**	**(3.9)**	**49**	**(4.0)**	**84**	**(3.0)**	**90**	**(3.0)**
Pericardial effusion	2	(1.3)	10	(0.8)	14	(0.5)	16	(0.5)
Gastrointestinal disorders	**12**	**(7.8)**	**76**	**(6.2)**	**231**	**(8.3)**	**243**	**(8.2)**
Abdominal pain	1	(0.6)	8	(0.6)	27	(1.0)	28	(0.9)
Colitis	2	(1.3)	9	(0.7)	32	(1.1)	34	(1.2)
Diarrhoea	6	(3.9)	7	(0.6)	36	(1.3)	42	(1.4)
Nausea	0	(0.0)	14	(1.1)	33	(1.2)	33	(1.1)
Vomiting	1	(0.6)	9	(0.7)	32	(1.1)	33	(1.1)
General disorders and administration site conditions	**8**	**(5.2)**	**103**	**(8.4)**	**213**	**(7.6)**	**221**	**(7.5)**
Asthenia	1	(0.6)	16	(1.3)	34	(1.2)	35	(1.2)
Fatigue	2	(1.3)	37	(3.0)	69	(2.5)	71	(2.4)
Pain	0	(0.0)	15	(1.2)	23	(0.8)	23	(0.8)
Hepatobiliary disorders	**1**	**(0.6)**	**9**	**(0.7)**	**43**	**(1.5)**	**44**	**(1.5)**
Infections and infestations	**19**	**(12.3)**	**108**	**(8.8)**	**220**	**(7.9)**	**239**	**(8.1)**
Lower respiratory tract infection	2	(1.3)	5	(0.4)	5	(0.2)	7	(0.2)
Lung infection	3	(1.9)	6	(0.5)	9	(0.3)	12	(0.4)
Pneumonia	3	(1.9)	51	(4.1)	75	(2.7)	78	(2.6)
Respiratory tract infection	2	(1.3)	6	(0.5)	7	(0.3)	9	(0.3)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**14**	**(1.1)**	**38**	**(1.4)**	**38**	**(1.3)**
Investigations	**12**	**(7.8)**	**54**	**(4.4)**	**130**	**(4.6)**	**142**	**(4.8)**
Alanine aminotransferase increased	2	(1.3)	9	(0.7)	25	(0.9)	27	(0.9)
Aspartate aminotransferase increased	2	(1.3)	9	(0.7)	24	(0.9)	26	(0.9)
Transaminases increased	2	(1.3)	2	(0.2)	2	(0.1)	4	(0.1)
Metabolism and nutrition disorders	**16**	**(10.4)**	**97**	**(7.9)**	**233**	**(8.3)**	**249**	**(8.4)**
Decreased appetite	2	(1.3)	15	(1.2)	26	(0.9)	28	(0.9)
Dehydration	2	(1.3)	9	(0.7)	28	(1.0)	30	(1.0)
Diabetes mellitus	2	(1.3)	1	(0.1)	3	(0.1)	5	(0.2)
Hyperglycaemia	4	(2.6)	12	(1.0)	29	(1.0)	33	(1.1)
Hyperkalaemia	2	(1.3)	0	(0.0)	4	(0.1)	6	(0.2)
Hypoalbuminaemia	2	(1.3)	5	(0.4)	15	(0.5)	17	(0.6)
Hypokalaemia	2	(1.3)	11	(0.9)	25	(0.9)	27	(0.9)
Hyponatraemia	5	(3.2)	24	(1.9)	62	(2.2)	67	(2.3)
Musculoskeletal and connective tissue disorders	**5**	**(3.2)**	**56**	**(4.5)**	**126**	**(4.5)**	**131**	**(4.4)**
Back pain	2	(1.3)	20	(1.6)	38	(1.4)	40	(1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(1.9)**	**28**	**(2.3)**	**79**	**(2.8)**	**82**	**(2.8)**
Nervous system disorders	**3**	**(1.9)**	**34**	**(2.8)**	**108**	**(3.9)**	**111**	**(3.8)**
Psychiatric disorders	**1**	**(0.6)**	**14**	**(1.1)**	**27**	**(1.0)**	**28**	**(0.9)**
Renal and urinary disorders	**1**	**(0.6)**	**18**	**(1.5)**	**38**	**(1.4)**	**39**	**(1.3)**
Reproductive system and breast disorders	**3**	**(1.9)**	**1**	**(0.1)**	**4**	**(0.1)**	**7**	**(0.2)**
Pelvic pain	2	(1.3)	0	(0.0)	2	(0.1)	4	(0.1)
Respiratory, thoracic and mediastinal disorders	**25**	**(16.2)**	**158**	**(12.8)**	**244**	**(8.7)**	**269**	**(9.1)**
Chronic obstructive pulmonary disease	6	(3.9)	12	(1.0)	14	(0.5)	20	(0.7)
Dyspnoea	3	(1.9)	48	(3.9)	78	(2.8)	81	(2.7)
Pleural effusion	6	(3.9)	23	(1.9)	37	(1.3)	43	(1.5)
Pneumonitis	4	(2.6)	24	(1.9)	34	(1.2)	38	(1.3)
Pulmonary embolism	4	(2.6)	31	(2.5)	46	(1.6)	50	(1.7)
Respiratory failure	1	(0.6)	13	(1.1)	15	(0.5)	16	(0.5)
Skin and subcutaneous tissue disorders	**7**	**(4.5)**	**14**	**(1.1)**	**40**	**(1.4)**	**47**	**(1.6)**
Rash	2	(1.3)	4	(0.3)	9	(0.3)	11	(0.4)
Vascular disorders	**2**	**(1.3)**	**40**	**(3.2)**	**84**	**(3.0)**	**86**	**(2.9)**
Hypertension	2	(1.3)	13	(1.1)	32	(1.1)	34	(1.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[a] Includes all subjects who received at least one dose of MK-3475 in KN001 Part C, F1, F2, F3 and KN010.
[b] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, and KN010.
[c] 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, and KN024.
(KN024 Database Cutoff Date: 09MAY2016).
(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).

Adverse Events of Special Interest (AEOSI)

The analysis of AEOSI was the primary method of assessing irAEs and was based on a compiled list of preferred AE terms potentially associated with an immune aetiology. The list of terms is updated periodically based on emerging pembrolizumab safety data.

The currently applied AEOSI term list is reported below:

Table 33: Adverse Events of Special Interest Preferred Terms (v10.2 RMST 02-MAY-2016)

Important identified risks
Pneumonitis Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis, and Idiopathic pneumonia syndrome
Colitis Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive
Hepatitis Hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury
Nephritis Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome
Endocrine disorders Adrenal insufficiency: Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency Hypophysitis: Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis Hyperthyroidism: Hyperthyroidism, Basedow's disease, Thyrotoxic crisis Hypothyroidism: Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism Thyroiditis: Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute Type I Diabetes Mellitus: Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus
Other immune-mediated events
Uveitis Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis
Pancreatitis Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising
Myositis Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy
Guillain-Barré Syndrome Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome
Skin **Any grade from Severe cutaneous reactions SMQ narrow:** Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalized, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Oculomucocutaneous syndrome, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis and Toxic skin eruption **If ≥ Grade 3:** Any event from the Epidermal and dermal conditions HLGT of the Skin and subcutaneous tissue disorders SOC.
Infusion reactions Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction
Important potential risks
Myasthenic syndrome Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia

Abbreviations: HLGT = high level group terms; SMQ = standardized MedDRA query; SOC = system organ class.

AEOSI were more common among pembrolizumab-treated subjects compared to SOC-treated subjects (29.2% vs. 4.7%, respectively). A majority of these events were Grade 1 or 2 in severity, with 9.7% of pembrolizumab-treated subjects experiencing Grade 3 to 5 AEOSI. There were no deaths reported due to AEOSI in either treatment group. Six (3.9%) subjects discontinued due to drug-related AEOSI in the pembrolizumab arm and none in the SOC arm.

Table 34: Subjects With Adverse Events by AEOSI Category (Incidence > 0% in One or More Treatment Groups) AsaT Population

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more AEOSI	45	(29.2)	7	(4.7)
with no AEOSI	109	(70.8)	143	(95.3)
Colitis	**3**	**(1.9)**	**0**	**(0.0)**
Colitis	2	(1.3)	0	(0.0)
Enterocolitis	1	(0.6)	0	(0.0)
Hyperthyroidism	**12**	**(7.8)**	**2**	**(1.3)**
Hyperthyroidism	12	(7.8)	2	(1.3)
Hypophysitis	**1**	**(0.6)**	**0**	**(0.0)**
Hypophysitis	1	(0.6)	0	(0.0)
Hypothyroidism	**14**	**(9.1)**	**2**	**(1.3)**
Hypothyroidism	14	(9.1)	2	(1.3)
Infusion Reactions	**7**	**(4.5)**	**2**	**(1.3)**
Drug hypersensitivity	0	(0.0)	1	(0.7)
Hypersensitivity	4	(2.6)	0	(0.0)
Infusion related reaction	3	(1.9)	1	(0.7)
Myositis	**3**	**(1.9)**	**0**	**(0.0)**
Myopathy	1	(0.6)	0	(0.0)
Myositis	2	(1.3)	0	(0.0)
Nephritis	**1**	**(0.6)**	**0**	**(0.0)**
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)
Pancreatitis	**1**	**(0.6)**	**0**	**(0.0)**
Pancreatitis	1	(0.6)	0	(0.0)
Pneumonitis	**9**	**(5.8)**	**1**	**(0.7)**
Interstitial lung disease	1	(0.6)	0	(0.0)
Pneumonitis	8	(5.2)	1	(0.7)
Skin	**6**	**(3.9)**	**0**	**(0.0)**
Psoriasis	1	(0.6)	0	(0.0)
Rash	2	(1.3)	0	(0.0)
Rash generalised	1	(0.6)	0	(0.0)
Rash maculo-papular	1	(0.6)	0	(0.0)
Toxic skin eruption	1	(0.6)	0	(0.0)
Thyroiditis	**4**	**(2.6)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(0.6)	0	(0.0)
Thyroiditis	3	(1.9)	0	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.6)**	**0**	**(0.0)**
Diabetic ketoacidosis	1	(0.6)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Skin-A and Skin-B categories are combined as Skin category.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Table 35: Subjects With Grade 3-5 AEOSI by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) - ASaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	15	(9.7)	1	(0.7)	16	(5.3)
with no adverse events	139	(90.3)	149	(99.3)	288	(94.7)
Pneumonitis	4	(2.6)	1	(0.7)	5	(1.6)
Skin-A	5	(3.2)	0	(0.0)	5	(1.6)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Skin-B	1	(0.6)	0	(0.0)	1	(0.3)
Type 1 Diabetes Mellitus	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae]

The concomitant systemic corticosteroid use for AEOSI is summarized in the following table.

Table 36: Use of concomitant corticosteroids for AEOSI

AEOSI	Subjects with ≥ 1 event	Treated with systemic corticosteroids n (%)	Duration of corticosteroid treatment median days
Pneumonitis	9	8 (88.9%)	4-5 (range 1-19)*
Colitis	3	2 (66.7%)	1
Myositis	3	2 (66.7%)	13 (range 5-20)
Skin	6	1 (16.7%)	3
Nephritis	1	1 (100%)	11
Pancreatitis	1	1 (100%)	8
Hypothyreoidism	14	0	-
Hyperthyreoidism	12	0	-
Thyroiditis	4	0	-
Hypophysitis	1	0	-
Diabetes mellitus	1	0	-
Infusion reactions	7	1 (14.3%)	1

Source: CSR Table 14-29 to Table 14-52; *For 2 of 10 pneumonitis episodes (obviously one patient had two events) a low starting dose was used (30 mg/day), for all other patients a high starting dose of corticosteroid treatment was applied (defined as ≥ 40 mg/day prednisone or equivalent).

- Pneumonitis

Table 37: Subjects with adverse events by maximum toxicity grade – AEOSI - Pneumonitis (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	9	(5.8)	54	(4.4)	94	(3.4)	103	(3.5)
Grade 1	1	(0.6)	10	(0.8)	22	(0.8)	23	(0.8)
Grade 2	4	(2.6)	19	(1.5)	36	(1.3)	40	(1.4)
Grade 3	2	(1.3)	14	(1.1)	25	(0.9)	27	(0.9)
Grade 4	2	(1.3)	7	(0.6)	7	(0.3)	9	(0.3)
Grade 5	0	(0.0)	4	(0.3)	4	(0.1)	4	(0.1)
with no adverse events	145	(94.2)	1,178	(95.6)	2,705	(96.6)	2,850	(96.5)

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

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

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

Grades are based on NCI CTCAE version 4.03..

[a] Includes all subjects who received at least one dose of MK-3475 in KN001 Part C, F1, F2, F3 and KN010.

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

[c] 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, and KN024.

(KN024 Database Cutoff Date: 09MAY2016) (KN001 Database Cutoff Date for Melanoma: 18APR2014). (KN001 Database Cutoff Date for Lung Cancer: 23JAN2015). (KN002 Database Cutoff Date: 28FEB2015). (KN006 Database Cutoff Date: 03MAR2015). (KN010 Database Cutoff Date: 30SEP2015).

The median time to onset of pneumonitis was 3.1 months (range 2 days to 19.3 months). The median duration was 1.8 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 42 (1.4%) patients. Pneumonitis resolved in 61 patients.

- Colitis

Table 38: Subjects with adverse events by maximum toxicity grade – AEOSI - Colitis (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	3	(1.9)	12	(1.0)	48	(1.7)	51	(1.7)
Grade 1	0	(0.0)	3	(0.2)	6	(0.2)	6	(0.2)
Grade 2	1	(0.6)	1	(0.1)	10	(0.4)	11	(0.4)
Grade 3	2	(1.3)	8	(0.6)	30	(1.1)	32	(1.1)
Grade 4	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
with no adverse events	151	(98.1)	1,220	(99.0)	2,751	(98.3)	2,902	(98.3)

Same notes as Table 38

The median time to onset of colitis was 3.5 months (range 7 days to 16.2 months). The median duration was 1.4 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 15 (0.5%) patients. Colitis resolved in 43 patients.

- Hepatitis

Table 39: Subjects with adverse events by maximum toxicity grade – AEOSI - Hepatitis (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	0	(0.0)	3	(0.2)	19	(0.7)	19	(0.6)
Grade 1	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Grade 2	0	(0.0)	2	(0.2)	4	(0.1)	4	(0.1)
Grade 3	0	(0.0)	1	(0.1)	12	(0.4)	12	(0.4)
Grade 4	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
with no adverse events	154	(100.0)	1,229	(99.8)	2,780	(99.3)	2,934	(99.4)

Same notes as Table 38

The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hepatitis resolved in 15 patients.

- Nephritis

Table 40: Subjects with adverse events by maximum toxicity grade – AEOSI - Nephritis (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	1	(0.6)	1	(0.1)	9	(0.3)	10	(0.3)
Grade 1	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Grade 2	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.1)
Grade 3	1	(0.6)	1	(0.1)	4	(0.1)	5	(0.2)
Grade 4	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
with no adverse events	153	(99.4)	1,231	(99.9)	2,790	(99.7)	2,943	(99.7)

Same notes as Table 38

The median time to onset of nephritis was 5.0 months (range 12 days to 12.8 months). The median duration was 2.5 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of pembrolizumab in 3 (0.1%) patients. Nephritis resolved in 6 patients.

- Endocrinopathies

Table 41: Subjects with adverse events by maximum toxicity grade – AEOSI - Hypophysitis (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	1	(0.6)	3	(0.2)	17	(0.6)	18	(0.6)
Grade 1	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Grade 2	0	(0.0)	0	(0.0)	6	(0.2)	6	(0.2)
Grade 3	1	(0.6)	3	(0.2)	8	(0.3)	9	(0.3)
Grade 4	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
with no adverse events	153	(99.4)	1,229	(99.8)	2,782	(99.4)	2,935	(99.4)

Same notes as Table 38

The median time to onset of hypophysitis was 4.0 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hypophysitis resolved in 7 patients, 2 with sequelae.

Table 42: Subjects with adverse events by maximum toxicity grade – AEOSI - Hyperthyroidism (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	12	(7.8)	43	(3.5)	96	(3.4)	108	(3.7)
Grade 1	8	(5.2)	28	(2.3)	70	(2.5)	78	(2.6)
Grade 2	4	(2.6)	13	(1.1)	22	(0.8)	26	(0.9)
Grade 3	0	(0.0)	2	(0.2)	4	(0.1)	4	(0.1)
with no adverse events	142	(92.2)	1,189	(96.5)	2,703	(96.6)	2,845	(96.3)
Same notes as Table 38								

The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.0 months (range 10 days to 15.0+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (<0.1%) patients. Hyperthyroidism resolved in 82 (76%) patients.

All subjects in the pembrolizumab arm who developed hyperthyroidism or hypothyroidism were assessed for a history of thyroid disorders, history of radiation to the neck/thyroid gland, and baseline thyroid stimulating hormone. Of the 12 subjects who developed hyperthyroidism, all had a normal TSH level at baseline and none had received radiation to their neck or thyroid gland prior to the onset of their hyperthyroidism. One subject did have a history of goiter; however, this subject had a normal TSH at baseline and was on no thyroid therapy prior to the first dose of pembrolizumab. Furthermore, the majority of the hyperthyroidism cases was Grade 1, did not require treatment interruption or steroid therapy, and responded to anti-thyroid therapy. Eleven of the twelve cases of hyperthyroidism in the pembrolizumab arm had resolved at the time of the database cut-off.

Table 43: Subjects with adverse events by maximum toxicity grade – AEOSI - Hypothyroidism (ASAT population)

	KN024 data for MK-3475		Established Safety Dataset within Lung Indication for MK-3475[a]		Reference Safety Dataset for MK-3475[b]		Cumulative Running Safety Dataset for MK-3475[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		1,232		2,799		2,953	
with one or more adverse events	14	(9.1)	98	(8.0)	237	(8.5)	251	(8.5)
Grade 1	6	(3.9)	28	(2.3)	60	(2.1)	66	(2.2)
Grade 2	8	(5.2)	69	(5.6)	174	(6.2)	182	(6.2)
Grade 3	0	(0.0)	1	(0.1)	3	(0.1)	3	(0.1)
with no adverse events	140	(90.9)	1,134	(92.0)	2,562	(91.5)	2,702	(91.5)
Same notes as Table 38								

The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One patient (< 0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 49 (20%) patients.

In the 14 subjects who developed hypothyroidism, 7 subjects had a preceding history of hyperthyroidism that developed while on pembrolizumab. Of the remaining 7 subjects, one had a history of hypothyroidism and was on thyroid replacement prior to the first dose of pembrolizumab. A second subject had a mildly elevated TSH at baseline but otherwise no history of thyroid disorders or radiation to the neck. The remaining five subjects had no medical history of thyroid abnormalities, had not received radiation to the neck and had normal TSH levels prior to the first dose of pembrolizumab. Steroid treatment was not required

for the treatment of any of the hypothyroidism cases. Clinically significant hypothyroidism responded appropriately to thyroid replacement therapy.

Adverse drug reactions

The MAH has updated the list of adverse drug reaction in section 4.8 of the SmPC on the basis of the 2,953 patients treated with pembrolizumab in clinical trials.

Tabulated list of adverse reactions

Adverse reactions reported in 2,953 patients treated with pembrolizumab in clinical trials are reported in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 44: Adverse reactions in patients treated with pembrolizumab in clinical trials

Blood and lymphatic system disorders	
Common	anaemia [n=102 (3.5%)]
Uncommon	neutropenia [n=9 (0.3%)], leukopenia [n=16 (0.5%)], thrombocytopenia [n=23 (0.8%)], lymphopenia [n=16 (0.5%)], eosinophilia [n=17 (0.6%)]
Rare	immune thrombocytopenic purpura [n=1 (<0.1%)], haemolytic anaemia [n=1 (<0.1%)]
Immune system disorders	
Common	infusion related reaction[a] [n=77 (2.6%)]
Endocrine disorders	
Common	hyperthyroidism [n=108 (3.7%)], hypothyroidism[b] [n=251 (8.5%)]
Uncommon	hypophysitis[c] [n=18 (0.6%)], adrenal insufficiency [n=15 (0.5%)], thyroiditis [n=14 (0.5%)]
Metabolism and nutrition disorders	
Common	decreased appetite [n=269 (9.1%)]
Uncommon	type 1 diabetes mellitus[d] [n=7 (0.2%)], hyponatraemia [n=22 (0.7%)], hypokalaemia [n=18 (0.6%)], hypocalcaemia [n=22 (0.7%)]
Psychiatric disorders	
Uncommon	insomnia [n=27 (0.9%)]
Nervous system disorders	
Common	headache [n=112 (3.8%)], dizziness [n=48 (1.6%)], dysgeusia [n=46 (1.6%)]
Uncommon	epilepsy [n=4 (0.1%)], lethargy [n=21 (0.7%)], neuropathy peripheral [n=28 (0.9%)]
Rare	Guillain-Barré syndrome [n=2 (<0.1%)], myasthenic syndrome [n=2 (<0.1%)]
Eye disorders	
Common	dry eye [n=32 (1.1%)]
Uncommon	uveitis[e] [n=14 (0.5%)]
Vascular disorders	
Uncommon	hypertension [n=14 (0.5%)]
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[f] [n=103 (3.5%)], dyspnea [n=113 (3.8%)], cough [n=117 (4.0%)]
Gastrointestinal disorders	
Very common	diarrhoea [n=365 (12.4%)], nausea [n=319 (10.8%)]
Common	colitis[g] [n=51 (1.7%)], vomiting [n=111 (3.8%)], abdominal pain[h] [n=114 (3.9%)], constipation [n=96 (3.3%)], dry mouth [n=78 (2.6%)]
Uncommon	pancreatitis[i] [n=10 (0.3%)]
Rare	small intestinal perforation [n=1 (<0.1%)]
Hepatobiliary disorders	
Uncommon	hepatitis[j] [n=19 (0.6%)]
Skin and subcutaneous tissue disorders	
Very common	rash[k] [n=564 (19.1%)], pruritus[l] [n=515 (17.4%)]
Common	severe skin reactions[m] [n=52 (1.8%)], vitiligo[n] [n=194 (6.6%)], dry skin [n=98 (3.3%)], erythema [n=49 (1.7%)], eczema [n=31 (1.0%)]
Uncommon	lichenoid keratosis[o] [n=11 (0.4%)], psoriasis [n=14 (0.5%)], alopecia [n=24 (0.8%)], dermatitis [n=11 (0.4%)], dermatitis acneiform [n=28 (0.9%)], hair colour changes [n=16 (0.5%)], papule [n=11 (0.4%)]
Rare	erythema nodosum [n=2 (<0.1%)]
Musculoskeletal and connective tissue disorders	
Very common	arthralgia [n=294 (10.0%)]
Common	myositis[p] [n=160 (5.4%)], musculoskeletal pain[q] [n=116 (3.9%)], pain in extremity [n=44 (1.5%)], arthritis[r] [n=48 (1.6%)]

Uncommon	tenosynovitis[s] [n=11 (0.4%)]
Renal and urinary disorders	
Uncommon	nephritis[t] [n=10 (0.3%)]
General disorders and administration site conditions	
Very common	fatigue [n=694 (23.5%)]
Common	asthenia [n=223 (7.6%)], oedema[u] [n=97 (3.3%)], pyrexia [n=142 (4.8%)], influenza like illness [n=47 (1.6%)], chills [n=81 (2.7%)]
Investigations	
Common	alanine aminotransferase increased [n=107 (3.6%)], aspartate aminotransferase increased [n=102 (3.5%)], blood alkaline phosphatase increased [n=38 (1.3%)], blood creatinine increased [n=38 (1.3%)]
Uncommon	amylase increased [n=5 (0.2%)], blood bilirubin increased [n=27 (0.9%)], hypercalcaemia [n=6 (0.2%)]

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

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

Serious adverse event / deaths / other significant events

The table below reports the number and percentage of subjects (incidence ≥1% in one or more treatment groups) with SAEs up to 90 days after the last dose of study medication for each treatment group in the AsaT population.

Table 45: Subjects With Serious Adverse Events by decreasing incidence (Incidence ≥1% in one or more treatment groups) AsaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	68	(44.2)	66	(44.0)	134	(44.1)
with no adverse events	86	(55.8)	84	(56.0)	170	(55.9)
Pneumonia	3	(1.9)	9	(6.0)	12	(3.9)
Pleural effusion	5	(3.2)	3	(2.0)	8	(2.6)
Pneumonitis	7	(4.5)	1	(0.7)	8	(2.6)
Anaemia	2	(1.3)	5	(3.3)	7	(2.3)
Chronic obstructive pulmonary disease	4	(2.6)	1	(0.7)	5	(1.6)
Back pain	1	(0.6)	3	(2.0)	4	(1.3)
Diarrhoea	3	(1.9)	1	(0.7)	4	(1.3)
Hyponatraemia	4	(2.6)	0	(0.0)	4	(1.3)
Lower respiratory tract infection	2	(1.3)	2	(1.3)	4	(1.3)
Lung infection	2	(1.3)	2	(1.3)	4	(1.3)
Pulmonary embolism	2	(1.3)	2	(1.3)	4	(1.3)
Acute kidney injury	0	(0.0)	3	(2.0)	3	(1.0)
Cardiac failure	1	(0.6)	2	(1.3)	3	(1.0)
Febrile neutropenia	0	(0.0)	3	(2.0)	3	(1.0)
Hypercalcaemia	0	(0.0)	3	(2.0)	3	(1.0)
Hyperglycaemia	3	(1.9)	0	(0.0)	3	(1.0)
Pancytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Pyrexia	2	(1.3)	1	(0.7)	3	(1.0)
Thrombocytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Urinary tract infection	1	(0.6)	2	(1.3)	3	(1.0)
Alanine aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Atrial fibrillation	0	(0.0)	2	(1.3)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Haemoptysis	2	(1.3)	0	(0.0)	2	(0.7)
Nausea	0	(0.0)	2	(1.3)	2	(0.7)
Pulmonary oedema	0	(0.0)	2	(1.3)	2	(0.7)
Pulmonary sepsis	0	(0.0)	2	(1.3)	2	(0.7)
Respiratory tract infection	0	(0.0)	2	(1.3)	2	(0.7)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Drug-related SAEs

Table 46: Subjects With Drug-Related Serious Adverse Events by decreasing incidence (Incidence >0% in one or more treatment groups) AsaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	33	(21.4)	31	(20.7)	64	(21.1)
with no adverse events	121	(78.6)	119	(79.3)	240	(78.9)
Pneumonitis	7	(4.5)	1	(0.7)	8	(2.6)
Anaemia	1	(0.6)	4	(2.7)	5	(1.6)
Diarrhoea	3	(1.9)	1	(0.7)	4	(1.3)
Febrile neutropenia	0	(0.0)	3	(2.0)	3	(1.0)
Pancytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Pneumonia	0	(0.0)	3	(2.0)	3	(1.0)
Thrombocytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Alanine aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Lower respiratory tract infection	2	(1.3)	0	(0.0)	2	(0.7)
Lung infection	0	(0.0)	2	(1.3)	2	(0.7)
Acute hepatic failure	1	(0.6)	0	(0.0)	1	(0.3)
Aspartate aminotransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	1	(0.3)
Cellulitis	0	(0.0)	1	(0.7)	1	(0.3)
Cerebrovascular accident	1	(0.6)	0	(0.0)	1	(0.3)
Death	0	(0.0)	1	(0.7)	1	(0.3)
Diabetic ketoacidosis	1	(0.6)	0	(0.0)	1	(0.3)
Enterocolitis	1	(0.6)	0	(0.0)	1	(0.3)
Face oedema	1	(0.6)	0	(0.0)	1	(0.3)
Fatigue	1	(0.6)	0	(0.0)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Gastric ulcer	1	(0.6)	0	(0.0)	1	(0.3)
Hepatic enzyme increased	1	(0.6)	0	(0.0)	1	(0.3)
Hyperthyroidism	1	(0.6)	0	(0.0)	1	(0.3)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Hypovolaemia	1	(0.6)	0	(0.0)	1	(0.3)
Infusion related reaction	1	(0.6)	0	(0.0)	1	(0.3)
Leukocytosis	0	(0.0)	1	(0.7)	1	(0.3)
Lichenoid keratosis	1	(0.6)	0	(0.0)	1	(0.3)
Malignant neoplasm progression	0	(0.0)	1	(0.7)	1	(0.3)
Musculoskeletal pain	1	(0.6)	0	(0.0)	1	(0.3)
Nausea	0	(0.0)	1	(0.7)	1	(0.3)
Neutropenic sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Oedema peripheral	1	(0.6)	0	(0.0)	1	(0.3)
Organising pneumonia	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Pericarditis	1	(0.6)	0	(0.0)	1	(0.3)
Platelet count decreased	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary embolism	1	(0.6)	0	(0.0)	1	(0.3)
Pulmonary sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Pyrexia	0	(0.0)	1	(0.7)	1	(0.3)
Rash	1	(0.6)	0	(0.0)	1	(0.3)
Respiratory tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Skin infection	0	(0.0)	1	(0.7)	1	(0.3)
Stomatitis	0	(0.0)	1	(0.7)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)
Transaminases increased	1	(0.6)	0	(0.0)	1	(0.3)
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Vasospasm	0	(0.0)	1	(0.7)	1	(0.3)
Vomiting	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Deaths

Overall, there were 16 deaths (9 in the pembrolizumab arm and 7 in the SOC arm) due to an AE, including 4 events, 1 in the pembrolizumab arm (sudden death) and 3 in the SOC arm (pulmonary sepsis, death, pulmonary alveolar haemorrhage) considered by Investigators as related to the study treatment.

Table 47: Subjects with AEs resulting in Death by decreasing incidence (Incidence >0% in One or More Treatment Groups) AsaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	9	(5.8)	7	(4.7)	16	(5.3)
with no adverse events	145	(94.2)	143	(95.3)	288	(94.7)
Cardiac arrest	1	(0.6)	1	(0.7)	2	(0.7)
Acute respiratory failure	1	(0.6)	0	(0.0)	1	(0.3)
Cardiac failure	0	(0.0)	1	(0.7)	1	(0.3)
Cardio-respiratory arrest	0	(0.0)	1	(0.7)	1	(0.3)
Death	0	(0.0)	1	(0.7)	1	(0.3)
General physical health deterioration	1	(0.6)	0	(0.0)	1	(0.3)
Haemorrhagic stroke	1	(0.6)	0	(0.0)	1	(0.3)
Multiple organ dysfunction syndrome	1	(0.6)	0	(0.0)	1	(0.3)
Neutropenic sepsis	1	(0.6)	0	(0.0)	1	(0.3)
Pneumonia	1	(0.6)	0	(0.0)	1	(0.3)
Pneumonia streptococcal	1	(0.6)	0	(0.0)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary embolism	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Respiratory failure	1	(0.6)	0	(0.0)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

One death was considered related to pembrolizumab treatment by the Investigator. However, in the opinion of the MAH, based on the clinically relevant information currently available for this individual case, the reported event was considered unlikely related to the study medication. A causality assessment is limited by confounding factors including recent ECG findings of myocardial infarction, internal jugular vein clot, history of diabetes mellitus, and the underlying metastatic malignancy.

Laboratory findings

A shift analysis on laboratory abnormalities with the highest CTCAE grade was performed. A clinically meaningful worsening was defined as a shift from less than Grade 3 to Grade 3, 4, or 5 or a shift from Grade 0 to Grade 2. No clinically meaningful change in the percentage of subjects with worsening of laboratory abnormalities was observed for subjects treated with pembrolizumab.

The most frequently reported laboratory abnormalities in pembrolizumab arm were magnesium decreased (41.7%), glucose increased (35.9%), lymphocytes decreased (35.8%), albumin decreased (33.3%), phosphate decreased (33.3%) and haemoglobin decreased (31.7%).

The most frequently reported laboratory abnormalities in the SOC arm were leukocytes decreased (80%), haemoglobin decreased (73.9%), glucose increased (52.3%) lymphocytes decreased (47.5%), phosphate

decreased (42.9%) and neutrophils decreased (33.3%).

Safety in special populations

Age

Table 48: AE Summary by Age (ASaT Population)

	Pembrolizumab								SOC							
	<=65		65-74		75-84		85 +		<=65		65-74		75-84		85 +	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	77		54		20		3		64		65		19		2	
with one or more adverse events	73	(94.8)	52	(96.3)	20	(100.0)	3	(100.0)	62	(96.9)	62	(95.4)	19	(100.0)	2	(100.0)
who died	4	(5.2)	4	(7.4)	0	(0.0)	1	(33.3)	2	(3.1)	3	(4.6)	1	(5.3)	1	(50.0)
with serious adverse events	32	(41.6)	25	(46.3)	10	(50.0)	1	(33.3)	24	(37.5)	30	(46.2)	11	(57.9)	1	(50.0)
discontinued‡ due to an adverse event	5	(6.5)	6	(11.1)	3	(15.0)	0	(0.0)	10	(15.6)	8	(12.3)	3	(15.8)	0	(0.0)
CNS (confusion/extrapyramidal)	8	(10.4)	4	(7.4)	3	(15.0)	2	(66.7)	1	(1.6)	7	(10.8)	4	(21.1)	1	(50.0)
AE related to falling	5	(6.5)	9	(16.7)	0	(0.0)	0	(0.0)	4	(6.3)	5	(7.7)	2	(10.5)	0	(0.0)
CV events	13	(16.9)	9	(16.7)	4	(20.0)	1	(33.3)	10	(15.6)	14	(21.5)	5	(26.3)	1	(50.0)
Cerebrovascular events	3	(3.9)	2	(3.7)	1	(5.0)	0	(0.0)	3	(4.7)	2	(3.1)	0	(0.0)	0	(0.0)
Infections	29	(37.7)	21	(38.9)	6	(30.0)	1	(33.3)	22	(34.4)	30	(46.2)	13	(68.4)	1	(50.0)

‡ Study medication withdrawn.
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, SAEs were followed 90 days after last dose of study treatment
(Database Cutoff Date: 09MAY2016).

Gender

Table 49: Adverse Event Summary by Gender - Study KEYNOTE-024 (ASaT Population)

	Pembrolizumab				SOC			
	M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	92		62		95		55	
with one or more adverse events	89	(96.7)	59	(95.2)	93	(97.9)	52	(94.5)
with no adverse event	3	(3.3)	3	(4.8)	2	(2.1)	3	(5.5)
with drug-related† adverse events	71	(77.2)	42	(67.7)	87	(91.6)	48	(87.3)
with serious adverse events	39	(42.4)	29	(46.8)	45	(47.4)	21	(38.2)
with serious drug-related adverse events	19	(20.7)	14	(22.6)	24	(25.3)	7	(12.7)
who died	6	(6.5)	3	(4.8)	7	(7.4)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	1	(1.6)	3	(3.2)	0	(0.0)
discontinued‡ due to an adverse event	5	(5.4)	9	(14.5)	15	(15.8)	6	(10.9)
discontinued due to a drug-related adverse event	3	(3.3)	8	(12.9)	11	(11.6)	5	(9.1)
discontinued due to a serious adverse event	4	(4.3)	9	(14.5)	9	(9.5)	2	(3.6)
discontinued due to a serious drug-related adverse event	2	(2.2)	8	(12.9)	6	(6.3)	1	(1.8)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Table 50: Adverse Event Summary by Gender - Subjects Treated with pembrolizumab from KN024, KN001, KN002, KN006 and KN010 (ASaT Population)

	KN024 data for MK-3475				Reference Safety Dataset for MK-3475[b]			
	M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	92		62		1,659		1,140	
with one or more adverse events	89	(96.7)	59	(95.2)	1,616	(97.4)	1,111	(97.5)
with no adverse event	3	(3.3)	3	(4.8)	43	(2.6)	29	(2.5)
with drug-related[†] adverse events	71	(77.2)	42	(67.7)	1,239	(74.7)	823	(72.2)
with toxicity grade 3-5 adverse events	51	(55.4)	31	(50.0)	759	(45.8)	514	(45.1)
with toxicity grade 3-5 drug-related adverse events	25	(27.2)	16	(25.8)	251	(15.1)	135	(11.8)
with serious adverse events	39	(42.4)	29	(46.8)	636	(38.3)	405	(35.5)
with serious drug-related adverse events	19	(20.7)	14	(22.6)	184	(11.1)	97	(8.5)
who died	6	(6.5)	3	(4.8)	69	(4.2)	41	(3.6)
who died due to a drug-related adverse event	0	(0.0)	1	(1.6)	9	(0.5)	1	(0.1)
discontinued[‡] due to an adverse event	5	(5.4)	9	(14.5)	197	(11.9)	137	(12.0)
discontinued due to a drug-related adverse event	3	(3.3)	8	(12.9)	98	(5.9)	48	(4.2)
discontinued due to a serious adverse event	4	(4.3)	9	(14.5)	155	(9.3)	98	(8.6)
discontinued due to a serious drug-related adverse event	2	(2.2)	8	(12.9)	72	(4.3)	29	(2.5)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[b] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
(KN024 Database Cutoff Date: 09MAY2016).
(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).

ECOG PS

Table 51: Adverse Event Summary by ECOG status (ASaT Population)

	Pembrolizumab						SOC					
	0		1		2		0		1		2	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	54		99		1		53		97		0	
with one or more adverse events	53	(98.1)	95	(96.0)	0	(0.0)	49	(92.5)	96	(99.0)	0	
with no adverse event	1	(1.9)	4	(4.0)	1	(100.0)	4	(7.5)	1	(1.0)	0	
with drug-related[†] adverse events	37	(68.5)	76	(76.8)	0	(0.0)	46	(86.8)	89	(91.8)	0	
with serious adverse events	22	(40.7)	46	(46.5)	0	(0.0)	15	(28.3)	51	(52.6)	0	
with serious drug-related adverse events	13	(24.1)	20	(20.2)	0	(0.0)	6	(11.3)	25	(25.8)	0	
who died	1	(1.9)	8	(8.1)	0	(0.0)	1	(1.9)	6	(6.2)	0	
who died due to a drug-related adverse event	0	(0.0)	1	(1.0)	0	(0.0)	1	(1.9)	2	(2.1)	0	
discontinued[‡] due to an adverse event	6	(11.1)	8	(8.1)	0	(0.0)	8	(15.1)	13	(13.4)	0	
discontinued due to a drug-related adverse event	5	(9.3)	6	(6.1)	0	(0.0)	6	(11.3)	10	(10.3)	0	
discontinued due to a serious adverse event	5	(9.3)	8	(8.1)	0	(0.0)	5	(9.4)	6	(6.2)	0	
discontinued due to a serious drug-related adverse event	4	(7.4)	6	(6.1)	0	(0.0)	4	(7.5)	3	(3.1)	0	

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-neplus]

Table 52: Grade 3-5 AEs summary by ECOG status (ASaT Population)

	pembrolizumab				SOC			
	0		1		0		1	
	n	%	n	%	n	%	n	%
Subject population	54		100		53		97	
with ≥1 grade 3-5 AEs	23	(42.6)	59	(59.0)	32	(60.4)	77	(79.4)
with no AEs	31	(57.4)	41	(41.0)	21	(39.6)	20	(20.6)
Subject population	54		100		53		97	
with ≥1 drug-related grade 3-5 AEs	13	(24.1)	28	(28.0)	23	(43.4)	57	(58.8)
with no AEs	41	(75.9)	72	(72.0)	30	(56.6)	40	(41.2)

Table made by the Assessor

Region

Table 53: Adverse Event Summary by Region (US-Ex-US) - ASaT Population

	Pembrolizumab				SOC			
	US		Ex-US		US		Ex-US	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	20		134		21		129	
with one or more adverse events	20	(100.0)	128	(95.5)	20	(95.2)	125	(96.9)
with no adverse event	0	(0.0)	6	(4.5)	1	(4.8)	4	(3.1)
with drug-related† adverse events	14	(70.0)	99	(73.9)	19	(90.5)	116	(89.9)
with serious adverse events	13	(65.0)	55	(41.0)	6	(28.6)	60	(46.5)
with serious drug-related adverse events	6	(30.0)	27	(20.1)	2	(9.5)	29	(22.5)
who died	1	(5.0)	8	(6.0)	0	(0.0)	7	(5.4)
who died due to a drug-related adverse event	1	(5.0)	0	(0.0)	0	(0.0)	3	(2.3)
discontinued‡ due to an adverse event	4	(20.0)	10	(7.5)	1	(4.8)	20	(15.5)
discontinued due to a drug-related adverse event	4	(20.0)	7	(5.2)	0	(0.0)	16	(12.4)
discontinued due to a serious adverse event	4	(20.0)	9	(6.7)	0	(0.0)	11	(8.5)
discontinued due to a serious drug-related adverse event	4	(20.0)	6	(4.5)	0	(0.0)	7	(5.4)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Table 54: Adverse Event Summary by Region (EU-Ex-EU) - ASaT Population

	Pembrolizumab				SOC			
	EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	79		75		79		71	
with one or more adverse events	75	(94.9)	73	(97.3)	76	(96.2)	69	(97.2)
with no adverse event	4	(5.1)	2	(2.7)	3	(3.8)	2	(2.8)
with drug-related† adverse events	53	(67.1)	60	(80.0)	68	(86.1)	67	(94.4)
with serious adverse events	38	(48.1)	30	(40.0)	41	(51.9)	25	(35.2)
with serious drug-related adverse events	17	(21.5)	16	(21.3)	18	(22.8)	13	(18.3)
who died	8	(10.1)	1	(1.3)	5	(6.3)	2	(2.8)
who died due to a drug-related adverse event	0	(0.0)	1	(1.3)	2	(2.5)	1	(1.4)
discontinued‡ due to an adverse event	7	(8.9)	7	(9.3)	15	(19.0)	6	(8.5)
discontinued due to a drug-related adverse event	4	(5.1)	7	(9.3)	12	(15.2)	4	(5.6)
discontinued due to a serious adverse event	6	(7.6)	7	(9.3)	9	(11.4)	2	(2.8)
discontinued due to a serious drug-related adverse event	3	(3.8)	7	(9.3)	6	(7.6)	1	(1.4)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Histology

Table 55: Adverse Event Summary by Histology (ASaT Population)

	Pembrolizumab				SOC			
	Squamous		Non-Squamous		Squamous		Non-Squamous	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	29		125		27		123	
with one or more adverse events	27	(93.1)	121	(96.8)	27	(100.0)	118	(95.9)
with no adverse event	2	(6.9)	4	(3.2)	0	(0.0)	5	(4.1)
with drug-related† adverse events	19	(65.5)	94	(75.2)	26	(96.3)	109	(88.6)
with serious adverse events	14	(48.3)	54	(43.2)	13	(48.1)	53	(43.1)
with serious drug-related adverse events	8	(27.6)	25	(20.0)	7	(25.9)	24	(19.5)
who died	1	(3.4)	8	(6.4)	1	(3.7)	6	(4.9)
who died due to a drug-related adverse event	0	(0.0)	1	(0.8)	1	(3.7)	2	(1.6)
discontinued‡ due to an adverse event	2	(6.9)	12	(9.6)	2	(7.4)	19	(15.4)
discontinued due to a drug-related adverse event	2	(6.9)	9	(7.2)	1	(3.7)	15	(12.2)
discontinued due to a serious adverse event	1	(3.4)	12	(9.6)	2	(7.4)	9	(7.3)
discontinued due to a serious drug-related adverse event	1	(3.4)	9	(7.2)	1	(3.7)	6	(4.9)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Discontinuation due to adverse events

Treatment interruption due to AEs occurred in 53 patients (34.4%) in the pembrolizumab arm and 51 patients (34.0%) in the SOC arm. The most common AEs leading to pembrolizumab interruption were diarrhoea (4.5%), dyspnoea (3.2%), ALT aminotransferase increased (1.9%), chronic obstructive pulmonary disease (1.9%), and transaminases increased (1.9%). In patients treated with SOC the most

common AEs leading to treatment interruption were neutropenia (8.0%), neutrophil count decreased (7.3%), anemia (6.7%), and platelet count decreased (4.0%).

The incidence of drug-related treatment discontinuation due to AE was 7.1% in the pembrolizumab arm and 10.7% in the SOC group.

Table 56: Subjects with drug-related AEs resulting in treatment discontinuation by decreasing incidence (Incidence >0% in one or more treatment groups) - ASaT Population

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	11	(7.1)	16	(10.7)	27	(8.9)
with no adverse events	143	(92.9)	134	(89.3)	277	(91.1)
Pneumonitis	6	(3.9)	0	(0.0)	6	(2.0)
Fatigue	1	(0.6)	2	(1.3)	3	(1.0)
Blood creatinine increased	0	(0.0)	2	(1.3)	2	(0.7)
Vomiting	1	(0.6)	1	(0.7)	2	(0.7)
Acute kidney injury	0	(0.0)	1	(0.7)	1	(0.3)
Alanine aminotransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Blood creatine increased	0	(0.0)	1	(0.7)	1	(0.3)
Creatinine renal clearance decreased	0	(0.0)	1	(0.7)	1	(0.3)
Decreased appetite	0	(0.0)	1	(0.7)	1	(0.3)
Enanthema	0	(0.0)	1	(0.7)	1	(0.3)
Febrile neutropenia	0	(0.0)	1	(0.7)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Hypoacusis	0	(0.0)	1	(0.7)	1	(0.3)
Hypoxia	0	(0.0)	1	(0.7)	1	(0.3)
Lethargy	0	(0.0)	1	(0.7)	1	(0.3)
Leukocytosis	0	(0.0)	1	(0.7)	1	(0.3)
Nausea	0	(0.0)	1	(0.7)	1	(0.3)
Peripheral sensory neuropathy	0	(0.0)	1	(0.7)	1	(0.3)
Platelet count decreased	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Respiratory tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)
Transaminases increased	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified 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: 09MAY2016).

Source: [P024V01MK3475: analysis-adsl; adae] [P024V01MK3475: tabulations-aeplus]

Post marketing experience

No new data regarding post marketing experience have been submitted as part of this application

2.5.1. Discussion on clinical safety

Safety data from patients in the pivotal KEYNOTE-024 study, comparing pembrolizumab to SOC chemotherapy (5 optional platinum-based doublets) in previously untreated NSCLC patients, have been submitted. Overall, 154 patients were treated with pembrolizumab and 150 patients received SOC (cut-off date 9 May 2016). In addition, analyses on the overall safety database, including data from 2,953 patients who received pembrolizumab across studies KN001, KN002, KN006, KN010 and KN024 have been submitted to support the update of Section 4.8 of the SmPC.

The median exposure to treatment was doubled for patients in the pembrolizumab arm compared to that in the SOC arm (214.00 days vs 106.00 days, respectively). Although the number of patients and the provided data for long-term exposure of pembrolizumab are limited in the first-line NSCLC setting, the safety data base can be considered sufficient to support this extension of indication, taking the overall safety data and the already available data for NSCLC into account. The safety data for NSCLC will be further expanded by

several currently on-going phase III studies in NSCLC in the 1L and adjuvant setting (pembrolizumab treatment with 200 mg flat dose three-weekly in all ongoing studies).

No major differences in baseline characteristics were observed across arms, with the exception of smoking status and brain metastases ("never-smokers": 12.6% vs 3.2%; brain metastases: 6.6% vs 11.7%, in SOC and pembrolizumab arms, respectively).

Overall, the safety of pembrolizumab positively compares with that of SOC chemotherapy. Although in the two arms a comparable number of patients experienced AEs (96.1% with pembrolizumab and 96.7% with SOC), a lower rate of drug-related AEs (73.4% vs 90%), drug-related Grade ≥3 AEs (26.6% vs 53.3%), and treatment discontinuation due to drug-related AEs (7.1% vs 10.7%) occurred in patients treated with pembrolizumab compared to chemotherapy.

Pembrolizumab showed a safety profile consistent with what previously reported, and well different from that of chemotherapy. The analysis of risk difference between arms for the most common AEs was clearly in favour of pembrolizumab for some events (i.e, *Blood creatinine increased*, *Stomatitis*, *White blood cell count decreased*, *Dysgeusia*, *Platelet count decreased*, *Thrombocytopenia*, *Decreased appetite*, *Neutrophil count decreased*, *Fatigue*, *Vomiting*, *Neutropenia*, *Nausea* and *Anaemia*), while was in favour of chemotherapy for others (i.e, *Pruritus*, *Rash* and *Nasopharyngitis*).

In the pembrolizumab arm, the most commonly reported AEs were *Dyspnoea* (22.1%), *Diarrhoea* (20.8%), *Constipation* (20.8%), *Fatigue* (20.8%) and *Decreased appetite* (20.1%), while in patients treated with SOC chemotherapy the most frequent AEs were *Anaemia* (52.7%), *Nausea* (46.7%), *Fatigue* (35.3%), *Decreased appetite* (32.7%), *Neutropenia* (24%), *Vomiting* (24%), *Constipation* (22.7%) and *Diarrhoea* (22%). In terms of drug-related AEs, the most frequently reported were *Diarrhoea* (14.3%) *Fatigue* (10.4%) and *Pyrexia* (10.4%) with pembrolizumab, while in the chemotherapy arm *Anaemia* (44%), *Nausea* (43.3%), *Fatigue* (28.7%), *Decreased appetite* (26%), *Neutropenia* (22.7%) and *Vomiting* (20%) were more commonly observed.

A lower rate of drug-related Grade≥3 AEs was reported with pembrolizumab compared to the chemotherapy arm (26.6% vs 53.3%). The drug-related Grade≥3 AEs occurred more commonly in patients treatment with pembrolizumab were *Diarrhoea* (3.9% vs 1.3%) and *Pneumonitis* (2.6% vs 0.7%).

As expected, a higher incidence of AEOSI, including immune-mediated AEs, was registered in the pembrolizumab arm compared to chemotherapy (29.2% vs 4.7%), and the most frequently reported events were *Hypothyroidism* (9.1% vs 1.3%), *Hyperthyroidism* (7.8% vs 1%), *Pneumonitis* (5.8% vs 0.7%) and *Infusion reactions* (4.5% vs 1.3%). Events were mostly mild, and Grade ≥3 AEOSI was reported in 9.7% of patients treated with pembrolizumab.

In line with previously submitted data of pembrolizumab in NSCLC patients, the most common drug-related SAE was *Pneumonitis* (4.5%); *Anaemia* (2.7%) was the most frequently reported with chemotherapy. Overall, 16 patients (9 in the pembrolizumab arm and 7 in the control group) died due to AEs. None of the AE leading to death occurred more than once. Four fatal cases, including 1 patient treated with pembrolizumab (sudden death), were considered related to study treatment by the investigator.

In pembrolizumab treated patients, no clinically meaningful change in the percentage of subjects with worsening of laboratory abnormalities was observed.

No major and unexpected differences in the tolerability of pembrolizumab treatment were observed across the different class of age and ECOG PS categories. On the contrary, the gender appear to influence the pembrolizumab safety, with a higher rate of female compared to male patients who discontinued pembrolizumab due to AEs (14.5% vs 5.4%), drug-related AEs (12.9% vs 3.3%), SAEs (14.5% vs 4.3%) and drug-related SAEs (12.9% vs 2.2%). Despite an higher incidence of discontinuations of pembrolizumab due to AEs observed in female patients compared to male patients in KEYNOTE-024 (14.5% vs 5.4%), the

overall incidence of adverse events was similar in both genders. Based on a review of the narratives for female subjects discontinued due to AEs, not all reported discontinuations are definitely lead by AE, lowering the rate of "true" discontinuations due to AEs to a level (8%) similar to that observed in the reference safety data set, where there was no difference between gender (11.9% in males and 12% in females). Moreover, difference of incidence between the genders might be exaggerated due to the small patient numbers in KN-024. This view is supported by analyses of the much larger reference safety dataset, where meaningful differences in the safety profile between female and male subjects cannot be demonstrated. In addition, no imbalances were observed in the second-line NSCLC study (KEYNOTE-010). Therefore, the higher rate of discontinuations due to AEs in female subjects in KN-024 is most likely a chance finding due to imprecise data collection/entry and small patient numbers.

2.5.2. Conclusions on clinical safety

Based on the submitted data, no new pembrolizumab safety concerns arise. Overall, the safety profile of pembrolizumab compares favourably with SOC chemotherapy in first-line NSCLC.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

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 4.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 4.2 with the following content. Data from study P024 have been included in different sections of the RMP:

Safety concerns

No new safety concerns have been identified. The list of safety concerns as approved in the previous version of the RMP is considered still valid for the extension of indication.

Summary of safety concerns	
Important identified risks	**Immune-Related Adverse Reactions** - Immune-related pneumonitis - Immune-related colitis - Immune-related hepatitis - Immune-related nephritis - Immune-related endocrinopathies • Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) • Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) • Type 1 diabetes mellitus - Other immune-related adverse reactions • Uveitis

Summary of safety concerns	
	• Myositis • Pancreatitis • Severe Skin Reactions • Guillain-Barre Syndrome **Infusion-Related Reactions**
Important potential risks	**Immune-Related Adverse Events** • Gastrointestinal perforation secondary to colitis **Immunogenicity**
Missing information	- Safety in patients with moderate or severe hepatic impairment - Safety in patients with severe renal impairment - Safety in patients with active systemic autoimmune disease - Safety in patients with HIV or Hepatitis B or Hepatitis C - Safety in pediatric patients - Reproductive and lactation data - Long term safety - Safety in various ethnic groups - Potential pharmacodynamic interaction with systemic immunosuppressants - Safety in patients with previous hypersensitivity to another monoclonal antibody - Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs

Pharmacovigilance plan

The MAH does not propose any new additional pharmacovigilance activities for the new indication, which is acceptable. The PRAC Rapporteur, having considered the updated data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Activity/Study title (type of activity, study title, category 1-3)*	Objectives*	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Validation report for anti-MK-3475 neutralizing antibody assay (Category 3)	To validate the assay for the determination of neutralizing capacity of anti-MK-3475 antibodies and to report the results in an assay validation report.	Important potential risk (Immunogenicity)	Started	Final report September 2016
Clinical trial Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung	To evaluate and characterize the tolerability and safety profile of single agent MK-3475 in adult patients with unresectable advanced carcinoma (including NSCLC or MEL).	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks	Started	Final report December 2016

Activity/Study title (type of activity, study title, category 1-3)*	Objectives*	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Carcinoma (P001) (Category 3)		(Immune-related adverse events, Immunogenicity) -Long term safety		
Clinical trial Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma (P002) (Category 3)	To evaluate the progression-free-survival (PFS) in patients with ipilimumab refractory advanced MEL receiving either MK-3475 or chemotherapy.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events, Immunogenicity) -Long term safety	Started	Final report January 2017
Clinical trial A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to IPI in Patients with Advanced Melanoma (P006) (Category 3)	To evaluate progression-free-survival (PFS) in patients with advanced MEL receiving either MK-3475 or IPI	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events, Immunogenicity) -Long term safety	Started	Final report January 2017
Clinical trial A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (P010) (Category 3)	To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions -Important potential risks (Immune-related adverse events, Immunogenicity) -Long term safety	Started	Final report August 2019
Clinical trial A Randomized	To compare the Progression Free Survival (PFS) per RECIST 1.1 as	-Important identified risks	Started	Final report September

Activity/Study title (type of activity, study title, category 1-3)*	Objectives*	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (P024) (Category 3)	assessed by blinded independent central radiologists' review in subjects with PDL1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	(Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events, Immunogenicity) -Long term safety		2018
Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (P042) (Category 3)	To compare the overall survival (OS) in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events, Immunogenicity) -Long term safety	Started	Final report December 2019
Clinical trial A Phase I/II Study of Pembrolizumab (MK-3475) in Children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma (P051) (Category 3)	To define the rate of dose-limiting toxicities (DLTs) at the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab when administered as monotherapy to children from 6 months to < 18 years of age pooled across all indications including advanced melanoma or a PD-l1 positive advanced, relapsed or refractory solid tumour or lymphoma	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events) - Safety in paediatric patients	Started	Final report July 2019

*Only the first primary objective was included

**Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

The risk minimisation measures have not changed. The PRAC Rapporteur, having considered the updated

data submitted, is of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk		
Immune-related Pneumonitis	The risk of the immune-related adverse reaction of pneumonitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Colitis	The risk of the immune-related adverse reaction of colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Hepatitis	The risk of the immune-related adverse reaction of hepatitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Nephritis	The risk of the immune-related adverse reaction of nephritis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Endocrinopathies	The risk of the immune-related endocrinopathies [Hypophysitis (including hypopituitarism and secondary adrenal insufficiency); Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis); Type 1 Diabetes Mellitus] associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4 and 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Other Immune-related adverse reactions	The risk of other immune-related adverse reactions (uveitis, myositis, pancreatitis, severe skin reactions, Guillain-Barre syndrome) associated with the use of pembrolizumab is	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	
Infusion-Related Reactions	The risk of infusion-related reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Important Potential Risk		
Gastrointestinal perforation secondary to colitis	The risk of the immune-related adverse event of gastrointestinal perforation secondary to colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	None
Immunogenicity	The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 4.8.	None
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	The missing information of safety in these patients is described in the SmPC, Section 4.2, 4.4.	None
Safety in patients with active systemic autoimmune disease	The missing information of safety in patients with active systemic autoimmune disease is described in the SmPC, Section 4.4, 5.1	None
Safety in patients with HIV or Hepatitis B or Hepatitis C	The missing information of safety in patients with patients with HIV or Hepatitis B or Hepatitis C is described in the SmPC, Section 4.4, 5.1.	None
Safety in Pediatric patients	The missing information of safety in pediatric patients is described in the SmPC, Section 4.2	None
Reproductive and lactation data	Use during pregnancy and use in nursing mothers is described in the SmPC, Section 4.6, 5.3	None
Long term safety	None	None
Safety in various ethnic groups	None	None
Potential pharmacodynamic interaction with systemic immunosuppressants	The missing information of potential pharmacodynamic interaction with systemic immunosuppressants is described in the SmPC, Section 4.4, 4.5	None
Safety in patients with previous	The missing information of safety in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
hypersensitivity to another monoclonal antibody	patients with previous hypersensitivity to another monoclonal antibody is described in the SmPC, Section 4.4, 5.1	
Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs	The missing information of safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs is described in the SmPC, Section 4.4, 5.1	None

2.7. Update of the Product information

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

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable because of the limited impact of this variation on the Keytruda PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication application is for the treatment of adult patients with stage IV NSCLC patients previously untreated for their metastatic disease. The sought indication is for patients with tumour expressing PD-L1 (TPS≥50%), measured in tumour tissue by IHC using the Dako Commercial Ready Assay (CRA), and not harbouring EGFR activating mutations and ALK translocations.

The aim of therapy in this setting is to prolong progression free-survival and overall survival, with no addition of major treatment-related toxicity.

3.1.2. Available therapies and unmet medical need

The prognosis of advanced NSCLC is poor and more than 80% of patients experience multiple severe cancer-related symptoms.

Platinum-based doublet chemotherapy (four to a maximum of six cycles) is still the standard of care for the first line treatment of NSCLC not harbouring EGFR activating mutations and ALK translocations, with no major differences in efficacy across combinations. The strategy of maintenance treatment, either as maintained use of an agent included in first-line treatment (“*continuation maintenance”*) or as introduction

of a new agent after 4 cycles of platinum-based chemotherapy (*"switch maintenance"*) has been explored and an improvement has been reported with pemetrexed (both continuation and switch maintenance, only in non-squamous histology) and erlotinib (switch maintenance in patients with stable disease after first-line chemotherapy).

Available systemic therapy, except that for tumors not harbouring EGFR sensitizing mutations or ALK rearrangements, can only determine a limited improvement in survival up to 8–12 months, with an enhanced symptom control and a better quality of life in 60%–70% despite treatment toxicity (Leighl NB. et al, 2012).

3.1.3. Main clinical studies

The pembrolizumab efficacy and safety data in the first line NSCLC setting are based on one single, well designed, phase III, randomized, pivotal study (KEYNOTE-024) conducted in PD-L1 strongly positive (TPS≥50%) NSCLC patients, comparing pembrolizumab to a SOC platinum-based doublet that was selected by the investigator at the time of randomization among 5 different options (pemetrexed 500 mg/m^2 plus carboplatin AUC 5 to 6 mg/mL/min or cisplatin 75 mg/m^2 day 1, for 4 to 6 cycles followed by optional maintenance pemetrexed, in non-squamous histologies only; gemcitabine 1250 mg/m^2 days 1 and 8 plus carboplatin AUC 5 to 6 mg/mL/min or cisplatin 75 mg/m^2 day 1, for 4 to 6 cycles; paclitaxel 200 mg/m^2 plus carboplatin AUC 5 to 6 mg/mL/min day 1, for 4 to 6 cycles, followed by optional maintenance pemetrexed only in non-squamous histologies).

3.2. Favourable effects

Median PFS (primary endpoint) was 10.3 months with pembrolizumab vs 6.0 months with SOC chemotherapy (HR: 0.50, p<0.001), with 6-month and 12-month PFS rates of 62.1% vs 50.3% and 47% vs 15%, respectively.

The HR for OS (secondary endpoint) was 0.60 (95% CI: 0.41-0.89; one-sided logrank p-value =0.005) with 12-month OS rate of 69.9% vs 54.2% in pembrolizumab and SOC chemotherapy arm.

3.3. Uncertainty in the knowledge about the beneficial effects

There are no additional remaining uncertainties and limitations that have an impact on the benefit/risk balance.

3.4. Unfavourable effects

Despite the comparable number of patients experiencing AEs across arms (96.1% with pembrolizumab and 96.7% with SOC), a lower rate of drug-related AEs (73.4% vs 90%), drug-related Grade ≥3 AEs (26.6% vs 53.3%), and treatment discontinuation due to drug-related AEs (7.1% vs 10.7%) occurred with pembrolizumab compared to chemotherapy.

In the pembrolizumab arm, the most commonly reported drug-related AEs were *Diarrhoea* (14.3%), *Fatigue* (10.4%) and *Pyrexia* (10.4%).

A lower rate of drug-related Grade≥3 AEs was reported with pembrolizumab compared to the chemotherapy arm (26.6% vs 53.3%). The drug-related Grade≥3 AEs occurred more commonly in patients treatment with pembrolizumab were *Diarrhea* (3.9% vs 1.3%) and *Pneumonitis* (2.6% vs 0.7%).

As expected, a higher incidence of AEOSI, including immune-mediated AEs, was registered in the pembrolizumab arm compared to chemotherapy (29.2% vs 4.7%), and the most frequently reported events were *Hypothyroidism* (9.1% vs 1.3%), *Hyperthyroidism* (7.8% vs 1%), *Pneumonitis* (5.8% vs 0.7%) and

Infusion reactions (4.5% vs 1.3%). Events were mostly mild, and Grade ≥3 AEOSI was reported in 9.7% of patients treated with pembrolizumab.

In line with previously submitted data of pembrolizumab in NSCLC patients, the most common drug-related SAE was *Pneumonitis* (4.5%).

3.5. Uncertainty in the knowledge about the unfavourable effects

There are no additional remaining uncertainties or limitations that have an impact on the benefit/risk balance.

3.6. Effects Table

Table 57: Effects Table for Keytruda for the treatment of first-line patients with PD-L1 TPS≥50% metastatic NSCLC (data cut-off: 9 May 2016)

Effect	Short Description	Unit	Pembrolizumab 200 mg Q3W	SOC chemotherapy	Uncertainties / Strength of evidence
Favourable Effects					
PFS	duration of survival without progression from randomization to PD or death whichever occurred first	months (95% CI)	10.3 (6.7,...)	6.0 (4.2, 6.2)	Results from final PFS analysis. Clinically meaningful improvement in all efficacy parameters.
OS	duration of survival from randomization to death regardless of cause	Nr of events (%) months (95% CI)	44 (29%) not reached (...,...)	64 (42%) not reached (9.4,...)	OS analysis performed with 63% of planned events (IA2): HR: 0.60 (0.41, 0.89), p-value=0.005, despite a not negligible rate of crossover (44%).
	OS rate at 12 months	%	69.9	54.2	
ORR	Confirmed CR + PR	% (95% CI)	44.8 (36.8, 53.0)	27.8 (20.8, 35.7)	
Response duration	Duration of CR/PR until documented PD	months (range)	not reached (1.9+-14.5)	6.3 (2.1+-12.6+)	
Unfavourable Effects					
Tolerability	drug related AEs	%	73.4	90	The safety of pembrolizumab positively compares with that of SOC chemotherapy.
	drug related Gr≥3 AE	%	26.6	53.3	
	drug related SAEs	%	21.4	20.7	
	death drug related	%	0.6	2	
	discontinuation drug related AEs	%	7.1	10.7	
Drug-related AEs	Incidence of Nausea	%	9.7	43.3	
	Incidence of Vomiting	%	2.6	20	
	Incidence of Fatigue	%	10.4	28.7	
	Incidence of Neutropenia	%	0.6	22.7	
	Incidence of Pneumonitis	%	5.8	0.7	

	Incidence of Infusion reactions	%	4.5	1.3	No new safety concerns
	Incidence of Hypothyroidism	%	9.1	1.3	
	Incidence of Hyperthyroidism	%	7.8	1.3	
	Incidence of Skin AEs*	%	3.9	0	

CI: Confidence Interval; HR: Hazard Ratio; LS: Least Squares; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 items; EORTC QLQ-L13: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Lung Cancer 13 items; * Psoriasis, Rash, Rash generalised, Rash macula-papular, Toxic skin eruption.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clinically significant improvement was reported with pembrolizumab compared to SOC, with a PFS gain of 4.3 months and 40% decreased risk of death. The advantage in OS was observed despite the not negligible rate of patients (44%) who crossed over to pembrolizumab, thus further emphasizing the contribution of pembrolizumab as first line treatment.
A lower rate of drug-related AEs, drug-related Grade ≥3 AEs, and treatment discontinuation due to drug-related AEs was observed in patients treated with pembrolizumab compared to SOC chemotherapy. The pembrolizumab safety profile is quite consistent with that of other PD-1 checkpoint inhibitors. No new pembrolizumab safety concern emerged.

3.7.2. Balance of benefits and risks

This is the first trial showing a clinically relevant advantage in PFS and OS compared to the recognized SOC chemotherapy in first line NSCLC patients. The pembrolizumab safety profile was consistent with that previously reported and overall positively compares with toxicity related to SOC chemotherapy in terms of frequency and severity.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

Conclusions

The overall B/R of Keytruda for the treatment of PD-L1 strongly positive (TPS≥50%) NSCLC patients is positive.

4. Recommendations

Outcome

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

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

Extension of Indication to include first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP version 4.2 was agreed during the procedure.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.