EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/546566/2016
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0007

Marketing authorisation holder (MAH): Merck Sharp & Dohme Limited

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

%CV	coefficient of variation of between-subject distributions of parameters
%SE	relative standard error (%)
ADA	anti-drug antibodies
AE	adverse event
AEOSI	adverse events of special interest
ALT	alanine transaminase
ALP	alkaline phosphatase
APaT	All Patients as Treated
AST	aspartate transaminase
AUC	area under the concentration-time curve
AUC0-28	area under the concentration-time curve from day 0 up to day 28
AUCss, 6wk	area under the concentration-time curve at steady state over a 6-week interval
CD	cluster of differentiation
CI	confidence interval
CL	Clearance
Cmax	maximum observed serum concentration
CR	Complete Response
CRA	commercial ready assay
CTA	clinical trial assay
Ctrough	concentration at the end of the dosing interval
CV	coefficient of variation
CYP	cytochrome P450
DCR	Disease control rate
DTL	drug tolerance level
ECG	Electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
Emax	maximum effect parameter
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set
FcRn	neonatal fragment crystallizable receptor

FFPE	formalin-fixed, paraffin embedded
GMR	geometric mean ratio
hERG	human ether-à-go-go-related gene
HRQoL	health-related quality-of-life
IHC	immunohistochemistry
irRC	immune-related Response Criteria
IC50	concentration at which 50% of maximum inhibition is achieved
IgG	immunoglobulin G
IL-2	Interleukin-2
Imax	maximum inhibition parameter
IPI	ipilimumab
IRC	Independent Review Committee
IV	Intravenous
KD	tumour reduction rate
KL	Tumour growth rate
mAb	monoclonal antibody
MD	multiple dose
MDRD	modification of diet in renal disease
N	Number
ORR	Objective Response Rate
PD	Progressive Disease
PR	Partial Response
SAE	Serious Adverse Event
TKI	tyrosine kinase inhibitor
TPS	Tumour Proportion Score

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 9 January 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 a new indication for Keytruda in second line Non-Small Cell Lung Cancer (NSCLC); as a consequence, sections 4.1, 4.2 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

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 CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

A Scientific Advice, related to clinical development in NSCLC and to the study design of the pivotal KEYNOTE- 010 (P010) trial, was received from the CHMP. The originally proposed study was revised taking into account most of the feedback received.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	9 January 2016
Start of procedure	30 January 2016
CHMP Rapporteur's preliminary assessment report circulated on	24 March 2016
CHMP Co-Rapporteur's preliminary assessment report circulated on	23 March 2016
PRAC Rapporteur's preliminary assessment report circulated on	1 April 2016
PRAC RMP advice and assessment overview adopted by PRAC	14 April 2016
CHMP Joint Rapporteur's updated assessment report circulated on	22 April 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	28 April 2016
MAH's responses submitted to the CHMP on	4 May 2016
CHMP Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 May 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 May 2016
PRAC RMP advice and assessment overview adopted by PRAC	9 June 2016
CHMP opinion:	23 June 2016

2. Scientific discussion

2.1. Introduction

Keytruda (pembrolizumab, MK-3475) is a humanized monoclonal antibody blocking 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-tumor activity. A Marketing Authorization was granted on July 17, 2015 in the EU as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.

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 non-small cell lung cancer (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).

In approximately two thirds of patients, NSCLC is diagnosed at an advanced stage. The standard of care for first-line treatment of advanced NSCLC is still platinum-based doublets, to which bevacizumab

and/or maintenance therapy in patients with good performance status can be added. In case of epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements, approved target therapy agents are available.

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 already approved for the treatment of locally advanced or metastatic squamous and non-squamous NSCLC after prior chemotherapy.

The current application is a type II variation to extend the indication in treatment of advanced Non-Small Cell Lung Carcinoma (NSCLC) in adults with tumours expressing PD-L1 who have received at least one prior chemotherapy regimen. The application is based on results from the study KEYNOTE-010 “A Phase II/III Randomized Trial of Two Doses of MK-3475 versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer”, with supportive data from the phase I trial KEYNOTE-001, cohorts C and F.

The MAH applied for the following indication:

KEYTRUDA is indicated for the treatment of advanced non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA.

The CHMP recommended the following 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 approved therapy for these mutations prior to receiving KEYTRUDA.

In order to be treated with Keytruda, patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see sections 4.2 and 5.1 of the SmPC).

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-P010V01 [Ref. 5.3.5.1: P010V01]	II-III	Worldwide Argentina, Autralia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Republic of Korea, Luthuania, Netherlands, Portugal, Russian Federation, Spain, Taiwan, United Kingdom, United States,	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 (NSCLC)	Randomized,parallel, open-label, active controlled, Phase 2/3 trial of intravenous (IV) pembrolizumab at two dosing schedules versus (vs) docetaxel in subjects with NSCLC with PD-L1 positive tumors who had experienced disease progression after platinum-containing systemic therapy.	Pembrolizumab: - 2 mg/kg every 3 weeks (IV) - 10 mg/kg every 3 weeks (IV) Docetaxel: -75 mg/m^2 every 3 weeks (IV)	Males/females Age: 18 and older Subjects with progressive, locally advanced metastatice non-small cell lung cancer who are positive for PD-L1 expression (>1% TPS)	Pembrolizumab 2 mg/kg: 345 subjects randomized, 339 treated Pembrolizumab 10 mg/kg: 346 subjects randomized, 343 treated Docetaxel 75 mg/m^2: 343 subjects randomized, 309 treated
3475-P001V04 [Ref. 5.3.5.2: P001V04]	I	Worldwide United States, France, Italy, Korea, Spain, United Kingdom, Canada, Norway, Taiwan, Australia	Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Cancer	Part C: Subjects with advanced NSCLC with prior systemic therapy, non-randomized Part F: F-1: Subjects with PD-L1 positive NSCLC with no prior systemic therapy, randomized to 2 dosing schedules F-2 positive, randomized: Subjects with PD-L1 positive NSCLC with prior systemic therapy, randomized to 2 dosing schedules F-2 negative: Subjects with PD-L1 negative NSCLC with prior systemic therapy, non-randomized cohort F-2 positive, non-randomized: PD-L1 positive NSCLC subjects with prior systemic therapy, non-randomized F-3: Subjects with PD-L1 positive NSCLC with prior systemic therapy, non-randomized	10 mg/kg Q3W Amendment 06 2 mg/kg Q3W 10 mg/kg Q2W and 10 mg/kg Q3W Amendment 07 onwards 10 mg/kg Q3W and 10 mg/kg Q2W 10 mg/kg Q3W and 10 mg/kg Q2W 10 mg/kg Q2W 10 mg/kg Q3W 2 mg/kg Q3W	Male and female subjects ≥18 years of age on the day of consent with Progressive Locally Advanced or Metastatic Non-Small Cell Lung Cancer	As of 23-Jan-2015 **Part C**: 38 subjects **Part F-1**: 2 mg/kg Q3W, 6 subjects 10 mg/kg Q2W, 46 subjects 10 mg/kg Q3W, 49 subjects **Part F-2 positive randomized:** 10 mg/kg Q2W, 113 subjects 10 mg/kg Q3W. 167 subjects **Part F-2 negative:** 10 mg/kg Q2W, 43 subjects **Part F-2 positive non-randomized:** 10 mg/kg Q3W, 33 subjects **Part F-3:** 2 mg/kg Q3W, 55 subjects

Table 1: Clinical Development Program for pembrolizumab in NSCLC

Study	Design	Subject Population	Primary Endpoint(s)	Status
KEYNOTE-001	Phase 1, open label study of pembrolizumab in multiple expansion cohorts	Progressive locally advanced or metastatic carcinomas, primarily melanoma or NSCLC; 5 parts with unique study objectives and designs: Part C and Part F enrolled subjects with NSCLC subjects exclusively	ORR	Enrollment complete; study ongoing
KEYNOTE-010	Phase 2/3 randomized study of two doses of pembrolizumab vs. docetaxel	NSCLC with PD-L1 TPS≥1%; experienced disease progression after platinum-containing systemic therapy	OS, PFS	Complete
KEYNOTE-021	Phase 1/2, open-label study of two dose schedules of pembrolizumab in combination with chemotherapy or immunotherapy (multiple cohorts; 2 parts)	Locally advanced or metastatic NSCLC	PFS, ORR	Enrollment ongoing
KEYNOTE-024	Phase 3 randomized, open-label study of pembrolizumab vs. platinum-based chemotherapy	Metastatic NSCLC with PD-L1 TPS≥50%; no prior systemic therapy for metastatic disease; no *EGFR* sensitizing mutations or *ALK* gene rearrangements	PFS	Enrollment complete; study ongoing
KEYNOTE-042	Phase 3 randomized open-label study of pembrolizumab vs. platinum-based chemotherapy	Advanced or metastatic NSCLC with PD-L1 TPS≥1%; no prior systemic therapy for advanced/ metastatic disease; no *EGFR* sensitizing mutations or *ALK* gene rearrangements	OS	Enrollment ongoing
KEYNOTE-091	Phase 3 randomized placebo-controlled study of pembrolizumab vs. placebo for one year after completion of surgical resection and adjuvant chemotherapy (if received)	Early stage NSCLC (Stage IB [T ≥ 4 cm] to II-IIIA) with complete surgical resection; PD-L1 TPS≥1%	DFS	Enrollment ongoing
KEYNOTE-189	Phase 3 randomized placebo-controlled study of platinum plus pemetrexed chemotherapy with or without pembrolizumab	Metastatic non-squamous NSCLC eligible for first-line therapy	PFS	Start-up

Abbreviations: *ALK* = *anaplastic lymphoma kinase*; DFS = disease-free survival; *EGFR* = *epidermal growth factor receptor*; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival; T = tumor size; TPS = tumor proportion score.

2.3.2. Pharmacokinetics

The updated clinical pharmacology results supporting this submission include:

• pharmacokinetic data from P010;

• updated exposure-response analysis for efficacy (tumor size, pooling data from P010 together with P001 in NSCLC)

• an updated program-wide evaluation of exposure-response for immune-related adverse events based on available data in NSCLC and melanoma patients (P001, P002, P006, and P010)

• An updated program-wide evaluation of immunogenicity.

The submitted analyses incorporating new data from the study P010 are shown in the following table.

Table 2: Analysis datasets, included study parts, key variables and data cut-off dates (new to this submission)

Analysis	Reference ID	Parts included	Total N included in analysis	Key variables included in dataset	Data cut-off date
Population PK (update 5)[f]	**0473LK**	**A, A1, A2, B1, B2, B3, C, D, F1, F2 and F3 from P001, and P002,,P006, P010**	**2856**	**MK-3475 concentration, baseline demographics**	**P001V02; 18-April-2014 P001V04, 23-January-2015 P002V01; 12-May-2014 P006V02; 03-March-2015 P010V01; 30-September-2015**
ADA (Melanoma + NSCLC)[f]	**047VSL**	**B1, B2, B3, D from P001[g], C and F from P001[g], and P002, P006, P010**	**2910**	**MK-3475 concentration, ADA sample results**	**P001V02; 18-April-2014 P001V04, 23-January-2015 P002V01; 12-May-2014 P006V02; 03-March-2015 P010V01; 30-September-2015**
Tumor size reduction NSCLC (update 5)[f]	**0473KZ**	**C, F1, F2, and F3 from P001 and P010**	**1151**	**Tumor size (sum of longest dimensions), MK- 3475 exposure parameters, baseline demographics**	**P001V04, 23-January-2015 P010V01; 30-September-2015**
PK-AE MEL and NSCLC (update 4)[f]	**0473LR**	**P001, P002, P006 and P010**	**2767**	**AE data (grouped), MK-3475 exposure parameters, baseline demographics**	**P001V02; 18-April-2014 P001V04, 23-January-2015 P002V01; 12-May-2014 P006V02; 03-March-2015 P010V01; 30-September-2015**

Absorption

Keytruda is administered via the i.v. route and is therefore completely (100%) bioavailable.

Distribution

The volume of distribution of Keytruda at steady state is small (7.4L).

Elimination

Keytruda is eliminated by catabolism. The systemic clearance of Keytruda is ~0.2 L/day (CV: 37%) and the terminal half-life (t½) is ~27 days (CV: 38%).

Dose proportionality and time dependencies

Exposure to Keytruda (Cmax and AUC) increased linearly dose proportionally within the dose range for efficacy (1 mg/kg to 10 mg/kg).

Upon repeated dosing, the clearance of Keytruda was found to be independent of time, and systemic accumulation was approximately 2.1-fold when administered every 3 weeks.

Special populations

The impact of intrinsic factors on pembrolizumab exposure from the definitive population PK analysis (report 0473LK) is described below (see also section 2.3.4 for a detailed description of population PK report 0473LK).

Exploratory analysis of covariates

Based on established exposure bounds, no clinically relevant impact on exposure was identified for other intrinsic factors in the NSCLC population, including age, gender, race, renal impairment (eGFR), or mild hepatic impairment and markers of FcRn capacity (baseline albumin). Exploratory covariate evaluations were performed as exemplified for age (see figure below).

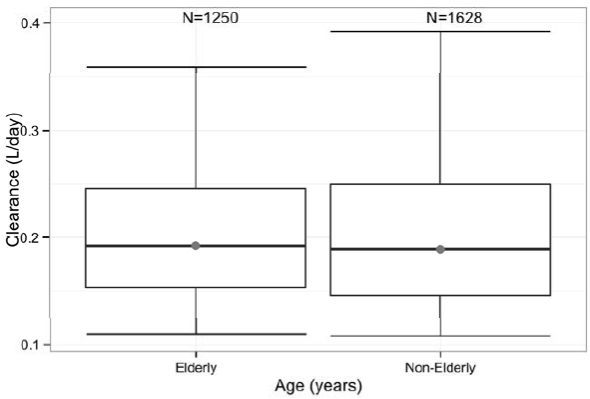
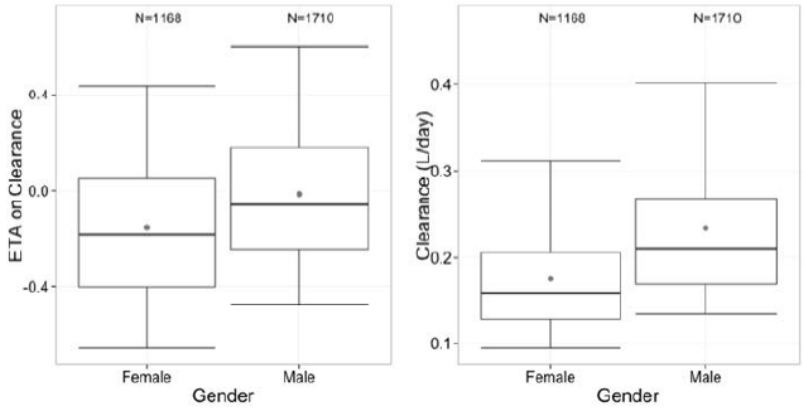


Figure 1: Effect of Age on pembrolizumab clearance (final data set)

The following shows plot of ETA on Clearance as well as Clearance versus gender.



Median for Clearance value for Male is 0.25 L/d whilst for female is 0.19L/d

Figure 2: Effect of Gender on pembrolizumab clearance

The newly included covariate race has a small impact on clearance (figure below).

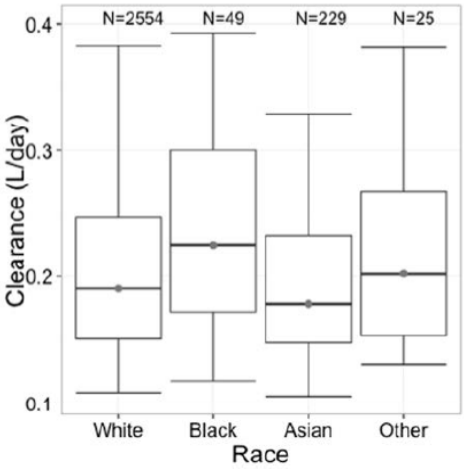


Figure 3: Effect of race on pembrolizumab clearance

Cancer type in the data set was classified in two categories: Melanoma and NSCLC.

The following displays the distribution of clearance and inter-individual variability versus cancer type. No impact of cancer type on clearance can be observed.

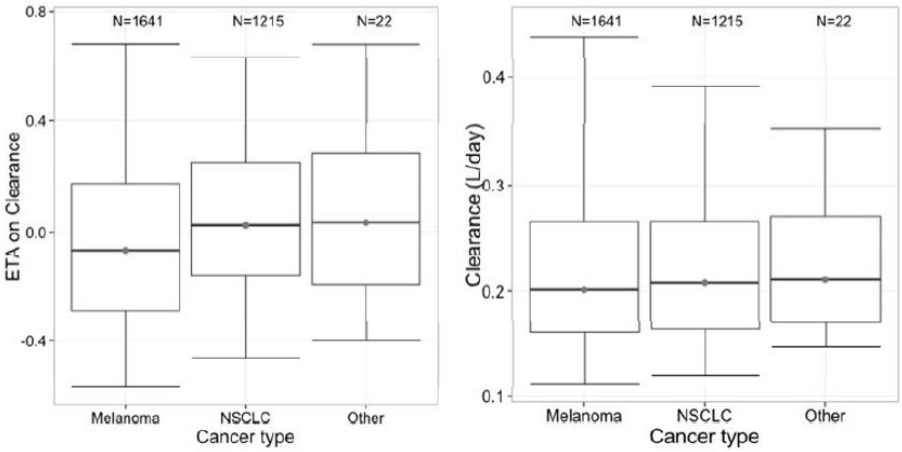


Figure 4: Distribution of cancer type versus PK parameters

The following figure illustrates the small difference in clearance between patients with different ECOG status.

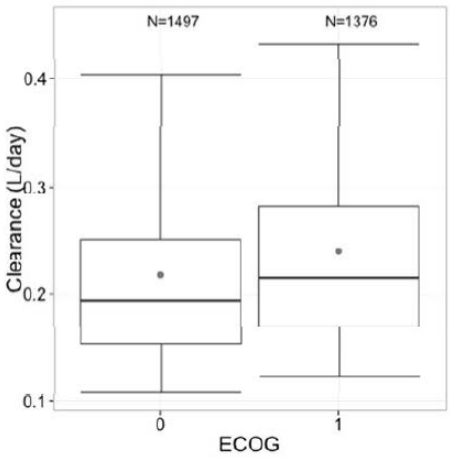


Figure 5: Effect of ECOG on clearance

Tumour burden showed a trend of correlation with clearance as well as inter-individual variability on clearance suggesting that Tumour burden might have an effect on clearance (figure below).

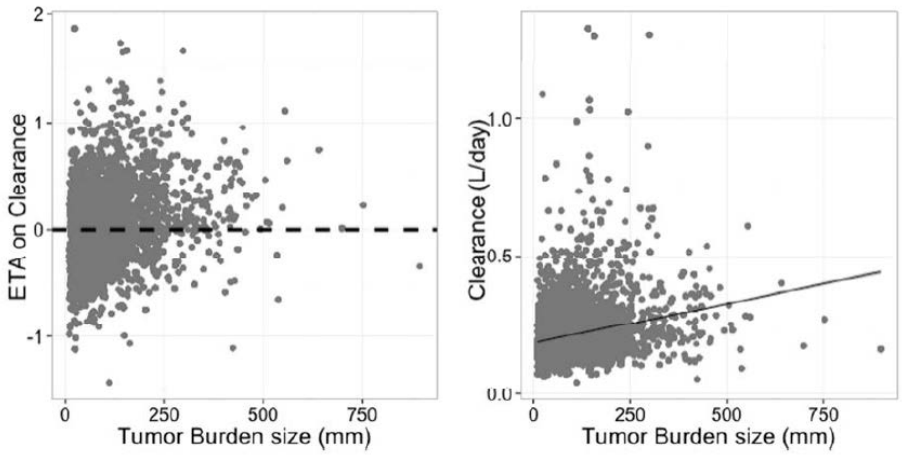


Figure 6: Effect of tumour burden on clearance

There appears to be no obvious trend between clearance and eGFR, either as a continuous covariate or as a categorical covariate broken out by impairment severity classification.

No effect on clearance is seen for mild and normal hepatic patients (Figure below, right). However for severe and moderate hepatic patients there appears to be an indication of a trend towards decreased clearance. Limited number of patients in Severe and Moderate hepatic categories were available in the pop PK analysis (table below).

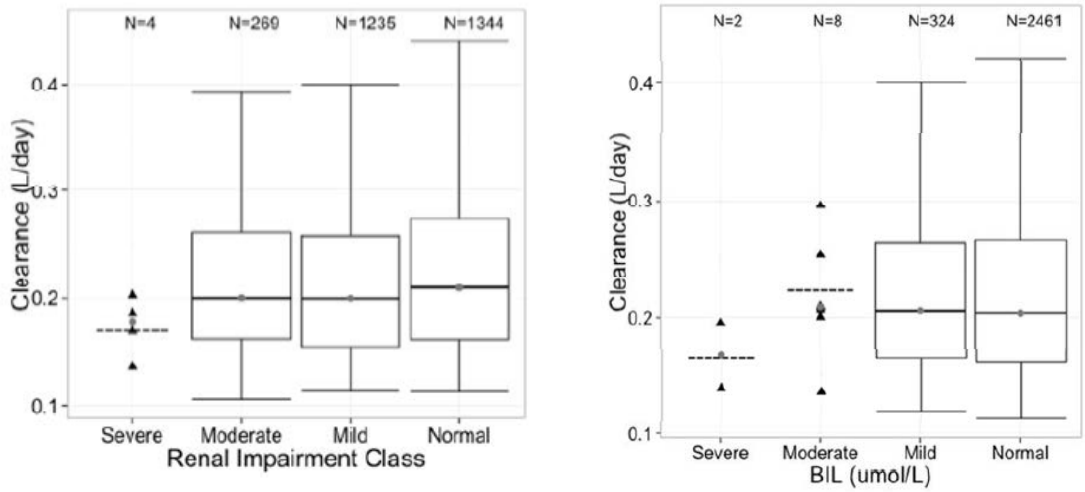


Figure 7: Effect of renal and hepatic impairment on pembrolizumab clearance

Table 3: Distribution of renal and hepatic impaired patients in the analysis dataset based on the classification by National Cancer Institute Organ Dysfunction Working Group.

Impairment		Normal	Mild	Moderate	Severe	Missing
Renal						
	[N]	1341	1219	267	4	25
	[%]	47	42.7	9.35	0.14	0.875
Hepatic						
	[N]	2445	319	8	2	82
	[%]	85.6	11.2	0.28	0.07	2.87

Statistical covariate analysis

Method

As an exploratory check intended to test stability of the key covariate findings, re-identification of covariates was performed using a stepwise selection procedure (Stepwise Covariate Model building, SCM) within PsN (psn.sourceforge.net). This procedure involves stepwise testing of linear and non-linear relationships in a forwards inclusion (ΔOFV of 6.63, $p < 0.01$ for 1 DF) and backwards exclusion (Δ OFV of 10.8, $p < 0.001$ for 1 DF) procedure. The categorical covariates Gender (on CL and Vc) and ECOG performance status, Co-administered drugs, Cancer type, Race, PDL1, Smoking Status on CL were tested as well as the continuous covariates Albumin and AST (on CL and Vc) and Bilirubin, eGFR, Tumour burden and Age on CL. Weight was included as structural covariate on clearance and volume.
The covariate 'prior IPI treatment status' was excluded from the present analysis, as it was specifically collected only in the melanoma trials. In addition, to all previous covariates, Race (White/Asian) was added due to the number of Asian subjects that were recruited in P010.
As in the previous analysis, highly correlated (ALP, ALT) and covariates with missing values (IgG) were excluded.

Results

The following table provides the final list of statistically significant covariates selected by the SCM algorithm.

Table 4: Results from covariate analysis

Covariates	Clearance	Central Volume
Age	No[a]	No
Gender	**Yes**	**Yes**
eGFR	**Yes**	No
AST	No	No
Albumin	**Yes**[b]	**Yes**
Bilirubin	Yes	No
Race	No	No
Cancer type	**Yes**	No
Use of glucocorticoids	No	No
BSLD	**Yes**	No
Baseline ECOG performance	**Yes**	No

[a]No means covariate was not found statistically significant according to SCM algorithm
[b]Yes means covariate was retained by SCM algorithm

Since no new covariates were selected compared to the previous population PK analysis, no assessment of clinical relevance of the covariate effects was performed. Specifically, the newly added covariate race was not picked up as having statistically-significant impact on clearance or volume of distribution and was therefore not assessed for clinical relevance.
The final model was fitted to 1000 bootstrap replicate datasets to assess consistency of the parameter estimates and their precision with those obtained in the previous population PK analysis. The mean parameter estimates and associated 95% CIs were along with the bootstrap estimates from the previous population PK analysis. Results indicate robust consistency between the two analyses, with confidence intervals for most of the parameter estimates showing large overlap.

Pharmacokinetic interaction studies
No pharmacokinetic drug interaction studies have been performed *in vitro* and *in vivo.*

Pharmacokinetics using human biomaterials
No pharmacokinetics using human biomaterials have been performed.

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 integrated immunogenicity evaluation has been performed across data from studies P001, P002, P006 and P010. The studies included in the analysis are summarized in the following table.

Table 5: Analysis datasets, included study parts, indication and data cut-off dates – Immunogenicity evaluation

Analysis	Parts included	Indication	Subjects included in dataset	Data cut-off date
P001 CSR V02[a]	B and D	Melanoma	653	18-April-2014
P001 CSR V04[b]	C and F	NSCLC	559	23-January-2015
P002 CSR V01	N/A	Melanoma	441	12-May-2014
P006 CSR V02	N/A	Melanoma	553	03-March-2015
P010 CSR V01	N/A	NSCLC	704	30-September-2015

a: In the CSR P001 V02, the data cut-off used for ADA samples was Dec 31st 2013 instead of the data cut-off date for other analysis April 18th 2014. At that time ADA samples up to data cut-off Dec 31st 2013 were available. In the current analysis the ADA samples with data cut-off April 18th 2014 are available and included in the analysis.
b: In the CSR P001 V04, the data cut-off used for ADA samples was Dec 31st 2013 instead of the data cut-off date for other analysis January 23rd 2015. At that time ADA samples up to data cut-off Dec 31st 2013 were available. In the current analysis the ADA samples with data cut-off January 23rd 2015 are available and included in the analysis.
N/A: Not Applicable

Data source [Appendix 7]

In the new database, a total of 11886 samples from 2910 subjects were available.

The immunogenicity categorization was to include only subjects who received treatment and had a post-treatment ADA sample available. The overall immunogenicity incidence was defined as the proportion of treatment-emergent positive subjects to the total number of evaluable subjects.

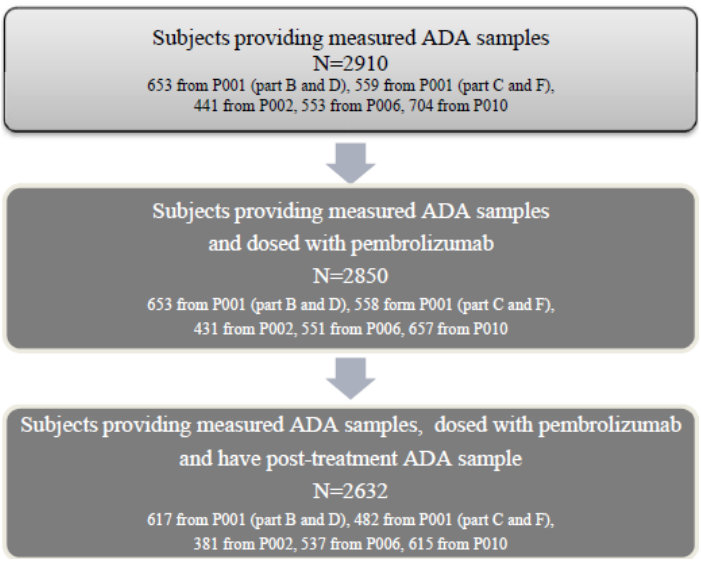


Figure 8: Flow charts of subjects included in immunogenicity analysis

The immunogenicity analysis as presented contained 2632 subjects (1535 melanoma and 1097 NSCLC assessable subjects).

Twenty nine (29) subjects had one or more samples that tested positive in the tier 2 confirmatory assay for antibodies against pembrolizumab. In the subgroup of NSCLC subjects, 16 of the 653 evaluable subjects tested positive for treatment-emergent antibodies to pembrolizumab during treatment with pembrolizumab (16 with treatment emergent positive status, 6 with non-treatment emergent positive status and 631 with negative immunogenicity status, red rectangles), yielding an incidence rate of 2.5% and compared to 631 negative and 444 inconclusive subjects.

An overview of the immunogenicity evaluation stratified by treatment and indication is presented in the table reported below.

Table 6: Summary of subject immunogenicity results (pooled analysis of P001, P002, P006, and P010)

Pooled analysis (P001, P002, P006, P010) Stratified by treatment			
Immunogenicity status	All treatments	Treatment	
		2 mg/kg	10 mg/kg
Assessable subjects[a]	2632	706	1926
Inconclusive subjects[b]	1545	136	1409
Evaluable subjects[c]	**1087**	**570**	**517**
Negative[d]	1058 (97.3%)	555 (97.4%)	503 (97.3%)
Non-Treatment emergent positive[d]	10 (0.9%)	7 (1.2%)	3 (0.6%)
Treatment emergent Positive[d]	19 (1.7%)	8 (1.4%)	11 (2.1%)

Pooled analysis (P001, P002, P006, P010) Stratified by Treatment and Indication					
Immunogenicity status	All subjects	2 mg/kg		10 mg/kg	
		Melanoma	NSCLC	Melanoma	NSCLC
Assessable subjects[a]	2632	**345**	**361**	**1190**	**736**
Inconclusive subjects[b]	1545	124	12	977	432
Evaluable subjects[c]	**1087**	**221**	**349**	**213**	**304**
Negative[d]	1058 (97.3%)	219 (99.1%)	336 (96.3%)	208 (97.7%)	295 (97.0%)
Non-Treatment emergent positive[d]	10 (0.9%)	2 (0.9%)	5 (1.4%)	2 (0.9%)	1 (0.3%)
Treatment emergent Positive[d]	19 (1.7%)	0	8 (2.3%)	3 (1.4%)	8 (2.6%)

Individual analysis (P010) Stratified by Treatment			
Immunogenicity status	All treatments	2 mg/kg	10 mg/kg
Assessable subjects[a]	615	309	306
Inconclusive subjects[b]	98	10	88
Evaluable subjects[c]	**517**	**299**	**218**
Negative[d]	507 (98.1%)	290 (97.0%)	217 (99.5%)
Non-Treatment emergent positive[d]	5 (1.0%)	4 (1.3%)	1 (0.5%)
Treatment emergent Positive[d]	5 (1.0%)	5 (1.7%)	0

a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the 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.

Data source [Appendix 7]

As reported in the table above, the observed incidence of treatment emergent ADA in evaluable subjects was 1.7% (19 out of 1087, green rectangles). Of note, the previously reported value in the melanoma indication was 0.4 %.

At this time, results from the neutralizing assay are available from 4 subjects. For one of these subjects that was negative at ADA assay, sample was inadvertently tested in Neutralizing Assay and resulted to be positive. The remaining three subjects were negative in the neutralizing assay.

Evaluation of drug tolerance level

Interference by pembrolizumab in the ADA assays may occur, especially at concentrations above the drug tolerance level. Therefore, samples with a negative test result in the screening or confirmatory anti-pembrolizumab assay could only be conclusively confirmed to be negative in the case of a pembrolizumab concentration below the DTL. Furthermore, the immunogenicity status of a subject could only be conclusively confirmed to be negative if all pre-treatment and post-dose samples were negative in the confirmatory assay for antibodies against pembrolizumab and if the concentration of pembrolizumab in the last post-dose sample was below the drug tolerance level.

At the recommended dosing regimen of 2 mg/kg, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level for about 81% of the subjects.

Table 7: Overview of subjects with pembrolizumab concentrations relative to the DTL of the ADA assay in the last post-dose sample

	Treatment		
	All Treatments	**2 mg/kg**	**10 mg/kg**
Assessable Subjects[a]	2632	706	1926
Last postdose sample: Pembrolizumab conc. ≥ DTL	1369 (52.0%)[b]	117 (16.6%)[b]	1252 (65.0%)[b]
Last postdose sample: Pembrolizumab conc. unknown	183 (7.0%)[b]	20 (2.8%)[b]	163 (8.5%)[b]
Last postdose sample: Pembrolizumab conc. < DTL	**1087 (41.0%)[b]**	**569 (80.6%)[b]**	**511 (26.5%)[b]**

DTL: Drug Tolerance Level of the ADA assay.
a: Assessable subjects are subjects treated with pembrolizumab and with at least 1 postdose sample available.
b: Denominator was the number of assessable subjects.

Data source [Appendix 7]

Impact of ADA on MK-3475 exposure

The pembrolizumab exposure for ADA positive subjects was similar to the exposure observed for negative subjects treated with the same dose regimen (data not shown).

QTc evaluation

No new data on QTc has been submitted.

2.3.4. PK/PD modelling

An extension of the population PK analysis (044WBG using P001, P002 and P006 studies and submitted as part of EMEA/H/C/003820/II/0002, CHMP opinion adopted on 1 April 2016) was conducted. The present analysis (report 0473LK) also includes data from 657 NSCLC patients from protocol P010. In total 2856 subjects were included in the final analysis with the objectives to:

• Assess the appropriateness of the existing Pop PK model to characterize concentration data from Protocol 010.

• Generate exposure predictions for patients in Protocol 010 to support exposure-response analyses.

• Investigate the effects of race on pertinent PK parameters

The parameters from the initial and updated models are compared in the following table.

Table 8: Parameter estimates of Final Model and comparison with parameter estimates from report 044WBG between brackets

Parameters	Estimates	% RSE	Shrinkage
CL (L/day)[a]	0.210 [0.202]	1.47 [1.71]	
Vc (L)[b]	3.46 [3.53]	0.76 [0.926]	
Q (L/day)	0.782 [0.75]	3.30 [4.18]	
Vp (L)	3.88 [3.85]	1.90 [2.15]	
α for CL and Q[c]	0.595 [0.578]	6.40 [7.98]	
α for Vc or Vp[c]	0.537 [0.492]	4.69 [6.26]	
Albumin on CL	-0.909 [-0.854]	6.97 [8.85]	
Bilirubin on CL	-0.053 [-0.064]	33.5 [27.6]	
BSLD on CL	0.101 [0.093]	9.78 [12.4]	
eGFR on CL	0.121 [0.14]	19.8 [23.4]	
Female/Male on CL	-0.161 [-0.17]	9.13 [10.1]	
Cancer Type (Melanoma=1/NSCLC=2) on CL	0.074 [0.143]	24.6 [17.3]	
ECOG=1/ECOG=0 on CL	0.067 [0.07]	26.3 [29.1]	
Albumin on Vc	-0.218 [-0.18]	17.2 [28.3]	
Female/Male on Vc	-0.133 [-0.147]	8.57 [8.84]	
Random Effect	**Estimates (CV%)**	**%RSE**	
IIV on CL or Q	0.128 (36.9%[d])] [0.132 (37%)]	4.38 [5.37]	13.4 [15.0]
IIV on Vc or Vp	0.042 [0.036 (19%)]	7.23 [9.69]	28.4 [33.2]
Residual Error	**Estimates**	**% RSE**	
Proportional	-0.282 -0.298	1.75 [1.83]	11.1 [10.8]

[a]$CL=0.21\ (WGT/75)^{0.595} x(ALB/40)^{(-0.909)}\ x(BIL/8.55)^{(-0.053)} x(BSLD/85)^{0.101}\ x(eGFR/88.67)^{0.121} x[(1-0.161)$ if female]x[(1+0.074) if NSCLC] x[(1+0.06) if BECOGN=1]

[b]$Vc=3.53(WGT/75)^{0.537}\ x(ALB/40)^{(-0.218)}$ x[(1-0.133) if female]

[c]α= power value for weight-based scaling

[d]Percentage of coefficient of variation (%CV)

[e]model file; run4197

RSE: Relative standard error, CL: clearance, V_c: central volume, Q: inter-compartmental flow, V_p: peripheral volume, IIV: inter-individual variability' WGT: weight, ALB: Albumin, BIL:Bilirubin, BSLD: Baseline Tumor burden, eGFR: Glomerular filtration rate, BECOGN; Baseline ECOG Numeric,

Goodness of fit plots of the final model and visual predictive check (VPC) were performed (data not shown).

The MAH has explored a series of structural PK models incorporating time-dependency in clearance.

Results (data not shown) showed that there is a pattern in time-dependent clearance with response categories (progressive disease, stable disease, complete and partial disease).

Exploratory Re-check of Covariate Findings

To confirm consistency in covariate relationships between the model based on the updated dataset and the previous analysis, an exploratory covariate analysis was conducted. In addition to all previous covariates, RACE (White/Asian) was added due to the number of Asian subjects recruited in P010 (see table below).

Table 9: Results of the final covariate evaluation

Covariates	Clearance	Central Volume
Age	No[a]	No
Gender	**Yes**	**Yes**
eGFR	**Yes**	No
AST	No	No
Albumin	**Yes**[b]	**Yes**
Bilirubin	Yes	No
Race	No	No
Cancer type	**Yes**	No
Use of glucocorticoids	No	No
BSLD	**Yes**	No
Baseline ECOG performance	**Yes**	No

[a]No means covariate was not found statistically significant according to SCM algorithm
[b]Yes means covariate was retained by SCM algorithm

Bootstrap

The final model was also fitted to 1000 bootstrap replicate datasets to assess consistency of the parameter estimates and their precision with those obtained in the previous population PK analysis (data not shown).

Simulations to Illustrate the PK Profile of Pembrolizumab

The model was used to simulate typical concentration-time profiles for different dosing regimens of pembrolizumab. This included a comparison of the exposures that would be generated by a fixed dose regimen of 200 mg Q3W with those for the weight-based doses included in the current dataset.

The table below presents values of derived parameters (C_{max}, C_{trough}, AUC) at steady state obtained from model-based simulations. Typical patient receiving dosing regiments of 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W were simulated 1000 times using the final model.

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

Exposure parameter	pembrolizumab dose regimen		
	2 mg/kg Q3W	200 mg Q3W	10 mg/kg Q3W
C_{max} (µg/mL)	67.5 (48.1; 98.1)	90 (62.6; 130)	337 (240; 488)
C_{trough} (µg/mL)	23.5 (10.4; 47.3)	31.2 (13.2; 63.2)	117 (52.1; 236)
AUCss, 6-week (µg·day/mL)	1434 (796; 2568)	1905(1037; 3415)	7190 (4001; 12775)

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.

The following figure presents comparison of predicted pembrolizumab concentration-time profiles between previous analysis (PA) [044WBG] and Protocol 10 (P10) from the current model for the dosing regimen of 2 mg/kg Q3W.

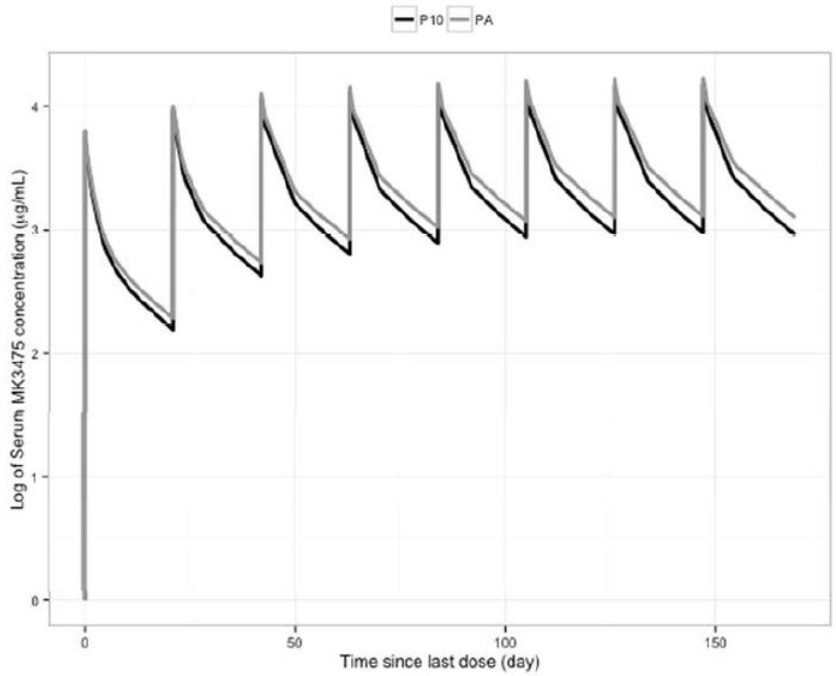


Figure 9: Comparison of pembrolizumab PK-profile between PA and (P10) patient for dosing of 2 mg/kg Q3W dosing regimen

Exposure-response analysis

A Model-based analysis of the relationship between pembrolizumab exposure and efficacy in patients with NSCLC in PN001 and PN010 was performed (report 0473KZ)

Data for this analysis were derived from patients treated on cohorts C and F of Protocol 001 (PN001) and pembrolizumab-treated arms of Protocol 010 (PN010). In total, 550 subjects received pembrolizumab treatment on PN001 and 682 on PN010. The tumour size exposure-response modelling analysis dataset consists of a subset of these 'all patients as treated' (APaT) set including only those patients who had a baseline tumour size assessment and were evaluable for pharmacokinetic analysis.

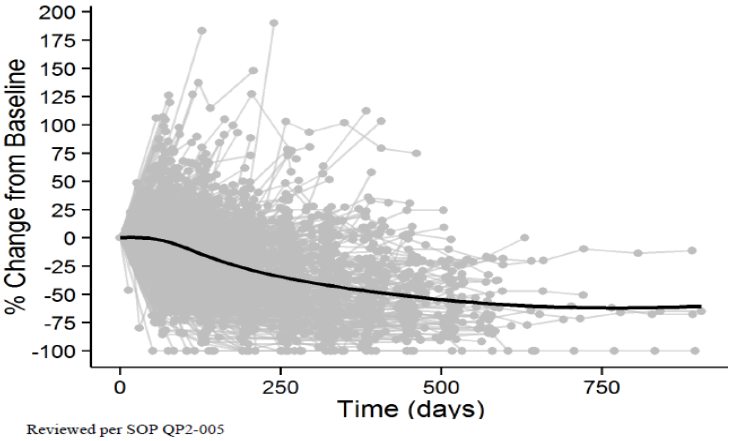
Results:

There were 4,554 observations from 1,151 patients comprising the FAS dataset used in the tumour size exposure-response analysis described in this report. Of these 1,151 patients, 84 had a tumour size measurement at a follow-up of at least 28 weeks but no measurements within a 26-30 week (i.e. 28 ± 2 week) window. 697 patients in the dataset had maximum follow-up less than 28 ± 2 weeks. This left 370 patients who had at least one tumour size measurement within 26-30 week (i.e. 28 ± 2 week) from baseline and also an $AUC_{ss\text{-}6weeks}$ value. Of these 370 patients, 173 were considered TPS ≥50%, 156 were TPS 1-49%, 25 were TPS<1% (PD-L1 negative), and 16 were PD-L1 unknown.

Exploratory plots were generated to gain insight in the overall pattern of change in tumour size over time and to investigate trends of response to treatment vs. exposure. The visual exploration was supported by the results of a simple linear regression where appropriate.

Exploration of longitudinal tumour size for NSCLC

Plots of tumour size change versus time illustrate the individual patterns of NSCLC longitudinal tumour size during treatment with pembrolizumab are shown below.



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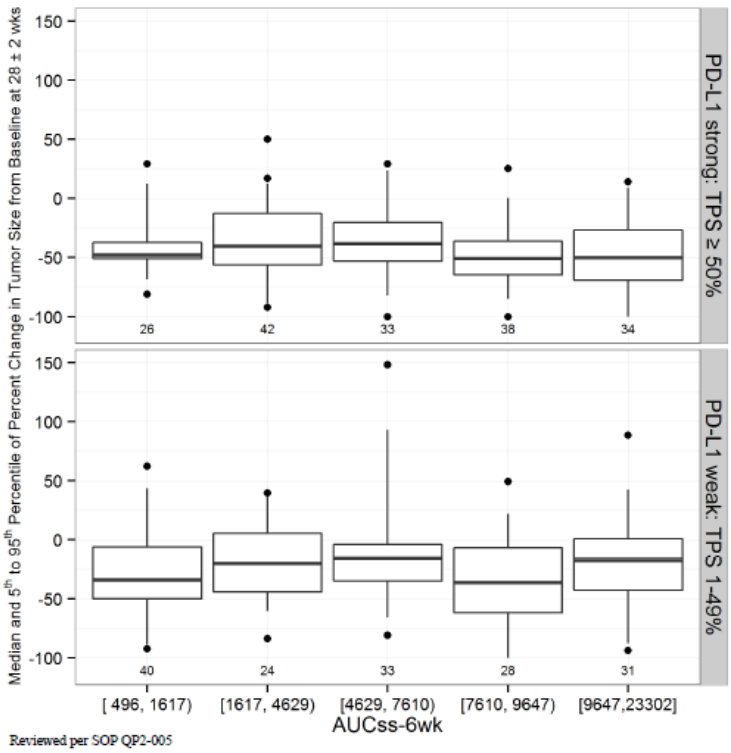
The black solid line is a loess smooth showing the overall trend in observed data.

Figure 10: Observed percent change in tumour size (sum of the longest diameter, SLD) from baseline vs. time since baseline scan for all patients

Exploration of Exposure-response at Week 28

Percent changes of tumour size from baseline at 28 weeks after the baseline scan versus pembrolizumab $AUC_{ss\text{-}6weeks}$ and stratified by PD-L1 expression were explored (data not shown).

The linear regression slope estimates for prior treated were modest and not significantly different from 0 ($p>0.05$) and there was no clear evidence of exposure dependency in response as also shown by the similar distribution of individual tumour response values across the $AUC_{ss\text{-}6weeks}$ quintiles (see figure below)).



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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 11: 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

Exposure response and covariate analysis:

The covariate analysis was performed to identify factors that are influential in determining response. An overview of patients and study specific factors that were pertinent to the covariate analysis is shown in the table below.

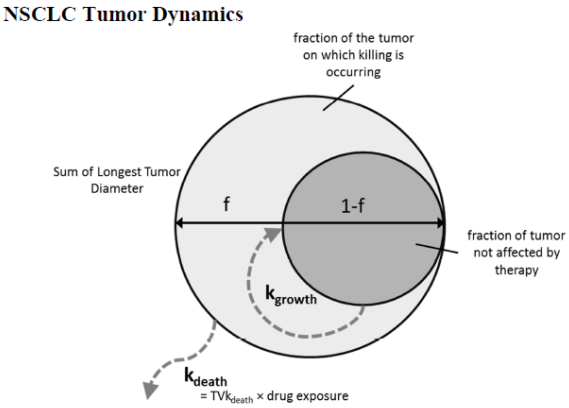
Table 11: Overview of categorical covariates for NSCLC population with observable baseline tumour size measurement (N=1151)

Covariates	Number of Subjects(%)	Total
Baseline ALK mutational status		
Wild Type	1011 (87.84%)	
Mutation/translocation	13 (1.13%)	
Unknown	127 (11.03%)	1151
Baseline EGFR mutation status		
No	957 (83.15%)	
Yes	125 (10.86%)	
Unknown	69 (5.99%)	1151
Baseline ECOG Numeric		
[0] Normal Activity	397 (34.49%)	
[1] Symptoms, but ambulatory	752 (65.33%)	
Unknown	2 (0.17%)	1151
Baseline Smoking Status		
Non-smoking	238 (20.68%)	
Former/current smoking	913 (79.32%)	1151
Gender		
Male	662 (57.52%)	
Female	489 (42.48%)	1151
Number of Lines Prior Therapy		
Treatment Naive	98 (8.51%)	
1 prior treatment	534 (46.39%)	
2 prior treatments	252 (21.89%)	
3 prior treatments	151 (13.12%)	
4 or more prior treatments	116 (10.08%)	1151
PD-L1 expression level: (PDL1SWN)		
PDL1 Strong	427 (37.1%)	
Weak	576 (50.04%)	
Negative	91 (7.91%)	
Unknown	57 (4.95%)	1151
Race		
American Indian or Alaskan Native	6 (0.52%)	
Asian	201 (17.46%)	
Black or African American	39 (3.39%)	
Multiracial	5 (0.43%)	
Native Hawaiian or other Pacific Islander	3 (0.26%)	
White	879 (76.37%)	
Unknown	18 (1.56%)	1151

Evaluation of covariate effects on tumour size model parameter estimates

An automated stepwise forward inclusion ($p<0.01$) / backward elimination ($p<0.001$) elimination procedure was applied to test for significant covariates on the model parameters using the Stepwise Covariate Modelling (SCM) routine implemented in PsN.

The figure below illustrates the structural components for describing NSCLC tumour dynamics:



$$Tumor\ size = Baseline * \left[(1-f) * e^{kgrowth * \text{time}} + f * e^{-kdeath * \max(0, time - delay)}\right]$$

f = fraction of the tumour on which removal is occurring (individual parameters assumed to be logit normally distributed and thus constrained between 0 and 1).

k_{growth} = Tumour growth rate (constrained to be positive, with individual parameters lognormally distributed)

'Baseline' is the baseline tumour size. In the current implementation, this is fixed to observed value and not estimated.

k_{death} = Tumour kill rate (constrained to be positive, with individual parameters log normally distributed) that captures the kinetics of the net tumour removal in the responding portion of the tumour

delay = Delay in the onset of drug activity for tumour killing interpreted as the time required for immune system activation (constrained to be positive, with individual parameters log normally distributed)

max(0,time-delay) = To constrain the system to avoid evaluating the model at negative times (i.e. tumour size before baseline), any scenario where delay>time, time = 0

Figure 12: Structural components describing NSCLC tumour dynamics

The final results of the Stepwise Covariate Modelling are summarised in the table below.

Table 12: Documentation of the key SCM results

SCM Procedure Summary			
Forward Addition	Relationship added during each round	Change in OFV	p-value
	PD-L1* on f	58	1.68E-12
	EGFR** on k_{growth}	17	0.000216
	Age on k_{growth}	14	0.000151
Backward Elimination	Relationship dropped during each round	Change in OFV	p-value
	None		
*PD-L1 expression level grouped into one of four categories using a proportion score (TPS) reflecting the percentage of tumor cells exhibiting membranous staining. **EGFR treated as a binary variable, either mutated or wild-type.			

Examination of plots of the distributions of *post hoc* individual parameters against covariates (see figure below) indicate that higher levels of PD-L1 expression are associated with a higher fraction of tumour being responsive to therapy, and mutated EGFR status, and younger age are associated with higher k_{growth}.

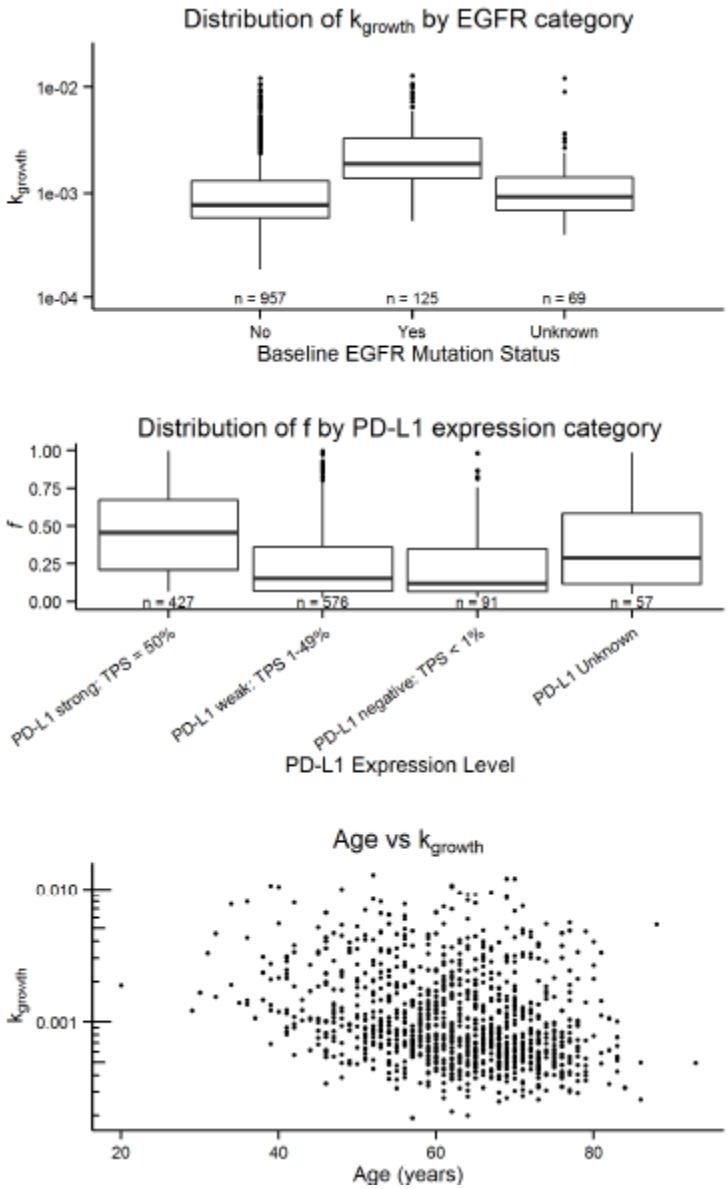
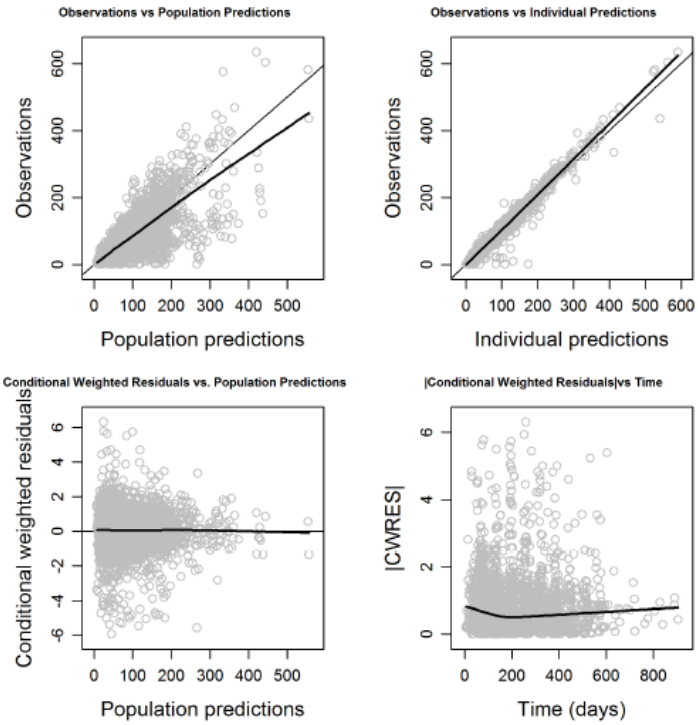


Figure 13: Distributions of final model post-hoc parameter distributions against covariate levels that were identified as being statistical significant during the automated covariate search

Final tumour size model

Goodness of fit plots and VCP for the final model are shown below:



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Top left, Observed versus population predicted tumor size (SLD; mm) for the final model. Top right, Observed versus individual predicted tumor size for the final model. Bottom left, Conditional weighted residual (CWRES) versus population predicted tumor size for the final model. Bottom right, CWRES versus time in days for the final model. Solid black lines in in all panels represent the LOWESS smooth and the solid grey line in top two plots represent line of unity. Time is in days since baseline scan.

Figure 14: Goodness-of-fit plots of the NSCLC tumour size (final model)

Exposure-response Simulations

Per RECIST 1.1 criteria, a maximum of five representative target lesions (and up to two lesions per organ) are identified and monitored for follow-up. Target lesions are evaluated based on change in SLD and patient response classified as either Complete Response (CR; disappearance of all target lesions), Partial Response (PR; 30% decrease in SLD of target lesions), Progressive Disease (PD; 20% increase in SLD of target lesions), and Stable Disease (SD; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD).

Simulations were first conducted at 1 mg/kg Q3W, 2 mg/kg Q3W, 10 mg/kg Q3W and 200 mg Q3W, drawing from subjects with PD-L1 TPS ≥50%, and from subjects with TPS≥1% (data not shown).

The simulated median response rates for PD-L1 TPS ≥50% patients and TPS ≤1% at week 28 were reported below.

Table 13: Simulated median response rates at week 28

	TPS ≥50%	TPS ≤1%
2 mg/kg Q3W	36.5% (90% CI: 31.6 – 41.1%)	27.3% (90% CI: 23.3 – 31%)
10 mg/kg Q3W	40.1% (90% CI: 35.7 – 44.8%)	30.3% (90% CI: 26.2 –33.7%)

Exposure-Adverse Event analysis

An exposure-adverse event analysis of pembrolizumab in a pooled dataset of patients with advanced melanoma and NSCLC form P001, P002, P006 and P0101 studies was performed (report 0473LR) to further characterize the exposure response relationship for pembrolizumab for relevant adverse events

in a pooled dataset across melanoma and NSCLC indications and to estimate the impact of other predictors on the occurrence of the adverse events of interest.

Data from 2530 patients, who received at least one dose of pembrolizumab and had a measured baseline tumour value, was used for this exposure safety analysis. Consistent with overall safety analyses presented elsewhere, a group of AEs of special interest (AEOSI) was defined, as a broad category of potentially immune related adverse events, excluding mild dermatological disorders. The AEOSI group was used as the dependent variable in this analysis.

Simulation

Simulations were used to characterize the typical probability of experiencing an AEOSI event as a function of exposure taking into account the estimated parameter uncertainty from the variance-covariance matrix and the influence of any significant covariate from the final model. Simulations were performed on the basis of the final model.

Covariates

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. A specific component of the covariate analysis was to assess the importance of time (duration of treatment) for the occurrence of AEOSI.

Exploratory analysis

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 same covariates as mentioned above).

The AUC values were divided into bins based on the percentiles and the number of bins depended on the total number of patients in order to have sufficient patients per bin or percentile.

Results

The results of the stepwise covariate analysis (first forward addition, data not shown) 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.

The table reported below summarizes the estimated parameters from the final model.

The inclusion of the covariate for treatment duration rendered the linear exposure response relationship insignificant (p=0.56 based on log likelihood ratio test versus a model with the slope value fixed at zero), as also indicated by the large % relative standard error (RSE) for the parameter estimate.

Table 14: Parameter estimates of the final AEOSI logistic regression model

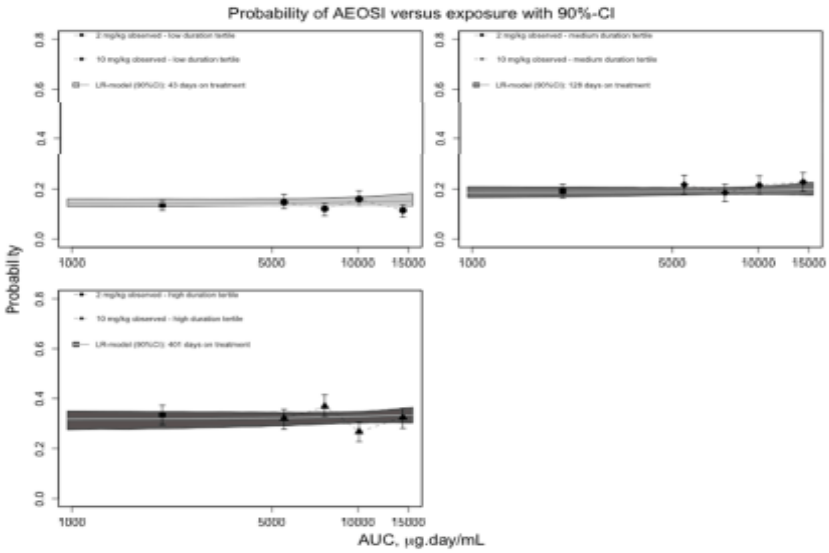
Parameter	Estimate	RSE (%)
Intercept	-1.18	8.87
Slope (AUC effect)	0.00000581	173
Treatment duration on intercept	-0.00232	16.9

Apart from the exposure-response slope, the other two parameters (intercept and effect of treatment duration on intercept) were estimated with good precision (low %RSE).

When forcing the non-significant regression slope with AUC on the final model, this was estimated to be 0.00000581 mL/(µg.day) (173% RSE). This translates into predicted probabilities of having a potentially immune related AE ranging from 18.6 to 19.7% for the 10th and 90th percentiles of AUC6wks values, respectively, in the pooled analysis dataset.

Model Qualification

Before using the logistic regression model for simulation purposes a visual predictive check (VPC) for the final model based on the full dataset. Data sets were simulated based on the estimates of the parameters and the accompanied uncertainties from the final model. The VPC was performed by simulating 10000 subjects. The 5th, 50th and 95th-percentiles were calculated from the simulated profiles and were super-imposed on the raw data (divided into different bins: one for 2 mg/kg and 4 equally sized bins for 10 mg/kg, each for three different categories of treatment duration) to allow assessment of model predictability. The VPC for the final model including a non-significant exposure to pembrolizumab and incidence of AEOSI is displayed below.



Note: Markers represent observed incidence of AEOSI for different AUC bins – AUC estimates associated with 2 mg/kg treatment or quantiles of AUC estimates associated with 10 mg/kg. Error bars represent 95% confidence interval of the incidence at each AUC bin.

Figure 15: Visual predictive checkof the final logistic regression model including a non-significant exposure-response relationship for the incidence of AEOSI

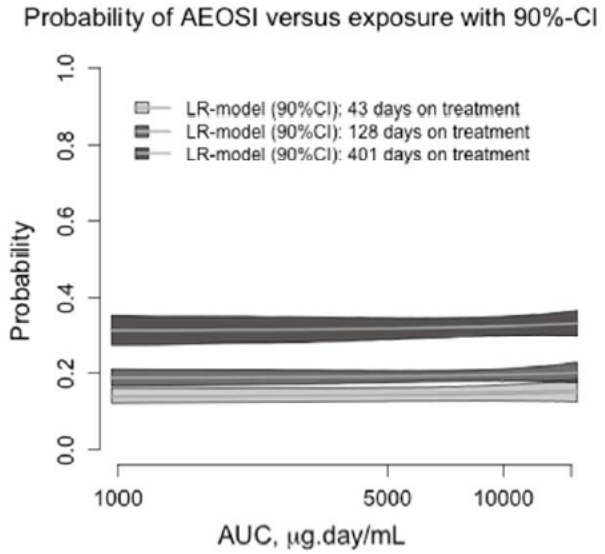
SIMULATIONS

Data Sets

The simulation datasets included 10000 subjects and exposure as the predictor variable. In addition, treatment duration was included, since it was a significant covariate in the model.

Simulation Results

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



The median (90% CI) simulated probability of experiencing an AE of the AEOSI group during 199 days of treatment (median treatment duration in dataset) for an exposure equal to the median AUC6wks for 2 mg/kg Q3W, 10 mg/kg Q3W or 10 mg/kg Q2W was 0.19 (0.17 – 0.21), 0.19 (0.18 – 0.21) and 0.20 (0.18-0.22), respectively. Thus, simulations indicate AEOSI occurrence to remain similar with increasing exposure.

Figure 16: Simulated probability of experiencing an AE for the AEOSI group in function of exposure and duration of treatment with associated 90% CI's

2.3.5. Discussion on clinical pharmacology

An updated clinical pharmacology dossier was submitted as part of this application.

Immunogenicity evaluation

An integrated immunogenicity evaluation has been performed across data from studies P001, P002, P006 and P010. The immunogenicity analysis as presented in this report contained 2632 subjects (1535 melanoma and 1097 NSCLC assessable subjects). The observed incidence of treatment emergent ADA in evaluable subjects was 1.7%, slightly increased relative to previously reported values (0.4 %) in melanoma indication. This slight higher incidence of ADA in NSCLC relative to the melanoma indication is likely the result 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 and the considerably longer treatment durations included in the current analysis.

At the recommended dosing regimen of 2 mg/kg, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level (<DTL) for about 81% of the subjects. Considering all treatments regimen, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level for about 41% of the subjects and for the dosing regimen of 10mg/kg the percentage of subjects with a pembrolizumab concentration <DTL in the last post-dose samples was of about 27%.

The new assay with this high drug tolerance level allows conclusive assessment of the immunogenicity potential of pembrolizumab based on trough samples in 81% of patients at the proposed dose regimen of 2 mg/kg Q3W. At the dose of 10 mg/kg results from a high percentage of patients resulted inconclusive, but also considering the clinical data supporting the use of the 2 mg dose, this issue is no longer pursued.

The MAH is actually validating a new designed assay for the evaluation of neutralizing antibody (only data from 4 of the positive subjects are available at present). This validation will be finalized by end of 2Q 2016 and the MAH will submit the final results by 3Q 2016 (see RMP).

The pembrolizumab exposure for ADA positive subjects was similar to the exposure observed for negative subjects treated with the same dose regimen as already observed in the previous analysis. There was no evidence of an altered pharmacokinetic with anti-pembrolizumab binding antibody development.

Population PK Analysis

An extension of the population PK analysis was conducted. The present analysis (report 0473LK) has built on the previous one that was updated and expanded to include data from 657 NSCLC patients from protocol P010 for a total of 2856 subjects included in the final analysis. Parameter estimates from both models are very similar.

The addition of PK data from P010 did not alter the previous population PK data for pembrolizumab (report 044WBG) in a significant way. Race (white or Asian) as a covariate did not have a statistically significant impact on clinical exposure.

Most intrinsic factors seem to have no relevant impact on pembrolizumab exposure (clearance). Specifically, age has no impact on exposure. Gender (independent of body weight), tumour type, renal and hepatic impairment, disease and albumin, while statistically significant, have at most small and not clinically relevant impact on exposure based on the established clinical bounds.

Visualization of the impact of albumin on clearance has been provided further to CHMP request. Provided data show that the lower the albumin level, the higher the corresponding clearance. Clearance values have been stratified by low (< 0.35 g/dL) and normal range albumin (> 0.35 g/dL). Post-hoc median clearance value in subjects with low albumin is approximately one third higher compared to subjects with normal range albumin. The MAH's explanation that albumin and the associated clearance variations likely reflect variation in disease severity (extent of cachexia and enhanced catabolism as a marker of end-stage cancer) is plausible. Data from subjects with severe hepatic and renal impairment were too sparse to draw a clinical conclusion from the data with respect to severe impairment. The influence of bilirubin as a marker for hepatic impairment could be associated with albumin.

The effect of all statistically significant covariates was judged clinically not important, as the geometric mean ratio (GMR) of exposures and their computed 95% CIs remained within the established clinical bounds interval of 0.5 to 5, based on clinical dose- and exposure-response data. No high correlations were found between Albumin and Bilirubin (i.e. correlation coefficient=0.088) or any of the other covariates included in the formal covariate testing.

PK/PD modelling

Visual predictive checks were carried out to check the ability of the model to describe the new data from P010; those were stratified by dose. As acknowledged by the MAH, the VPCs demonstrate an under-prediction of pembrolizumab concentration at later time point. Further to the CHMP request, the MAH evaluated the potential for time-dependency in pembrolizumab PK to account for the discrepancy demonstrated by the VPC. An exploratory Kaplan-Meier of OS showed that the overall survival was associated with pembrolizumab clearance but not exposure (lower pembrolizumab clearance is associated with improved survival) and subjects with an initial higher CL tend to stay in the trial for shorter duration and therefore contribute less to PK concentration-time data than patients with lower CL. A series of structural PK models incorporating time-dependency in clearance have been explored. Results showed that there is a pattern in time-dependent clearance with response categories

(progressive disease, stable disease, complete and partial disease), consistent with the hypothesized association between CL and OS.

It is assumed that all patients starting treatment have higher clearance values probably because they are in a more advanced cachectic state (hyper-catabolism) associated with a more severe disease. If patients have a beneficial response to the drug, the hyper-catabolism may be reduced (cachectic state may be improved), while the cachectic state and so the hyper –catabolism increases in progressing patients. It can be hypothesised that variations on clearance (the dependency of clearance on albumin levels has also been shown) reflect variations in disease severity (extent of cachexia and hyper-catabolism) is possible.

As acknowledged by the MAH, the ETA shrinkage of the empirical Bayes estimates from the exposure-response model of tumor size is moderate to high. Shrinkage was assigned to an unavoidable effect of sparse and heterogeneous data available at individual patient level. Provided qq plots showed deviations from normality of the random effect distributions on k_{growth} (ETA1), fraction dying, f (ETA3) and especially k_{death} (ETA2). Given that some shrinkage appears to be unavoidable, model predictions should be trusted with caution.

Exposure-response analysis

A 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 was performed (report 0473KZ). There was no clear evidence of exposure dependency in response as also shown by the similar distribution of individual tumour response values across the $AUC_{ss\text{-}6weeks}$ quintiles. Plots of simulated response rate show that there is only a light exposure-response dependency in tumour size response across doses ranging from 2 mg/kg Q3W to 10 mg/kg Q3W. There is a little trend of increase in response and a parallel little decrease in progression both in patients with PD-L1 TPS ≥50% than in patients with PD-L1 TPS ≤1%.

The potential for exposure-dependency in OS in NSCLC patients from P010 was investigated using exploratory Kaplan-Meier (K-M) plots, stratified by $AUC_{ss\text{-}6weeks}$ quartile, thus comparing the OS with CL and exposure. The analysis considered a total of 651 patients (324 treated with a dose of 10 mg/kg Q3W and 327 patients with a dose of 2 mg/kg Q3W). Presented data show that the higher dose of 10 mg/kg Q3W has no noticeable beneficial effect in comparison to 2 mg/kg Q3W. Within each dose group, there appears to be a strong relationship between AUC and OS. Irrespective of dose, a high AUC (low clearance) is associated with higher rate of overall survival (OS).

OS of all four quartiles are comparable per dose group. In the pooled analysis, the survival curves associated within each quartile (e.g. 1st quartile of $AUC_{ss\text{-}6weeks}$ from the 2mg/kg dose versus the 10 mg/kg dose) are similar with overlapping confidence limits, despite the observed 5-fold difference in $AUC_{ss\text{-}6weeks}$ values. Moreover, the 2nd and 4th quartiles of AUC of the combined analysis (2 and 10 mg/kg doses) shows the lowest CL value together with the improved OS relative to the 1st and 3rd quartiles of AUC, suggesting that exposure-OS relationship is strongly associated with pembrolizumab's clearance rather to exposure.

Secondly, the lack of a clear exposure-response relationship was also demonstrated by simulated median response rates at week 28, where the predicted proportion of patients with progressing tumour growth has been shown to be quite similar across wide dose ranges and close to the maximal response plateau of efficacy at a 2 mg/kg Q3W dose. Thus, patients with low exposure (Q1, 2 mg/kg and 10 mg/kg group) regardless of PD-L1 expression have lower benefit regarding OS, but the data clearly indicate that dose adjustment would not alter this situation.

Subject age, EGFR mutation and PD-L1 expression status are significant predictors of tumour size response as suggested by the final results of the stepwise covariate model, and no other patient specific factors were found to be predictive of tumour size parameters.

Exposure-Adverse Event analysis

An exposure-adverse event analysis of pembrolizumab in a pooled dataset of patients with advanced melanoma and NSCLC form P001, P002, P006 and P010 studies was performed (report 0473LR).

The simulated analysis as well as the exploratory plots analysis demonstrated the absence of exposure-response relationship supporting the flat exposure-response of pembrolizumab for these types of AEs (AEOSI) within the tested dose range of 2 to 10 mg/kg.

In the updated graphs provided by the MAH, all the binned observed data fall within (or near) the 90% confidence interval from the model.

IHC to detect PD-L1 expression

To evaluate the clinical performance of CRA a bridging study was conducted with a retrospective testing of banked tissue samples using the CRA based on clinical outcomes from study P010 that enrolled on a Clinical Trial Assay. Overall, the bridging analysis to compare the two assays (CTA and CRA) shows an unidirectional trend versus a more stringent selection with the new assay, with the most evident discordance observed for 136 specimens resulted negative (TPS<1%) with CRA and previously classified as weakly positive (1-49%) with CTA. Analyses of OS and PFS based on PD-L1 expression detected by the new assay provided slightly stronger results than those obtained with the primary efficacy analysis conducted using CTA, especially in the overall population, and support the use of the new assay for the selection of patients. Whether, these results are driven solely by the difference in the monoclonal mouse anti PD-L1, or also by other factors is difficult to establish. Differences in the sample type used (tissue from resection vs biopsies) could have influenced the results.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics of pembrolizumab has been mainly characterised by means of a population PK model which is considered acceptable.

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

- To submit the validation report for anti-pembrolizumab neutralizing antibody assay by September 2016

2.4. Clinical efficacy

This application to extend the Keytruda therapeutic indication for the treatment of second line or greater advanced NSCLC with PD-L1 expression is based on efficacy results from the pivotal phase II/III trial KEYNOTE-010, comparing two pembrolizumab doses (2 mg/kg and 10 mg/kg, every 3 weeks) versus docetaxel. Data from the phase I study KEYNOTE-001 Cohorts C and F, enrolling previously treated NSCLC patients, were also submitted as supportive.

Study ID/ centres/ locations	Study design	Treatment	No of pts planned/ random/ treated	Demographics	Primary endpoint	Secondary endpoints
KEYNOTE-010 P010	Randomized (1:1:1), multicenter, open-label, adaptively designed phase II/III trial of	pembrolizumab 10 mg/kg Q3W	920/1034/991	Sex: 213M/133F Median age	OS, PFS	ORR, response duration

198 centers in 24 countries: Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Chile, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, Lithuania, Netherland, Portugal, Russia, South Africa, Spain, Taiwan, United Kingdom, United States *Study complete*	pembrolizumab at two dosing schedules vs docetaxel, in patients with PD-L1 positive NSCLC with disease progression after platinum containing therapy	pembrolizumab 2 mg/kg Q3W docetaxel 75 mg/m^2 Q3W		(min/max): 63 years (20-88) Sex: 212M/132F Median age (min/max): 63 years (29-82) Sex: 209M/134F Median age (min/max): 62 years (33-82)		
KEYNOTE-001 P001 <u>Cohorts C and F</u> 44 centers in 10 countries: Australia, Canada, France, Italy , Korea, Norway, Spain, Taiwan, United Kingdom United States *Enrollment complete; study ongoing*	Multicenter, open-label, phase I, multiple expansion cohorts Cohort A: solid tumors Cohort B: adv. melanoma **Cohort C: NSCLC ≥*2 prior therapy*** Cohort D: adv. Melanoma **Cohort F: NSCLC** *-F1: PD-L1+ treatment naive* *-F2: PD-L1+, ≥1/2 prior therapy* *or* *PD-L1-, ≥2 prior therapy* *-F3: PD-L1-, ≥1 prior therapy*	<u>Cohort C:</u> Pembrolizumab 10 mg/kg Q3W <u>Cohort F:</u> F1: Pembrolizumab 2 mg/kg Q3W 10 mg/kg Q3W 10 mg/kg Q2W F2: Pembrolizumab 10 mg/kg Q3W 10 mg/kg Q2W or 10 mg/kg Q2W F3: Pembrolizumab 2 mg/kg Q3W	<u>Cohort C:</u> 41/38 <u>Cohort F:</u> F1: 103/101 F2: 318/313 43/43 F3: 55/55	Sex: 289M/261F Median age (min/max): 64 years (28-93)	ORR, DCR	PFS, OS, correlation between biomarkers and anti-tumor activity

In study P001, an additional cohort (Part E), designed to characterize pembrolizumab in combination with chemotherapy in NSCLC patients was originally planned. However, no patients were enrolled and, as suggested by FDA, this cohort was removed and set up as a stand-alone study (KEYNOTE-021).

2.4.1. Dose response study(ies)

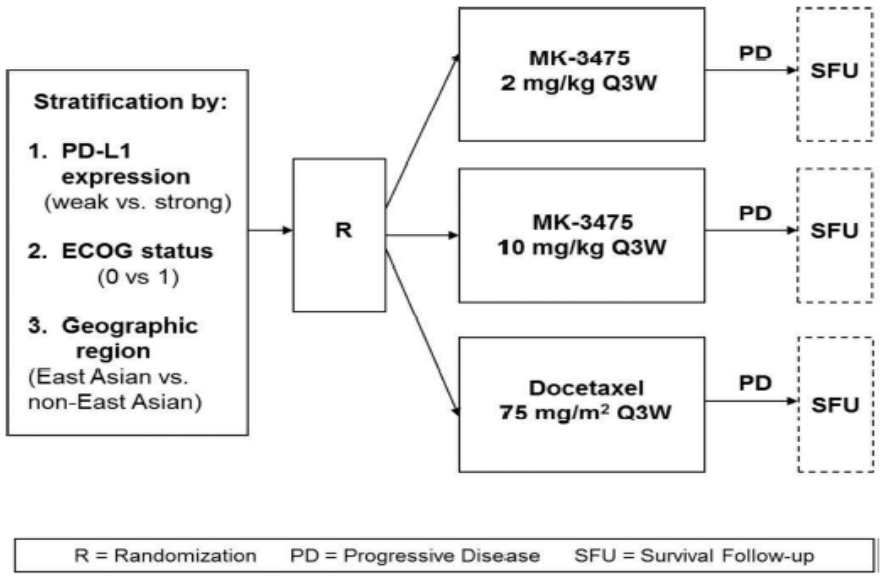
No additional dose-response study was performed, and data are limited to those submitted at the time of the initial Marketing Authorisation Application, from the escalation Part A of the phase I P001 trial.

In the trial P010, submitted as pivotal to support this extension of indication, 2 pembrolizumab doses (2 mg/kg Q3W and 10 mg/kg Q3W), including that already recommended for the treatment of melanoma patients, were tested with an opportunity to drop a poorly performing dose early in the study.

2.4.2. Main study

A Phase II/III Randomized Trial of Two Doses of MK-3475 versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (KEYNOTE-010, P010).

Methods



Study participants

Key inclusion criteria were:

- Histologically or cytologically confirmed diagnosis of NSCLC with at least one measurable lesion as defined by RECIST 1.1. The target lesion(s) should also have bi-dimensional measurability for irRC evaluation on study.
- Investigator determined radiographic progression per RECIST 1.1 (from at least 2 dates) after treatment with at least two cycles of a platinum-containing doublet for stage IIIB/IV or recurrent disease. Completion of treatment with a platinum-containing doublet as adjuvant therapy within one year of signing informed consent will satisfy the prior treatment requirement.
    - Subjects with an EGFR sensitizing mutation must also be able to demonstrate progression of disease on the EGFR tyrosine kinase inhibitor (either erlotinib, gefitinib, or afatinib).
    - Subjects with an ALK translocation must also be able to demonstrate progression of disease on crizotinib.

  Subjects with an EGFR sensitizing mutation or with an ALK translocation may have been treated previously with the tyrosine kinase inhibitor separately from the platinum-containing doublet; the order of treatment does not matter, but progression of disease as determined by RECIST 1.1 must be demonstrable for both regimens. An exception to this rule is the patient whose NSCLC tumour has an EGFR sensitizing mutation who receives four cycles of a platinum doublet, does not experience progression of disease, and begins therapy with an EGFR tyrosine kinase inhibitor as a maintenance therapy within 28 days of the last administration of the platinum doublet chemotherapy. For this patient, only one set of images demonstrating

progression on the EGFR tyrosine kinase inhibitor is required for submission to the independent imaging vendor for the patient to be eligible.

- PD-L1 positive (either strongly or weakly) tumour as determined by IHC at a central laboratory. If the initial tumour specimen is not classified as PD-L1 positive by the central laboratory, a newly obtained specimen may be submitted for testing.
- Age ≥18 years
- ECOG performance status of ≤ 1
- Newly obtained formalin fixed tissue from a recent biopsy of a tumour lesion not previously irradiated, for PD-L1 biomarker analysis. For patients in whom obtaining a new tumour biopsy will be medically inappropriate, an archival formalin-fixed, paraffin-embedded tumour specimen for PD-L1 could be submitted if agreed by the study clinical director.
    - Investigators must be able to produce the source documentation of the EGFR mutation status or ALK translocation status. If unable to test for these molecular changes, formalin-fixed paraffin-embedded tumour tissue of any age should be submitted to a central laboratory .
    - If a patient is known to have one molecular alteration (either sensitizing EGFR mutation or ALK translocation), then testing for the other alteration is not required.
    - If a patient is known to have a mutation in KRAS, then testing for an EGFR mutation or for an ALK translocation will not be required, given that all of these molecular alterations are mutually exclusive in patients with non-squamous NSCLC.
    - For patients enrolled who are known to have a tumour of predominantly squamous histology, molecular testing for EGFR mutation and ALK translocation will not be required as this is not standard of care and is not part of current diagnostic guidelines.

Main exclusion criteria were:

- Prior therapy with docetaxel for NSCLC.
- Systemic steroid therapy within three days prior to the first dose of trial treatment or any other form of immunosuppressive medication.
- Need of any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC or radiation therapy).
- Prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (e.g., cetuximab), major surgery within 3 weeks; thoracic radiation therapy of > 30 Gy within 6 months; prior tyrosine kinase inhibitor therapy or completed palliative radiotherapy within 7 days.
- 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) or participation in another pembrolizumab clinical trial.
- Known history of prior malignancy except if the patient has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy. The time requirement does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancer.

- Known active central nervous system metastases and/or carcinomatous meningitis.
- Active autoimmune disease, or documented history of autoimmune disease, or syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Subjects that require inhaled steroid or local steroid injections will not be excluded from the study. Subjects with hypothyroidism not from autoimmune disease and stable on hormone replacement will not be excluded from the study.
- Interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids.

Treatments

Pembrolizumab (2 mg/kg or 10 mg/kg) was administered IV every 3 weeks as a 30 minute infusion, with a time window of -5 and +10 minutes.

Docetaxel 75 mg/m^2 was administered IV over 1 hour every 3 weeks. Pre-medications, including oral or injectable steroids, were administered as per standard practice.

Patients randomised to docetaxel were pre-medicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional pre-medications were administered as per standard practice.

Treatment with pembrolizumab or docetaxel was planned to be continued until two years or less in case of documented disease progression, unacceptable AEs, intercurrent illness that prevented further administration of treatment, Investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or discontinuation due to administrative reasons. Treatment could be interrupted for clinically stable patients assigned who experienced disease progression. The decision to continue or discontinue treatment in the trial could be deferred until confirmation of disease progression per irRC at least 28 day from the date of radiological disease progression. In case of no disease progression confirmation, treatment could be resumed.

Objectives

Primary Objectives:

- To compare the OS and PFS per RECIST 1.1 by independent radiologists' review of previously treated NSCLC patients in the strongly positive (TPS≥50%) PD-L1 stratum.
- To evaluate OS and PFS per RECIST 1.1 by independent radiologists' review in the PD-L1 positive population.

Safety and tolerability profile of pembrolizumab in previously treated subjects with NSCLC in the TPS ≥ 50% stratum and in the overall population was also among primary objectives.

Secondary Objectives:

- To evaluate ORR and response duration in the strongly positive (TPS≥50%) PD-L1 stratum and in the overall positive (TPS≥1%) study population.

Exploratory Objectives:

- To evaluate PFS, ORR, response duration per immune-related response criteria (irRC) by Investigators' review in the TPS≥50% stratum and in overall positive study population

(TPS≥1%).

- To evaluate the influence of age of tumour specimen (archival vs new) submitted for PD-L1 analysis on the primary endpoints PFS and OS.
- To evaluate tumour volumetric changes and to explore correlation of tumour volumetric changes with OS in the TPS≥50% stratum.
- To evaluate changes in HRQoL assessments from baseline, and to characterize utilities and healthcare resource utilization in the TPS≥50% stratum and in the TPS>1% population.

Outcomes/endpoints

The primary endpoints were OS and PFS using IRC assessment per RECIST 1.1 in the TPS≥50% stratum and the TPS≥1% population.

The secondary endpoints were ORR and time to response by IRC assessment by RECIST 1.1.

The changes in HRQoL were assessed using the electronic EORTC Quality of Life Questionnaire Core 30 items (eEORTC QLQ-C30) and the electronic EORTC Quality of Life Questionnaire Lung Cancer 13 items (eEORTC QLQ-LC13).

Patients were evaluated every 9 weeks (63±7 days) with radiographic imaging to assess response to treatment. Investigators made all treatment-based decisions using the irRC.

Treatment with pembrolizumab or docetaxel was continued until two years of therapy had been administered, documented disease progression, unacceptable AEs, intercurrent illness that prevented further administration of treatment, Investigator's decision, subject withdrew consent, pregnancy, noncompliance, or for administrative reasons.

Pembrolizumab-treated patients who attained an Investigator-determined confirmed complete response (CR) per irRC could have considered stopping trial treatment. In case of radiographic disease progression these patients were eligible for re-treatment for up to one year with pembrolizumab at the Investigator discretion (Second Course Phase).

Participation in this trial was dependent upon supplying tumour tissue for PD-L1 analysis. Specimens were evaluated at a central laboratory facility for PD-L1 expression status in a prospective manner. Only patients whose tumours expressed PD-L1 were eligible for randomization in this study.

PD-L1 -expression

The PD-L1 expression levels were measured in NSCLC tumour tissues by IHC performed on tumour tissue on glass slides. Tumour tissue was analysed by the Dako Clinical Trial Assay (CTA) by using the 22C3 clone against PD-L1.

All scoring was performed by pathologists. An evaluable sample must have contained a minimum of 100 tumour cells. The slides were evaluated using several scoring methods. A tumour proportion score (TPS) reflecting the percentage of tumour cells exhibiting membranous staining was selected as the scoring method to use for the assay. Tumours with at least 1% positive staining for PD-L1 were considered positive. Since the Biomarker Training Set defined the optimal cutpoint as TPS≥50%, subjects with tumour PD-L1 expression above this cutpoint were referred to as strongly positive for PD-L1 expression. Those subjects with tumours who had a TPS between 1% and 49% are referred to as weakly positive for PD-L1 expression. Tumours with <1% tumour cells positive for PD-L1 staining were considered negative.

After the study had started, the Sponsor became aware that PD-L1 antigens on the cut slides have the stability window of 6 months for the CTA. Therefore, those subjects who submitted tumour sample slides out of the stability window were excluded from the FAS analysis.

Sample size

The sample size was targeted to be approximately 460 for strongly PD-L1 positive patients (TPS≥50%), and was projected to be approximately 920 patients for the overall population (TPS≥1%), based on an expected rate of strongly PD-L1 positive patients of around 50%.

The study was designed as event driven, with the number of patients and follow-up time subject to change, and would be complete after approximately 200 deaths observed across the three arms in the TPS≥50% stratum (approximately 140 deaths between one pembrolizumab arm and the docetaxel arm under the alternative hypothesis). With 140 deaths between one pembrolizumab arm and the docetaxel arm, the study had over 81% power to detect a 0.55 hazard ratio at the final analysis, where 0.825% alpha was allocated to the two pembrolizumab vs. docetaxel comparisons using Hochberg procedure.

The sample size calculation is based on the following assumptions for subjects in the strongly positive PD-L1 stratum: 1) overall survival follows an exponential distribution with a median of 9 months in the control arm, 2) the hazard ratio between pembrolizumab and control is 0.60, 3) an enrollment period of 16 months and a minimum of 8 months follow-up after enrollment completion, 4) a dropout rate of 2% in 12 months. The assumed median overall survival time of 9 months for docetaxel treated patients is based on historical data, and the possible positive prognostic nature of high PD-L1 expression levels. The median OS in docetaxel could be greater or less than 9 months in patients with strongly positive PD -L1 expression, if PD-L1 expression is prognostic for docetaxel.

Randomisation

Patients were randomly assigned to treatment arms (ratio 1:1:1) via a central Interactive Voice Response System (IVRS)/Interactive Voice and Web Response System (IXRS) in block of six in each stratum. They were stratified according to PD-L1 expression, as tumour proportion score (TPS) ≥50% vs 1-49%, ECOG PS (0 vs 1), and Region (East Asia vs not East Asia).

Blinding (masking)

The study was conducted in an open label fashion, with a blinded independent radiologist review of responses.

The extent of tumour PD-L1 expression in randomized subjects was double-blinded. The subject, the Investigator, and Sponsor personnel or delegate(s) who were involved in the treatment or clinical evaluation of the subjects were unaware of the PD-L1 status.

Statistical methods

The primary efficacy analyses are based on the Intention to Treat (ITT) population in the strongly positive PD-L1 stratum and the overall positive PD-L1 population. A supportive analysis was conducted in the Full Analysis Set (FAS) population that excludes those who did not meet the critical eligibility criteria or discontinued before receiving any dose of assigned treatment. All Patients Population (APaT) was used for the primary analysis of safety data. The Kaplan-Meier method is used to estimate the survival (PFS and OS) curves, as well as the overall survival rate at 1 year by treatment group. The treatment difference in OS and PFS is assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling with a single treatment covariate is used

to assess the magnitude of the treatment difference (i.e., the hazard ratio and 95% confidence interval). The same stratification factors used for randomization are applied to both the stratified log-rank test and the stratified Cox model. The model based approach to handling missing data is used for the primary outcomes. To control for bias induced by non-study treatment (i.e patients in the docetaxel arm may receive other PD-1 treatment after discontinuation), it was planned to use a Rank Preserving Structural Failure Time (RPSFT) model. To further account for the possible confounding effect, an OS sensitivity analysis censoring patients at the time of initiation of new therapy and an additional analysis that treats initiation of new therapy as a time-dependent binary covariate were also planned. In case the proportional hazards assumption doesn't hold it was planned to conduct Fleming and Harrington's weighted logrank test or other methods, as appropriate, after proper adjustment of the crossover effect over time. Restricted mean survival time (RMST) estimate of OS and PFS over time was also calculated as an exploratory analysis.

Three PFS sensitivity analyses with a different set of censoring rules and PD event definitions under various scenarios were planned. The censoring rules for the primary and sensitivity PFS analyses are summarized in the following table.

Table 15: Censoring rules for Primary and Sensitivity PFS analyses

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2	**Sensitivity Analysis 3**
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	**Censored at last disease assessment**
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	**Censored at last disease assessment**
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death	**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	**Progressed at date of documented PD or death**

An exploratory analysis of pooled pembrolizumab arm vs. docetaxel was carried out for PFS or OS at the second interim and the final analyses in the strongly positive PD-L1 stratum as well as the overall PD-L1 positive population. The same stratified Cox proportional hazard model as that for the primary analysis was used to assess the magnitude of the treatment difference. The Kaplan-Meier method was used to estimate the survival curves.

For comparison of the ORR between the treatment groups, the stratified Miettinen and Nurminen's method was used. The same stratification factors used for randomization were applied to the analysis. A 95% confidence interval for the difference in response rates between each pembrolizumab arm and the control was provided. A p-value for this difference was provided for dose selection at interim analyses. A subgroup ORR analysis is performed in patients followed up for 27 weeks, including early drop-outs. Subjects with missing data were considered non-responders.

Response duration was summarized descriptively using Kaplan-Meier medians and quartiles. Non-responders were excluded in this analysis.

EORTC-QLQC30, EORTC QLQ LC-13, EuroQoL EQ-5D, Health Economic Assessment were summarized as part of the exploratory analysis.

Interim Analyses

Two planned interim analyses occurred during the conduct of this trial. The table below summarizes the strategy and timing of each interim analysis. The eDMC reviewed the data, and the study continued until the final analysis.

Table 16: Strategy and planning of interim analyses

Interim Analysis	Key Endpoint(s)	Anticipated Time of Analysis from Study Start	Sample Size Expected at Time of Analysis (3 Arms)	Primary Purpose
1	ORR	App. 10 months	120 in the TPS≥50% stratum with 3 months of minimum follow up	Discontinue one pembrolizumab arm for lack of efficacy OR discontinue both arms for futility
2 (primary PFS analysis and contingent OS analysis)	PFS, OS	App 19 months	App 414 (around 175 PFS events across the 3 arms) in the TPS≥50% stratum	Demonstrate superiority of pembrolizumab in PFS Demonstrate superiority of pembrolizumab in OS after approximately 120 deaths have been observed across 3 arms in TPS≥50% stratum
Final	OS, PFS	App. 30 months	App. 460 (around 200 OS events across 3 arms) in TPS≥50% stratum	Demonstrate superiority of pembrolizumab in OS Demonstrate long-3term PFS effect of pembrolizumab

App. = approximately; ORR = overall response rate; OS = overall survival; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival.
Source: Appendix [16.1.9]

Multiplicity Adjustment

A predefined strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple efficacy endpoints, multiple target groups and interim analyses is taken into account (see figure below). At each analysis, the Hochberg step-up procedure is used for PFS and OS testing in the strongly positive PD-L1 stratum, giving equal weights to the two pembrolizumab arms, if neither is prior discontinued. At each analysis, a gate-keeping testing procedure is used for adjustment over the strongly positive PD-L1 stratum and the overall PD-L1 positive population. If both pembrolizumab arms demonstrate superior PFS in the strongly positive stratum, PFS is then tested in the overall PD-L1 positive population at the same alpha level. The same approach is applied at the second interim analysis for OS, while at the final analysis, a Bonferroni correction is used to adjust for the OS tests in strongly positive PD-L1 stratum and in the overall PD-L1 positive population; the level of significance for OS in the final analysis is set at 0.825% (i.e. 1.65/2) in light of the results observed for the PSF at the second interim and final analysis in both populations. Indeed, the strongly positive PD-L1 stratum and the overall PD-L1 positive population was planned to be tested at $\alpha'/2$ each, where α' will be between 1.65% and 2.00% and the actual alpha level depends on whether or not both MK-3475 arms are superior in PFS for the overall positive population at the second interim analysis and the final analysis.

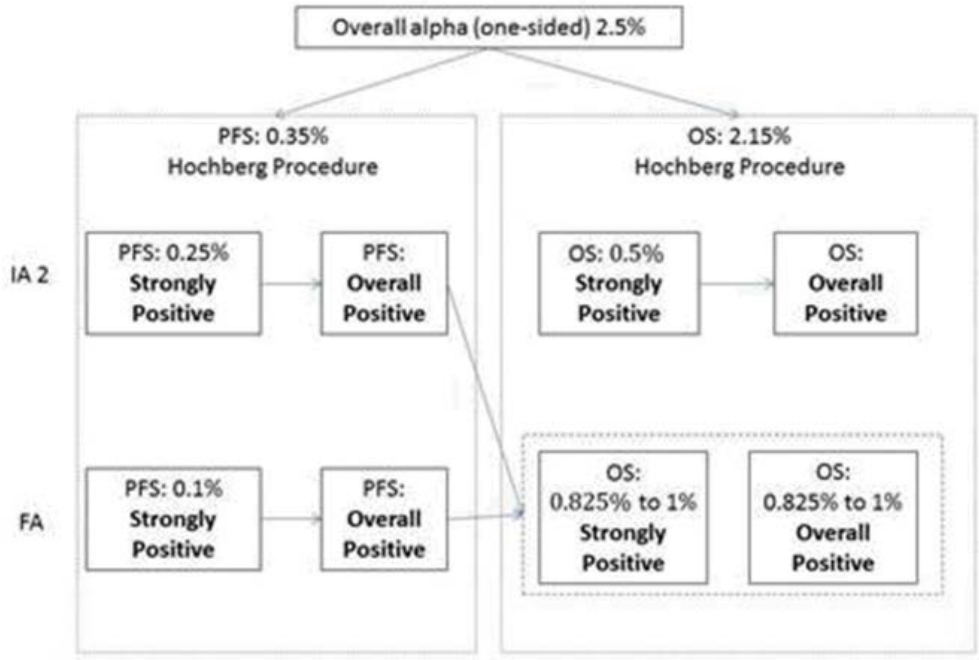


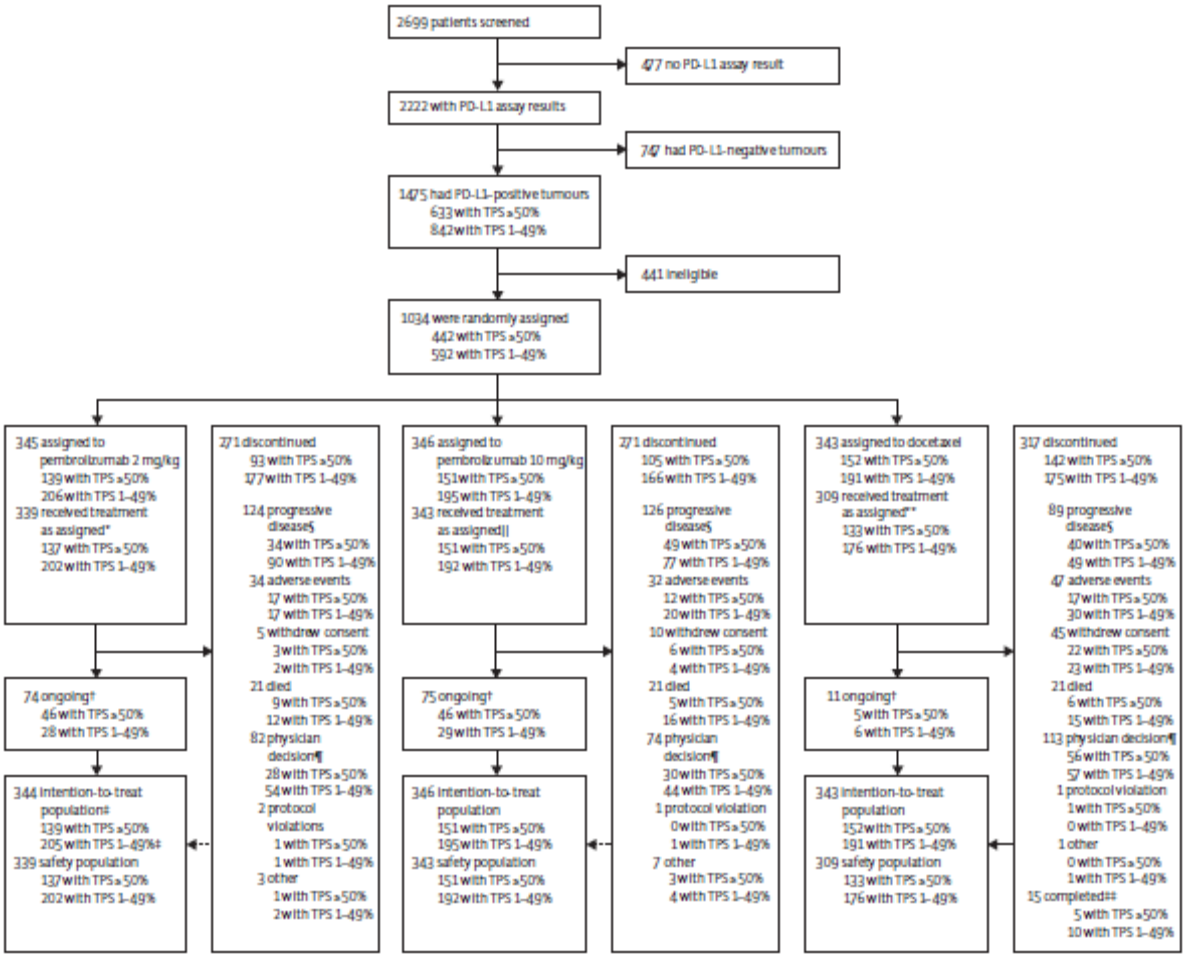
Figure 17: Strategy to address multiplicity adjustment

Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint is estimated and plotted within each category of the following classification variables: age category (≤65 vs. >65 years), sex (female, male), race (white, non-white), ECOG status (0 vs. 1), geographic region of enrolling site (East Asia, non-East Asia), ethnicity (East Asian, non-East Asian), previous chemotherapy regimen (types with greater than 10% subjects in the control group), ALK translocation status (translocated vs. wild type), EGFR mutation status (wild type vs. mutant), age of tumour specimen (archival vs. new).

Results

Participant flow



Herbst RS, Lancet 2015

In the pembrolizumab 2 mg/kg arm, one patient was excluded from efficacy analysis due to GCP non-compliance issue of the enrolling site.

Recruitment

The study was conducted in 198 trial centres in 24 countries. Overall, 1034 PD-L1 positive (TPS>1%) patients were enrolled from 28 August 2013 to 27 February 2015. The highest enrolling country was the US with a total of 224 subjects and the top recruiter site was in the Netherlands (25 patients).

Conduct of the study

A total of 11 protocol amendments, including global and country-specific changes, were implemented during the study. The original protocol (dated 16 November 2012) specified the inclusion of squamous NSCLC patients who experienced disease progression after a platinum-containing systemic therapy.

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

Protocol Amendment	Most relevant changes
#01 (25 April 2013)	- study population was expanded to include all NSCLC histologies, provided that tumors were PD-L1 positive. - primary statistical analyses were changed from an all-comers population to PD-L1 strongly positive patients.

	- changed PFS to primary endpoint, and ORR to secondary endpoint. - increase of sample size, from 408 to 660 patients. - pembrolizumab 2 mg/kg Q3W arm was replaced with a 10 mg/kg Q2W - unblinding of pembrolizumab treatment arms. -addition of analysis of OS and PFS in the weakly positive PD-L1 stratum. - in EGFR mutated or ALK positive patients, demonstration of progression of disease also respectively on EGFR tyrosine kinase inhibitor (either erlotinib or gefitinib) or crizotinib. -removal of criterion excluding patients with symptomatic ascites or pleural effusion. - changed time period of the first dose of trial treatment (from 3 weeks to 6 months) for the exclusion of patients with previous radiation therapy of > 30 Gy. - changed criteria from 4 to 2 weeks of stable brain metastases prior to the first dose of trial treatment, allowing patients inclusion - update of first interim analysis to facilitate decisions in both strongly and weakly positive PD-L1 subgroups. Second interim analysis has been changed to be based on PFS events.
#2 (13 May 2013)	Country specific (Brazil)
# 3 (24 June 2013)	-the pembrolizumab 10 mg/kg every 2 weeks arm was dropped and replaced with a 2 mg/kg every 3 weeks arm. -Added clinical stability criteria for treatment after initial disease progression. -update of power, sample size (from 660 to 920), and assumptions for power calculation. -update of timing of interim analyses, criteria for futility and study arm discontinuation at interim analysis 1, and empirical hazard ratio for significance at interim and final analyses.
#4 (25 June 2013)	Country specific (US and Netherlands)
#5 (09 July 2013)	Country specific (Brazil)
#6 (02 August 2013)	Country specific (US) - changed primary analysis population to PD-L1 positive from strongly PD-L1 positive. Increased target hazard ratio in OS.
#7 (24 February 2014)	Country specific (Germany) -confirmatory imaging of disease progression 9 weeks after initial documentation.
#8 (10 April 2014)	-implementation of stratification by PD-L1 status as strong positive vs weak positive -newly obtained biopsies were required for PD-L1 analyses. An archival sample may be submitted if medically inappropriate to perform a new biopsy. -confirmatory imaging for progression of disease between 4 and 6 weeks from the initial date of progression.
#9 (19 May 2014)	Country specific (Germany)
#10 (06 July 2014)	-The evaluation of OS and PFS in PD-L1 positive patients was moved from secondary to primary objectives. - Updated diagram and multiplicity control strategy for IA2 and final analysis; Updated power calculation for OS analyses; Updated timing of interim and final analyses.
#11 (3 September 2015)	Country specific (Germany)

The first patients were screened under Amendment #3 (global) and #4 (country-specific). A total of 441 patients were enrolled prior to the implementation of PD-L1 status stratification factor, as for Amendment #8. Collaborative partner audits and the Investigator site compliance (14 sites) were conducted specific to study P010.

Two formal interim analyses occurred during the conduct of this trial. The first interim analysis (futility) was performed on 01-Nov-2014 after 120 subjects in the TPS≥50% stratum had completed a minimum of 3 months of follow-up; based on data, the eDMC recommended to continue the study with no modifications.

The second interim analysis (31-Jul-2015) was triggered after approximately 175 PFS events per RECIST 1.1 by independent radiologists' review across the three study arms in the TPS≥50% stratum,

and based on data it was decided to continue the study.

The final analysis (30-Sep-2015) was carried out when 204 deaths occurred across the 3 study arms in the TPS≥50% stratum.

Baseline data

In study P010, for the PD-L1 analysis a new tumour sample was available for 578 (55.95%) patients and an archival tumour sample was provided for 455 (44.05%) patients. The baseline characteristics for patients with PD-L1 TPS ≥50% and TPS ≥1% are shown below:

Table 17: Baseline patient characteristics

	TPS≥50%				TPS≥1%		
	pembrolizumab 2mg/kg Q3W N (%)	pembrolizumab 10mg/kg Q3W N (%)	Docetaxel 75mg/m² Q3W N (%)		pembrolizumab 2mg/kg Q3W N (%)	pembrolizumab 10mg/kg Q3W N (%)	Docetaxel 75mg/m² Q3W N (%)
Subjects in population	**139**	**151**	**152**		**344**	**346**	**343**
Gender							
Male	81 (58.3)	89 (58.9)	93 (61.2)		212 (61.6)	213 (61.6)	209 (60.9)
Female	58 (41.7)	62 (41.1)	59 (38.8)		132 (38.4)	133 (38.4)	134 (39.1)
Age (years)							
<65	84 (60.4)	81 (53.6)	96 (63.2)		201 (58.4)	194 (56.1)	209 (60.9)
≥65	55 (39.6)	70 (46.4)	56 (36.8)		143 (41.6)	152 (43.9)	134 (39.1)
Mean	62.1	62.9	60.9		62.1	62.3	61.6
SD	9.5	9.9	9.9		9.6	9.7	9.8
Median	62.0	64.0	60.0		63.0	63.0	62.0
Range	30-82	20-86	33-82		29-82	20-88	33-82
Race							
American Indian/ Alaska Native	0	0	0		2 (0.6)	3 (0.9)	0
Asian	27 (19.4)	28 (18.5)	29 (19.1)		73 (21.2)	72 (20.8)	72 (21.0)
Black/African American	5 (3.6)	5 (3.3)	1 (0.7)		13 (3.8)	8 (2.3)	7 (2.0)
Multiple	1 (0.7)	0	0		1 (0.3)	2 (0.6)	1 (0.3)
Native Hawaiian/ Other Pacific Islander	1 (0.7)	0	1 (0.7)		2 (0.6)	0	1 (0.3)
White	102 (73.4)	111 (73.5)	117 (77.0)		246 (71.5)	250 (72.3)	251 (73.2)
Missing	3 (2.2)	7 (4.6)	4 (2.6)		7 (2.0)	11 (3.2)	11 (3.2)
Ethnicity							
Hispanic/Latino	10 (7.2)	7 (4.6)	6 (3.9)		23 (6.7)	16 (4.6)	13 (3.8)
Not Hispanic/Latino	121 (87.1)	129 (85.4)	135 (88.8)		303 (88.1)	293 (84.7)	307 (89.5)
Not reported	1 (0.7)	10 (6.6)	8 (5.3)		7 (2.0)	25 (7.2)	14 (4.1)
Unknown	6 (4.3)	4 (2.6)	1 (0.7)		10 (2.9)	10 (2.9)	3 (0.9)
Missing	1 (0.7)	1 (0.7)	2 (1.3)		1 (0.3)	2 (0.6)	6 (1.7)
Region							
Non-East Asian	118 (84.9)	126 (83.4)	126 (82.9)		280 (81.4)	282 (81.5)	281 (81.9)
East Asian	21 (15.1)	25 (16.6)	26 (17.1)		64 (18.6)	64 (18.5)	62 (18.1)
Smoker							
Never smoker	26 (18.7)	29 (19.2)	34 (22.4)		63 (18.3)	60 (17.3)	67 (19.5)
Current/Ex smoker	112 (80.6)	122 (80.8)	113 (74.3)		279 (81.1)	285 (82.4)	269 (78.4)
Missing	1 (0.7)	0	5 (3.3)		2 (0.6)	1 (0.3)	7 (2.0)
ECOG							
0	47 (33.8)	47 (31.1)	49 (32.2)		112 (32.6)	120 (34.7)	116 (33.8)
1	91 (65.5)	104 (68.9)	102 (67.1)		229 (66.6)	225 (65.0)	224 (65.3)
2	1 (0.7)	0	1 (0.7)		3 (0.9)	1 (0.3)	1 (0.3)
3	0	0	0		0	0	1 (0.3)

ECOG							
Missing	0	0	0		0	0	1 (0.3)
Cancer Stage							
IA	0	0	0		1 (0.3)	0	0
IB	1 (0.7)	0	1 (0.7)		1 (0.3)	0	1 (0.3)
IIB	0	0	0		1 (0.3)	0	0
IIIA	1 (0.7)	2 (1.3)	4 (2.6)		5 (1.5)	4 (1.2)	8 (2.3)
IIIB	6 (4.3)	12 (7.9)	9 (5.9)		21 (6.1)	26 (7.5)	22 (6.4)
IV	131 (94.2)	137 (90.7)	138 (90.8)		315 (91.6)	316 (91.3)	312 (91.0)
Metastatic Staging							
M0	8 (5.8)	14 (9.3)	14 (9.2)		29 (8.4)	30 (8.7)	31 (9.0)
M1	36 (25.9)	29 (19.2)	40 (26.3)		95 (27.6)	80 (23.1)	80 (23.3)
M1A	20 (14.4)	34 (22.5)	22 (14.5)		62 (18.0)	65 (18.8)	62 (18.1)
M1B	75 (54.0)	74 (49.0)	76 (50.0)		158 (45.9)	171 (49.4)	170 (49.6)
Baseline Tumor Size (mm)							
Subject with data	135	149	133		335	338	308
Mean	101.6	91.7	98.5		98.7	94.2	91.6
SD	64.2	54.6	60.3		61.0	55.4	54.9
Median	82.0	78.0	90.0		86.0	80.0	78.0
Range	10-345	11-258	13-290		10-345	11-326	13-290
Brain Metastasis							
Yes	32 (23)	23 (15.2)	23 (15.1)		56 (16.3)	48 (13.9)	48 (14.0)
No	107 (77.0)	128 (84.8)	129 (84.9)		288 (83.7)	298 (86.1)	295 (86.0)
Non Small Cell Histology							
Squamous	29 (20.9)	41 (27.2)	26 (17.1)		76 (22.1)	80 (23.1)	66 (19.2)
Non-squamous	95 (68.3)	98 (64.9)	111 (73.0)		240 (69.8)	244 (70.5)	240 (70.0)
Mixed	0	3 (2.0)	2 (1.3)		3 (0.9)	3 (0.9)	4 (1.2)
Other	4 (2.9)	2 (1.3)	3 (2.0)		6 (1.7)	3 (0.9)	6 (1.7)
Unknown	11 (7.9)	7 (4.6)	10 (6.6)		19 (5.5)	16 (4.6)	27 (7.9)
PD-L1 Status							
Weakly positive	0	0	0		205 (59.6)	195 (56.4)	191 (55.7)
Strongly positive	139 (100)	151 (100)	152 (100)		139 (40.4)	151 (43.6)	152 (44.3)
EGFR Mutation							
Mutant	8 (5.8)	13 (8.6)	12 (7.9)		28 (8.1)	32 (9.2)	26 (7.6)
Wild Type	119 (85.6)	127 (84.1)	131 (86.2)		293 (85.2)	288 (83.2)	294 (85.7)
Undetermined	7 (5.0)	6 (4.0)	4 (2.6)		15 (4.4)	17 (4.9)	13 (3.8)
Missing	5 (3.6)	5 (3.3)	5 (3.3)		8 (2.3)	9 (2.6)	10 (2.9)
ALK Translocation Status							
Mutant	2 (1.4)	2 (1.3)	1 (0.7)		2 (0.6)	4 (1.2)	2 (0.6)
Wild Type	120 (86.3)	131 (86.8)	137 (90.1)		307 (89.2)	305 (88.2)	310 (90.4)
Undetermined	11 (7.9)	10 (6.6)	7 (4.6)		22 (6.4)	26 (7.5)	20 (5.8)
Missing	6 (4.3)	8 (5.3)	7 (4.6)		13 (3.8)	11 (3.2)	11 (3.2)
Prior Lines of Systemic Therapy							
Adjuvant	2 (1.4)	4 (2.6)	3 (2.0)		6 (1.7)	7 (2.0)	3 (0.9)
Neo-adjuvant	0	1 (0.7)	0		1 (0.3)	1 (0.3)	0
1st line	97 (69.8)	104 (68.9)	109 (71.7)		243 (70.6)	235 (67.9)	235 (68.5)
2nd line	30 (21.6)	26 (17.2)	25 (16.4)		66 (19.2)	69 (19.9)	75 (21.9)
3rd line	9 (6.5)	13 (8.6)	11 (7.2)		18 (5.2)	27 (7.8)	20 (5.8)
4th line	1 (0.7)	1 (0.7)	2 (1.3)		6 (1.7)	3 (0.9)	6 (1.7)
5th line or greater	0	2 (1.3)	2 (1.3)		3 (0.9)	4 (1.2)	3 (0.9)
Missing	0	0	0		1 (0.3)	0	1 (0.3)
Prior Adjuvant/Neo-adjuvant therapy							
Yes	7 (5.0)	11 (7.3)	9 (5.9)		20 (5.8)	26 (7.5)	18 (5.2)
No	132 (95.0)	140 (92.7)	143 (94.1)		324 (94.2)	320 (92.5)	325 (94.8)
Prior Chemotherapy							
Yes	137 (98.6)	146 (96.7)	149 (98.0)		335 (97.4)	337 (97.4)	339 (98.8)
No	2 (1.4)	5 (3.3)	3(2.0)		9 (2.6)	9 (2.6)	4 (1.2)
Prior Immunotherapy							
Yes	1 (0.7)	1 (0.7)	0		2 (0.6)	1 (0.3)	1 (0.3)
No	138 (99.3)	150 (99.3)	152 (100)		342 (99.4)	345 (99.7)	342 (99.7)
Prior EGFR TKI Therapy							
Yes	14 (10.1)	20 (13.2)	21 (13.8)		40 (11.6)	56 (16.2)	47 (13.7)
No	125 (89.9)	131 (86.8)	131 (86.2)		304 (88.4)	290 (83.8)	296 (86.3)
Prior ALK inhibitor Therapy							
Yes	3 (2.2)	3 (2.0)	1 (0.7)		3 (0.9)	5 (1.4)	2 (0.6)
No	136 (97.8)	148 (98.0)	151 (99.3)		341 (99.1)	341 (98.6)	341 (99.4)

Numbers analysed

The ITT population in the strongly positive PD-L1 stratum (TPS ≥50%) and the overall PD-L1 positive population (TPS ≥1%) served as the primary population for the efficacy analyses.

A supportive efficacy analysis was conducted in the Full Analysis Set (FAS) that excluded patients who did not meet the key eligibility criteria or discontinued before receiving any dose of assigned treatment. The FAS population was also used for the pre-specified exploratory PRO analysis.

Primary safety analyses were carried out in all randomized subjects who received at least one dose of treatment (APaT population) in the TPS≥50% stratum and the TPS>1% population.

Table 18: Study Populations (TPS≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 2 mg/kg Q3W	MK-3475 10 mg.kg Q3W	Total
Study Population	n	n	n	n
Randomized patients	343	345	346	1034
ITT Population	343	344	346	1033
All Patients as Treated (APaT)	309	339	343	991
Full analysis set (FAS) that excludes randomized who did not meet the eligibility criteria or discontinued before receiving any study medication	300	331	333	964
Site 805 was closed for enrollment due to GCP non-compliance issue and one subject enrolled at the site was excluded from efficacy analysis.				
Database Cutoff Date: 30SEP2015				

Table 19: Study Populations (Subjects with TPS ≥ 50%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 2 mg/kg Q3W	MK-3475 10 mg.kg Q3W	Total
Study Population	n	n	n	n
Randomized patients	152	139	151	442
ITT Population	152	139	151	442
All Patients as Treated (APaT)	133	137	151	421
Full analysis set (FAS) that excludes randomized who did not meet the eligibility criteria or discontinued before receiving any study medication	130	134	149	413
Site 805 was closed for enrollment due to GCP non-compliance issue and one subject enrolled at the site was excluded from efficacy analysis.				
Database Cutoff Date: 30SEP2015				

Outcomes and estimation

Overall Survival

Table 20: Analysis of Overall Survival - Subjects with TPS ≥ 50%, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	152	86 (56.6)	1091.6	7.9	8.2 (6.4, 10.7)	46.0 (36.9, 54.7)	---	---
MK-3475 2 mg/kg Q3W	139	58 (41.7)	1221.0	4.8	14.9 (10.4, .)	68.3 (59.4, 75.6)	0.54 (0.38, 0.77)	0.00024
MK-3475 10 mg/kg Q3W	151	60 (39.7)	1406.8	4.3	17.3 (11.8, .)	66.4 (57.8, 73.7)	0.50 (0.36, 0.70)	0.00002
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.12 (0.77, 1.62)	0.53513

†From product-limit (Kaplan-Meier) method for censored data.
‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive)
§One-sided p-value based on log-rank test.
‖Two-sided p-value based on log-rank test.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

	Docetaxel 75 mg/m2 Q3W (N=152)	MK-3475 2 mg/kg Q3W (N=139)	MK-3475 10 mg/kg Q3W (N=151)	MK-3475 Pooled (N=290)
OS rate at 6 Months in (95% CI)†	61.2 (52.5, 68.8)	75.4 (67.3, 81.7)	77.7 (70.1, 83.6)	76.6 (71.2, 81.1)
OS rate at 9 Months in (95% CI)†	46.0 (36.9, 54.7)	68.3 (59.4, 75.6)	66.4 (57.8, 73.7)	67.2 (61.2, 72.5)
OS rate at 12 Months in (95% CI)†	38.0 (28.9, 47.1)	53.4 (43.1, 62.6)	58.1 (48.8, 66.3)	55.9 (49.1, 62.2)

†From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

Table 21: Analysis of Overall Survival - Subjects with TPS ≥ 1%, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	343	193 (56.3)	2411.2	8.0	8.5 (7.5, 9.8)	46.6 (40.5, 52.5)	---	---
MK-3475 2 mg/kg Q3W	344	172 (50.0)	2928.7	5.9	10.4 (9.4, 11.9)	59.2 (53.5, 64.5)	0.71 (0.58, 0.88)	0.00076
MK-3475 10 mg/kg Q3W	346	156 (45.1)	3063.1	5.1	12.7 (10.0, 17.3)	61.5 (55.7, 66.7)	0.61 (0.49, 0.75)	<0.00001
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.17 (0.94, 1.45)	0.15511

†From product-limit (Kaplan-Meier) method for censored data.
‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive)
§One-sided p-value based on log-rank test.
‖Two-sided p-value based on log-rank test.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

	Docetaxel 75 mg/m2 Q3W (N=343)	MK-3475 2 mg/kg Q3W (N=344)	MK-3475 10 mg/kg Q3W (N=346)	MK-3475 Pooled (N=690)
OS rate at 6 Months in (95% CI)†	64.2 (58.6, 69.2)	72.5 (67.4, 76.9)	74.4 (69.4, 78.7)	73.5 (70.0, 76.6)
OS rate at 9 Months in (95% CI)†	46.6 (40.5, 52.5)	59.2 (53.5, 64.5)	61.5 (55.7, 66.7)	60.3 (56.3, 64.1)
OS rate at 12 Months in (95% CI)†	34.6 (28.4, 40.8)	43.2 (37.0, 49.3)	52.3 (46.2, 58.1)	47.8 (43.5, 52.1)

†From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

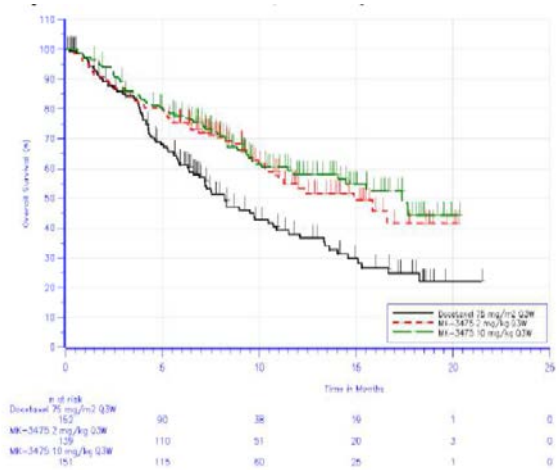


Figure 18: Kaplan-Meier of OS subjects with TPS ≥ 50%, ITT population

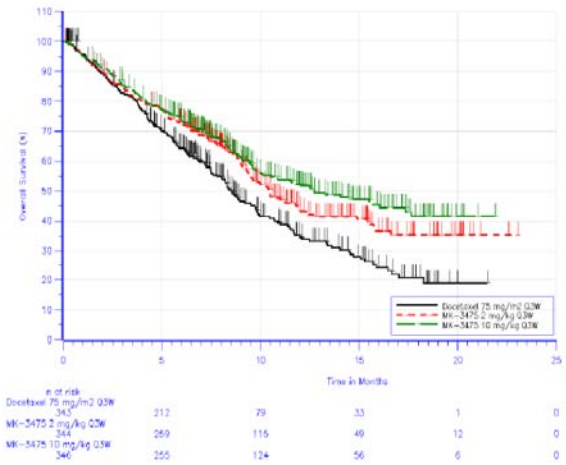


Figure 19: Kaplan-Meier of OS subjects with TPS ≥ 1%, ITT population

Progression Free Survival

Table 22: Analysis of PFS based on IRC assessment per RECIST 1.1 - Subjects with TPS ≥ 50%, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Months 9 in %[†] (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Docetaxel 75 mg/m2 Q3W	152	118 (77.6)	648.1	18.2	4.1 (3.6, 4.3)	19.2 (12.6, 26.8)	—	—
MK-3475 2 mg/kg Q3W	139	89 (64.0)	803.7	11.1	5.2 (4.0, 6.5)	36.0 (27.5, 44.5)	0.58 (0.43, 0.77)	0.00009
MK-3475 10 mg/kg Q3W	151	97 (64.2)	943.1	10.3	5.2 (4.1, 8.1)	37.8 (29.6, 45.9)	0.59 (0.45, 0.78)	0.00007
Pairwise Comparison							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.00 (0.74, 1.35)	0.99358

IRC: Independent Review Committee.
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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive)
[§] One-sided p-value based on log-rank test.
[‖] Two-sided p-value based on log-rank test.
Database Cutoff Date: 30SEP2015

Data Source: [Sec. 5.3.5.1.P010V01.16.4]

	Docetaxel 75 mg/m2 Q3W (N=152)	MK-3475 2 mg/kg Q3W (N=139)	MK-3475 10 mg/kg Q3W (N=151)	MK-3475 Pooled (N=290)
PFS rate at 6 Months in (95% CI)[†]	32.5 (24.5, 40.6)	47.3 (38.6, 55.4)	47.1 (38.8, 54.9)	47.2 (41.2, 52.9)
PFS rate at 9 Months in (95% CI)[†]	19.2 (12.6, 26.8)	36.0 (27.5, 44.5)	37.8 (29.6, 45.9)	36.9 (31.0, 42.8)
PFS rate at 12 Months in (95% CI)[†]	10.7 (5.6, 17.5)	28.2 (19.5, 37.5)	33.1 (24.9, 41.5)	30.9 (24.9, 37.1)

[†] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 30SEP2015

Table 23: Analysis of PFS based on IRC assessment per RECIST 1.1 - Subjects with TPS ≥ 1%, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Months 9 in %[†] (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Docetaxel 75 mg/m2 Q3W	343	257 (74.9)	1368.1	18.8	4.0 (3.1, 4.2)	15.9 (11.5, 20.9)	—	—
MK-3475 2 mg/kg Q3W	344	266 (77.3)	1676.2	15.9	3.9 (3.1, 4.1)	23.1 (18.4, 28.0)	0.88 (0.73, 1.04)	0.06758
MK-3475 10 mg/kg Q3W	346	255 (73.7)	1817.6	14.0	4.0 (2.6, 4.3)	27.4 (22.5, 32.6)	0.79 (0.66, 0.94)	0.00462
Pairwise Comparison							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.09 (0.91, 1.30)	0.34431

IRC: Independent Review Committee.

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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian)and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive)

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

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

Database Cutoff Date: 30SEP2015

Data Source: [Sec. 5.3.5.1.P010V01.16.4]

	Docetaxel 75 mg/m2 Q3W (N=343)	MK-3475 2 mg/kg Q3W (N=344)	MK-3475 10 mg/kg Q3W (N=346)	MK-3475 Pooled (N=690)
PFS rate at 6 Months in (95% CI)[†]	34.3 (28.8, 39.8)	35.1 (30.0, 40.3)	39.5 (34.3, 44.8)	37.3 (33.7, 41.0)
PFS rate at 9 Months in (95% CI)[†]	15.9 (11.5, 20.9)	23.1 (18.4, 28.0)	27.4 (22.5, 32.6)	25.2 (21.8, 28.8)
PFS rate at 12 Months in (95% CI)[†]	8.6 (5.1, 13.1)	17.5 (13.1, 22.4)	22.9 (18.1, 28.1)	20.2 (16.8, 23.7)

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

Database Cutoff Date: 30SEP2015

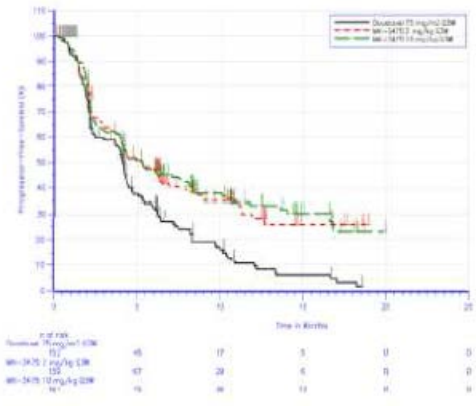


Figure 20: Kaplan- Meier of PFS (IRC assessment) subjects with TPS ≥50%, ITT population

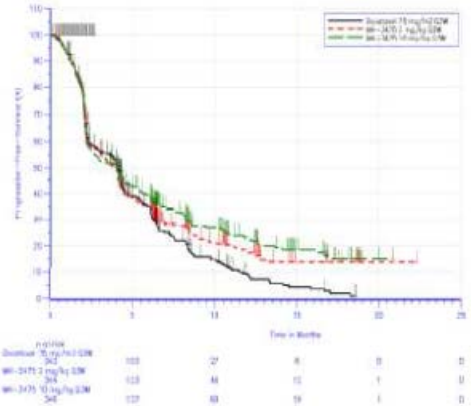


Figure 21: Kaplan- Meier of PFS (IRC assessment) subjects with TPS ≥1%, ITT population

Overall Response Rate

Table 24: Analysis of Overall Response Based on IRC Assessment RECIST 1.1 - Subjects with TPS ≥ 50%, ITT Population

Treatment	N	Number of Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Docetaxel	
				Estimate(95% CI)[†]	p-Value[††]
Docetaxel 75 mg/m2 Q3W	152	12	7.9 (4.1,13.4)		
MK-3475 2 mg/kg Q3W	139	42	30.2 (22.7,38.6)	23.3 (14.8,32.1)	<0.00001
MK-3475 10 mg/kg Q3W	151	44	29.1 (22.0,37.1)	22.2 (14.0,30.7)	<0.00001
Pairwise Comparison				Estimate (95% CI)[†]	p-Value[§]
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W				-2.3 (-12.7,8.2)	0.66608

IRC = Independent Review Committee
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive and Unknown Positive) ; if no patients are in one of the treatment groups 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.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0.
Database Cutoff Date: 30SEP2015

Data Source: [Sec. 5.3.5.1.P010V01.16.4]

Table 25: Analysis of Overall Response Based on IRC Assessment RECIST 1.1 - Subjects with TPS ≥ 1%, ITT Population

Treatment	N	Number of Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Docetaxel	
				Estimate(95% CI)[†]	p-Value[††]
Docetaxel 75 mg/m2 Q3W	343	32	9.3 (6.5,12.9)		
MK-3475 2 mg/kg Q3W	344	62	18.0 (14.1,22.5)	8.7 (3.6,13.9)	0.00045
MK-3475 10 mg/kg Q3W	346	64	18.5 (14.5,23.0)	9.1 (4.1,14.3)	0.00024
Pairwise Comparison				Estimate (95% CI)[†]	p-Value[§]
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W				0.5 (-5.3,6.2)	0.87591

IRC = Independent Review Committee
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive and Unknown Positive) ; if no patients are in one of the treatment groups 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.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0.
Database Cutoff Date: 30SEP2015

Data Source: [Sec. 5.3.5.1.P010V01.16.4]

Duration of Response

Table 26: Summary of Time to Response and Response Duration - Subjects with TPS ≥ 50%, Responders in ITT Population

	Docetaxel 75 mg/m2 Q3W (N=152)	MK-3475 2 mg/kg Q3W (N=139)	MK-3475 10 mg/kg Q3W (N=151)	MK-3475 Pooled (N=290)
IRC Assessment per RECIST 1.1				
Number of Patients with Response[†]	12	42	44	86
Time to Response [†] (days)				
Mean (SD)	94 (55)	84 (31)	85 (62)	84 (49)
Median (Range)	65 (59-247)	65 (38-141)	64 (44-440)	64 (38-440)
Response Duration[‡] (days)				
Median (Range)[§]	246 (63+ - 268+)	Not reached (20+ - 512+)	Not reached (64+ - 542+)	Not reached (20+ - 542+)
Number of Response Ongoing [‖] (%)	4 (33)	32 (76)	33 (75)	65 (76)
Investigator Assessment per irRC				
Number of Patients with Response[†]	18	46	48	94
Time to Response [†] (days)				
Mean (SD)	87 (46)	80 (44)	87 (49)	84 (46)
Median (Range)	63 (57-197)	64 (38-317)	65 (37-253)	64 (37-317)
Response Duration[‡] (days)				
Median (Range)[§]	132 (65+ - 450+)	504 (20+ - 512+)	Not reached (64+ - 542+)	504 (20+ - 542+)
Number of Response Ongoing [‖] (%)	6 (33)	33 (72)	32 (67)	65 (69)

[†] Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
[‡] From product-limit (Kaplan-Meier) method for censored data.
[§] "+" indicates there is no progressive disease by the time of last disease assessment.
[‖] Ongoing response includes all responders who are alive, progression free, did not initiate new anti-cancer therapies and have not been detemined to be lost to follow-up.
Database Cutoff Date: 30SEP2015

Data Source: [Sec. 5.3.5.1.P010V01.16.4]

Table 27: Summary of Time to Response and Response Duration - Subjects with TPS ≥ 1%, Responders in ITT Population

	Docetaxel 75 mg/m2 Q3W (N=343)	MK-3475 2 mg/kg Q3W (N=344)	MK-3475 10 mg/kg Q3W (N=346)	MK-3475 Pooled (N=690)
IRC Assessment per RECIST 1.1				
Number of Patients with Response*	32	62	64	126
Time to Response † (days)				
Mean (SD)	99 (60)	86 (36)	97 (81)	92 (63)
Median (Range)	65 (41-250)	65 (38-217)	64 (44-444)	64 (38-444)
Response Duration‡ (days)				
Median (Range)§	189 (43+ - 268+)	Not reached (20+ - 610+)	Not reached (64+ - 542+)	Not reached (20+ - 610+)
Number of Response Ongoing ‖ (%)	11 (34)	45 (73)	46 (72)	91 (72)
Investigator Assessment per irRC				
Number of Patients with Response*	35	72	73	145
Time to Response † (days)				
Mean (SD)	84 (43)	85 (46)	92 (59)	88 (53)
Median (Range)	62 (41-197)	64 (35-317)	65 (37-381)	64 (35-381)
Response Duration‡ (days)				
Median (Range)§	150 (32+ - 450+)	Not reached (20+ - 547+)	Not reached (64+ - 542+)	Not reached (20+ - 547+)
Number of Response Ongoing ‖ (%)	12 (34)	51 (71)	46 (63)	97 (67)

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.
‖ Ongoing response includes all responders who are alive, progression free, did not initiate new anti-cancer therapies and have not been determined to be lost to follow-up.
Database Cutoff Date: 30SEP2015

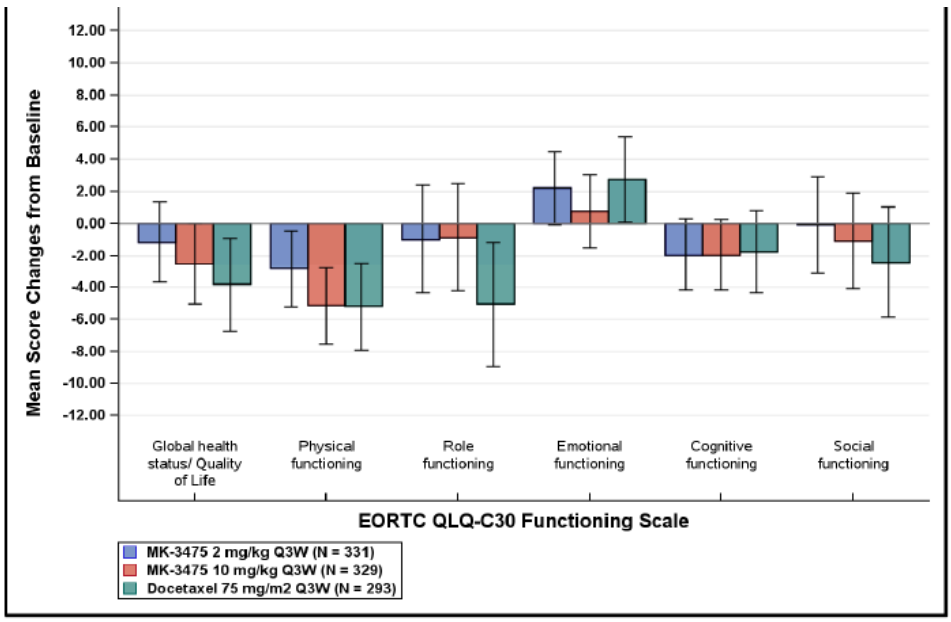
Data Source: [Sec. 5.3.5.1.P010V01.16.4]

Patient Reported Outcome (PRO) Analyses

There were three electronic questionnaires used in this study: eEORTC QLQ-C30, eEORTC QLQ-LC13, and eEQ-5D-3L.

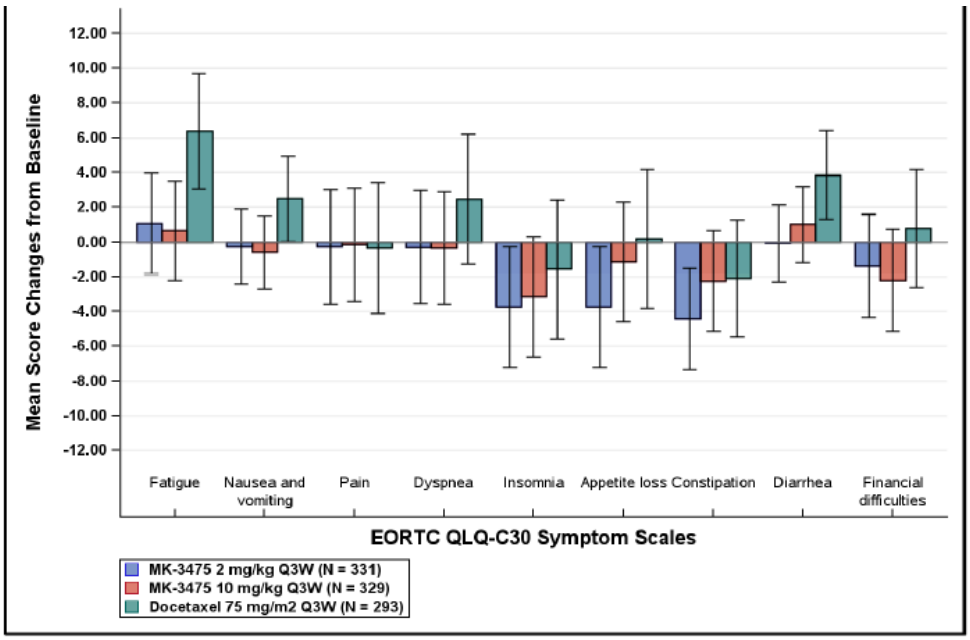
The primary analysis approach for the pre-specified exploratory PRO endpoints was based on a quality of life related FAS population, including all randomized subjects who received at least one dose of study medication and completed at least one PRO assessment.

- eEORTC QLQ-C30 Analyses are summarised in the below figures.



*For global health status/quality of life score and all functional scales, a higher score denotes better HRQoL or function, and a higher negative score denotes worse HRQoL or functions.

Figure 22: Change from baseline for EORTC QLQ-C30 functioning scale at week 12 – FAS population, TPS≥ 1%



*For different symptoms scales, a higher score denotes worse symptoms.

Figure 23: Change from baseline for EORTC QLQ-C30 symptom scales at week 12 – FAS population, TPS≥ 1%

- eEORTC QLQ-LC13 Analyses.

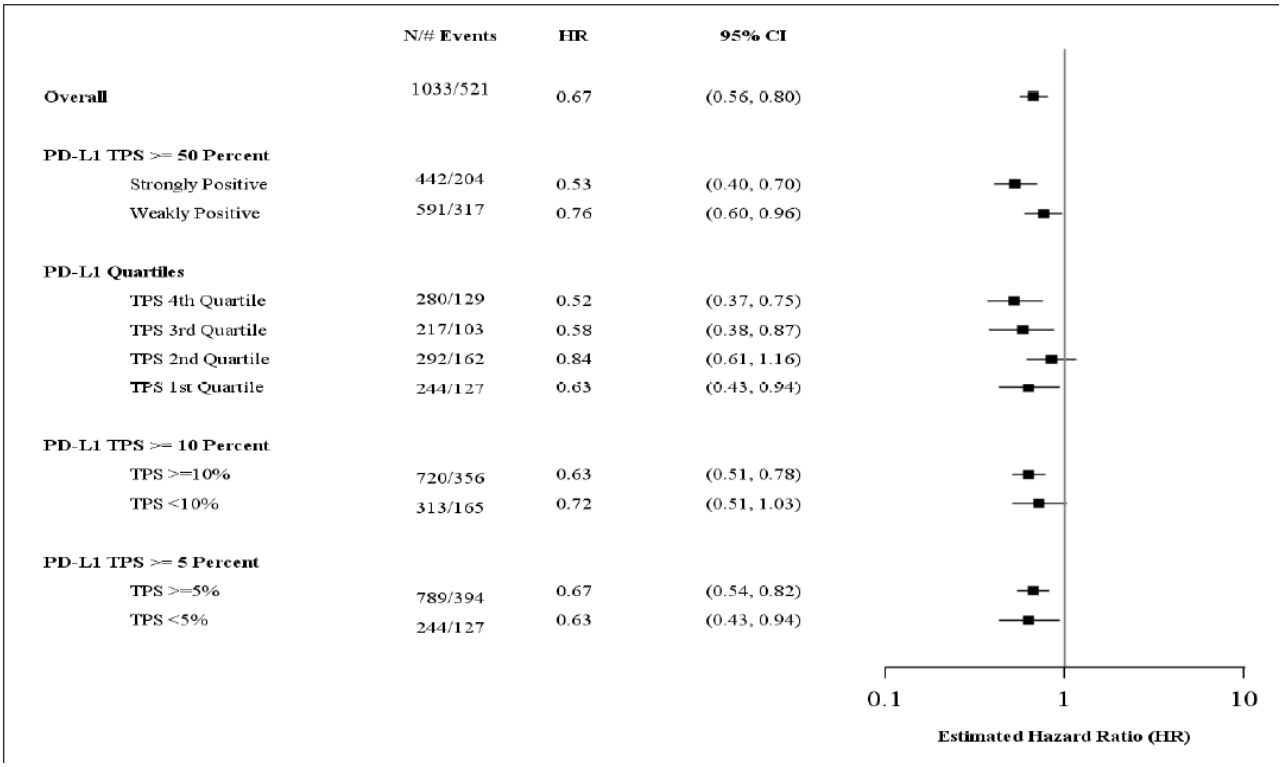
Subjects in both pembrolizumab arms had a numerical improvement from baseline to Week 12 in most EORTC lung cancer symptoms. This improvement was more pronounced for the 2 mg/kg dose in the TPS≥50% stratum. In contrast, subjects in the docetaxel arm had a numerical worsening from baseline in most EORTC lung cancer symptoms. With few exceptions, both pembrolizumab arms had a superior numerical change from baseline in EORTC lung cancer symptom scores compared to docetaxel and many of these achieved statistical significance. Compared to docetaxel, pembrolizumab also increased the time to true deterioration in the QLQ-LC13 composite endpoint of cough, dyspnea and chest pain. Unlike traditional deterioration, true deterioration requires a second adjacent 10 points or more score decrease from baseline under right-censoring rule.

- Summary of eEQ-5D-3L Analysis

The eEQ-5D provides data for use in economic models and analyses on health utilities or quality-adjusted life years. Minimal descriptive statistics were included in the PRO SAP for eEQ-5D. Results from eEQ-5D VAS analyses are consistent with the results of EORTC QLQ-C30 analyses (data not shown).

Ancillary analyses

Efficacy by PD-L1 expression status



Strongly positive = TPS≥50%; weakly positive = TPS 1-49%%; TPS 1st quartile = TPS <5%; TPS 2nd quartile = 35% > TPS ≥ 5%; TPS 3rd quartile = 80% > TPS ≥ 35%; TPS 4th quartile = TPS ≥ 80%.

Figure 24: Forest Plot of OS Hazard Ratio by subgroup factors pembrolizumab treatment group pooled vs docetaxel ITT population (TPS ≥ 1%)

Efficacy results for weakly positive (1%≤ TPS <50%) stratum

In the weakly positive (1%≤ TPS <50%) stratum, both pembrolizumab doses were superior to docetaxel in terms of **OS** by individual arms (HR 0.79, 95% CI: 0.61, 1.04 for pembrolizumab 2 mg/kg and HR 0.71, 95% CI: 0.53, 0.94 for pembrolizumab 10 mg/kg) and by pooled analysis (HR 0.76, 95% CI: 0.60, 0.96 for pooled pembrolizumab). The median OS for pembrolizumab was 9.4 months and 10.8 months for the 2 mg and 10 mg groups, respectively, compared to 8.6 months for docetaxel.

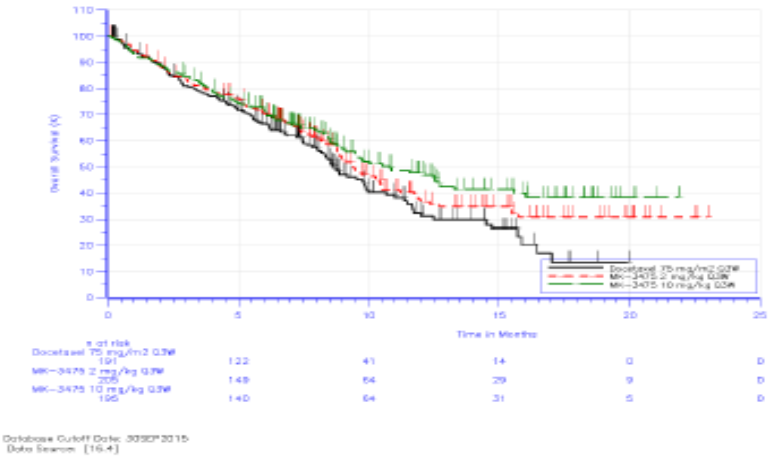


Figure 25: Kaplan-Meier of Overall Survival - Subjects with 1% ≤TPS < 50%, ITT Population

Table 28: OS Rate at 6,9,12 Months - Subjects with 1% ≤ TPS < 50%, ITT Population

	Docetaxel 75 mg/m2 Q3W (N=191)	MK-3475 2 mg/kg Q3W (N=205)	MK-3475 10 mg/kg Q3W (N=195)	MK-3475 Pooled (N=400)
OS rate at 6 Months in (95% CI)[1]	66.5 (59.0, 72.9)	70.5 (63.6, 76.3)	71.9 (64.9, 77.7)	71.2 (66.4, 75.4)
OS rate at 9 Months in (95% CI)[1]	47.0 (38.8, 54.8)	53.3 (45.7, 60.3)	57.6 (49.7, 64.6)	55.3 (49.9, 60.4)
OS rate at 12 Months in (95% CI)[1]	31.2 (22.9, 39.8)	36.7 (29.1, 44.4)	47.8 (39.6, 55.5)	42.0 (36.4, 47.5)
[1] From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 30SEP2015				

Data Source: [16.4]

In the weakly positive (1%≤ TPS <50%) stratum, the HR for **PFS** was 1.07 (95% CI: 0.85, 1.34) for the pembrolizumab 2 mg/kg Q3W and 0.99 (95% CI: 0.78, 1.25) for the pembrolizumab 10 mg/kg Q3W arm, compared to docetaxel.

Figure 26: Kaplan-Meier of Progression-Free Survival Based on IRC Assessment per RECIST 1.1 - Subjects with 1% ≤TPS < 50%, ITT Population

Table 29: PFS rate over time based on IRC Assessment per RECIST 1.1 - Subjects with 1% ≤ TPS < 50%, ITT Population

	Docetaxel 75 mg/m2 Q3W (N=191)	MK-3475 2 mg/kg Q3W (N=205)	MK-3475 10 mg/kg Q3W (N=195)	MK-3475 Pooled (N=400)
PFS rate at 6 Months in (95% CI)[1]	35.8 (28.4, 43.3)	27.0 (21.0, 33.3)	33.7 (27.0, 40.5)	30.2 (25.7, 34.9)
PFS rate at 9 Months in (95% CI)[1]	12.3 (7.0, 19.1)	14.6 (9.8, 20.3)	19.2 (13.5, 25.6)	16.8 (13.0, 21.1)
PFS rate at 12 Months in (95% CI)[1]	5.8 (1.9, 12.7)	10.4 (6.3, 15.6)	14.9 (9.7, 21.2)	12.6 (9.2, 16.6)
[1] From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 30SEP2015				

Table 30: Analysis of Overall Response Based on IRC Assessment RECIST 1.1 - Subjects with 1% ≤ TPS < 50%, ITT Population

Treatment	N	Number of Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Docetaxel	
				Estimate(95% CI)†	p-Value††
Docetaxel 75 mg/m2 Q3W	191	20	10.5 (6.5,15.7)		
MK-3475 2 mg/kg Q3W	205	20	9.8 (6.1,14.7)	-0.6 (-6.8,5.5)	0.57192
MK-3475 10 mg/kg Q3W	195	20	10.3 (6.4,15.4)	0.1 (-6.3,6.3)	0.48964
Pairwise Comparison				Estimate (95% CI)†	p-Value§
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W				0.6 (-5.4,6.8)	0.84210

IRC = Independent Review Committee
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive and Unknown Positive) ; if no patients are in one of the treatment groups 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.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

Table 31: Summary of Time to Response and Response Duration - Subjects with 1% ≤TPS <50 %, Responders in ITT Population

	Docetaxel 75 mg/m2 Q3W (N=191)	MK-3475 2 mg/kg Q3W (N=205)	MK-3475 10 mg/kg Q3W (N=195)	MK-3475 Pooled (N=400)
IRC Assessment per RECIST 1.1				
Number of Patients with Response[†]	20	20	20	40
Time to Response [†] (weeks)				
Mean (SD)	15 (9)	13 (6)	18 (16)	15 (12)
Median (Range)	9 (6-36)	9 (7-31)	9 (7-63)	9 (7-63)
Response Duration[‡] (weeks)				
Median (Range)[§]	26 (6+ - 31)	46 (9+ - 87+)	45 (13+ - 74+)	46 (9+ - 87+)
Number of Response Ongoing (%)	12 (60)	13 (65)	13 (65)	26 (65)
Investigator Assessment per irRC				
Number of Patients with Response[†]	17	26	25	51
Time to Response [†] (weeks)				
Mean (SD)	12 (6)	13 (7)	14 (11)	14 (9)
Median (Range)	9 (6-27)	9 (5-31)	9 (7-54)	9 (5-54)
Response Duration[‡] (weeks)				
Median (Range)[§]	21 (5+ - 55)	Not reached (9+ - 78+)	61 (9+ - 74+)	63 (9+ - 78+)
Number of Response Ongoing (%)	9 (53)	19 (73)	15 (60)	34 (67)

[†] Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
[‡] From product-limit (Kaplan-Meier) method for censored data.
[§] "+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

Results from a subgroup analysis for squamous and non-squamous NSCLC by PD-L1 status are shown in the following Table.

Table 32: subgroup analysis for squamous and non-squamous NSCLC by PD-L1 status

	Squamous NSCLC	Non-squamous NSCL	NSCLC overall
TPS ≥ 50%	HR 0.73	HR 0.44*	HR 0.53
TPS ≥ 1%	HR 0.74	HR 0.63	HR 0.67
TPS 1-49%	HR 0.73	HR 0.72*	HR 0.76

* Excluding Subjects with EGFR Mutation

OS Kaplan Meier curves and HRs based on histology, pembrolizumab dose and PD-L1 status are shown below.

Table 33: Subgroup analyses of OS Hazard Ratios by pembrolizumab dose, PD-L1 status and histology

Histology	PD-L1	Pembrolizumab Dose	N	Events	OS HR	Lower CI	Upper CI
Squamous	≥1%	2	142	83	0.88	0.55	1.39
Squamous	≥1%	10	146	84	0.67	0.43	1.04
Adenocarcinoma	≥1%	2	471	237	0.67	0.52	0.87
Adenocarcinoma	≥1%	10	473	223	0.58	0.44	0.76
Squamous	≥50%	2	55	30	0.92	0.41	2.04
Squamous	≥50%	10	67	34	0.62	0.30	1.26
Adenocarcinoma	≥50%	2	199	95	0.49	0.32	0.75
Adenocarcinoma	≥50%	10	203	95	0.45	0.29	0.69
Squamous	1-49%	2	87	53	0.83	0.47	1.48
Squamous	1-49%	10	79	50	0.69	0.38	1.23
Adenocarcinoma	1-49%	2	272	142	0.77	0.55	1.08
Adenocarcinoma	1-49%	10	270	128	0.68	0.48	0.98

N includes subjects in the pembrolizumab and docetaxel arms combined.
Events includes the total number of subjects in the pembrolizumab and docetaxel arms that died.
The OS HR is a comparison of pembrolizumab vs docetaxel.
OS=overall survival, HR=hazard ratio, CI=95% confidence interval.

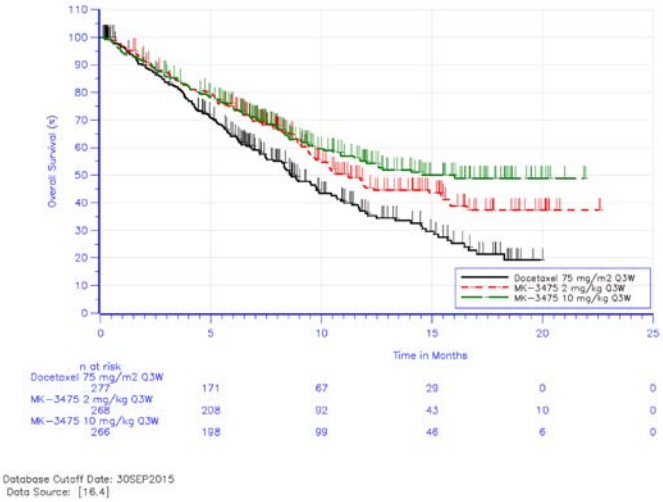


Figure 27: Kaplan-Meier of Overall Survival Non-Squamous Subjects, ITT Population (TPS >= 1%)

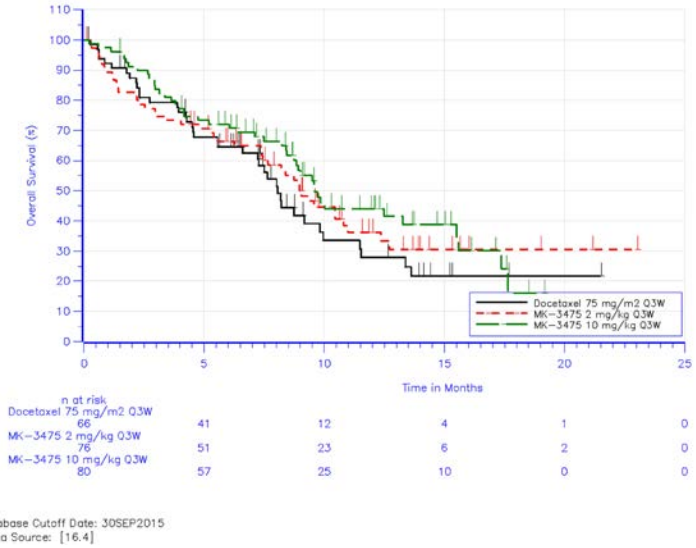


Figure 28: Kaplan-Meier of Overall Survival Squamous Subjects, ITT Population (TPS >= 1%)

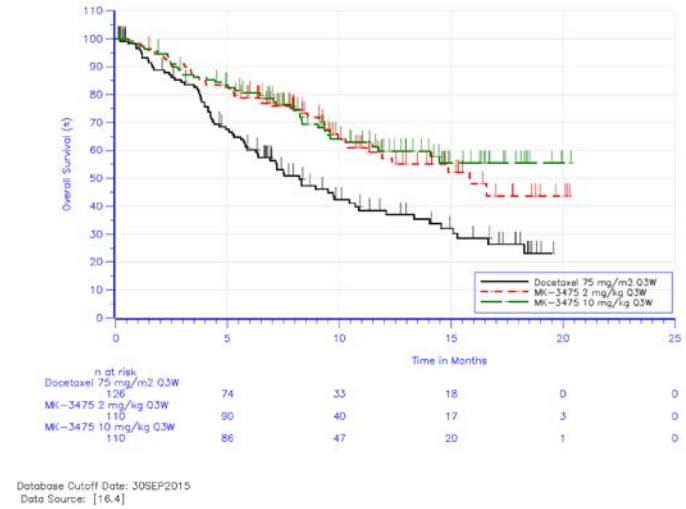


Figure 29: Kaplan-Meier of Overall Survival Non-Squamous Subjects with TPS >=50%, ITT Population

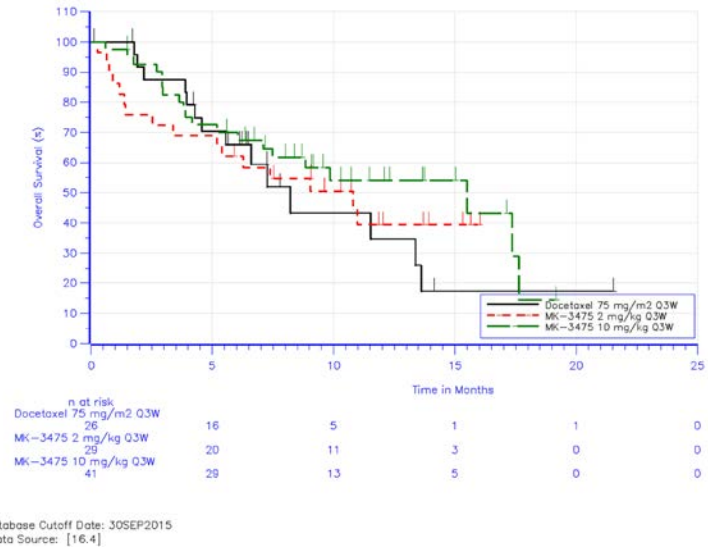


Figure 30: Kaplan-Meier of Overall Survival Squamous Subjects With TPS>=50%, ITT Population

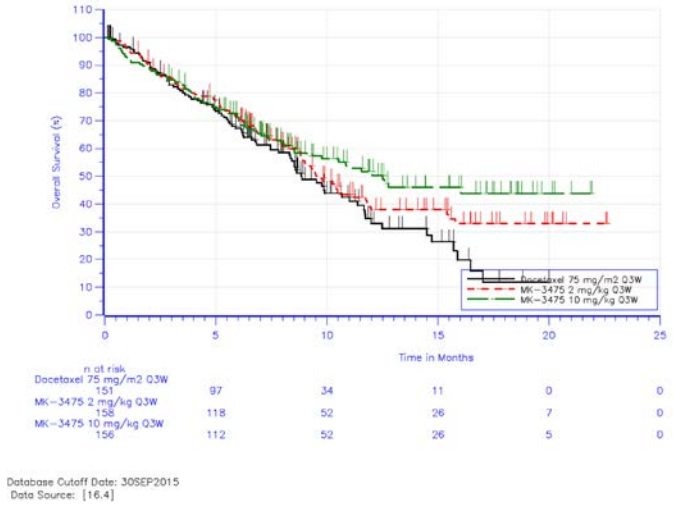


Figure 31: Kaplan-Meier of Overall Survival Non-Squamous Subjects with TPS = 1-49%, ITT Population

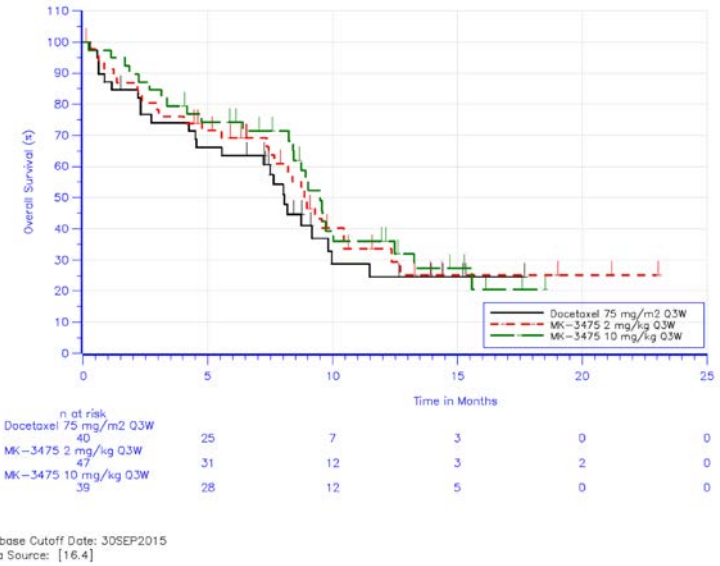


Figure 32: Kaplan-Meier of Overall Survival Squamous Subjects With TPS < 50%, ITT Population

PFS Sensitivity Analyses

Investigator Assessment per irRC

TPS≥50% Stratum:

Table 34: Analysis of Progression-Free Survival Based on Investigator Assessment per irRC Subjects with TPS ≥ 50%, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 9 in %† (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	152	116 (76.3)	665.8	17.4	4.3 (4.0, 5.4)	15.6 (9.5, 23.0)	---	---
MK-3475 2 mg/kg Q3W	139	82 (59.0)	871.6	9.4	6.9 (5.3, 8.6)	40.3 (31.1, 49.4)	0.51 (0.38, 0.69)	<0.00001
MK-3475 10 mg/kg Q3W	151	93 (61.6)	1008.9	9.2	7.3 (5.3, 8.4)	40.6 (32.0, 49.0)	0.50 (0.38, 0.67)	<0.00001
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg.kg Q3W							0.98 (0.72, 1.34)	0.91595

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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive) if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
§ One-sided p-value based on log-rank test.
‖ Two-sided p-value based on log-rank test.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

The results of the analyses of PFS for the TPS≥50% stratum based on Investigator assessment by irRC in the FAS population are consistent with the results in the ITT population with only minimal differences. The HR for PFS was 0.52 (95% CI: 0.38, 0.71) with a one-sided p-value of 0.00001 in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm. The HR for PFS was 0.52 (95%CI: 0.39, 0.69) with a one-sided p-value of <0.00001 in the pembrolizumab 10 mg/kg Q3W arm vs. the docetaxel arm.

TPS≥1% Population

Table 35: Analysis of Progression-Free Survival Based on Investigator Assessment per irRC Subjects with TPS ≥ 1%, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Months 9 in %[†] (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Docetaxel 75 mg/m2 Q3W	343	253 (73.8)	1450.5	17.4	4.4 (4.0, 5.5)	16.2 (11.7, 21.2)	---	---
MK-3475 2 mg/kg Q3W	344	244 (70.9)	1858.3	13.1	4.9 (4.0, 5.9)	28.4 (23.2, 33.9)	0.76 (0.64, 0.92)	0.00174
MK-3475 10 mg/kg Q3W	346	241 (69.7)	1930.2	12.5	4.9 (4.0, 6.2)	30.4 (25.2, 35.8)	0.72 (0.60, 0.87)	0.00023
Pairwise Comparison							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg.kg Q3W							1.04 (0.87, 1.25)	0.65966

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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive) if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

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

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

Database Cutoff Date: 30SEP2015

Data Source: [16.4]

The results of analyses of PFS for the TPS≥1% population by Investigator assessment by irRC in the FAS population are consistent with the results in the ITT population with only minimal differences. The HR for PFS was 0.77 (95% CI: 0.64, 0.92) with a one-sided p-value of 0.00240 in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm. The HR for PFS was 0.73 (95% CI: 0.61, 0.88) with a one-sided p-value of 0.00048 in the pembrolizumab 10 mg/kg Q3W arm vs. the docetaxel arm.

Sensitivity Censoring Rule analyses

Subjects with TPS ≥ 50%, ITT Population IRC assessment per RECIST 1.1			
	pembrolizumab 2 mg/kg Q3W	pembrolizumab 10 mg/kg Q3W	docetaxel
N. patients	139	151	152
Censoring rule 1*			
N. events (%)	88 (63.3)	94 (62.3)	110 (72.4)
Median PFS (months) (95% CI)	5.2 (4.0, 6.5)	5.2 (4.0, 7.6)	4.1 (3.6, 4.3)
PFS rate at months 9 (%) (95% CI)	35.5 (27.0, 44.1)	36.8 (28.6, 45.0)	14.1 (8.0, 21.9)
HR treatment vs docetaxel (95% CI)	0.58 (0.43, 0.78)	0.57 (0.43, 0.76)	
p-value (one sided, log-rank test)	0.00012	0.00005	
Censoring rule 2°			
N. events (%)	104 (74.8)	113 (74.8)	136 (89.5)
Median PFS (months) (95% CI)	4.4 (3.6, 6.1)	4.3 (3.7, 5.6)	3.8 (2.2, 4.2)
PFS rate at months 9 (%) (95% CI)	29.4 (21.7, 37.4)	30.5 (23.1, 38.3)	14.2 (8.9, 20.7)
HR treatment vs docetaxel (95% CI)	0.60 (0.46, 0.79)	0.62 (0.48, 0.80)	
p-value (one sided, log-rank test)	0.00010	0.00011	
Censoring rule 3•			
N. events (%)	89 (64.0)	97 (64.2)	118 (77.6)
Median PFS (months) (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
PFS rate at months 9 (%) (95% CI)	36.3 (27.8, 44.8)	37.9 (29.8, 46.0)	19.2 (12.6, 26.8)
HR treatment vs docetaxel (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	
p-value (one sided, log-rank test)	0.00008	0.00007	
Subjects with TPS ≥ 1%, ITT Population IRC assessment per RECIST 1.1			
	pembrolizumab 2 mg/kg Q3W	pembrolizumab 10 mg/kg Q3W	docetaxel
N. patients	344	346	343
Censoring rule 1*			
N. events (%)	260 (75.6)	248 (71.7)	240 (70.0)
Median PFS (months) (95% CI)	3.8 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.0, 4.2)
PFS rate at months 9 (%) (95% CI)	22.2 (17.5, 27.2)	26.9 (21.9, 32.1)	12.4 (8.2, 17.6)
HR treatment vs docetaxel (95% CI)	0.86 (0.72, 1.03)	0.78 (0.65, 0.94)	
p-value (one sided, log-rank test)	0.05435	0.00381	
Censoring rule 2°			
N. events (%)	288 (83.7)	285 (82.4)	308 (89.8)
Median PFS (months) (95% CI)	3.6 (2.9, 4.0)	3.7 (2.5, 4.2)	3.5 (2.5, 4.0)
PFS rate at months 9 (%) (95% CI)	20.1 (15.8, 24.7)	22.5 (18.0, 27.3)	10.4 (7.3, 14.2)
HR treatment vs docetaxel (95% CI)	0.80 (0.68, 0.94)	0.75 (0.63, 0.88)	
p-value (one sided, log-rank test)	0.00371	0.00025	
Censoring rule 3•			
N. events (%)	266 (77.3)	255 (73.7)	257 (74.9)
Median PFS (months) (95% CI)	3.9 (3.1, 4.1)	4.0 (2.7, 4.3)	4.0 (3.4, 4.2)
PFS rate at months 9 (%)	23.2	27.7	15.9

(95% CI)	(18.6, 28.2)	(22.8, 32.9)	(11.5, 20.9)
HR treatment vs docetaxel (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	
p-value (one sided, log-rank test)	0.06816	0.00400	

*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.
° 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 same as the second sensitivity analysis except that it censors at the last disease assessment when there is No PD and no death and new anticancer treatment is initiated.

Restricted Mean Survival Times Analysis of PFS in TPS≥50% Stratum

Comparison of restricted mean survival times (RMST) of PFS provides an assessment of treatment effect over a time interval. It provides an alternative estimate of the treatment effect that is robust to the proportional hazard assumption. The treatment effect of pembrolizumab on PFS was demonstrated by Kaplan-Meier analysis where a separation of the curves was observed after Month 3 and continued all the way towards the tail end when the majority of subjects in the docetaxel arm had PFS events. The mean PFS up to a certain follow-up time provides meaningful additional information compared to the median PFS in this situation, e.g., the RMST at Month 6 was 4.18 and 4.16 for pembrolizumab 2 mg/kg and 10 mg/kg, respectively, compared to 3.78 for docetaxel. The differences between pembrolizumab and docetaxel RMST values continue to increase at each subsequent time point.

Subgroups analyses

Data from the 2 mg/kg and 10 mg/kg were pooled for the subgroup analyses.

OS subgroups analysis

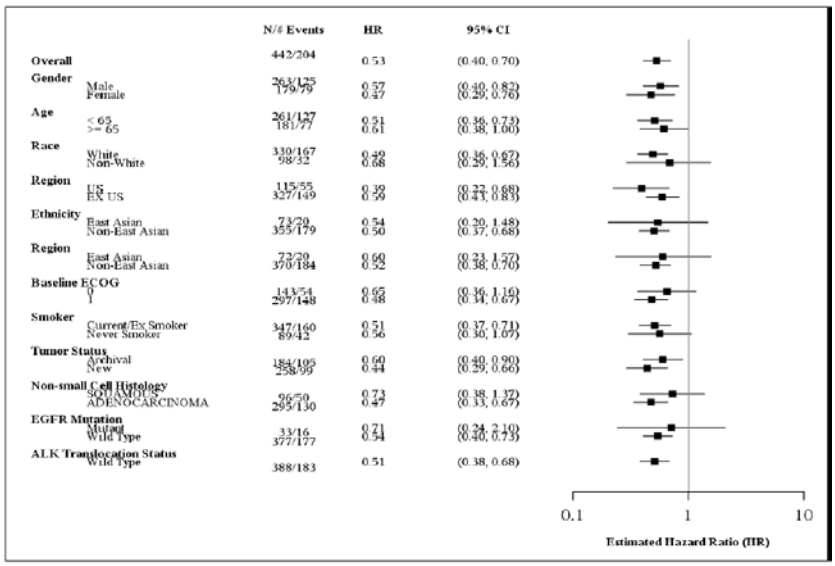


Figure 33: Forest Plot of OS HR by subgroup factors - Pembrolizumab treatment groups pooled vs docetaxel –ITT population (TPS≥ 50%)

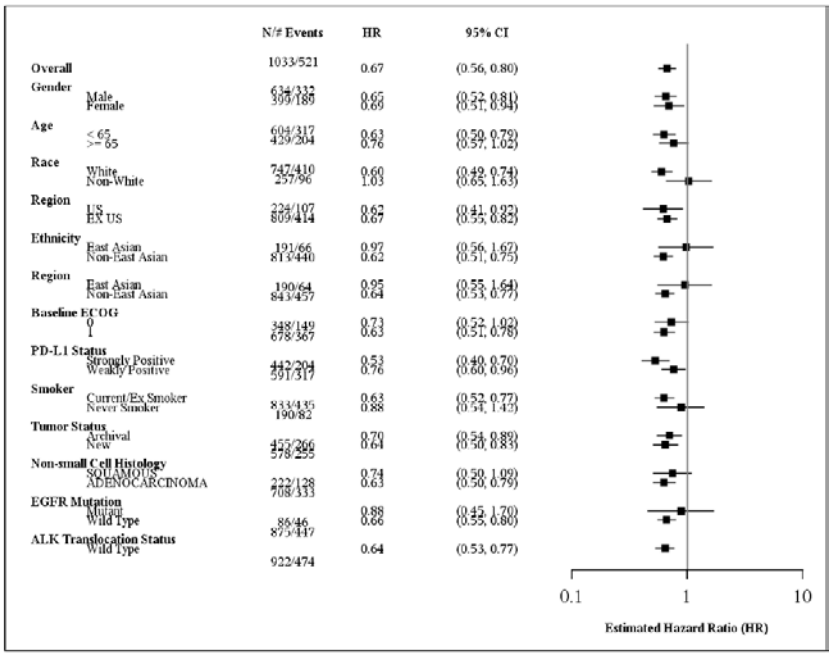


Figure 34: Forest Plot of OS HR by subgroup factors - Pembrolizumab treatment groups pooled vs docetaxel –ITT population (TPS≥ 1%)

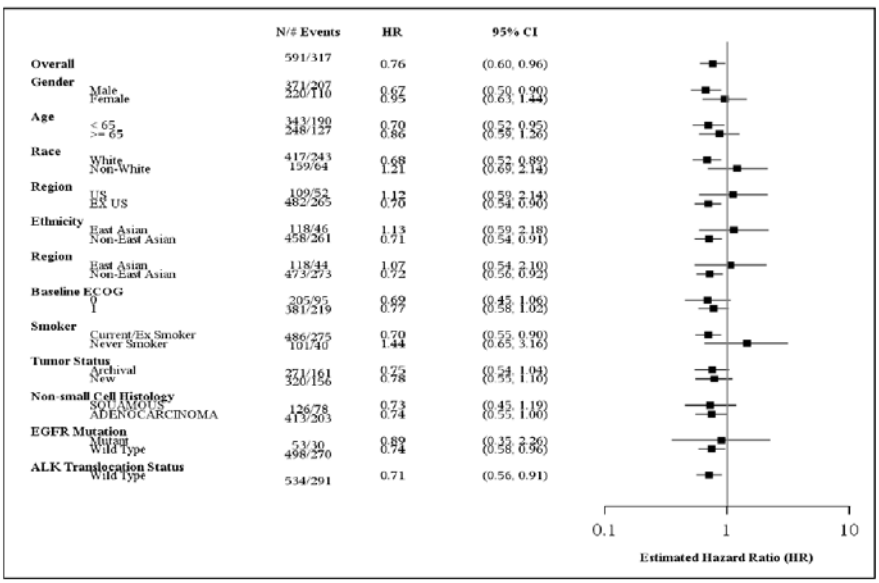


Figure 35: Forest Plot of OS HR by subgroup factors - Pembrolizumab treatment groups pooled vs docetaxel –ITT population (1%≤TPS<50%)

PFS subgroups analysis

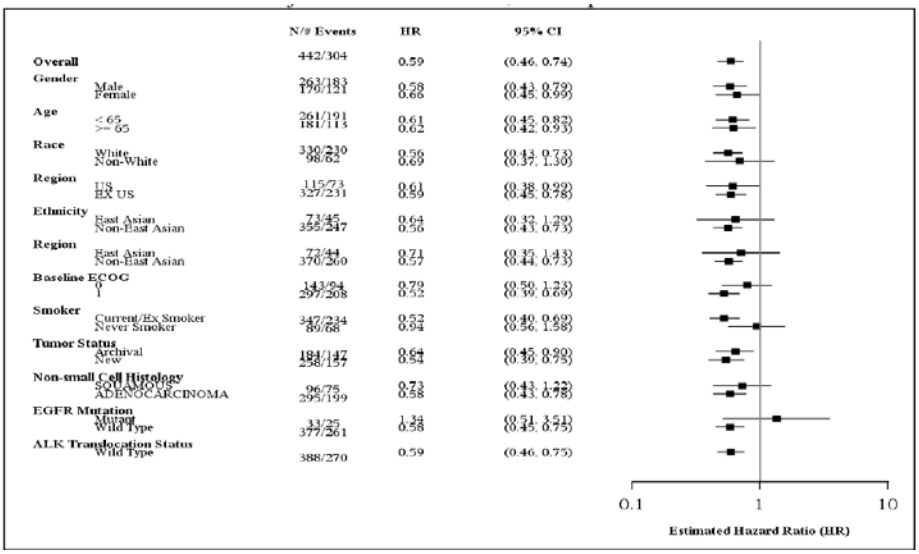


Figure 36: Forest Plot of PFS HR by subgroup factors - IRC assessment (primary censoring rule) – Pembrolizumab treatment groups pooled vs docetaxel –ITT population (TPS≥ 50%)

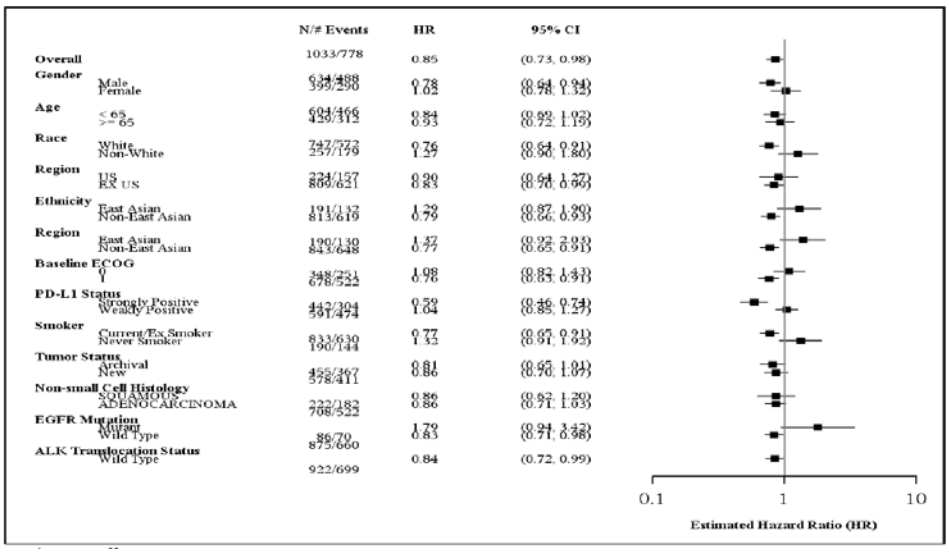


Figure 37: Forest Plot of PFS HR by subgroup factors - IRC assessment (primary censoring rule) – Pembrolizumab treatment groups pooled vs docetaxel –ITT population (TPS≥ 1%)

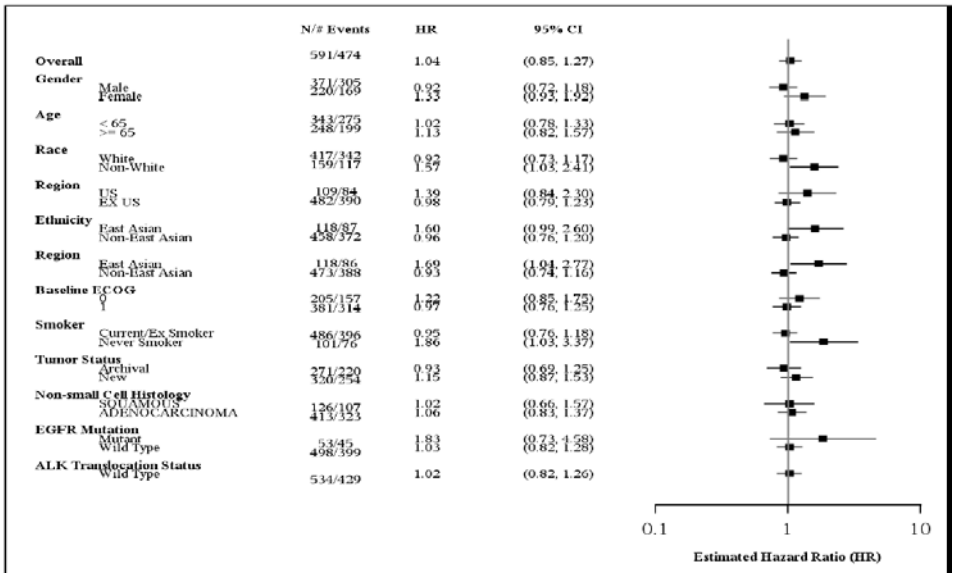


Figure 38: Forest Plot of PFS HR by subgroup factors - IRC assessment (primary censoring rule) – Pembrolizumab treatment groups pooled vs docetaxel –ITT population (1%≤TPS<50%)

ORR subgroups analysis

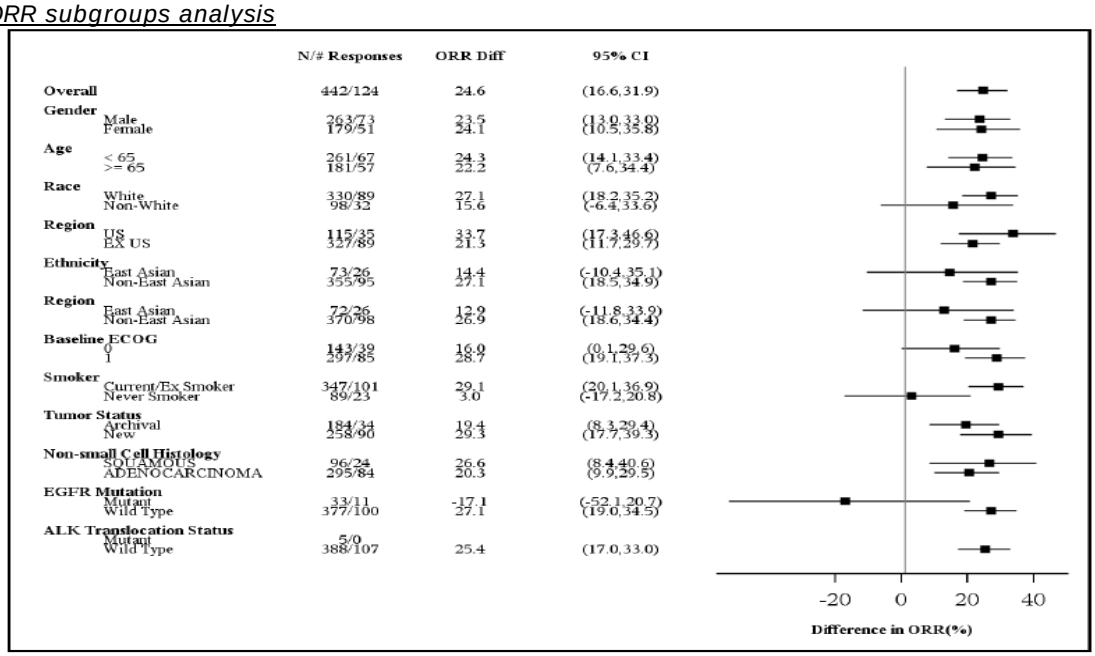


Figure 39: Forest Plot of ORR by subgroup factors - IRC assessment – Pembrolizumab treatment groups pooled vs docetaxel –ITT population (TPS≥ 50%)

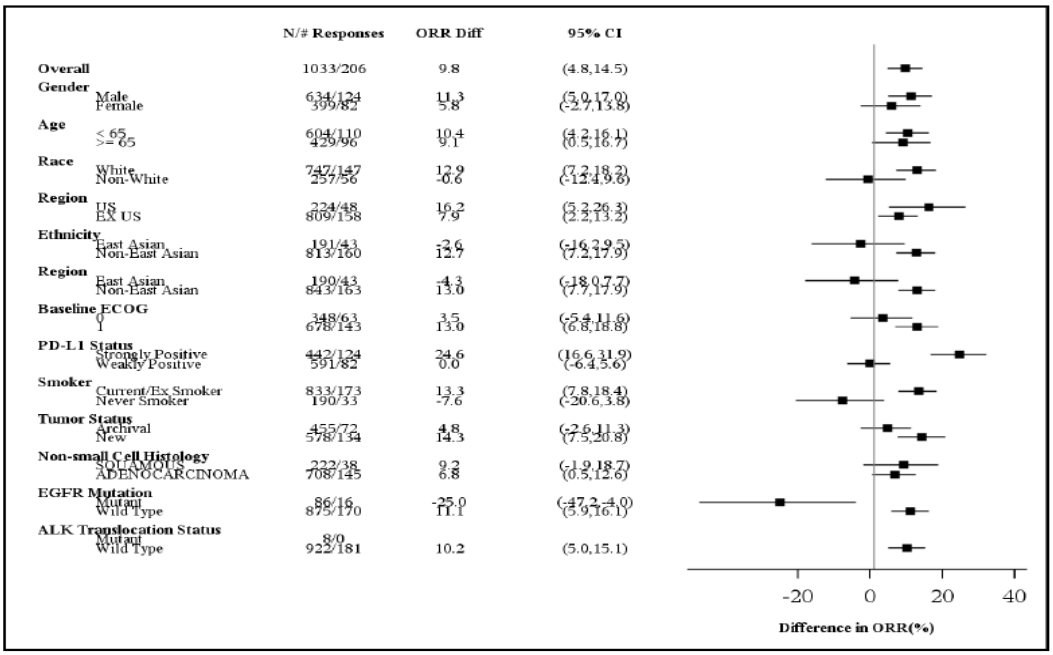


Figure 40: Forest Plot of ORR by subgroup factors - IRC assessment – Pembrolizumab treatment groups pooled vs docetaxel –ITT population (TPS≥ 1%)

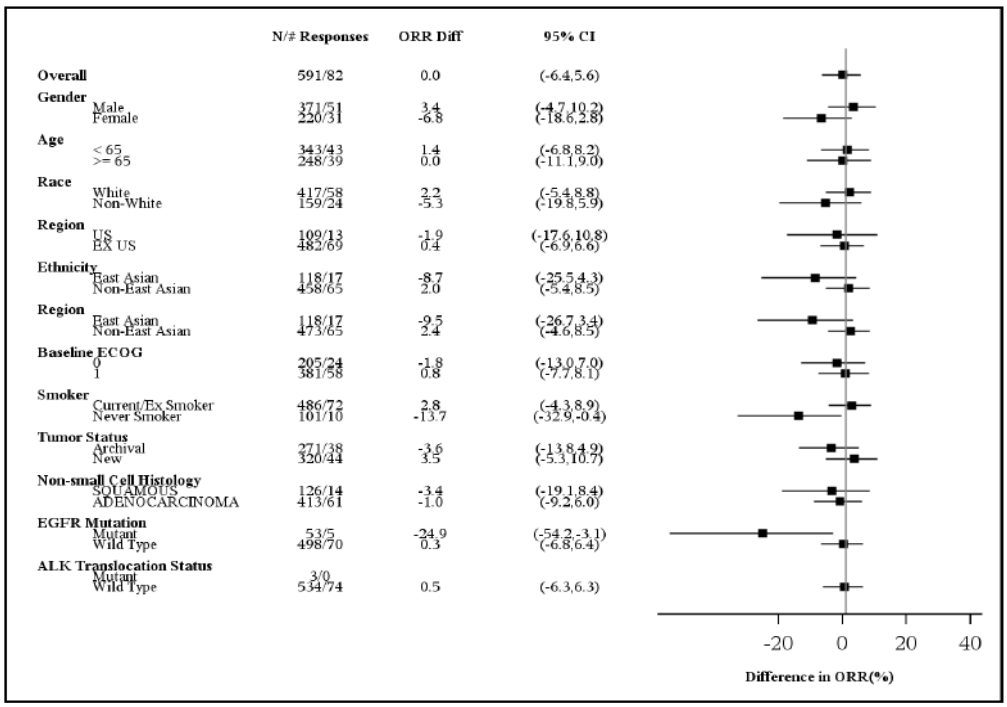


Figure 41: Forest Plot of ORR by subgroup factors - IRC assessment – Pembrolizumab treatment groups pooled vs docetaxel – ITT population (1%≤TPS<50%)

Table 36: Subgroup analysis in subjects with one and ≥2 lines of prior therapy

	1 line of prior therapy		≥ 2 lines of prior therapies	
Pembrolizumab	2 mg/m² (n=243)	10 mg/m² (n=235)	2 mg/m² (n=93)	10 mg/m² (n=103)
OS (HR vs. docetaxel)	0.63	0.51	1.21	0.81
PFS (HR vs. docetaxel)	0.84	0.72	1.05	0.97

ORR (difference in % vs. docetaxel)	12.7	13.1	-0.6	2.2

Summary of main study

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

Table 37: Summary of Efficacy for trial KEYNOTE-010

Title: *A Phase II/III Randomized Trial of Two Doses of MK-3475 versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer*			
Study identifier	KEYNOTE-010 EudraCT NUMBER: 2012-004391-19		
Design	Open-label, randomized (1:1:1) phase 2/3 trial of IV pembrolizumab at two dosing schedules vs docetaxel, in PD-L1 positive NSCLC patients who experienced disease progression after platinum-containing systemic therapy.		
Hypothesis	Superiority		
Treatments groups	pembrolizumab 2 mg/kg		IV infusion given once every 3 weeks 345 patients randomized
	pembrolizumab 10 mg/kg		IV infusion given once every 3 weeks 346 patients randomized
	docetaxel		75 mg/m^2 by IV infusion over 1 hour once every 3 weeks 343 patients randomized
Endpoints and definitions	Co-Primary endpoint	OS	the time from randomization to death due to any cause.
	Co-Primary endpoint	PFS	the time from randomization to documented PD or death due to any cause, whichever occurred first, per RECIST 1.1 based on blinded independent radiologists' review.
	Secondary endpoint	ORR	proportion of patients in the analysis population with a CR or PR, based on blinded independent radiologists' review per RECIST 1.1.
	Secondary endpoint	Response duration	time from first documented evidence of CR or PR until disease progression or death.
Database lock	30 September 2015		

Results and Analysis

Analysis description	**Primary Analysis**			
Time point description	Median follow up: 13.1 months			
Analysis population	Intent to treat: **TPS ≥ 50%**			
Descriptive statistics and effect estimate per comparison	Treatment group	pembrolizumab 2 mg/kg Q3W	pembrolizumab 10 mg/kg Q3W	docetaxel
	Number of subject	139	151	152
	Co-primary endpoints			
	OS N. with events n (%)	58 (41.7)	60 (39.7)	86 (56.6)
	Median OS months (95% CI)	14.9 (10.4,..)	17.3 (11.8,..)	8.2 (6.4, 10.7)
	Hazard Ratio treatment vs docetaxel (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	
	p-value (one sided log-rank test)	0.00024	0.00002	
	PFS (IRC RECIST 1.1) N. with events (%)	89 (64.0)	97 (64.2)	118 (77.6)
	Median PFS months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)

	Hazard Ratio treatment vs docetaxel (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	
	p-value (one sided log-rank test)	0.00009	0.00007	
	Secondary endpoints			
	ORR (IRC-RECIST 1.1) (95% CI)	30.2 (22.7, 38.6)	29.1 (22.0, 37.1)	7.9 (4.1, 13.4)
	Difference % vs docetaxel (95% CI)	23.3 (14.8, 32.1)	22.2 (14.0, 30.7)	
	p-value (one sided)	<0.00001	<0.00001	
	Response Duration (IRC-RECIST 1.1) Pts with response (n)	42	44	12
	Median in days (range)	Not reached (20+-512+)	Not reached (64+-542+)	246 (63+-268+)
	Median time to response in days (range)	65 (38-141)	64 (44-440)	65 (59-247)
Analysis population	**TPS ≥ 1%**			
Descriptive statistics and effect estimate per comparison	Treatment group	pembrolizumab 2 mg/kg Q3W	pembrolizumab 10 mg/kg Q3W	docetaxel
	Number of subject	344	346	343
	Co-primary endpoints			
	OS N. with events n (%)	172 (50.0)	156 (45.1)	193 (56.3)
	Median OS months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
	Hazard Ratio treatment vs docetaxel (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	
	p-value (one sided log-rank test)	0.00076	<0.00001	
	PFS (IRC RECIST 1.1) N. with events (%)	266 (77.3)	255 (73.7)	257 (74.9)
	Median PFS months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
	Hazard Ratio treatment vs docetaxel (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	
	p-value (one sided log-rank test)	0.06758	0.00462	
	Secondary endpoints			
	ORR (IRC-RECIST 1.1) (95% CI)	18.0 (14.1, 22.5)	18.5 (14.5, 23.0)	9.3 (6.5, 12.9)
	Difference % vs docetaxel (95% CI)	8.7 (3.6, 13.9)	9.1 (4.1, 14.3)	
	p-value (one sided)	0.00045	0.00024	
	Response Duration (IRC-RECIST 1.1) Pts with response (n)	62	64	32
	Median in days (range)	Not reached (20+-610+)	Not reached (64+-542+)	189 (43+-268+)
	Median time to response in days (range)	65 (38-217)	64 (44-444)	65 (41-250)

Clinical studies in special populations

Table 38: Efficacy results by age categories

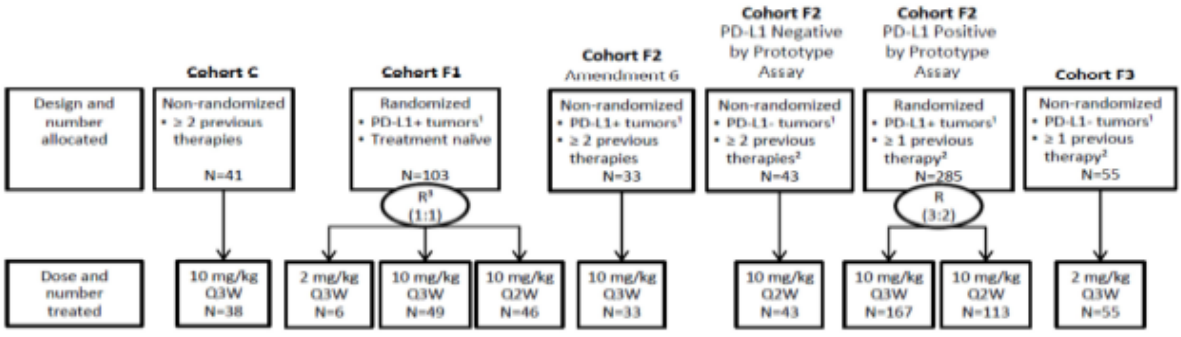
		TPS ⩾ 50%		TPS >1%	
Pembrolizumab		2 mg/m²	10 mg/m²	2 mg/m²	10 mg/m²
OS (HR vs. docetaxel)	<65 years	0.63	0.43	0.69	0.55
	65-74 years	0.31	0.86	0.76	0.79
	75-84 years	0.56	0.26	0.78	0.31
PFS (HR vs. docetaxel)	<65 years	0.67	0.61	0.88	0.78
	65-74 years	0.58	0.82	1.04	0.99
	75-84 years	0.46	0.32	0.61	0.48
ORR (difference in % vs. docetaxel)	<65 years	19.8	24.2	8.1	10.4
	65-74 years	26.7	17.7	5.2	5.5
	75-84 years	34.8	29.5	21.2	23.3

Supportive study

To support the claimed indication, an interim CSR from the NSCLC parts (Cohort C and Cohort F) of the multicenter, open label phase I P001 trial, whose data on melanoma patients were submitted at the time of the initial Marketing Authorisation Application, was provided with a minimum of 6-months of follow-up (database cut-off of 23-Jan-2015).

Different pembrolizumab doses and schedules were tested across NSCLC Cohorts: 10 mg/kg every 3 weeks, in patients with prior systemic therapy (Cohort C), PD-L1 positive treatment naïve patients (Cohort F1) and PD-L1 positive previously treated patients (Cohort F2); 10 mg/kg every 2 weeks in PD-L1 positive treatment naïve patients (Cohort F1) and in previously-treated patients both PD-L1 negative or positive (Cohort F2); 2 mg/kg every 3 weeks in PD-L1 positive treatment naïve patients (Cohort F1) and PD-L1 positive previously treated patients.

A total of 560 NSCLC patients were allocated to Cohorts C and F of study P001.



- Response assessment:
  - Primary measure: ORR by RECIST v 1.1 per independent central review
  - Secondary measure: immune-related response criteria (irRC) per investigator assessment
- Pembrolizumab was given until disease progression, unacceptable toxicity, or death

IRC = Independent central review; irRC = Immune-related response criteria; ORR = Overall response rate; PD-L1 = Programmed cell death 1 ligand; Q2W = every 2 weeks; Q3W = every 3 weeks; R = Randomized.
[1]Tumor PD-L1 expression was determined by a prototype assay to inform enrollment. Samples were independently reanalyzed using a clinical trial/market-ready immunohistochemistry assay.
[2]Including ≥ therapy with platinum-containing doublet.
[3]First 11 subjects randomized to 2mg/kg Q3W or 10 mg/kg Q3W. The remaining 92 subjects were randomized to 10mg/kg Q2W or Q3W.

Figure 42: Study P001- NSCLC Expansion Cohorts (N=560 allocated)

The median duration of follow up is 15.7 months (range 10.0 to 32.3 months) for Cohort C, Cohort F2, and Cohort F1. Due to the late starting of enrollment, Cohort F-3 has a median follow-up of 7.7 months (range 6.4 to 9.7 months).

The baseline characteristics were well balanced across the dosing arms. Overall, the median age was 64 years; most of patients were former smokers (66.9%) and had metastatic disease (96.2%). The non-squamous was the most common histology (81.1%), and in the majority of patients (67.2%) ≥2 prior lines of therapy were administered. Fifty-eight (10.5%) patients presented baseline brain metastases.

The study primary endpoint was ORR, based on RECIST 1.1 by IRC. The secondary measure for assessment of tumor response (ORR) was based on irRC by Investigator assessment. Disease control rate (DCR), duration of response, and PFS based on both RECIST 1.1 and irRC, and OS were evaluated as secondary endpoints.

The pre-specified primary efficacy analysis was conducted in the *Previously Treated Primary Efficacy Population*, a subset of 61 patients in Cohort F2 comprising the Biomarker Validation Set who had tumor PD-L1 expression ≥50% at baseline, as determined by a different IHC assay using the 22C3 clone, a Market-Ready Assay. All patients previously received a platinum-based chemotherapy and experienced progression.

Supportive analyses were also conducted in *Previously Treated Validation Population* including 223 patient from Cohort F2 who progressed after at least platinum-based cytotoxic chemotherapy, were part of the Biomarker Validation Set and had PD-L1 expression ≥1% at baseline (patients).

Table 39: Efficacy results in Previously Treated Primary Efficacy Population (61 patients PD-L1 ≥50%) and Previously Treated Validation Population (223 patients PD-L1 ≥1%) (All Subject as Treated)

Parameter	***Previously Treated Primary Efficacy Population*** **(n=61 PD-L1 ≥50%)**	***Previously Treated Validation Population*** **(n=223 PD-L1 ≥1%)**
ORR RECIST 1.1 by IRC (%) 95% CI	42.6 (30.0, 55.9)	22.9 (17.5, 28.9)
ORR irRC by Investigator (%) 95% CI	45.9 (33.1, 59.2)	26.9 (21.2, 33.2)
DCR RECIST 1.1 by IRC (%) median (range)	57.4 (44.1, 70.0)	51.1 (44.4, 57.9)
Response duration RECIST 1.1 by IRC (months) median (range)	Not reached (2.1+-13.4+)	Not reached (1.0+-13.4+)
PFS RECIST 1.1 by IRC (months) median (95%CI)	6.3 (2.1, 10.7)	4.1 (2.3, 4.5)
OS (months) median (95%CI)	15.5 (11.1, …)	15.5 (11.3, …)

The *Total Previously Treated Efficacy Population* included any subject from Part C or Cohort F2 who experienced progression of disease after at least platinum-based cytotoxic chemotherapy and was part of the Biomarker Training or Validation Set (394 patients). One hundred-thirteen of these patients were strongly PD-L1 positive (TPS ≥50%).

Table 40: Summary of Best Overall Response Based on IRC Assessment per RECIST 1.1 - Total Previously-Treated Efficacy Population by PD-L1 (Irrespective of Stability Window) (All Subjects as Treated)

Response Evaluation	PS>=50% (N=113)			PS=1-49% (N=144)			PS<1% (N=86)			Unknown (N=51)			Total (N=394)		
	n	%	95% CI†	n	%	95% CI†	n	%	95% CI†	n	%	95% CI†	n	%	95% CI†
Complete Response (CR)	1	0.9	(0.0, 4.8)	0	0.0	(0.0, 2.5)	0	0.0	(0.0, 4.2)	2	3.9	(0.5, 13.5)	3	0.8	(0.2, 2.2)
Partial Response (PR)	40	35.4	(26.6, 45.0)	19	13.2	(8.1, 19.8)	7	8.1	(3.3, 16.1)	7	13.7	(5.7, 26.3)	73	18.5	(14.8, 22.7)
Overall Response (CR+PR)	**41**	**36.3**	**(27.4, 45.9)**	**19**	**13.2**	**(8.1, 19.8)**	**7**	**8.1**	**(3.3, 16.1)**	**9**	**17.6**	**(8.4, 30.9)**	**76**	**19.3**	**(15.5, 23.5)**
Stable Disease (SD)	18	15.9	(9.7, 24.0)	36	25.0	(18.2, 32.9)	19	22.1	(13.9, 32.3)	14	27.5	(15.9, 41.7)	87	22.1	(18.1, 26.5)
NonCR/NonPD (NN)	3	2.7	(0.6, 7.6)	7	4.9	(2.0, 9.8)	4	4.7	(1.3, 11.5)	4	7.8	(2.2, 18.9)	18	4.6	(2.7, 7.1)
Disease Control (CR+PR+SD+NN)	**62**	**54.9**	**(45.2, 64.2)**	**62**	**43.1**	**(34.8, 51.6)**	**30**	**34.9**	**(24.9, 45.9)**	**27**	**52.9**	**(38.5, 67.1)**	**181**	**45.9**	**(40.9, 51.0)**
Progressive Disease (PD)	34	30.1	(21.8, 39.4)	62	43.1	(34.8, 51.6)	41	47.7	(36.8, 58.7)	15	29.4	(17.5, 43.8)	152	38.6	(33.7, 43.6)
Non-evaluable (NE)	3	2.7	(0.6, 7.6)	3	2.1	(0.4, 6.0)	1	1.2	(0.0, 6.3)	1	2.0	(0.0, 10.4)	8	2.0	(0.9, 4.0)
No Assessment	14	12.4	(6.9, 19.9)	17	11.8	(7.0, 18.2)	14	16.3	(9.2, 25.8)	8	15.7	(7.0, 28.6)	53	13.5	(10.2, 17.2)

Only confirmed responses are included in this table.
†Based on binomial exact confidence interval method.
Database Cutoff Date: 23JAN2015

Data Source: [Sec. 5.3.5.2.P001V04.16.4]

Table 41: Summary of Time to Response and Response Duration IRC Assessment per RECIST 1.1 in subjects with confirmed response - Total Previously-Treated Efficacy Population by PD-L1 (Irrespective of Stability Window) (All Subjects as Treated)

	PS>=50% (N=113)	PS=1-49% (N=144)	PS<1% (N=86)	Unknown (N=51)	Total (N=394)
Number of Subjects with Response†	41	19	7	9	76
Time to Response† (months)					
Mean (SD)	2.5 (1.3)	3.5 (2.0)	3.1 (1.1)	7.0 (7.1)	3.4 (3.0)
Median (Range)	2.1 (1.4-7.0)	2.2 (1.9-8.1)	3.3 (1.6-4.2)	4.1 (2.0-19.4)	2.1 (1.4-19.4)
Response Duration‡ (months)					
Median (Range)§	23.3 (2.1+ - 23.3)	12.5 (1.9+ - 12.5)	Not reached (1.0+ - 15.6+)	Not reached (4.0 - 14.5+)	23.3 (1.0+ - 23.3)
Number of Non-progressing (non-PD) Subjects (%)	31 (76)	15 (79)	6 (86)	7 (78)	59 (78)

† 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 non-PD at the last assessment (censored) for the patient with the minimum and maximum response duration within the treatment group.
Database Cutoff Date: 23JAN2015

Data Source: [16.4]

Table 42: Summary of PFS based on IRC Assessment per RECIST 1.1 - Total Previously-Treated Efficacy Population by PD-L1 (Irrespective of Stability Window) (All Subjects as Treated)

	PS>=50% (N=113)	PS=1-49% (N=144)	PS<1% (N=86)	Unknown (N=51)	Total (N=394)
Number (%) of PFS Events	78 (69.0)	122 (84.7)	77 (89.5)	36 (70.6)	313 (79.4)
Person-Months	807	615	334	336	2091
Event Rate/100 Person-Months (%)	9.7	19.8	23.1	10.7	15.0
Median PFS (Months)§	5.0	2.3	2.1	4.0	3.0
95% CI for Median PFS§	(2.3,8.6)	(2.1,3.6)	(2.0,3.1)	(2.3,10.2)	(2.2,4.0)
PFS rate at 3 Months in % §	56.3	45.7	40.0	60.4	49.3
PFS rate at 6 Months in % §	49.0	27.2	20.2	42.9	34.0

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
§ From product-limit (Kaplan-Meier) method for censored data.
(Database Cutoff Date: 23JAN2015)

Data Source: [16.4]

Table 43: Summary of Overall Survival - Total Previously-Treated Efficacy Population by PD-L1 (Irrespective of Stability Window) (All Subjects as Treated)

	PS>=50% (N=113)	PS=1-49% (N=144)	PS<1% (N=86)	Unknown (N=51)	Total (N=394)
Death (%)	54 (47.8)	84 (58.3)	56 (65.1)	29 (56.9)	223 (56.6)
Median Survival (Months)[§]	15.7	8.8	8.6	13.1	11.3
95% CI for Median Survival[§]	(11.1,.)	(6.2,14.3)	(5.5,12.0)	(5.7,20.2)	(8.8,14.0)
OS rate at 6 Months in % [§]	72.4	58.9	57.8	62.3	63.0
OS rate at 12 Months in % [§]	57.7	45.8	39.2	53.1	48.7

OS: Overall survival.
[§] From product-limit (Kaplan-Meier) method for censored data.
(Database Cutoff Date: 23JAN2015)

Data Source: [16.4]

Cohort F-3 (PD-L1 positive previously treated population - 2 mg/kg Q3W)

Cohort F-3 was added with the last amendment to the protocol to study the likely dose for pembrolizumab in subjects with NSCLC, i.e., 2 mg/kg Q3W, therefore follow up is shortest in these subjects with a minimum of 27 weeks of follow up. The inclusion criteria for Cohort F-3 are identical to Cohort F-2. The only difference between these cohorts is that in F-3, all subjects received pembrolizumab 2 mg/kg Q3W, and in F-2 all subjects received pembrolizumab 10 mg/kg Q3W or Q2W.

For Cohort F-3 (n=55) the cumulative ORR at Week 27 was 14.7% (95% CI: 7.6, 27.3) compared to 21.1% (95% CI: 16.8, 26.5) for PD-L1 pos. subjects of F2 (n=280). 6-month PFS rates were 33.6% for Cohort F-3 and 37.2% for Cohort F-2. Cohort F-3 had a 6-month OS rate of 58.8%, and the randomized subjects of Cohort F-2 had an OS rate of 66.0%.

Development of Companion diagnostic

Dako has been collaborating with MSD in the development of a companion diagnostic immunohistochemical (IHC) assay, PD-L1 IHC 22C3 pharmDx, to detect PD-L1 protein expression in formalin-fixed, paraffin embedded (FFPE) Non-Small Cell Lung Carcinoma (NSCLC) tissue samples.

This commercial ready assay (CRA) (abbreviated 'Dako PD-L1 CRA' in this document) uses an anti PD-L1 mouse monoclonal antibody MEB037.22C3.138 ('22C3') that is optimized for automated use on the Dako Autostainer Link 48 platform for detection of PD-L1 expression.

An immunohistochemistry (IHC) clinical trial assay (CTA) (abbreviated 'Dako PD-L1 CTA' in this document), was used to screen patients prior to enrolment into the pembrolizumab KEYNOTE 010 (see clinical efficacy).

The primary difference between Dako PD-L1 CTA and Dako PD-L1 CRA is that the primary antibody for the CTA IHC assay was supplied by Merck, whereas the primary antibody for the CRA IHC assay is manufactured by Dako.

Table 44: CTA and CRA similarities and differences

Parameter	CTA	CRA
Scoring Criteria	The same scoring criteria was used for both CTA and CRA pathology review. Evaluation of PD-L1 staining in tumor cells. Mononuclear inflammatory cells or stroma not included.	
Location of PD-L1 Performance (staining and evaluation)	LabCorp- Los Angeles, CA, USA	
Use in Keynote-010	Prospective PD-L1 IHC testing of patient specimens for enrollment eligibility for Keynote study P010.	Retrospective PD-L1 IHC testing of banked, unstained patient specimens from Keynote study P010.

A bridging study was conducted to establish the clinical performance of the CRA, in conjunction with an accompanying statistical analysis plan (SAP). (*Retrospective Testing of Banked NSCLC Tissue Samples Using PD-L1 IHC 22C3 pharmDx CRA to compare and Evaluate Clinical Performance Based on Clinical Outcomes from Clinical Study MK-3475- 010/KEYNOTE-010 that enrolled on a CTA)*.

The primary objectives in the SAP were:

1. To estimate agreement between the CTA and the CRA for the IHC outcomes of being "PD-L1 Negative" or "PD-L1 Positive" or "PD-L1 Strongly Positive" (1% and 50% cut-off points).

2. To test the primary hypotheses of KEYNOTE-010 comparing pembrolizumab to docetaxel within the "PD-L1 positive" and "PD-L1 strongly positive" subpopulations with respect to the CRA under an intent-to-treat (ITT) framework.

3. To conduct a sensitivity analysis to understand the plausible range for the hazard ratio estimated based on the CRA in the "PD-L1 positive" and "PD-L1 strongly positive" subpopulations under an intent-to-diagnose (ITD) framework.

Results

Bridging Analysis

Dako PD-L1 CTA was used as the reference study and negative percent agreement (NPA) and positive percent agreement (PPA) estimates were calculated for tumour proportion score 1% (cut-off for PD-L1 positive) and 50% (cut-off for PD-L1 strongly positive) along with 95% confidence intervals.

Agreement Estimates

Results in the panels using the 1% and 50% cut-offs are reflected in the table below.

For the 1% cut-off, PD-L1 positive is defined as TPS $\geqslant$ 1% and PD-L1 negative is defined as TPS < 1%, and for the 50% cut-off PD-L1 positive is defined as TPS $\geqslant$ 50% and PD-L1 negative is defined as TPS < 50%. Note that the category of TPS 1-49% is considered to be PD-L1 positive for the 1% cut-off, and is considered to be PD-L1 negative for the 50% cut-off.

Table 45: Performance summary at cut-offs 1% and 50% PD-L1 expression

Panel 6. Performance Summary, Cutoff = 1%

CTA (Reference Method)	CRA		Total	Performance Characteristic [95% Confidence Interval]
	Negative	Positive		
Negative	294	17	311	NPA=94.5% [91.4%-96.6%]
Positive	139	557	696	PPA=80.0% [76.9%-82.8%]
Total	433	574	1,007	

Panel 7. Performance Summary, Cutoff = 50%

CTA (Reference Method)	CRA		Total	Performance Characteristic [95% Confidence Interval]
	Negative	Positive		
Negative	697	12	709	NPA=98.3% [97.1%-99.0%]
Positive	80	218	298	PPA=73.2% [67.9%-77.9%]
Total	777	230	1,007	

Imputation Analysis

Template Title: Study Report
Template No/Rev: TX01177.02
Effective Date: See ECO C18835
Document Type: Template

Of the 2699 patients in the data set received, 477 patients (none of which belong to the ITT) had no CTA or CRA PD-L1 score and were excluded from all subsequent evaluation. For the remaining 2222

patients, referred to hereafter as the imputation analysis set (IAS), all CTA or CRA scores lying outside the 6-month stability window were set to missing.

Panel 8 and 9 show the resulting breakdown of the CTA and CRA PD-L1 status variables in the IAS and ITT respectively.

Table 46: PD-L1 status breakdown for CTA vs. CRA for IAS patients

	CRA PD-L1 Status			
CTA PD-L1 Status	NEGATIVE	WEAKLY POSITIVE	STRONGLY POSITIVE	MISSING
NEGATIVE	294	17	0	404
WEAKLY POSITIVE	136	250	12	427
STRONGLY POSITIVE	3	77	218	323
MISSING	2	1	0	58

Table 47: PD-L1 status breakdown for CTA vs. CRA for ITT patients

	CRA PD-L1 Status			
CTA PD-L1 Status	NEGATIVE	WEAKLY POSITIVE	STRONGLY POSITIVE	MISSING
NEGATIVE	0	0	0	0
WEAKLY POSITIVE	92	193	4	293
STRONGLY POSITIVE	2	56	159	218
MISSING	0	1	0	15

Four distinct discordant groups were identified as highlighted in the table below.

Table 48: Overview of CTA vs. CRA agreement within the stability window

	CRA PD-L1 Status		
CTA PD-L1 Status	TPS < 1%	TPS 1-49%	TPS ≥ 50%
TPS < 1%	294	17	0
TPS 1-49%	136	250	12
TPS ≥ 50%	3	77	218

Blue, purple, red and green highlights indicate discordant specimens from various categories.

For the 1% cut-off:

- Of the 136 specimens that were PD-L1 positive with TPS 1-49% by Dako PD-L1 CTA and became PD-L1 negative by Dako PD-L1 CRA, accounting for 95% of the discordant specimens in this category.

- Of the 17 specimens that were PD-L1 negative by Dako PD-L1 CTA and became PD-L1 positive with TPS 1-49% by Dako PD-L1 CRA, accounting for 94% of the discordant specimens in this category.

For the 50% cut-off:

- Of the 77 that were PD-L1 positive with Dako PD-L1 CTA and became PD-L1 negative with TPS 1-49% by Dako PD-L1 CRA, accounting for 61% of the discordant specimens in this category.

- Of the 12 specimens that were PD-L1 negative and had TPS 1-49% by Dako PD-L1 CTA and became PD-L1 positive by Dako PD-L1 CRA, accounting for 83% of the discordant specimens in this category.

Analysis of Overall Survival (OS) and Progression Free Survival (PFS):

For the bridging study, results from the analysis of overall survival (OS) in Panel 12-14 show that for the patients with a CRA measurement that was within the stability window (the complete case analysis) both the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W doses are superior to docetaxel at the significance threshold of nominal p-value <0.00825 (pre-specified in the protocol for the primary analyses in using the CTA) for both the strongly positive and positive PD-L1 status definitions.

Table 49: Analysis of OS subjects with CRA strongly positive (TPS ≥50%), within stability window (Panel 12)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	47	25 (53.2)	244.4	10.2	7.2 (4.4, 8.3)	31.3 (14.6, 49.6)	---	---
MK-3475 2 mg/kg Q3W	56	18 (32.1)	426.8	4.2	Not Reached (9.3,	67.5 (52.8, 78.5)	0.45 (0.24, 0.84)	0.00541
MK-3475 10 mg/kg Q3W	60	19 (31.7)	492.1	3.9	Not Reached (8.3,	64.9 (49.5, 76.6)	0.29 (0.15, 0.56)	0.00006
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.29 (0.66, 2.54)	0.44670

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

‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status as assigned by the IVRS system (Strongly Positive , Weakly Positive, and Unknown Positive, where "Unknown" means PD-L1 status as Strongly or Weakly positive by the CTA was unknown at time of enrollment).

§One-sided p-value based on log-rank test.

‖Two-sided p-value based on log-rank test.

Database Cutoff Date: 30SEP2015

Table 50: Analysis of OS subjects with CRA positive (TPS ≥1%), within stability window (Panel 13)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	131	67 (51.1)	732.7	9.1	7.5 (6.3, 9.9)	42.2 (31.5, 52.5)	---	---
MK-3475 2 mg/kg Q3W	140	59 (42.1)	1088.0	5.4	11.8 (9.6, .)	64.2 (54.9, 72.0)	0.54 (0.37, 0.78)	0.00045
MK-3475 10 mg/kg Q3W	142	59 (41.5)	1076.2	5.5	12.0 (8.7, .)	57.8 (48.0, 66.4)	0.57 (0.39, 0.82)	0.00115
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.02 (0.71, 1.47)	0.91537

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

‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status as assigned by the IVRS system (Strongly Positive , Weakly Positive, and Unknown Positive, where "Unknown" means PD-L1 status as Strongly or Weakly positive by the CTA was unknown at time of enrollment).

§One-sided p-value based on log-rank test.

‖Two-sided p-value based on log-rank test.

Database Cutoff Date: 30SEP2015

Table 51: Analysis of OS subjects with CRA negative (TPS <1%), within stability window (Panel 14)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	23	13 (56.5)	99.8	13.0	6.2 (2.0, 8.8)	19.9 (3.6, 45.6)	---	---
MK-3475 2 mg/kg Q3W	38	24 (63.2)	250.3	9.6	6.8 (5.3, 9.3)	35.6 (19.1, 52.5)	0.61 (0.29, 1.29)	0.09627
MK-3475 10 mg/kg Q3W	33	15 (45.5)	236.6	6.3	9.6 (6.8, .)	59.3 (38.8, 75.0)	0.53 (0.22, 1.28)	0.07739
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg/kg Q3W							1.73 (0.87, 3.43)	0.11489

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

‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status as assigned by the IVRS system (Strongly Positive , Weakly Positive, and Unknown Positive, where "Unknown" means PD-L1 status as Strongly or Weakly positive by the CTA was unknown at time of enrollment).

§One-sided p-value based on log-rank test.

‖Two-sided p-value based on log-rank test.

Database Cutoff Date: 30SEP2015

Panels 17-19 show the complete case analyses for progression-free survival based on central assessment per RECIST 1.1. The point estimates and trend are generally consistent with those analyses conducted based on CTA regardless of sample stability. However, due to reduced sample size, only the MK-3475 10 mg/kg vs. docetaxel comparison in the PD-L1 strongly positive patients met the

significance threshold of nominal p-value < 0.001 (pre-specified in the protocol for the primary analyses in patients irrespective of stability window).

Table 52: Analysis of PFS subjects with CRA strongly positive (TPS≥ 50%), within stability window (Panel 17)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 4 in % † (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	47	33 (70.2)	155.0	21.3	3.9 (2.0, 4.3)	45.0 (29.3, 59.5)	---	---
MK-3475 2 mg/kg Q3W	56	33 (58.9)	301.6	10.9	5.9 (4.2, 9.0)	68.8 (54.7, 79.3)	0.47 (0.28, 0.80)	0.00221
MK-3475 10 mg/kg Q3W	60	34 (56.7)	339.3	10.0	4.8 (2.8, .)	61.3 (47.7, 72.3)	0.41 (0.24, 0.70)	0.00037
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg.kg Q3W							0.99 (0.59, 1.66)	0.96475

IRC: Independent Review Committee.

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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status as assigned by the IVRS system (Strongly Positive , Weakly Positive, and Unknown Positive, where "Unknown" means PD-L1 status as Strongly or Weakly positive by the CTA was unknown at time of enrollment).

§ One-sided p-value based on log-rank test.

‖ Two-sided p-value based on log-rank test.

Database Cutoff Date: 30SEP2015

Table 53: Analysis of PFS subjects with CRA positive (TPS ≥1%), within stability window (Panel 18)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 4 in % † (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	131	94 (71.8)	444.6	21.1	3.8 (2.2, 4.2)	46.5 (37.2, 55.4)	---	---
MK-3475 2 mg/kg Q3W	140	97 (69.3)	686.6	14.1	4.9 (4.1, 6.2)	61.6 (52.9, 69.1)	0.68 (0.50, 0.92)	0.00578
MK-3475 10 mg/kg Q3W	142	103	677.3	15.2	4.0 (2.2, 4.6)	50.8 (42.3, 58.7)	0.79 (0.59, 1.06)	0.05767
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg.kg Q3W							0.90 (0.67, 1.19)	0.44912

IRC: Independent Review Committee.

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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status as assigned by the IVRS system (Strongly Positive , Weakly Positive, and Unknown Positive, where "Unknown" means PD-L1 status as Strongly or Weakly positive by the CTA was unknown at time of enrollment).

§ One-sided p-value based on log-rank test.

‖ Two-sided p-value based on log-rank test.

Database Cutoff Date: 30SEP2015

Table 54: Analysis of PFS subjects with CRA negative (TPS <1%), within stability window (Panel 19)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 4 in % † (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	23	15 (65.2)	69.8	21.5	2.8 (1.3, 6.4)	40.0 (19.3, 60.0)	---	---
MK-3475 2 mg/kg Q3W	38	35 (92.1)	127.6	27.4	2.2 (1.9, 3.3)	31.6 (17.7, 46.4)	1.38 (0.69, 2.75)	0.82193
MK-3475 10 mg/kg Q3W	33	27 (81.8)	110.7	24.4	2.1 (1.9, 6.0)	35.0 (19.3, 51.2)	1.26 (0.59, 2.69)	0.74335
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 2 mg/kg Q3W vs. MK-3475 10 mg.kg Q3W							1.43 (0.82, 2.49)	0.21119

IRC: Independent Review Committee.

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 ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status as assigned by the IVRS system (Strongly Positive , Weakly Positive, and Unknown Positive, where "Unknown" means PD-L1 status as Strongly or Weakly positive by the CTA was unknown at time of enrollment).

§ One-sided p-value based on log-rank test.

‖ Two-sided p-value based on log-rank test.

Database Cutoff Date: 30SEP2015

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study P010 is a randomized trial comparing two pembrolizumab doses (2 mg/kg and 10 mg/kg, every 3 weeks) versus docetaxel in locally advanced or metastatic (Stage IIIB/IV) PD-L1 positive (TPS≥1%) NSCLC patients previously treated with at least two cycles of a platinum-containing doublet. Patients with sensitizing EGFR mutation or ALK translocation were eligible provided they had progressed on both TKIs and platinum-based chemotherapy: although this inclusion may have introduced some further heterogeneity in the patient population, it is considered acceptable as it increases the external validity of the trial. Overall, the eligibility criteria are acceptable. The choice to include all NSCLC histologies limited to PD-L1 positive (TPS≥1%) tumours is based on data accumulating from Study P001 supporting the potential predictive value of PD-L1 expression regardless the histology, and is acceptable. Patients with brain metastases (non-active) were eligible, which is acceptable. From Amendment #8 onwards, i.e after the enrolment of the first 441 patients, newly obtained biopsies were required for the evaluation of PD-L1 expression. However, for patients in whom obtaining a new biopsy was deemed inappropriate, archival tissue was accepted. Whether changes in PD-L1 expression are to be expected during the natural course of the disease (i.e. in treatment naïve and after platinum-based chemotherapy and/or TKIs) is at present unknown.
The primary objectives of the study were to compare the OS and PFS per RECIST 1.1 by independent radiologists' review of previously treated NSCLC patients with tumour samples designated as strongly positive (TPS≥50%) PD-L1 stratum, and in the overall patient population that had tumour samples which were designated as PD-L1 positive. Safety and tolerability profile of pembrolizumab was also among primary objectives. ORR, response duration and changes in HRQoL were among secondary objectives.

The sample size was targeted to be approximately 460 for strongly PD-L1 positive patients (TPS≥50%), and the study had over 81% power to detect a 0.55 hazard ratio at the final analysis, where 0.825% alpha was allocated to the two pembrolizumab vs. docetaxel comparisons using Hochberg procedure. In the protocol the MAH provided also the Minimum Detectable Hazard Ratios (MDHR) for positive OS and PFS in the PD-L1 strongly positive stratum at the final analysis. The target MDHR was stronger for OS (<0.675, i.e. >4.3 m of improvement) with regard to PFS (<0.787, i.e. >2.4 m of improvement) which is not surprising based on the mechanism of action of pembrolizumab compared to docetaxel, and the higher probability to induce durable responses and thus show a higher probability to show a benefit in the long run. Therefore, OS analyses are expected to capture the benefit of the therapy better than PFS analyses.

Two planned interim analyses occurred during the conduct of this trial. Interim Analysis 1(IA1) was performed after 120 subjects in the strongly positive (TPS≥50%) PD-L1 stratum completed a minimum of 3 months of follow-up, ant its primary objective of IA1 was to stop the study for futility or discontinue one pembrolizumab arm if it was less efficacious than the other pembrolizumab arm based on ORR in the strongly positive (TPS≥50%) PD-L1 stratum. However, after IA1 the study continued without modifications. Interim Analysis 2 (IA2) was planned at the time of primary PFS analysis after approximately 175 PFS events had occurred in the strongly positive (TPS≥50%) PD-L1 stratum. The eDMC reviewed the data, and the study continued until the final analysis. The statistical methods are overall acceptable.

The statistical analyses for the primary endpoints and for the secondary and exploratory endpoints, including the sensitivity analyses and the censoring rules, are adequate for the type of variables

analyzed. Results of OS sensitivity analyses, censoring at the time new anti-cancer therapy and subsequent immunotherapy started were provided. The significant benefit in OS was confirmed in both TPS⩾1% and TPS⩾50%. Comparison of restricted mean survival times (RMST) of PFS, which provides an alternative estimate of the treatment effect that is robust to the proportional hazard assumption, has been planned and submitted.

The multiplicity strategy is overall acceptable. In light of the results observed for the PSF at the second interim and at the final analysis, the level of significance in the final analysis in both populations is set at 0.825% (p=0.00825) for OS and 0.1% (p=0.001) for PFS.

A total of 1034 patients were randomised 1:1:1 to pembrolizumab 2 mg/kg (n=344), to pembrolizumab 10 mg/kg (n=346) and to docetaxel (n=343). Screen failure was mostly due to not meeting the inclusion criteria of PD-L1 positivity (830 patients), or to unavailability of tissue for PD-L1 biomarker analysis (260). In addition, the presence of known active CNS metastases and/or carcinomatous meningitis excluded patients from enrolment in the trial (78 patients). The rate of PD-L1 strongly (TPS≥50%) and weakly positive (TPS 1>49%) was around 40% and 60%, respectively, in both the overall PD-L1 positive screened (1475) and enrolled subjects (1034); this consistency is reassuring with regard to the representativeness of the ITT population (i.e. there is no apparent overrepresentation of strongly positive patients), which is deemed very important for the reliability of the results in the overall population of patients that have tumours expressing PD-L1. It is noted that a higher number of patients did not receive treatment as assigned in the control arm. Furthermore, a quite higher number of patients in the docetaxel arm discontinued treatment for reason other than progressive disease, namely withdrawal of consent and physician's decision. In the context of an open label trial this is likely occurring due to patients and physicians' awareness of the treatment assigned.

Overall, there are no meaningful imbalances in patients' baseline characteristics among treatment arms, and the enrolled population is representative of real life EU patients. Not all enrolled patients met key eligibility criteria (e.g. prior chemotherapy, ECOG PS, etc.). However, the numbers are quite limited and supportive efficacy analysis (FAS) was conducted excluding those patients not meeting the key eligibility criteria or discontinued before receiving any dose of assigned treatment, and has been provided.

Data from the phase I study KEYNOTE-001 Cohorts C and F, enrolling previously treated NSCLC patients, were also submitted as supportive.

Efficacy data and additional analyses

A statistically significant and clinically meaningful benefit in OS has been observed for both pembrolizumab arms over docetaxel in subjects with TPS≥50% (HR of 0.54, p=0.00024, and 0.50, p=0.00002, for pembrolizumab 2 mg/kg and 10 mg/kg Q3W vs docetaxel, respectively), and in the overall population of subjects with TPS≥1% (HR of 0.71, p=0.00076, and 0.61, p<0.00001, for pembrolizumab 2 mg/kg and 10 mg/kg Q3W vs docetaxel, respectively).

A statistically significant difference has been observed for PFS in the strongly positive subgroup only, with HRs of 0.58 and 0.59 for pembrolizumab 2 mg/kg and 10 mg/kg vs docetaxel, respectively. The median PFS was 5.2 months for pembrolizumab 2 mg/kg and 10 mg/kg, and 4.1 months for docetaxel. The Kaplan-Meier PFS curves show a clear separation only after some months, and this pattern is observed also in the overall population PD-L1 positive population. In both subjects with TPS≥50% and the overall study population of subjects with TPS≥1% there is a trend to an increase in the difference in the rate of event-free patients between the experimental and the control arms at subsequent time points.

Supportive pre-specified sensitivity analyses for PFS were provided. The PFS results based on

Investigator assessment by irRC were similar to the results by IRC assessment per RECIST 1.1 in both the TPS≥50% and TPS≥1%population. The PFS sensitivity censoring rule analyses confirm the results of the primary analysis, with a reduced, but still clinically significant advantage also in the strongly PD-L1 positive population. The RMST analysis of PFS provided to account the possible violation of proportional hazard assumption show that the differences between pembrolizumab and docetaxel RMST values continue to increase over time, which support the potential benefit of pembrolizumab based on its mechanism of action compared to docetaxel and its ability to induce more durable responses.

No meaningful differences have been observed between the two pembrolizumab dose levels for both OS and PFS.

The OS results observed in the overall population are clearly driven by the effect observed in the strongly positive subgroup. However, when taking into account the complementary weakly positive subgroup (for which a formal analysis was not planned) the visual inspection of OS survival curves shows a separation of the curves over time with a trend to an increase in the difference in the rate of patients alive between the experimental and the control arms at subsequent time points. When analysing the PFS Kaplan Meier curves in the complementary weakly positive population, the curves appear superimposed with no apparent benefit for the experimental arms over docetaxel. However, based on the different mechanism of action and expected pattern of response to pembrolizumab and docetaxel it is not unexpected that OS analysis may capture the potential benefit of pembrolizumab better than PFS. Indeed, as reported below, the duration of response observed with pembrolizumab is much longer than what observed with docetaxel, even in the weakly positive subgroup.

The ORR was higher for pembrolizumab in TPS≥50% subjects (30.2% and 29.1% in the 2 mg/kg and 10 mg/kg arms, respectively, vs 7.9% in the docetaxel arm, p=<0.00001), and in the overall population (18% and 18.5% in the 2 mg/kg and 10 mg/kg arms, respectively, vs 9.3% in the docetaxel arm), with no difference observed between the two pembrolizumab dose levels. In the complementary weakly positive subgroup no difference in terms of ORR was observed between pembrolizumab and docetaxel (9.8% and 10.3% in the 2 mg/kg and 10 mg/kg arms, respectively, vs 10.5% in the docetaxel arm). However, the duration of response based on IRC assessment was almost double in pembrolizumab treated subjects compared to docetaxel even in the weakly positive subgroup (46 and 45 weeks in the 2 mg/kg and 10 mg/kg arms, respectively, vs 26 weeks in the docetaxel arm).

The treatment effect of pembrolizumab was superior for subjects with TPS≥50% compared to the overall study population with TPS≥1% across all endpoints (OS, PFS and ORR). However, also for the overall study population with TPS≥1% statistically significant and clinically meaningful HRs for OS are demonstrated for the pembrolizumab treatment groups in comparison to the docetaxel arm, supported by a numerically superior (although not statistically significant) HR for PFS. For both primary endpoints, the Kaplan-Meier curves demonstrated separation after several months without crossing of the curves.

The MAH provided additional analyses to inform on the impact of various tumour PD-L1 expression levels on efficacy. Forest plots of OS are presented for subgroups with TPS 1-49% (“weakly positive”), with TPS 1st to 4th quartiles and for different cut-offs of TPS (≥5 % and ≥10 %). The HR results indicate that an OS benefit is demonstrated for all subgroups and that the superior treatment effect of pembrolizumab over docetaxel does not appear to be driven solely by the subgroups with high tumour expression levels. However, with regard to the endpoints PFS (HR) and ORR, subjects in the 1%≤TPS <50% stratum did not derive superior benefit from pembrolizumab compared to docetaxel in exploratory analyses (with crossing of Kaplan-Meier curves for PFS). But longer response duration for

pembrolizumab compared to docetaxel was also confirmed in this subgroup, likely contributing to the effect on OS.

Based on preliminary efficacy results of P001, two different pembrolizumab doses were evaluated in study P010. The KM curves for both pembrolizumab groups are superimposed in the initial parts and separate after some months, both for the OS and the PFS curves. From the visual inspection of the curves, the higher pembrolizumab dose group of 10 mg/kg appears to be slightly superior compared to the dose of 2 mg/kg in all figures. However, pairwise comparisons did not show meaningful HRs for OS or PFS for the pembrolizumab 2 mg/kg group relative to the 10 mg/kg group (range of HRs 1.0 – 1.17). Additionally, ORR did not differ between both pembrolizumab dose groups. Exposure-response analyses indicated that there is little if any additional benefit available at higher exposures. Overall, the observed differences are considered small and not sufficient to object the dose selection of 2 mg/kg Q3W also for the NSCLC indication.

No major differences in OS across pembrolizumab doses can be highlighted based on tumour histology and PD-L1 expression. Although there is a general trend for a better efficacy of the 10 mg/kg Q3W particularly in PD-L1 weakly positive subjects with non-squamous histology, a dose–exposure response analysis by NSCLC histology based on KN010 shows no meaningful differences between the two pembrolizumab doses at each TPS cut points (>50% and >1%) for reduction in tumour size both in non-squamous and squamous histology. In particular, in the non-squamous subgroup there is a trend to an increased response in the lowest quintile in TPS 1-49%.

The lack of meaningful difference between the two pembrolizumab dose levels observed in all the efficacy analyses including Quality of life data further supports the adequacy of the 2 mg/kg Q3W dose level.

No new insights were provided from efficacy results submitted by the MAH for study KN010 using additional PD-L1 expression cut-off values (1% ≤TPS <10% and 10%≤ TPS <50%).

Consistently to what was observed in the primary analyses, the benefit observed in the strongly PD-L1 positive patients appears more robust also in subgroup analyses in comparison to the overall population and the complementary weakly positive subgroup.

In subgroup analyses, a reduced survival benefit of pembrolizumab compared to docetaxel was observed for patients who were never-smokers, patients with tumours harbouring EGFR activating mutations or East Asian patients who received at least platinum-based chemotherapy and a tyrosine kinase inhibitor; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

A consistent improvement in OS and PFS was reported with pembrolizumab over docetaxel in sensitivity analyses conducted excluding patients who discontinued study treatment due to consent withdrew or physician'decision.

Based on a subgroup analysis by the number of prior therapies (1 versus ≥2 lines), the superior benefit of pembrolizumab over docetaxel in the overall study population appears to be solely driven by the treatment effect in subjects with only one prior line of therapy. Patients with two or more lines of prior therapy do not seem to have a superior outcome with pembrolizumab compared to docetaxel. A reduced treatment effect in patients with more advanced disease is in line with what has been previously observed for nivolumab in the same indication and might be expected from the mode of action of checkpoint inhibitors that depends on an efficient immune system and requires a longer time to exert an effect.

As from the prior nivolumab experience, in non-squamous NSCLC the pembrolizumab effect seems to be determined by the level of PD-L1 expression, with an OS HR ranging from 0.67 to 0.49 at the dose

of 2 mg/kg and from 0.58 to 0.45 at 10 mg/kg based on TPS ≥1% and TPS ≥50%, respectively. On the other hands, the percentage of TPS is not related to OS benefit in squamous NSCLC.

In study KEYNOTE-010, patients were screened by an IHC clinical trial assay (Dako PD-L1 CTA) which is an earlier version of the companion diagnostic IHC assay (Dako PD-L1 CRA) proposed by the MAH. To evaluate the clinical performance of the commercial ready assay (CRA), a bridging study for KEYNOTE-010 retrospectively tested banked formalin fixed and paraffin embedded (FFPE) NSCLC tissue samples available from screened patients. Even if the variability of PD-L1 expression within the tumour and, consequently, the possibility of discordant results produced by analytical tests is acknowledged, overall the available efficacy outcomes, in terms of OS and PFS, support the use of Dako PD-L1 CRA (PD-L1 IHC 22C3 pharmDx) for the selection of NSCLC patients.

When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.

The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 have not been established.

Similarly to the melanoma indication, the MAH will further explore the value of biomarkers to predict the efficacy of pembrolizumab in NSCLC studies.

In the supportive study P001 a clear benefit in terms of ORR, PFS and OS has been observed for the strongly PD-L1 positive subgroup over the weakly positive or negative subgroups. The ORR was 36.3% in strongly PD-L1 positive, 13.2% in weakly PD-L1 positive and 8.1% in negative subjects (TPS<1%) PD-L1. Even though a similar median PFS and OS were observed in weakly PD-L1 positive and negative patients, the difference in PFS and OS rate tend to increase over time, with a higher rate for weakly PD-L1 positive vs negative subjects at 12 months.

2.4.4. Conclusions on the clinical efficacy

A statistically significant and clinically meaningful benefit in OS over docetaxel has been observed for both subjects with TPS≥50% and with TPS≥1% with pembrolizumab in the target population of adult patients with advanced NSCLC whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. A statistically significant difference has been observed for PFS in the strongly positive subgroup only. It can however be concluded that the benefit from pembrolizumab is not limited to the strongly positive subgroup.

There are no meaningful differences among the two pembrolizumab doses, supporting the proposed 2mg/kg Q3W dose, already recommended in the melanoma indication. Further support comes from the observation that statistical significance for PROs was achieved for the pembrolizumab 2 mg/kg dose only.
The CHMP considers the following measures necessary to address issues related to efficacy:

- The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically:

Although PD-L1 status is predictive of response in NSCLC patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD L1 obtained in the ongoing NSCLC studies (P001, P010, P024, and P042):

- Data on the Nanostring RNA gene signature

- IHC staining for PD-L2
- Data on RNA and proteomic serum profiling

Due date: 2Q 2020

2.5. Clinical safety

The known pembrolizumab safety profile, at present based on 1567 melanoma patients treated across studies KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 is mainly associated with immune-related adverse reactions and characterized by general (fatigue), gastrointestinal (diarrhoea and nausea), skin (rash and pruritus) and muskuloskeletal (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 submitted safety database includes 1232 NSCLC patients (from studies KEYNOTE-010 and KEYNOTE-001) and 1567 melanoma patients (from studies KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006) who received at least one pembrolizumab dose.

Patient exposure

In the pivotal NSCLC study P010, the mean treatment duration was higher in the pembrolizumab arms (155.4 days at 10 mg/kg Q3W and 151.1 days at 2 mg/kg Q3W) compared to docetaxel (81.6 days).

Overall, the mean exposure was greater in melanoma compared to NSCLC patients (227.80 days vs.160.25 days). In a total of 418 and 165 NSCLC patients the duration of exposure to pembrolizumab was ≥6 months and ≥12 months, respectively. Considering the pooled NSCLC and melanoma populations, 1153 and 600 patients were respectively exposed to pembrolizumab ≥6 months and ≥12 months.

Table 55: Summary of Drug Exposure (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010	PN001 Lung, PN010	PN001 Mel, PN002, PN006	PN001,PN002, PN006, PN010
	N=682	N=1232	N=1567	N=2799
Study Days On-Therapy (days)				
Mean	153.27	160.25	227.80	198.06
Median	106.00	106.00	155.00	127.00
SD	145.87	157.28	191.73	180.51
Range	1.00 to 681.00	1.00 to 925.00	1.00 to 862.00	1.00 to 925.00
Number of Administrations				
Mean	7.91	8.87	12.86	11.11
Median	6.00	6.00	9.00	7.00
SD	6.64	8.14	10.34	9.64
Range	1.00 to 30.00	1.00 to 45.00	1.00 to 59.00	1.00 to 59.00

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Table 56: Exposure and Duration (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

Duration of Exposure	P010 (N=682)		PN001 Lung, PN010 (N=1232)		PN001 Mel, PN002, PN006 (N=1567)		PN001,PN002, PN006, PN010 (N=2799)	
	n	Patient Years	n	Patient Years	n	Patient Years	n	Patient Years
> 0 m	682	286.2	1,232	540.5	1,567	977.2	2,799	1517.7
≥ 1 m	567	282.0	1,009	532.7	1,385	970.9	2,394	1503.6
≥ 3 m	369	251.0	648	475.4	1,008	904.1	1,656	1379.5
≥ 6 m	220	196.9	418	391.6	735	806.2	1,153	1197.8
≥ 12 m	73	96.8	165	216.5	435	583.7	600	800.3

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date +1.
(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Demographic and other baseline characteristics of patients in the pooled melanoma and NSCLC populations were mostly similar across tumour types. Mainly due to due to the differences in site selection and the natural history of disease, there were more Asian patients (17.4% vs 1.2%) and more subjects with ECOG PS 1 (65.5% vs 34.5) in the NSCLC studies compared to melanoma studies.

Table 57: Subject Characteristics (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001,PN002, PN006, PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
Gender								
Male	419	(61.4)	708	(57.5)	951	(60.7)	1,659	(59.3)
Female	263	(38.6)	524	(42.5)	616	(39.3)	1,140	(40.7)
Age (Years)								
<65	390	(57.2)	681	(55.3)	906	(57.8)	1,587	(56.7)
>=65	292	(42.8)	551	(44.7)	661	(42.2)	1,212	(43.3)
Mean	62.2		62.3		60.0		61.0	
SD	9.7		10.2		14.0		12.5	
Median	63.0		63.0		62.0		62.0	
Range	20 to 88		20 to 93		15 to 94		15 to 94	
Race								
American Indian Or Alaska Native	5	(0.7)	6	(0.5)	1	(0.1)	7	(0.3)
Asian	144	(21.1)	214	(17.4)	19	(1.2)	233	(8.3)
Black Or African American	21	(3.1)	41	(3.3)	7	(0.4)	48	(1.7)
Multiple	0	(0.0)	0	(0.0)	4	(0.3)	4	(0.1)
Multiracial	3	(0.4)	5	(0.4)	2	(0.1)	7	(0.3)
Native Hawaiian Or Other Pacific Islander	2	(0.3)	3	(0.2)	1	(0.1)	4	(0.1)
White	489	(71.7)	944	(76.6)	1,530	(97.6)	2,474	(88.4)
Missing	18	(2.6)	19	(1.5)	3	(0.2)	22	(0.8)
Ethnicity								
Hispanic Or Latino	38	(5.6)	67	(5.4)	61	(3.9)	128	(4.6)
Not Hispanic Or Latino	589	(86.4)	1,108	(89.9)	1,474	(94.1)	2,582	(92.2)
Not Reported	32	(4.7)	32	(2.6)	15	(1.0)	47	(1.7)
Unknown	20	(2.9)	20	(1.6)	17	(1.1)	37	(1.3)
Missing	3	(0.4)	5	(0.4)	0	(0.0)	5	(0.2)
Geographic Region								
US	144	(21.1)	492	(39.9)	758	(48.4)	1,250	(44.7)
Ex-US	538	(78.9)	740	(60.1)	809	(51.6)	1,549	(55.3)
ECOG								
0	231	(33.9)	422	(34.3)	1,024	(65.3)	1,446	(51.7)

1	450	(66.0)	807	(65.5)	540	(34.5)	1,347	(48.1)
2	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
null	0	(0.0)	2	(0.2)	3	(0.2)	5	(0.2)

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Adverse events

The primary analysis population for safety across clinical studies includes all patients who received at least one dose of pembrolizumab (APaT population).

In the pivotal NSCLC study P010, despite the longer exposure duration to pembrolizumab, overall AE counts were similar across all three arms. However, in the pembrolizumab arms fewer drug-related AEs, drug-related Grade ≥3 AEs, and discontinuations due to AEs or drug-related AEs occurred compared to the docetaxel arm. A slight excess of deaths due to AEs has been observed in the pooled pembrolizumab population compared to docetaxel arm (6.3% vs 4.9%); however, deaths due to drug-related adverse events were less frequently observed in the pooled experimental arms than with docetaxel (0.9% vs 1.6%).

Table 58: Study P010-AEs Summary - APaT population (TPS≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	309		682	
with one or more adverse events	297	(96.1)	661	(96.9)
with no adverse event	12	(3.9)	21	(3.1)
with drug-related[†] adverse events	251	(81.2)	441	(64.7)
with toxicity grade 3-5 adverse events	173	(56.0)	314	(46.0)
with toxicity grade 3-5 drug-related adverse events	109	(35.3)	98	(14.4)
with serious adverse events	107	(34.6)	246	(36.1)
with serious drug-related adverse events	42	(13.6)	71	(10.4)
who died	15	(4.9)	43	(6.3)
who died due to a drug-related adverse event	5	(1.6)	6	(0.9)
discontinued[‡] due to an adverse event	42	(13.6)	54	(7.9)
discontinued due to a drug-related adverse event	31	(10.0)	32	(4.7)
discontinued due to a serious adverse event	19	(6.1)	44	(6.5)
discontinued due to a serious drug-related adverse event	11	(3.6)	24	(3.5)

[†] 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.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source: [16.4]

The overall incidence of AEs and SAEs was similar for NSCLC patients in the APaT population compared to previously reported data in melanoma patients:

Table 59: Summary of Adverse Events (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001,PN002, PN006, PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	661	(96.9)	1,192	(96.8)	1,535	(98.0)	2,727	(97.4)
with no adverse event	21	(3.1)	40	(3.2)	32	(2.0)	72	(2.6)
with drug-related[†] adverse events	441	(64.7)	821	(66.6)	1,241	(79.2)	2,062	(73.7)
with toxicity grade 3-5 adverse events	314	(46.0)	568	(46.1)	705	(45.0)	1,273	(45.5)
with toxicity grade 3-5 drug-related adverse events	98	(14.4)	158	(12.8)	228	(14.6)	386	(13.8)
with non-serious adverse events	638	(93.5)	1,157	(93.9)	1,514	(96.6)	2,671	(95.4)
with serious adverse events	246	(36.1)	474	(38.5)	567	(36.2)	1,041	(37.2)
with serious drug-related adverse events	71	(10.4)	117	(9.5)	164	(10.5)	281	(10.0)
who died	43	(6.3)	62	(5.0)	48	(3.1)	110	(3.9)
who died due to a drug-related adverse event	6	(0.9)	9	(0.7)	1	(0.1)	10	(0.4)
discontinued[‡] due to an adverse event	54	(7.9)	139	(11.3)	195	(12.4)	334	(11.9)
discontinued due to a drug-related adverse event	32	(4.7)	57	(4.6)	89	(5.7)	146	(5.2)
discontinued due to a serious adverse event	44	(6.5)	111	(9.0)	142	(9.1)	253	(9.0)
discontinued due to a serious drug-related adverse event	24	(3.5)	44	(3.6)	57	(3.6)	101	(3.6)

[†] 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.

Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).

(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).

(MK-3475 PN002 Database Cutoff Date: 28FEB2015).

(MK-3475 PN006 Database Cutoff Date: 03MAR2015).

(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

In study P010, the most common AEs (>20%) were fatigue (25.1%), decreased appetite (24.6%) and dyspnea (22.9%) with pembrolizumab combined dose levels, and alopecia (34.0%), fatigue (32.0%) and diarrhea (25.9%) in the docetaxel arm. The exposure adjusted incidence of AEs showed across all treatment arms a more frequent reporting in the first 3 months followed by decreased frequency with each successive 3-month period. In the pembrolizumab arms, the most frequent Grade ≥3 AEs were pneumonia (5.3%), dyspnea (3.7%), and fatigue (3.1%), while with docetaxel Grade ≥3 AEs commonly reported were neutropenia (13.6%), neutrophil count decreased (6.5%), fatigue (5.5%), febrile neutropenia (5.5%), and pneumonia (5.5%).

In the overall pembrolizumab safety database, including both melanoma and NSCLC patients, the observed incidence of specific AEs occurred in ≥10% of patients is shown in the Table below.

Table 60: Subjects with Adverse Events (Incidence ≥10% in One or More Treatment Groups) (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	661	(96.9)	1,192	(96.8)	1,535	(98.0)	2,727	(97.4)
with no adverse events	21	(3.1)	40	(3.2)	32	(2.0)	72	(2.6)
Blood and lymphatic system disorders	**105**	**(15.4)**	**188**	**(15.3)**	**299**	**(19.1)**	**487**	**(17.4)**
Anaemia	66	(9.7)	135	(11.0)	212	(13.5)	347	(12.4)
Endocrine disorders	**83**	**(12.2)**	**136**	**(11.0)**	**199**	**(12.7)**	**335**	**(12.0)**
Eye disorders	**63**	**(9.2)**	**113**	**(9.2)**	**245**	**(15.6)**	**358**	**(12.8)**
Gastrointestinal disorders	**354**	**(51.9)**	**657**	**(53.3)**	**1,048**	**(66.9)**	**1,705**	**(60.9)**
Abdominal pain	38	(5.6)	83	(6.7)	191	(12.2)	274	(9.8)
Constipation	105	(15.4)	193	(15.7)	304	(19.4)	497	(17.8)
Diarrhoea	95	(13.9)	189	(15.3)	436	(27.8)	625	(22.3)
Nausea	139	(20.4)	247	(20.0)	438	(28.0)	685	(24.5)
Vomiting	88	(12.9)	157	(12.7)	230	(14.7)	387	(13.8)
General disorders and administration site conditions	**382**	**(56.0)**	**742**	**(60.2)**	**1,116**	**(71.2)**	**1,858**	**(66.4)**
Asthenia	76	(11.1)	132	(10.7)	230	(14.7)	362	(12.9)
Fatigue	171	(25.1)	374	(30.4)	670	(42.8)	1,044	(37.3)
Oedema peripheral	53	(7.8)	113	(9.2)	172	(11.0)	285	(10.2)
Pyrexia	77	(11.3)	145	(11.8)	212	(13.5)	357	(12.8)
Infections and infestations	**245**	**(35.9)**	**467**	**(37.9)**	**713**	**(45.5)**	**1,180**	**(42.2)**
Injury, poisoning and procedural complications	**65**	**(9.5)**	**121**	**(9.8)**	**241**	**(15.4)**	**362**	**(12.9)**
Investigations	**201**	**(29.5)**	**359**	**(29.1)**	**506**	**(32.3)**	**865**	**(30.9)**
Metabolism and nutrition disorders	**266**	**(39.0)**	**505**	**(41.0)**	**604**	**(38.5)**	**1,109**	**(39.6)**
Decreased appetite	168	(24.6)	310	(25.2)	320	(20.4)	630	(22.5)
Musculoskeletal and connective tissue disorders	**295**	**(43.3)**	**531**	**(43.1)**	**881**	**(56.2)**	**1,412**	**(50.4)**
Arthralgia	75	(11.0)	167	(13.6)	337	(21.5)	504	(18.0)
Back pain	73	(10.7)	133	(10.8)	216	(13.8)	349	(12.5)
Myalgia	35	(5.1)	73	(5.9)	180	(11.5)	253	(9.0)
Pain in extremity	42	(6.2)	69	(5.6)	168	(10.7)	237	(8.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**36**	**(5.3)**	**68**	**(5.5)**	**190**	**(12.1)**	**258**	**(9.2)**
Nervous system disorders	**207**	**(30.4)**	**386**	**(31.3)**	**651**	**(41.5)**	**1,037**	**(37.0)**
Headache	64	(9.4)	122	(9.9)	278	(17.7)	400	(14.3)
Psychiatric disorders	**106**	**(15.5)**	**208**	**(16.9)**	**315**	**(20.1)**	**523**	**(18.7)**
Renal and urinary disorders	**52**	**(7.6)**	**99**	**(8.0)**	**172**	**(11.0)**	**271**	**(9.7)**
Respiratory, thoracic and mediastinal disorders	**350**	**(51.3)**	**671**	**(54.5)**	**720**	**(45.9)**	**1,391**	**(49.7)**
Cough	130	(19.1)	256	(20.8)	359	(22.9)	615	(22.0)
Dyspnoea	156	(22.9)	286	(23.2)	248	(15.8)	534	(19.1)
Skin and subcutaneous tissue disorders	**222**	**(32.6)**	**419**	**(34.0)**	**941**	**(60.1)**	**1,360**	**(48.6)**
Pruritus	73	(10.7)	148	(12.0)	414	(26.4)	562	(20.1)
Rash	94	(13.8)	161	(13.1)	338	(21.6)	499	(17.8)
Vitiligo	1	(0.1)	1	(0.1)	170	(10.8)	171	(6.1)

Vascular disorders	**86**	**(12.6)**	**156**	**(12.7)**	**254**	**(16.2)**	**410**	**(14.6)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.
(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Overall, the most common AEs were fatigue (37.3%), nausea (24.5%), decreased appetite (22.5%), diarrhoea (22.3%), and cough (22.0%).

The Grade ≥3 AEs reported in NSCLC and melanoma populations are listed below:

Table 61: Subjects with Grade 3-5 Adverse Events (Incidence ≥1% in One or More Treatment Groups) (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	314	(46.0)	568	(46.1)	705	(45.0)	1,273	(45.5)
with no adverse events	368	(54.0)	664	(53.9)	862	(55.0)	1,526	(54.5)
Blood and lymphatic system disorders	**26**	**(3.8)**	**43**	**(3.5)**	**80**	**(5.1)**	**123**	**(4.4)**
Anaemia	16	(2.3)	27	(2.2)	63	(4.0)	90	(3.2)
Cardiac disorders	**23**	**(3.4)**	**49**	**(4.0)**	**35**	**(2.2)**	**84**	**(3.0)**
Pericardial effusion	7	(1.0)	10	(0.8)	4	(0.3)	14	(0.5)
Endocrine disorders	**4**	**(0.6)**	**8**	**(0.6)**	**18**	**(1.1)**	**26**	**(0.9)**
Gastrointestinal disorders	**42**	**(6.2)**	**76**	**(6.2)**	**156**	**(10.0)**	**232**	**(8.3)**
Abdominal pain	3	(0.4)	8	(0.6)	19	(1.2)	27	(1.0)
Colitis	4	(0.6)	9	(0.7)	23	(1.5)	32	(1.1)
Diarrhoea	3	(0.4)	7	(0.6)	29	(1.9)	36	(1.3)
Nausea	9	(1.3)	14	(1.1)	19	(1.2)	33	(1.2)
Vomiting	6	(0.9)	9	(0.7)	23	(1.5)	32	(1.1)
General disorders and administration site conditions	**55**	**(8.1)**	**104**	**(8.4)**	**110**	**(7.0)**	**214**	**(7.6)**
Asthenia	9	(1.3)	16	(1.3)	18	(1.1)	34	(1.2)
Fatigue	21	(3.1)	37	(3.0)	32	(2.0)	69	(2.5)
General physical health deterioration	6	(0.9)	9	(0.7)	15	(1.0)	24	(0.9)
Pain	4	(0.6)	15	(1.2)	8	(0.5)	23	(0.8)
Hepatobiliary disorders	**7**	**(1.0)**	**9**	**(0.7)**	**34**	**(2.2)**	**43**	**(1.5)**
Infections and infestations	**71**	**(10.4)**	**108**	**(8.8)**	**112**	**(7.1)**	**220**	**(7.9)**
Pneumonia	36	(5.3)	50	(4.1)	24	(1.5)	74	(2.6)
Injury, poisoning and procedural complications	**10**	**(1.5)**	**14**	**(1.1)**	**24**	**(1.5)**	**38**	**(1.4)**
Investigations	**32**	**(4.7)**	**54**	**(4.4)**	**76**	**(4.9)**	**130**	**(4.6)**

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**32**	**(4.7)**	**54**	**(4.4)**	**76**	**(4.9)**	**130**	**(4.6)**
Alanine aminotransferase increased	5	(0.7)	9	(0.7)	16	(1.0)	25	(0.9)
Aspartate aminotransferase increased	5	(0.7)	9	(0.7)	15	(1.0)	24	(0.9)
Metabolism and nutrition disorders	**58**	**(8.5)**	**97**	**(7.9)**	**136**	**(8.7)**	**233**	**(8.3)**
Decreased appetite	10	(1.5)	15	(1.2)	11	(0.7)	26	(0.9)
Dehydration	5	(0.7)	9	(0.7)	19	(1.2)	28	(1.0)
Hypercalcaemia	7	(1.0)	11	(0.9)	4	(0.3)	15	(0.5)
Hyperglycaemia	10	(1.5)	12	(1.0)	17	(1.1)	29	(1.0)
Hypokalaemia	7	(1.0)	11	(0.9)	14	(0.9)	25	(0.9)
Hyponatraemia	13	(1.9)	24	(1.9)	38	(2.4)	62	(2.2)
Musculoskeletal and connective tissue disorders	**32**	**(4.7)**	**56**	**(4.5)**	**70**	**(4.5)**	**126**	**(4.5)**
Arthralgia	7	(1.0)	11	(0.9)	6	(0.4)	17	(0.6)
Back pain	10	(1.5)	20	(1.6)	18	(1.1)	38	(1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**17**	**(2.5)**	**28**	**(2.3)**	**51**	**(3.3)**	**79**	**(2.8)**
Nervous system disorders	**23**	**(3.4)**	**34**	**(2.8)**	**74**	**(4.7)**	**108**	**(3.9)**
Psychiatric disorders	**11**	**(1.6)**	**14**	**(1.1)**	**13**	**(0.8)**	**27**	**(1.0)**
Renal and urinary disorders	**10**	**(1.5)**	**18**	**(1.5)**	**20**	**(1.3)**	**38**	**(1.4)**
Respiratory, thoracic and mediastinal disorders	**83**	**(12.2)**	**158**	**(12.8)**	**86**	**(5.5)**	**244**	**(8.7)**
Chronic obstructive pulmonary disease	8	(1.2)	12	(1.0)	2	(0.1)	14	(0.5)
Dyspnoea	25	(3.7)	48	(3.9)	30	(1.9)	78	(2.8)
Respiratory, thoracic and mediastinal disorders	**83**	**(12.2)**	**158**	**(12.8)**	**86**	**(5.5)**	**244**	**(8.7)**
Pleural effusion	10	(1.5)	23	(1.9)	14	(0.9)	37	(1.3)
Pneumonitis	14	(2.1)	24	(1.9)	10	(0.6)	34	(1.2)
Pulmonary embolism	18	(2.6)	31	(2.5)	15	(1.0)	46	(1.6)
Respiratory failure	4	(0.6)	13	(1.1)	2	(0.1)	15	(0.5)
Skin and subcutaneous tissue disorders	**7**	**(1.0)**	**14**	**(1.1)**	**26**	**(1.7)**	**40**	**(1.4)**
Vascular disorders	**26**	**(3.8)**	**40**	**(3.2)**	**44**	**(2.8)**	**84**	**(3.0)**
Hypertension	10	(1.5)	13	(1.1)	19	(1.2)	32	(1.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.
(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Overall, the most common Grade ≥3 AEs were anaemia (3.2%), dyspnoea (2.8%), pneumonia (2.6%), fatigue (2.5%), and hyponatremia (2.2%). Consistently with the natural history of NSCLC, a higher incidence of Grade ≥3 dyspnoea (3.9% vs. 1.9%) and pneumonia (4.1% vs. 1.5%) was reported in the NSCLC population compared to melanoma patients.

Drug-related AEs

In the pivotal NSCLC study P010, the most common drug-related AEs reported with pembrolizumab (combined arms) were fatigue (13.9%), decreased appetite (11.6%), nausea (10.0%), and rash (10.7%). In the docetaxel arm drug-related alopecia (32.7%), fatigue (24.6%), and diarrhoea (18.1%) were more frequently observed.

The overall incidence of drug-related AEs in lung and melanoma populations is reported in the Table

below:

Table 62: Subjects with Drug-Related Adverse Events (Incidence ≥5% in One or More Treatment Groups) (PN001, PN002, PN006 and PN010) - Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	441	(64.7)	821	(66.6)	1,241	(79.2)	2,062	(73.7)
with no adverse events	241	(35.3)	411	(33.4)	326	(20.8)	737	(26.3)
Blood and lymphatic system disorders	**41**	**(6.0)**	**68**	**(5.5)**	**89**	**(5.7)**	**157**	**(5.6)**
Endocrine disorders	**71**	**(10.4)**	**119**	**(9.7)**	**172**	**(11.0)**	**291**	**(10.4)**
Hypothyroidism	48	(7.0)	88	(7.1)	125	(8.0)	213	(7.6)
Eye disorders	**18**	**(2.6)**	**29**	**(2.4)**	**96**	**(6.1)**	**125**	**(4.5)**
Gastrointestinal disorders	**153**	**(22.4)**	**278**	**(22.6)**	**520**	**(33.2)**	**798**	**(28.5)**
Diarrhoea	46	(6.7)	93	(7.5)	250	(16.0)	343	(12.3)
Nausea	68	(10.0)	109	(8.8)	195	(12.4)	304	(10.9)
General disorders and administration site conditions	**180**	**(26.4)**	**355**	**(28.8)**	**720**	**(45.9)**	**1,075**	**(38.4)**
Asthenia	39	(5.7)	70	(5.7)	148	(9.4)	218	(7.8)
Fatigue	95	(13.9)	199	(16.2)	479	(30.6)	678	(24.2)
Investigations	**88**	**(12.9)**	**155**	**(12.6)**	**231**	**(14.7)**	**386**	**(13.8)**
Metabolism and nutrition disorders	**119**	**(17.4)**	**190**	**(15.4)**	**198**	**(12.6)**	**388**	**(13.9)**
Decreased appetite	79	(11.6)	135	(11.0)	120	(7.7)	255	(9.1)
Musculoskeletal and connective tissue disorders	**77**	**(11.3)**	**162**	**(13.1)**	**368**	**(23.5)**	**530**	**(18.9)**
Arthralgia	32	(4.7)	81	(6.6)	200	(12.8)	281	(10.0)
Myalgia	19	(2.8)	36	(2.9)	110	(7.0)	146	(5.2)
Nervous system disorders	**60**	**(8.8)**	**94**	**(7.6)**	**223**	**(14.2)**	**317**	**(11.3)**
Headache	14	(2.1)	24	(1.9)	87	(5.6)	111	(4.0)
Respiratory, thoracic and mediastinal disorders	**74**	**(10.9)**	**142**	**(11.5)**	**209**	**(13.3)**	**351**	**(12.5)**
Cough	11	(1.6)	24	(1.9)	88	(5.6)	112	(4.0)
Skin and subcutaneous tissue disorders	**148**	**(21.7)**	**282**	**(22.9)**	**738**	**(47.1)**	**1,020**	**(36.4)**
Pruritus	57	(8.4)	116	(9.4)	351	(22.4)	467	(16.7)
Rash	73	(10.7)	123	(10.0)	263	(16.8)	386	(13.8)
Vitiligo	1	(0.1)	1	(0.1)	158	(10.1)	159	(5.7)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.
(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

A lower incidence of drug-related AEs have been reported in NSCLC patients compared to melanoma patients, with particular regard to *Diarrhoea*, *Nausea*, *Asthenia*, *Fatigue*, and events in the SOCs *Nervous System Disorders*, and *Skin and Subcutaneous Tissue Disorders*.

The overall incidence of Grade ≥3 AEs considered drug-related by the Investigator is reported below for both lung and melanoma patients:

Table 63: Subjects with Grade ≥3 Drug-Related Adverse Events (Incidence >0% in One or More Treatment Groups) - PN001, PN002, PN006 and PN010 Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	98	(14.4)	158	(12.8)	228	(14.6)	386	(13.8)
with no adverse events	584	(85.6)	1,074	(87.2)	1,339	(85.4)	2,413	(86.2)
Blood and lymphatic system disorders	**7**	**(1.0)**	**13**	**(1.1)**	**15**	**(1.0)**	**28**	**(1.0)**
Anaemia	4	(0.6)	6	(0.5)	7	(0.4)	13	(0.5)
Autoimmune haemolytic anaemia	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Haemolytic anaemia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Immune thrombocytopenic purpura	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Leukopenia	1	(0.1)	3	(0.2)	0	(0.0)	3	(0.1)
Lymphopenia	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Microcytic anaemia	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Neutropenia	0	(0.0)	1	(0.1)	2	(0.1)	3	(0.1)
Pancytopenia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Thrombocytopenia	1	(0.1)	1	(0.1)	2	(0.1)	3	(0.1)
Cardiac disorders	**3**	**(0.4)**	**7**	**(0.6)**	**3**	**(0.2)**	**10**	**(0.4)**
Acute myocardial infarction	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Atrial fibrillation	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Atrioventricular block complete	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cardiac tamponade	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Myocardial infarction	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Pericardial effusion	1	(0.1)	2	(0.2)	2	(0.1)	4	(0.1)
Pericarditis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Ear and labyrinth disorders	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.0)**
Tinnitus	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Vertigo	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Endocrine disorders	**4**	**(0.6)**	**7**	**(0.6)**	**15**	**(1.0)**	**22**	**(0.8)**
Adrenal insufficiency	1	(0.1)	2	(0.2)	4	(0.3)	6	(0.2)
Hyperthyroidism	1	(0.1)	2	(0.2)	2	(0.1)	4	(0.1)
Hypophysitis	0	(0.0)	1	(0.1)	3	(0.2)	4	(0.1)
Hypopituitarism	2	(0.3)	2	(0.2)	3	(0.2)	5	(0.2)
Hypothyroidism	0	(0.0)	1	(0.1)	2	(0.1)	3	(0.1)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**2**	**(0.1)**
Eye pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Iritis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Gastrointestinal disorders	**11**	**(1.6)**	**21**	**(1.7)**	**56**	**(3.6)**	**77**	**(2.8)**
Abdominal pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Ascites	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Colitis	4	(0.6)	8	(0.6)	19	(1.2)	27	(1.0)
Diarrhoea	2	(0.3)	4	(0.3)	21	(1.3)	25	(0.9)
Dysphagia	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Enterocolitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Gastritis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Ileus	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Impaired gastric emptying	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Intestinal obstruction	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Intussusception	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Nausea	3	(0.4)	6	(0.5)	4	(0.3)	10	(0.4)
Oesophagitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Oral pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Rectal haemorrhage	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Small intestinal perforation	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Stomatitis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Vomiting	1	(0.1)	3	(0.2)	6	(0.4)	9	(0.3)
General disorders and administration site conditions	**13**	**(1.9)**	**19**	**(1.5)**	**31**	**(2.0)**	**50**	**(1.8)**
Asthenia	3	(0.4)	4	(0.3)	8	(0.5)	12	(0.4)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Axillary pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Chest pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Fatigue	10	(1.5)	14	(1.1)	16	(1.0)	30	(1.1)
General physical health deterioration	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Generalised oedema	0	(0.0)	1	(0.1)	2	(0.1)	3	(0.1)
Mucosal inflammation	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pyrexia	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Systemic inflammatory response syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Hepatobiliary disorders	**2**	**(0.3)**	**2**	**(0.2)**	**14**	**(0.9)**	**16**	**(0.6)**
Autoimmune hepatitis	1	(0.1)	1	(0.1)	7	(0.4)	8	(0.3)
Cholestasis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Drug-induced liver injury	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Hepatic function abnormal	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Hepatitis	0	(0.0)	0	(0.0)	3	(0.2)	3	(0.1)
Hyperbilirubinaemia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Liver disorder	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Immune system disorders	**0**	**(0.0)**	**1**	**(0.1)**	**3**	**(0.2)**	**4**	**(0.1)**
Anaphylactic reaction	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Drug hypersensitivity	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Serum sickness	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Infections and infestations	**7**	**(1.0)**	**9**	**(0.7)**	**10**	**(0.6)**	**19**	**(0.7)**
Bacterial sepsis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Clostridium difficile infection	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Diverticulitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Encephalitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Erysipelas	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Listeriosis	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Liver abscess	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Meningitis	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)
Meningitis listeria	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Pneumonia	6	(0.9)	6	(0.5)	2	(0.1)	8	(0.3)
Rash pustular	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Sinusitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Injury, poisoning and procedural complications	**2**	**(0.3)**	**2**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.1)**
Pneumonitis chemical	2	(0.3)	2	(0.2)	0	(0.0)	2	(0.1)
Investigations	**11**	**(1.6)**	**20**	**(1.6)**	**26**	**(1.7)**	**46**	**(1.6)**
Alanine aminotransferase increased	3	(0.4)	6	(0.5)	8	(0.5)	14	(0.5)
Amylase increased	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Aspartate aminotransferase increased	2	(0.3)	4	(0.3)	7	(0.4)	11	(0.4)
Blood albumin increased	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Blood alkaline phosphatase increased	2	(0.3)	3	(0.2)	0	(0.0)	3	(0.1)
Blood bilirubin increased	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)
Blood corticotrophin decreased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	1	(0.1)	3	(0.2)	4	(0.1)
Blood glucose increased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Blood lactate dehydrogenase increased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Blood prolactin increased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**11**	**(1.6)**	**20**	**(1.6)**	**26**	**(1.7)**	**46**	**(1.6)**
Gamma-glutamyltransferase increased	1	(0.1)	1	(0.1)	5	(0.3)	6	(0.2)
Hepatic enzyme increased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Intraocular pressure decreased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Lipase increased	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Liver function test abnormal	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Lymphocyte count decreased	2	(0.3)	2	(0.2)	2	(0.1)	4	(0.1)
Neutrophil count decreased	0	(0.0)	2	(0.2)	0	(0.0)	2	(0.1)
Platelet count decreased	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Transaminases increased	1	(0.1)	2	(0.2)	0	(0.0)	2	(0.1)
Weight decreased	1	(0.1)	2	(0.2)	0	(0.0)	2	(0.1)
Metabolism and nutrition disorders	**21**	**(3.1)**	**24**	**(1.9)**	**27**	**(1.7)**	**51**	**(1.8)**
Decreased appetite	4	(0.6)	5	(0.4)	3	(0.2)	8	(0.3)
Dehydration	0	(0.0)	1	(0.1)	2	(0.1)	3	(0.1)
Diabetes mellitus	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Diabetic ketoacidosis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Failure to thrive	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Hyperamylasaemia	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Hypercalcaemia	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Hyperglycaemia	1	(0.1)	1	(0.1)	3	(0.2)	4	(0.1)
Hypertriglyceridaemia	4	(0.6)	4	(0.3)	2	(0.1)	6	(0.2)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Hypokalaemia	1	(0.1)	1	(0.1)	6	(0.4)	7	(0.3)
Hyponatraemia	4	(0.6)	5	(0.4)	6	(0.4)	11	(0.4)
Hypophosphataemia	2	(0.3)	2	(0.2)	2	(0.1)	4	(0.1)
Insulin resistant diabetes	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Metabolic disorder	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Type 1 diabetes mellitus	2	(0.3)	2	(0.2)	1	(0.1)	3	(0.1)
Musculoskeletal and connective tissue disorders	**4**	**(0.6)**	**6**	**(0.5)**	**15**	**(1.0)**	**21**	**(0.8)**
Arthralgia	2	(0.3)	4	(0.3)	3	(0.2)	7	(0.3)
Arthritis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Back pain	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Bone pain	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Groin pain	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Muscular weakness	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Musculoskeletal pain	0	(0.0)	1	(0.1)	2	(0.1)	3	(0.1)
Myalgia	0	(0.0)	0	(0.0)	4	(0.3)	4	(0.1)
Pain in extremity	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Sjogren's syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Synovitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(0.3)**	**2**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.1)**
Malignant neoplasm progression	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Paraneoplastic syndrome	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Nervous system disorders	**3**	**(0.4)**	**4**	**(0.3)**	**11**	**(0.7)**	**15**	**(0.5)**
Amnesia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Brain oedema	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Cerebrovascular accident	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cognitive disorder	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Depressed level of consciousness	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Encephalopathy	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Epilepsy	0	(0.0)	0	(0.0)	3	(0.2)	3	(0.1)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Headache	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Lethargy	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Meningitis noninfective	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**3**	**(0.4)**	**4**	**(0.3)**	**11**	**(0.7)**	**15**	**(0.5)**
Myelitis transverse	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Presyncope	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Toxic leukoencephalopathy	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Psychiatric disorders	**2**	**(0.3)**	**2**	**(0.2)**	**2**	**(0.1)**	**4**	**(0.1)**
Confusional state	1	(0.1)	1	(0.1)	2	(0.1)	3	(0.1)
Disorientation	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Renal and urinary disorders	**2**	**(0.3)**	**3**	**(0.2)**	**4**	**(0.3)**	**7**	**(0.3)**
Acute kidney injury	1	(0.1)	1	(0.1)	2	(0.1)	3	(0.1)
Dysuria	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Tubulointerstitial nephritis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Reproductive system and breast disorders	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.0)**
Pruritus genital	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Respiratory, thoracic and mediastinal disorders	**17**	**(2.5)**	**31**	**(2.5)**	**21**	**(1.3)**	**52**	**(1.9)**
Chronic obstructive pulmonary disease	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cough	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Dysphonia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Dyspnoea	4	(0.6)	5	(0.4)	7	(0.4)	12	(0.4)
Hypoxia	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Interstitial lung disease	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)
Laryngeal inflammation	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pleural effusion	1	(0.1)	2	(0.2)	0	(0.0)	2	(0.1)
Pleuritic pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pneumonitis	12	(1.8)	22	(1.8)	10	(0.6)	32	(1.1)
Pulmonary embolism	1	(0.1)	2	(0.2)	0	(0.0)	2	(0.1)
Respiratory failure	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Skin and subcutaneous tissue disorders	**6**	**(0.9)**	**11**	**(0.9)**	**18**	**(1.1)**	**29**	**(1.0)**
Drug eruption	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Hyperkeratosis	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Lichen planus	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Lichenoid keratosis	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)
Pemphigoid	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Pruritus	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Psoriasis	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Rash	2	(0.3)	4	(0.3)	2	(0.1)	6	(0.2)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Rash generalised	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Rash maculo-papular	1	(0.1)	2	(0.2)	5	(0.3)	7	(0.3)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Vascular disorders	**4**	**(0.6)**	**7**	**(0.6)**	**5**	**(0.3)**	**12**	**(0.4)**
Arterial thrombosis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Embolism	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Hypertension	2	(0.3)	4	(0.3)	3	(0.2)	7	(0.3)
Peripheral ischaemia	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Vasculitis	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)

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

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

Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).

(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).

(MK-3475 PN002 Database Cutoff Date: 28FEB2015).

(MK-3475 PN006 Database Cutoff Date: 03MAR2015).

(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

No major differences in the incidence of Grade ≥ 3 Drug-Related AEs were observed between NSCLC and melanoma patients with the exception of events in the SOC *Respiratory, Thoracic and Mediastinal disorders* (2.5% vs 1.3%).

Adverse Events of Special Interest (AEOSI)

In the overall TPS≥1% population of study P010, AEOSI were more common among pembrolizumab-treated compared to docetaxel-treated patients (19.5% vs. 4.2%, respectively). The median time to onset of the first AEOSI occurrence was 64 days (range: 4 to 381 days) in pembrolizumab-treated patients and 85 days (range: 14 to 229 days) in docetaxel-treated patients.

Grade ≥3 AEOSI were reported in 5.3% of pembrolizumab-treated patients. No meaningful differences occurred between the pembrolizumab and docetaxel arms in the rates of deaths due to AEOSI (0.4% vs. 0.6%), discontinuations due to AEOSI (2.2% vs. 1.6%), or discontinuations due to AEOSI categorized as SAEs (1.5% vs. 1.0%). Fifteen patients (2.2%) discontinued pembrolizumab due to any AEOSI, regardless of causality, compared to 5 patients (1.6%) on docetaxel.

The most common AEOSI, occurring in >1% of subjects in the pooled pembrolizumab arms, included hypothyroidism (8.2% vs 0.3%), hyperthyroidism (4.7% vs 1%) and pneumonitis (4.5% vs 1.3%).

Hypothyroidism and hyperthyroidism, mainly Grade 1 or Grade 2 events and none worse than Grade 3, were in general readily managed with thyroid replacement therapy, treatment interruption, or both. Only one patient discontinued pembrolizumab (10 mg/kg Q3W) due to hypothyroidism.

A total of 31 patients (4.5%) on pembrolizumab and 6 (1.9%) on docetaxel experienced pneumonitis in the pivotal NSCLC P010. At the data cut-off date, 18 out of the 31 pembrolizumab treated completely recovered from pneumonitis with corticosteroid treatment and treatment interruption. Grade ≥3 pneumonitis was experienced by 14 (2.1%) patients compared to 2 (0.6%) patients on docetaxel. Three pembrolizumab-treated patients died due to pneumonitis possibly drug-related.

The incidence of selected and pre-specified AEs of potential immune aetiology was compared between the pooled pembrolizumab arms and the docetaxel arm. Results reported in the TPS≥1% population are shown in the Table below:

Table 64: Analysis of selected AEs - pembrolizumab groups pooled - APaT population (TPS≥1%)

			Difference in % vs Docetaxel 75 mg/m2 Q3W	
			Estimate	p-value[1]
Treatment	n	(%)	(95% CI)[1]	
Subjects in population				
MK-3475 Pooled	682			
Docetaxel 75 mg/m2 Q3W	309			
Grade ≥ 3 Diarrhea with a potential immunologic etiology				
MK-3475 Pooled	3	(0.4)	-2.1 (-4.6, -0.6)	0.003
Docetaxel 75 mg/m2 Q3W	8	(2.6)		
Grade ≥ 2 Colitis with a potential immunologic etiology				
MK-3475 Pooled	4	(0.6)	0.6 (-0.6, 1.7)	0.174
Docetaxel 75 mg/m2 Q3W	0	(0.0)		
Grade ≥ 2 Pneumonitis with a potential immunologic etiology				
MK-3475 Pooled	25	(3.7)	2.2 (-0.1, 4.1)	0.056
Docetaxel 75 mg/m2 Q3W	4	(1.3)		
Grade ≥ 3 Hypo- or hyperthyroidism with a potential immunologic etiology				
MK-3475 Pooled	1	(0.1)	0.2 (-1.1, 0.8)	0.485
Docetaxel 75 mg/m2 Q3W	0	(0.0)		

[1] Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive, Weakly Positive and Unknown Positive)

Every subject is counted a single time for each applicable specific adverse event category.

Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.

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

(Database Cutoff Date: 30SEP2015)

Data Source: [16.4]

Overall, infusion reactions were more frequent in the docetaxel arm than in the pooled pembrolizumab arms (5.2% vs. 1.8%, respectively). The majority of cases were Grade 1 or 2 in severity across treatment arms. The only two Grade 3 reported cases (anaphylactic reaction and drug hypersensitivity) occurred with pembrolizumab.

The number and rate of patients with specific identified AEOSI across clinical studies are reported below:

Table 65: Subjects with identified Adverse Events of Special Interest (incidence >0% in one or more treatment groups) - PN001, PN002, PN006 and PN010 Melanoma and Lung patients treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	142	(20.8)	244	(19.8)	352	(22.5)	596	(21.3)
with no adverse events	540	(79.2)	988	(80.2)	1,215	(77.5)	2,203	(78.7)
Adrenal Insufficiency	**5**	**(0.7)**	**9**	**(0.7)**	**13**	**(0.8)**	**22**	**(0.8)**
Adrenal insufficiency	5	(0.7)	9	(0.7)	11	(0.7)	20	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Colitis	**6**	**(0.9)**	**13**	**(1.1)**	**36**	**(2.3)**	**49**	**(1.8)**
Colitis	6	(0.9)	13	(1.1)	33	(2.1)	46	(1.6)
Colitis microscopic	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Enterocolitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**2**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Hepatic	**3**	**(0.4)**	**3**	**(0.2)**	**16**	**(1.0)**	**19**	**(0.7)**
Autoimmune hepatitis	3	(0.4)	3	(0.2)	9	(0.6)	12	(0.4)
Drug-induced liver injury	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Hepatitis	0	(0.0)	0	(0.0)	6	(0.4)	6	(0.2)
Hyperthyroidism	**32**	**(4.7)**	**43**	**(3.5)**	**53**	**(3.4)**	**96**	**(3.4)**
Hyperthyroidism	32	(4.7)	43	(3.5)	53	(3.4)	96	(3.4)
Hypophysitis	**2**	**(0.3)**	**3**	**(0.2)**	**14**	**(0.9)**	**17**	**(0.6)**
Hypophysitis	0	(0.0)	1	(0.1)	8	(0.5)	9	(0.3)
Hypopituitarism	2	(0.3)	2	(0.2)	6	(0.4)	8	(0.3)
Hypothyroidism	**56**	**(8.2)**	**98**	**(8.0)**	**139**	**(8.9)**	**237**	**(8.5)**
Hypothyroidism	56	(8.2)	98	(8.0)	138	(8.8)	236	(8.4)
Myxoedema	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Infusion Reactions	**12**	**(1.8)**	**31**	**(2.5)**	**39**	**(2.5)**	**70**	**(2.5)**
Anaphylactic reaction	2	(0.3)	2	(0.2)	1	(0.1)	3	(0.1)
Cytokine release syndrome	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Drug hypersensitivity	4	(0.6)	5	(0.4)	8	(0.5)	13	(0.5)
Hypersensitivity	1	(0.1)	8	(0.6)	14	(0.9)	22	(0.8)
Serum sickness	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Infusion related reaction	5	(0.7)	15	(1.2)	14	(0.9)	29	(1.0)
Myositis	**3**	**(0.4)**	**3**	**(0.2)**	**8**	**(0.5)**	**11**	**(0.4)**
Myopathy	2	(0.3)	2	(0.2)	1	(0.1)	3	(0.1)
Myositis	1	(0.1)	1	(0.1)	6	(0.4)	7	(0.3)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pancreatitis	**3**	**(0.4)**	**3**	**(0.2)**	**6**	**(0.4)**	**9**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pancreatitis	2	(0.3)	2	(0.2)	5	(0.3)	7	(0.3)
Pancreatitis acute	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Pneumonitis	**31**	**(4.5)**	**54**	**(4.4)**	**40**	**(2.6)**	**94**	**(3.4)**
Interstitial lung disease	3	(0.4)	4	(0.3)	3	(0.2)	7	(0.3)
Pneumonitis	28	(4.1)	50	(4.1)	37	(2.4)	87	(3.1)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal	**1**	**(0.1)**	**1**	**(0.1)**	**3**	**(0.2)**	**4**	**(0.1)**
Tubulointerstitial nephritis	1	(0.1)	1	(0.1)	3	(0.2)	4	(0.1)
Skin	**11**	**(1.6)**	**18**	**(1.5)**	**28**	**(1.8)**	**46**	**(1.6)**
Jaundice	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Rash pustular	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Contusion	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Pruritus genital	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Dermatitis	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Dermatitis bullous	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Dermatitis exfoliative	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)
Drug eruption	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Erythema	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Erythema multiforme	2	(0.3)	3	(0.2)	0	(0.0)	3	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Lichen planus	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Pemphigoid	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Pruritus	0	(0.0)	0	(0.0)	4	(0.3)	4	(0.1)
Psoriasis	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Rash	2	(0.3)	4	(0.3)	5	(0.3)	9	(0.3)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Rash generalised	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Rash maculo-papular	1	(0.1)	2	(0.2)	5	(0.3)	7	(0.3)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Skin lesion	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Toxic skin eruption	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Thyroiditis	**3**	**(0.4)**	**3**	**(0.2)**	**13**	**(0.8)**	**16**	**(0.6)**
Autoimmune thyroiditis	1	(0.1)	1	(0.1)	4	(0.3)	5	(0.2)
Thyroiditis	2	(0.3)	2	(0.2)	9	(0.6)	11	(0.4)
Type 1 Diabetes Mellitus	**3**	**(0.4)**	**3**	**(0.2)**	**3**	**(0.2)**	**6**	**(0.2)**
Diabetic ketoacidosis	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Type 1 diabetes mellitus	3	(0.4)	3	(0.2)	2	(0.1)	5	(0.2)
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**14**	**(0.9)**	**14**	**(0.5)**
Iridocyclitis	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Iritis	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Uveitis	0	(0.0)	0	(0.0)	10	(0.6)	10	(0.4)

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

An AEOSI category 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 version used is 18.0

Five additional cases (subject 000054 in PN001 with autoimmune nephritis, subject 000048 in PN001 with renal failure acute, subject 000058 in PN001 with renal failure, subject 368852 in PN006 with renal failure acute, subject 363218 in PN006 with renal failure) of the AEOSI-Renal were observed that are not reported on the table.

Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).

(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).

(MK-3475 PN002 Database Cutoff Date: 28FEB2015).

(MK-3475 PN006 Database Cutoff Date: 03MAR2015).

(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Due to coding issues and differing database locks, the following events for a small subset of terms were not included in the above table:

- Five additional cases in the AEOSI-Renal (Nephritis): autoimmune nephritis (Subject 000054 in Study P001), renal failure acute (Subject 000048 in Study P001), renal failure (Subject 000058 in Study P001), renal failure acute (Subject 368852 in Study P006), and renal failure (Subject 363218 in Study P006). Therefore, the incidence of AEOSI-Renal (Nephritis) in the pooled dataset of PN001, PN002, PN006, PN010 should have a count of 9 (0.3%).
- Subject 001734 in KEYNOTE-001 was counted within the AEOSI-Colitis. However, it was later determined that the patient had a grade 3 calcified fecalith, and was included in the summary

of colitis due to data entry errors. Therefore, the incidence of AEOSI-Colitis in the pooled dataset of PN001, PN002, PN006, PN010 should have a count of 48 (1.7%).

- Subject 361473 in KEYNOTE-006 had an event of anaphylactoid reaction that was not counted as an infusion-related reaction since this term was not listed as AEOSI-Infusion-Related Reactions at the time of reporting. This event was considered related to study drug, and led to treatment withdrawal. Therefore, the incidence of AEOSI-Infusion-Related Reactions in the pooled dataset of PN001, PN002, PN006, PN010 should have a count of 71 (2.5%).

Pneumonitis:

Pneumonitis occurred in 94 (3.4%) patients, including Grade 2, 3, 4 or 5 cases in 36 (1.3%), 25 (0.9%), 7 (0.3%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.

Colitis

Colitis occurred in 48 (1.7%) patients, including Grade 2, 3 or 4 cases in 10 (0.4%), 31 (1.1%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 15 (0.5%) patients. Colitis resolved in 41 patients.

Hepatitis

Hepatitis occurred in 19 (0.7%) patients, including Grade 2, 3 or 4 cases in 4 (0.1%), 12 (0.4%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab. 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

Nephritis occurred in 9 (0.3%) patients, including Grade 2, 3 or 4 cases in 3 (0.1%), 4 (0.1%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of pembrolizumab in 3 (0.1%) patients. Nephritis resolved in 5 patients.

Endocrinopathies

Hypophysitis occurred in 17 (0.6%) patients, including Grade 2, 3 or 4 cases in 6 (0.2%), 8 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 3.7 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.

Hyperthyroidism occurred in 96 (3.4%) patients, including Grade 2 or 3 cases in 22 (0.8%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) patients.

Hypothyroidism occurred in 237 (8.5%) patients, including Grade 2 or 3 cases in 174 (6.2%) and 3

(0.1%) patients, receiving pembrolizumab. 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 48 (20%) patients.

Serious adverse event / deaths / other significant events

SAEs occurred in the pivotal study P010 across the three treatment arms are reported in the Table below:

Table 66: Most common (≥1%) SAEs up to 90 days after last dose (Study P010) (All Causality and Treatment-Related) - Subjects with TPS ≥1%, APaT Population

	pembrolizumab 2 mg/kg (N=339)		pembrolizumab 10 mg/kg (N=343)		docetaxel (N=309)	
	All-Causality n (%)	**Drug Related n (%)**	**All Causality n (%)**	**Drug Related n (%)**	**All Causality n (%)**	**Drug Related n (%)**
Patients with ≥SAEs	115 (33.9)	32 (9.4)	131 (38.2)	39 (11.4)	107 (34.6)	42 (13.6)
Blood and lymphatic system disorders	5 (1.5)	0	7 (2.0)	3 (0.9)	19 (6.1)	15 (4.9)
Febrile neutropenia	1 (0.3)	0	1 (0.3)	0	11 (3.6)	10 (3.2)
Neutropenia	0	0	0	0	5 (1.6)	4 (1.3)
Cardiac disorders	14 (4.1)	0	14 (4.1)	3 (0.9)	8 (2.6)	2 (0.6)
Pericardial effusion	4 (1.2)	0	2 (0.6)	1 (0.3)	1 (0.3)	0
Endocrine disorders	2 (0.6)	2 (0.6)	5 (1.5)	5 (1.5)	0	0
Gastrointestinal disorders	11 (3.2)	4 (1.2)	10 (2.9)	1 (0.3)	13 (4.2)	4 (1.3)
General disorders and administration site conditions	14 (4.1)	1 (0.3)	10 (2.9)	3 (0.9)	10 (3.2)	4 (1.3)
Death	3 (0.9)	0	3 (0.9)	0	1 (0.3)	0
Pyrexia	2 (0.6)	0	3 (0.9)	1 (0.3)	4 (1.3)	1 (0.3)
Infection and infestations	29 (8.6)	3 (0.9)	37 (10.8)	3 (0.9)	38 (12.3)	12 (3.9)
Bronchitis	1 (0.3)	0	0	0	3 (1.0)	0
Lung infection	2 (0.6)	0	0	0	3 (1.0)	1 (0.3)
Pneumonia	15 (4.4)	3 (0.9)	21 (6.1)	3 (0.9)	16 (5.2)	4 (1.3)
Respiratory tract infection	3 (0.9)	0	3 (0.9)	0	3 (1.0)	1 (0.3)
Injury, poisoning and procedural complications	5 (1.5)	1 (0.3)	9 (2.6)	1 (0.3)	6 (1.9)	1 (0.3)
Investigations	6 (1.8)	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	5 (1.5)	2 (0.6)	14 (4.1)	6 (1.7)	8 (2.6)	4 (1.3)
Decreased appetite	1 (0.3)	1 (0.3)	0	0	3 (1.0)	1 (0.3)
Dehydration	1 (0.3)	0	2 (0.6)	0	4 (1.3)	3 (1.0)
Hypercalcaemia	1 (0.3)	0	5 (1.5)	0	0	0
Musculoskeletal and connective tissue disorders	10 (2.9)	4 (1.2)	8 (2.3)	1 (0.3)	4 (1.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.2)	0	6 (1.7)	1 (0.3)	2 (0.6)	0
Nervous system disorders	8 (2.4)	2 (0.6)	12 (3.5)	1 (0.3)	4 (1.3)	1 (0.3)
Psychiatric disorders	4 (1.2)	1 (0.3)	4 (1.2)	1 (0.3)	2 (0.6)	0
Renal and urinary disorders	4 (1.2)	1 (0.3)	4 (1.2)	0	3 (1.0)	1 (0.3)
Acute kidney injury	2 (0.6)	0	2 (0.6)	0	1 (0.3)	1 (0.3)
Tubulointestinal nephritis	1 (0.3)	1 (0.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	33 (9.7)	11 (3.2)	32 (9.3)	10 (2.9)	24 (7.8)	8 (2.6)
Chronic obstructive pulmonary disease	6 (1.8)	1 (0.3)	1 (0.3)	0	1 (0.3)	0
Dyspnoea	6 (1.8)	1 (0.3)	2 (0.6)	1 (0.3)	6 (1.9)	3 (1.0)
Haemoptysis	3 (0.9)	0	1 (0.3)	0	0	0
Pleural effusion	4 (1.2)	2 (0.6)	4 (1.2)	0	3 (1.0)	2 (0.6)
Pneumonitis	8 (2.4)	7 (2.1)	9 (2.6)	8 (2.3)	2 (0.6)	2 (0.6)
Pulmonary embolism	8 (2.4)	1 (0.3)	7 (2.0)	0	5 (1.6)	0
Vascular disorders	6 (1.8)	0	5 (1.5)	1 (0.3)	5 (1.6)	1 (0.3)

Table made by the CHMP Assessor. Source: Table 14.4.2-63 and Table 14.4.2-71

Among pembrolizumab-treated patients, the most common drug-related SAE was pneumonitis (2.2%), with all other drug-related SAEs occurred in less than 1% of patients. By contrast, in the docetaxel arm, the most frequent drug-related SAEs were febrile neutropenia (3.2%).

Overall, no major differences were registered based on pembrolizumab dose or PD-L1 expression in the pivotal NSCLC trial P010.

In the NSCLC population, the incidence of both All-Causality and Drug-related SAEs was consistent with that reported in melanoma studies. As expected, a higher rate of drug-related Pneumonitis was reported in NSCLC patients (2.4% vs 1.0%):

Table 67: Subjects With Serious Drug-Related AEs Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) - PN001, PN002, PN006 and PN010 Subjects Treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	71	(10.4)	117	(9.5)	164	(10.5)	281	(10.0)
with no adverse events	611	(89.6)	1,115	(90.5)	1,403	(89.5)	2,518	(90.0)
Endocrine disorders	**7**	**(1.0)**	**11**	**(0.9)**	**16**	**(1.0)**	**27**	**(1.0)**
Gastrointestinal disorders	**5**	**(0.7)**	**12**	**(1.0)**	**48**	**(3.1)**	**60**	**(2.1)**
Colitis	3	(0.4)	6	(0.5)	19	(1.2)	25	(0.9)
Diarrhoea	0	(0.0)	1	(0.1)	16	(1.0)	17	(0.6)
General disorders and administration site conditions	**4**	**(0.6)**	**7**	**(0.6)**	**17**	**(1.1)**	**24**	**(0.9)**
Metabolism and nutrition disorders	**8**	**(1.2)**	**11**	**(0.9)**	**14**	**(0.9)**	**25**	**(0.9)**
Respiratory, thoracic and mediastinal disorders	**21**	**(3.1)**	**40**	**(3.2)**	**26**	**(1.7)**	**66**	**(2.4)**
Pneumonitis	15	(2.2)	29	(2.4)	15	(1.0)	44	(1.6)

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

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

Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).

(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).

(MK-3475 PN002 Database Cutoff Date: 28FEB2015).

(MK-3475 PN006 Database Cutoff Date: 03MAR2015).

(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Deaths

Table 68: Subjects With Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) - PN001, PN002, PN006 and PN010 Subjects Treated with pembrolizumab (APaT Population)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	682		1,232		1,567		2,799	
with one or more adverse events	43	(6.3)	62	(5.0)	48	(3.1)	110	(3.9)
with no adverse events	639	(93.7)	1,170	(95.0)	1,519	(96.9)	2,689	(96.1)
Acute coronary syndrome	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Acute kidney injury	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Acute myocardial infarction	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Acute respiratory failure	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Anaemia	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Aspiration bronchial	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Brain oedema	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cachexia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Cardiac arrest	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Cardiac failure	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Cardiac failure congestive	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Cardiac tamponade	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Cardiopulmonary failure	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Cerebrovascular accident	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Completed suicide	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Death	6	(0.9)	8	(0.6)	9	(0.6)	17	(0.6)
Diffuse alveolar damage	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Dyspnoea	0	(0.0)	0	(0.0)	2	(0.1)	2	(0.1)
Embolism	1	(0.1)	3	(0.2)	0	(0.0)	3	(0.1)
Gastrointestinal perforation	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
General physical health deterioration	0	(0.0)	0	(0.0)	6	(0.4)	6	(0.2)
Generalised oedema	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Haemoptysis	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)

	P010		PN001 Lung, PN010		PN001 Mel, PN002, PN006		PN001 PN002 PN006 PN010	
	n	(%)	n	(%)	n	(%)	n	(%)
Haemorrhagic infarction	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Haemorrhagic stroke	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Haemothorax	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Hepatic failure	1	(0.1)	1	(0.1)	2	(0.1)	3	(0.1)
Hypoxia	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Infectious pleural effusion	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Interstitial lung disease	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Intestinal obstruction	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Intestinal perforation	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Lung infection	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Lung neoplasm malignant	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Lymphangiosis carcinomatosa	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Mental status changes	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Metastatic malignant melanoma	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Multi-organ failure	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Myocardial infarction	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)
Pneumocystis jirovecii pneumonia	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Pneumonia	7	(1.0)	8	(0.6)	2	(0.1)	10	(0.4)
Pneumonia aspiration	2	(0.3)	2	(0.2)	0	(0.0)	2	(0.1)
Pneumonitis	3	(0.4)	3	(0.2)	0	(0.0)	3	(0.1)
Pneumothorax	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Pulmonary embolism	1	(0.1)	2	(0.2)	1	(0.1)	3	(0.1)
Pulmonary haemorrhage	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Pulmonary oedema	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Respiratory distress	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Respiratory failure	2	(0.3)	6	(0.5)	0	(0.0)	6	(0.2)
Sepsis	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Septic shock	0	(0.0)	1	(0.1)	2	(0.1)	3	(0.1)
Soft tissue infection	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Spinal cord compression	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Traumatic intracranial haemorrhage	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Include all treated subjects in PN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in PN002 treated with Pembrolizumab in the original phase , and all subjects in PN006 and PN010 treated with Pembrolizumab.
(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN002 Database Cutoff Date: 28FEB2015).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Laboratory findings

In study P010, a shift analysis on laboratory abnormalities with the highest CTCAE Grade was performed. A clinically meaningful worsening in CTCAE grade, defined as a shift from less than Grade 3 to Grade ≥3 or a shift from Grade 0 to Grade 2, was reported for some laboratory test:

Table 69: Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-Baseline

Laboratory test	docetaxel (N=309)	pembrolizumab 2 mg/kg Q3W (N=339)	pembrolizumab 10 mg/kg Q3W (N=343)
Alanine Aminotransferase increased			
Improved from baseline	0	0	1 (0.3)
Worsened from baseline	29 (9.4)	77 (22.7)	69 (20.1)

Clinically meaningful worsened from baseline	2 (0.6)	16 (4.7)	15 (4.4)
Albumin decreased			
Improved from baseline	1 (0.3)	1 (0.3)	3 (0.9)
Worsened from baseline	98 (31.7)	108 (31.9)	116 (33.8)
Clinically meaningful worsened from baseline	25 (8.1)	33 (9.7)	30 (8.7)
Alkaline Phosphatase increased			
Improved from baseline	1 (0.3)	1 (0.3)	2 (0.6)
Worsened from baseline	50 (16.2)	87 (25.7)	101 (29.4)
Clinically meaningful worsened from baseline	3 (1.0)	17 (5.0)	18 (5.2)
Amylase increased			
Improved from baseline	0	0	0
Worsened from baseline	0	2 (0.6)	2 (0.6)
Clinically meaningful worsened from baseline	0	2 (0.6)	2 (0.6)
Aspartate Aminotransferase increased			
Improved from baseline	0	0	0
Worsened from baseline	36 (11.7)	86 (25.4)	84 (24.5)
Clinically meaningful worsened from baseline	4 (1.3)	15 (4.4)	15 (4.4)
Bilirubin increased			
Improved from baseline	0	0	0
Worsened from baseline	11 (3.6)	24 (7.1)	20 (5.8)
Clinically meaningful worsened from baseline	4 (1.3)	9 (2.7)	9 (2.6)
Calcium decreased			
Improved from baseline	0	0	0
Worsened from baseline	57 (18.4)	65 (19.2)	66 (19.2)
Clinically meaningful worsened from baseline	11 (3.6)	14 (4.1)	16 (4.7)
Calcium increased			
Improved from baseline	0	1 (0.3)	0
Worsened from baseline	22 (7.1)	33 (9.7)	39 (11.4)
Clinically meaningful worsened from baseline	3 (1.0)	6 (1.8)	11 (3.2)
Cholesterol			
Improved from baseline	2 (0.6)	0	1 (0.3)
Worsened from baseline	61 (19.7)	63 (18.6)	75 (21.9)
Clinically meaningful worsened from baseline	5 (1.6)	2 (0.6)	10 (2.9)
Creatinine increased			
Improved from baseline	3 (1.0)	0	0
Worsened from baseline	28 (9.1)	57 (16.8)	63 (18.4)
Clinically meaningful worsened from baseline	4 (1.3)	9 (2.7)	8 (2.3)
Gamma Glutamyl Transferase increased			
Improved from baseline	0	0	1 (0.3)
Worsened from baseline	2 (0.6)	3 (0.9)	7 (2.0)
Clinically meaningful worsened from baseline	2 (0.6)	3 (0.9)	6 (1.7)
Glucose decreased			
Improved from baseline	0	0	0
Worsened from baseline	8 (2.6)	27 (8.0)	16 (7.6)
Clinically meaningful worsened from baseline	2 (0.6)	6 (1.8)	5 (1.5)
Glucose increased			
Improved from baseline	4 (1.3)	4 (1.2)	2 (0.6)
Worsened from baseline	150 (48.5)	132 (38.9)	157 (45.8)
Clinically meaningful worsened from baseline	48 (15.5)	27 (8.0)	32 (9.3)
Hemoglobin decreased			
Improved from baseline	2 (0.6)	0	7 (2.0)
Worsened from baseline	170 (55.0)	128 (37.8)	121 (35.3)
Clinically meaningful worsened from baseline	28 (9.1)	24 (7.1)	15 (4.4)
Leukocytes decreased			
Improved from baseline	0	0	1 (0.3)
Worsened from baseline	73 (23.6)	18 (5.3)	25 (7.3)
Clinically meaningful worsened from baseline	58 (18.8)	4 (1.2)	5 (1.5)
Lymphocytes decreased			
Improved from baseline	2 (0.6)	9 (2.7)	3 (0.9)
Worsened from baseline	122 (39.5)	103 (30.4)	111 (32.4)
Clinically meaningful worsened from baseline	73 (23.6)	57 (16.8)	65 (19.0)
Magnesium decreased			
Improved from baseline	1 (0.3)	0	0
Worsened from baseline	40 (12.9)	67 (19.8)	64 (18.7)
Clinically meaningful worsened from baseline	6 (1.9)	9 (2.7)	10 (2.9)
Magnesium increased			
Improved from baseline	0	0	0
Worsened from baseline	8 (2.6)	13 (3.8)	18 (5.2)

Clinically meaningful worsened from baseline	1 (0.3)	2 (0.6)	3 (0.9)
Neutrophil decreased			
Improved from baseline	0	0	0
Worsened from baseline	73 (23.0)	14 (4.1)	24 (7.0)
Clinically meaningful worsened from baseline	65 (21.0)	6 (1.8)	10 (2.9)
Phosphate decreased			
Improved from baseline	0	3 (0.9)	1 (0.3)
Worsened from baseline	54 (17.5)	50 (14.7)	69 (20.1)
Clinically meaningful worsened from baseline	46 (14.9)	38 (11.2)	62 (18.1)
Platelet decreased			
Improved from baseline	0	0	0
Worsened from baseline	24 (7.8)	35 (10.3)	39 (11.4)
Clinically meaningful worsened from baseline	6 (1.9)	9 (2.7)	7 (2.0)
Potassium decreased			
Improved from baseline	0	1 (0.3)	0
Worsened from baseline	24 (7.8)	42 (12.4)	27 (7.9)
Clinically meaningful worsened from baseline	6 (1.9)	7 (2.1)	4 (1.2)
Potassium increased			
Improved from baseline	2 (0.6)	0	2 (0.6)
Worsened from baseline	47 (15.2)	60 (17.7)	56 (16.3)
Clinically meaningful worsened from baseline	8 (2.6)	15 (4.4)	19 (5.5)
Sodium decreased			
Improved from baseline	1 (0.3)	1 (0.3)	0
Worsened from baseline	77 (24.9)	99 (29.2)	115 (33.5)
Clinically meaningful worsened from baseline	8 (2.6)	28 (8.3)	29 (8.5)
Triglycerides			
Improved from baseline	2 (0.6)	4 (1.2)	1 (0.3)
Worsened from baseline	89 (28.8)	96 (28.3)	120 (35.0)
Clinically meaningful worsened from baseline	11 (3.6)	10 (2.9)	21 (6.1)

From Table 12-36 (CSR P010)

No clinically meaningful changes in the percentage of subjects with worsening of laboratory abnormalities was observed between the previously reported data in subjects with melanoma and the new data in subjects with NSCLC.

Safety in special populations

Safety was assessed in subgroups defined by intrinsic and extrinsic factors (age, gender, ECOG status, region and histology) in NSCLC patients treated with pembrolizumab in the KEYNOTE-001 and KEYNOTE-010 studies.

Age

In Study P010 the incidence of drug-related AEs and SAEs was slightly higher in patients ≥65 years compared to those aged <65 years in both docetaxel and pembrolizumab arms.

In the NSCLC population treated with pembrolizumab (Studies P001 and P010), the incidences of AEs, drug-related AEs, Grade ≥3 AEs, deaths, SAEs, and discontinuations due to AEs were slightly increased in older patients.

Table 70: Adverse Event Summary by Age – Studies P001 (Lung subjects) and P010 treated with pembrolizumab (APaT Population)

	Pem 2 mg/kg Q3W			Pem 10 mg/kg Q3W			Pem 10 mg/kg Q2W			Total		
	<65	65-74	75-84	<65	65-74	75-84	<65	65-74	75-84	<65	65-74	75-84
Subjects in population	231	128	41	339	228	60	111	64	25	681	420	126
with one or more AE n(%)	224 (97.0)	124 (96.9)	41 (100)	325 (95.9)	219 (96.1)	59 (98.3)	109 (98.2)	61 (95.3)	25 (100)	658 (96.6)	404 (96.2)	125 (99.2)
with no AE n(%)	7 (3.0)	4 (3.1)	0	14 (4.1)	9 (3.9)	1 (1.7)	2 (1.8)	3 (4.7)	0	23 (3.4)	16 (3.8)	1 (0.8)
with drug-related* AE n(%)	134 (58.0)	82 (64.1)	30 (73.2)	222 (65.5)	156 (68.4)	48 (80.0)	84 (75.7)	42 (65.6)	20 (80.0)	440 (64.6)	280 (66.7)	98 (77.8)

with SAE n(%)	78 (33.8)	50 (39.1)	17 (41.5)	123 (36.3)	93 (40.8)	30 (50.0)	39 (35.1)	32 (50.0)	11 (44.0)	240 (35.2)	175 (41.7)	58 (46.0)
with drug-related SAE n(%)	20 (8.7)	14 (10.9)	4 (9.8)	33 (9.7)	25 (11.0)	8 (13.3)	3 (2.7)	7 (10.9)	3 (12.0)	56 (8.2)	46 (11.0)	15 (11.9)
who died n(%)	11 (4.8)	4 (3.1)	4 (9.8	17 (5.0)	15 (6.6)	4 (6.7)	2 (1.8)	3 (4.7)	2 (8.0)	30 (4.4)	22 (5.2)	10 (7.9)
discontinued due to AE n(%)	18 (7.8)	15 (11.7)	5 (12.2)	37 (10.9)	25 (11.0)	8 (13.3)	15 (13.5)	11 (17.2)	5 (20.0)	70 (10.3)	51 (12.1)	18 (14.3)
discontinued due to drug-related AE n(%)	8 (3.5)	8 (6.3)	3 (7.3)	15 (4.4)	11 (4.8)	4 (6.7)	4 (3.6)	3 (4.7)	1 (4.0)	27 (4.0)	22 (5.2)	8 (6.3)
discontinued due to SAE n(%)	18 (7.8)	13 (10.2)	3 (7.3)	28 (8.3)	19 (8.3)	7 (11.7)	9 (8.1)	10 (15.6)	4 (16.0)	55 (8.1)	42 (10.0)	14 (11.1)
discontinued due to drug-related SAE n(%)	8 (3.5)	6 (4.7)	1 (2.4)	12 (3.5)	8 (3.5)	3 (5.0)	2 (1.8)	3 (4.7)	1 (4.0)	22 (3.2)	17 (4.0)	5 (4.0)

*Determined by the investigator to be related to the drug
MedDRA PTs"Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression"not related to the drug are excluded.
Include all treated subjects in PN001 Part C, F1, F2 F3 and all subjects in PN010 treated with pembrolizumab.
(MK-3475 PN001 Database Cutoff Date for Lung: 23 Jan 2015)
(MK-3475 PN010 Database Cutoff Date: 30 Sep 2015)

Table 71: AEs Summary by Age PN001 and PN010 Lung Subjects Treated with pembrolizumab 2 mg/kg Q3W

	Age (years)							
	<65		65-74		75-84		85 +	
	n	(%)	N	(%)	n	(%)	n	(%)
Subjects in population	231	(100.0)	128	(100.0)	41	(100.0)	0	(.)
with one or more adverse events	224	(97.0)	124	(96.9)	41	(100.0)	0	(.)
who died	11	(4.8)	4	(3.1)	4	(9.8)	0	(.)
with serious adverse events	78	(33.8)	50	(39.1)	17	(41.5)	0	(.)
discontinued‡ due to an adverse event	18	(7.8)	15	(11.7)	5	(12.2)	0	(.)
CNS (confusion/extrapyramidal)	17	(7.4)	15	(11.7)	2	(4.9)	0	(.)
AE related to falling	10	(4.3)	10	(7.8)	1	(2.4)	0	(.)
CV events	43	(18.6)	28	(21.9)	7	(17.1)	0	(.)
Cerebrovascular events	6	(2.6)	1	(0.8)	2	(4.9)	0	(.)
Infections	84	(36.4)	48	(37.5)	15	(36.6)	0	(.)

‡ Study medication withdrawn.
MedDRA preferred terms 'Malignant neoplasm progression' ,'Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment, SAEs were followed 90 days after last dose of study treatment
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Table 72: AEs Summary by Age PN001, PN002, PN006 and PN010 Melanoma and Lung Subjects Treated with pembrolizumab 2 mg/kg Q3W

	Age (years)							
	<65		65-74		75-84		85 +	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	437	(100.0)	221	(100.0)	80	(100.0)	2	(100.0)
with one or more adverse events	426	(97.5)	216	(97.7)	78	(97.5)	2	(100.0)
who died	18	(4.1)	10	(4.5)	7	(8.8)	0	(0.0)
with serious adverse events	161	(36.8)	91	(41.2)	37	(46.3)	2	(100.0)
discontinued‡ due to an adverse event	39	(8.9)	28	(12.7)	13	(16.3)	0	(0.0)
CNS (confusion/extrapyramidal)	45	(10.3)	30	(13.6)	3	(3.8)	2	(100.0)
AE related to falling	36	(8.2)	21	(9.5)	8	(10.0)	0	(0.0)
CV events	78	(17.8)	50	(22.6)	15	(18.8)	0	(0.0)
Cerebrovascular events	15	(3.4)	3	(1.4)	3	(3.8)	0	(0.0)
Infections	168	(38.4)	98	(44.3)	33	(41.3)	1	(50.0)

‡ Study medication withdrawn.

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

AEs were followed 30 days after last dose of study treatment, SAEs were followed 90 days after last dose of study treatment

(MK-3475 PN001 Database Cutoff Date for MEL: 18APR2014).

(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).

(MK-3475 PN002 Database Cutoff Date: 28FEB2015).

(MK-3475 PN006 Database Cutoff Date: 03MAR2015).

(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Gender

In Study P010, the overall incidence of AEs was similar between the genders in both treatment arms, with the exception of SAEs occurring more often in males than in females (38.7% vs 28% in docetaxel arm; 40.6% vs 28.9% in pooled pembrolizumab arms). A similar trend was observed in the NSCLC population (studies P001 and P010) with a slightly lower incidence of SAEs in female patients pembrolizumab treated.

ECOG Performance Status

The incidence of SAEs was slightly higher in the ECOG 1 than in the ECOG 0 populations in both the docetaxel (36.7% vs 30.4%) and the pembrolizumab arms (38.4% vs 31.6%) in study P010. In ECOG 1 NSCLC patients treated with pembrolizumab across studies P001 and P010 the tolerability was slightly reduced compared to that in ECOG 0 patients in terms of SAEs (40.5% vs 34.4%), discontinuation due to AEs (12.6% vs 8.8%) and discontinuation due to SAEs (10.2% vs 6.9%).

Region

NSCLC patients from North America, Europe, Asia and Australia participated in the studies. No major differences in safety were observed by Region (US and outside of US) both in study P010 among treatment arms and in the overall NSCLC population.

Histology

Table 73: Adverse Event Summary by Histology - All Subjects with NSCLC by dose (All Subject as Treated)

	MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W				MK-3475 10 mg/kg Q2W				Total			
	Squamous		Non-Squamous		Squamous		Non-Squamous		Squamous		Non-Squamous		Squamous		Non-Squamous	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	84		316		118		512		47		155		249		983	
with one or more adverse events	82	(97.6)	307	(97.2)	114	(96.6)	492	(96.1)	47	(100.0)	150	(96.8)	243	(97.6)	949	(96.5)
with no adverse event	2	(2.4)	9	(2.8)	4	(3.4)	20	(3.9)	0	(0.0)	5	(3.2)	6	(2.4)	34	(3.5)
with drug-related† adverse events	47	(56.0)	199	(63.0)	73	(61.9)	354	(69.1)	36	(76.6)	112	(72.3)	156	(62.7)	665	(67.7)
with serious adverse events	32	(38.1)	113	(35.8)	57	(48.3)	189	(36.9)	21	(44.7)	62	(40.0)	110	(44.2)	364	(37.0)
with serious drug-related adverse events	9	(10.7)	29	(9.2)	7	(5.9)	59	(11.5)	4	(8.5)	9	(5.8)	20	(8.0)	97	(9.9)
who died	8	(9.5)	11	(3.5)	11	(9.3)	25	(4.9)	1	(2.1)	6	(3.9)	20	(8.0)	42	(4.3)
discontinued‡ due to an adverse event	8	(9.5)	30	(9.5)	16	(13.6)	54	(10.5)	6	(12.8)	25	(16.1)	30	(12.0)	109	(11.1)
discontinued due to a drug-related adverse event	3	(3.6)	16	(5.1)	2	(1.7)	28	(5.5)	2	(4.3)	6	(3.9)	7	(2.8)	50	(5.1)
discontinued due to a serious adverse event	8	(9.5)	26	(8.2)	14	(11.9)	40	(7.8)	6	(12.8)	17	(11.0)	28	(11.2)	83	(8.4)
discontinued due to a serious drug-related adverse event	3	(3.6)	12	(3.8)	2	(1.7)	21	(4.1)	2	(4.3)	4	(2.6)	7	(2.8)	37	(3.8)

† 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.
Include all treated subjects in PN001 Part C, F1, F2, F3 and all subjects in PN010 treated with Pembrolizumab.
(MK-3475 PN001 Database Cutoff Date for Lung: 23JAN2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

Discontinuation due to adverse events

In study P010, AEs leading to treatment discontinuation occurred more frequently in the docetaxel arm (13.6%) compared to the pooled pembrolizumab arms (7.9%), with consistent results besides the degree of PD-L1 expression. Treatment discontinuation was slightly more frequent in the pembrolizumab arms due to events in the *Respiratory, thoracic and mediastinal disorders* SOC (2.9% vs 2.6%).

Due to AEs, the treatment was interrupted in 23.6% of patients in the docetaxel arm and in 22.9% in the pembrolizumab combined arms. The more frequently reported events leading to pembrolizumab interruption were in the SOCs *Infection and Infestations* (5.3%), *Respiratory, thoracic and mediastinal disorders* (3.7%) and *Metabolism and nutrition disorders* (3.4%). In the docetaxel arm, treatment was more commonly interrupted due to AEs in the SOCs *Infection and Infestations* (7.4%), *General disorders and administration site conditions* (5.8%) and *Respiratory, thoracic and mediastinal disorders* (4.2%).

No major differences were observed in AEs leading to discontinuation or interruption regardless of PD-L1 expression level.

The incidence of treatment discontinuations due to AEs reported in the NSCLC population (11.3%) was consistent with that previously reported in melanoma patients (12.4%). This was also observed in terms of drug-related AEs leading to treatment discontinuations (4.6% in NSCLC and 5.7% in melanoma populations).

Overall, across populations pembrolizumab discontinuation mostly occurred due to *Pneumonitis* (34 events, 1.2%).

Post marketing experience

The first annual Periodic Safety Update Report (PSUR) for pembrolizumab, covering the period from 04-Sep-2014 to 03-Sep-2015, has been assessed by the PRAC. Overall, 300 serious adverse drug

reactions and 527 non-serious drug reactions have been reported (EMEA/H/C/PSUSA/00010403/201509). No new safety concerns have been identified from the review of spontaneously reported cases for Keytruda as of 03-Sep-2015.

After the reporting period, 1 patient treated with pembrolizumab in the phase III melanoma study P006 experienced Grade 4 Guillain-Barré Syndrome (GBS) that was considered an Important Identified Risk and was added in the SmPC Sections 4.4 and 4.8 (Keytruda EMEA/H/C/003820/II/0002 adopted by the CHMP on 1 April 2016).

Pooled Data Across Indications to Support the Product Information

Safety data to support Section 4.8 of the SmPC were pooled across completed studies in multiple indications (studies P001 and P010 in NSCLC and studies P001, P002 and P006 in melanoma) using the pembrolizumab intended dose and regimen (2 mg/kg every 3 weeks).

2.5.1. Discussion on clinical safety

The pembrolizumab safety profile in NSCLC is based on data from 1232 patients treated in the pivotal phase II/III study (KEYNOTE-010, P010) and in the supportive phase I trial (KEYNOTE-001, P001). The majority of patients were previously treated with systemic therapy for locally advanced or metastatic NSCLC, with the exception of 101 patients in study P001 (Cohort F2) that were treatment-naïve.

A twice longer mean exposure to pembrolizumab than to docetaxel was registered in Study P010 (153.27 vs 81.6 days, respectively). In comparison to data in the melanoma population, the drug exposure and duration of exposure were lower in the NSCLC population. However, long term safety data (≥12 months) are available for 165 NSCLC patients.

No major differences in baseline characteristics were observed across NSCLC and melanoma patient populations, with the exception that there were more Asian patients (17.4% vs 1.2%) and more subjects with ECOG PS 1 (65.5% vs 34.5) in the NSCLC studies, due to the differences in site selection and the natural history of disease, compared to melanoma studies.

Overall, in the pivotal study P010 a lower rate of AEs, in particular drug-related and drug-related Grade ≥3, and treatment discontinuation occurred in patients treated with pembrolizumab compared to docetaxel.

No meaningful differences occurred in the safety profile of pembrolizumab-treated patients based on dose or level of PD-L1 expression in Study P010. However, in weakly PD-L1 positive patients, a higher rate of drug-related SAEs in the *Respiratory, thoracic and mediastinal disorders* SOC was registered in the two pembrolizumab arms (3.5% and 2.1% at dose 2 mg/kg and 10 mg/kg, respectively) compared to docetaxel (1.1%), mainly in terms of Pneumonitis (8 total cases with pembrolizumab vs one case in the control arm).

Pembrolizumab and docetaxel were characterized by a well different safety profile. The most commonly reported AEs belonging respectively to SOCs *General disorders and administration site conditions* (*Fatigue*, 25.1%), *Metabolism and nutrition disorders* (*Decreased Appetite*, 24.6%), *Respiratory, thoracic and mediastinal disorders* (*Dyspnoea*, 22.9%) and to SOCs *Skin and subcutaneous tissue disorders* (*Alopecia*, 34%), *General disorders and administration site conditions* (*Fatigue*, 32%), *Gastrointestinal disorders* (*Diarrhoea*, 25.9%). In terms of drug-related AEs, the most frequently reported were *Fatigue* (13.9%), *Decreased appetite* (11.6%), *Nausea* (10.0%), and *Rash* (10.7%) with pembrolizumab, while in the docetaxel arm drug-related *Alopecia* (32.7%), *Fatigue* (24.6%), and *Diarrhoea* (18.1%) were more commonly observed. As expected, a higher incidence of AEOSI, including immune-mediated AEs, was registered in the pembrolizumab arms compared to docetaxel (19.5% vs 4.2%), and the most frequently reported events were *Hypothyroidism* (8.2% vs

0.3%), *Hyperthyroidism* (4.7% vs 1%) and *Pneumonitis* (4.5% vs 1.3%). In addition, AEOSI occurred earlier with pembrolizumab than docetaxel, with a median time to first episode onset of 64 days (range: 4 to 381 days) and 85 days (range: 14 to 229 days), respectively. The most common drug-related SAEs were *Pneumonitis* (2.2%) with pembrolizumab and *Febrile neutropenia* (3.2%) with docetaxel. Overall, 43 deaths due to AEs were observed in the pembrolizumab arms (17 in the 2m/kg Q3W, and 26 in the 10 mg/kg Q3W) vs 15 in the docetaxel arm. However, only 6 deaths (3 in each pembrolizumab arm) were considered drug-related in the experimental arms vs 5 in the docetaxel arm. For 5 of the 6 cases, the event leading to the fatal outcome in the pembrolizumab arms was related to respiratory function (3 Pneumonitis and 2 Pneumonia). The information on the possible fatal outcome of Pneumonitis has been added to the Keytruda SmPC (Section 4.4) through Keytruda variation EMEA/H/C/003820/II/0002.

In the overall pembrolizumab database, a mostly overlapping safety profile was observed across melanoma and NSCLC populations. Overall, the occurrence of Adverse Events in the NSCLC population was quite similar to that in melanoma patients. In NSCLC patients the most common AEs were *Fatigue* (30.4%), *Decreased Appetite* (25.2%), *Dyspnoea* (23.2%), *Cough* (20.8%) and *Nausea* (20 %). An increased incidence of Grade ≥3 events in the SOC *Respiratory, thoracic and mediastinal disorders* occurred in NSCLC (*Dyspnoea* 3.9%, *Pneumonia* 4.1%) compared to melanoma patients (*Dyspnoea* 1.9%, *Pneumonia* 1.5%). The slightly lower incidence of drug-related events can be justified by the reduced exposure to pembrolizumab in NSCLC patients compared to melanoma patients. No major differences in the incidence of Grade ≥ 3 Drug-Related AEs were observed between NSCLC and melanoma patients with the exception of events in the SOC *Respiratory, Thoracic and Mediastinal disorders* (2.5% vs 1.3%).

The rates of AEOSI were consistent across patient populations, except for *Pneumonitis* occurring more frequently in NSCLC (4.4% vs 2.6%). In terms of drug-related SAEs, no major differences were reported among melanoma and NSCLC population, with the only exception of a higher rate of *Pneumonitis* in NSCLC patients (2.4% vs 1.0%):

The overall incidence of AEs resulting in deaths was slightly higher in NSCLC patients compared to that previously reported in melanoma (5.0% vs 3.1%), with in particular an increased number of respiratory fatalities (pneumonia, pneumonitis, and respiratory failure).

The tolerability of pembrolizumab treatment was slightly reduced in NSCLC patients ≥65 years and with ECOG PS 1. Available data do not allow to clearly differentiate the pembrolizumab safety profile based on histology. No new safety concerns were raised by post-marketing data.

Due to insufficient evidence to support a causal relationship with pembrolizumab, the MAH proposes to remove the terms Optic Neuritis and Rhabdomyolysis from the list of Other immune-related adverse reactions in section 4.4 of the SmPC. In the pooled locked datasets of studies P001, P002, P006, and P010, one drug-related AE of optic neuritis and one drug-related AE of rhabdomyolysis were registered.

The only drug-related AE of optic neuritis (Grade 2) occurred in a patient with a known history of sarcoidosis for whom the ophthalmologist raised the possible role of sarcoidosis in the aetiology of the event. The drug-related AE of rhabdomyolysis (Grade 3) was reported in a patient with a history of hypothyroidism and who was engaged in an intense physical workout a few days prior to development of the event. The CHMP agrees with the deletion of both Optic Neuritis and Rhabdomyolysis from section 4.4 of the SmPC

There was no evidence of an altered safety profile with anti-pembrolizumab binding antibody development.

2.5.2. Conclusions on clinical safety

Based on submitted data, no new pembrolizumab safety concerns arise from the NSCLC population. In comparison to data related to melanoma patients, an increased frequency of drug-related Pneumonitis and respiratory fatalities (pneumonia, pneumonitis, and respiratory failure) was reported. The information on the possible fatal outcome of Pneumonitis has been reflected in the Keytruda SmPC (Section 4.4) in the context of variation EMEA/H/C/003820/II/0002.

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 (RMP).

The PRAC considered that the RMP version 3.0 (dated 18 December 2015) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 01 April 2016.

The CHMP endorsed this advice without changes.

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

The CHMP endorsed the Risk Management Plan version 3.3 (dated 21 June 2016) with the following content:

Safety concerns

Table 74 Summary of the 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 • 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

Table 75 Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the PV Plan

Study / activity Type, title and category	Objectives *	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports
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 assay validation report Sep 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 Carcinoma (P001) (Category 3)	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 (Immune-related adverse events, Immunogenicity) -Long term safety	Started	Final Study Report Dec 2016
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 Study Report Jan 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 Study Report Jan 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 Study Report Aug 2019

Table 75 Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the PV Plan

Study / activity Type, title and category	Objectives *	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports
Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (P024) (Category 3)	To compare the Progression Free Survival (PFS) per RECIST 1.1 as 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.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events, Immunogenicity) -Long term safety	Started	Final Study Report Sep 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 Study Report Dec 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 tumor or lymphoma.	Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events) -Safety in pediatric patients	Started	Final Study Report July 2019
*Only the first primary objective was included (additional information can be found in Annex 6).				

Risk minimisation measures

Table 76 Summary Table of the Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related Pneumonitis	SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials

Table 76 Summary Table of the Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Immune-related Colitis	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	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	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 -Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis) - Type 1 Diabetes Mellitus	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 -Uveitis, Myositis, Pancreatitis, Severe Skin Reactions, Guillain-Barre Syndrome	SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Important Identified Risks: Infusion-Related Reactions		
Infusion-Related Reactions	SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Important Potential Risks: Immune-Related Adverse Events		
Gastrointestinal perforation secondary to colitis	SmPC, Section 4.4, 4.8	None
Important Potential Risks: Immunogenicity		
Immunogenicity	SmPC, Section 4.8.	None
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	SmPC, Section 4.2, 4.4.	None
Safety in patients with active systemic autoimmune disease	Section 4.4, 5.1.	None
Safety in patients with HIV or Hepatitis B or Hepatitis C	SmPC, Section 4.4, 5.1.	None
Safety in Pediatric patients	SmPC, Section 4.2.	None
Reproductive and lactation data	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	SmPC, Section 4.4, 4.5.	None
Safety in patients with previous hypersensitivity to another monoclonal antibody	SmPC, Section 4.4, 5.1.	None

Table 76 Summary Table of the Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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	SmPC, Section 4.4, 5.1.	None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, minor changes have been implemented in Annex II.

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 due to the minor changes introduced by this variation.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefit of Keytruda in the treatment of second line or greater advanced NSCLC with PD-L1 expression is based on data from the pivotal phase II/III trial KEYNOTE-010 (P010), and supportive data from the NSCLC Cohorts C and F of the phase I study KEYNOTE-001 (P001).

In the pivotal trial, a statistically significant and clinically meaningful benefit in OS has been observed for both pembrolizumab arms over docetaxel in subjects with TPS≥50% (HR of 0.54, p=0.00024, and 0.50, p=0.00002, for pembrolizumab 2 mg/kg and 10 mg/kg Q3W vs docetaxel, respectively), and in the overall population of subjects with TPS≥1% (HR of 0.71, p=0.00076, and 0.61, p<0.00001, for pembrolizumab 2 mg/kg and 10 mg/kg Q3W vs docetaxel, respectively).

A statistically significant difference has been observed for PFS in the strongly positive subgroup only (as per the CTA test used), with HRs of 0.58 and 0.59 for pembrolizumab 2 mg/kg and 10 mg/kg vs docetaxel, respectively.

Supportive pre-specified sensitivity analyses for PFS were provided, all of which support the results of the primary analysis.

OS results observed in the overall population are clearly driven by the effect observed in the strongly positive subgroup. However, the visual inspection of OS survival curves of the weakly positive subgroup (for which a formal analysis was not planned) shows a separation of the curves over time with a trend to an increase in the difference in the rate of alive patients between the experimental and

the control arms at subsequent time points.

The duration of response observed with pembrolizumab is much longer than what observed with docetaxel for all patients whose tumours express PD-L1.

Duration of response based on IRC assessment was almost double in pembrolizumab treated subjects compared to docetaxel even in the weakly positive subgroup (46 and 45 weeks in the 2 mg/kg and 10 mg/kg arms, respectively, vs 26 weeks in the docetaxel arm).

No meaningful difference has been observed between the two pembrolizumab dose levels for both OS and PFS. In general, secondary endpoints confirmed the benefit of pembrolizumab over docetaxel, with no difference observed between the two pembrolizumab dose levels. The lack of meaningful difference between the two pembrolizumab dose levels observed in all the efficacy analyses including Quality of life data further supports the adequacy of the 2 mg/kg Q3W dose level.

Uncertainty in the knowledge about the beneficial effects

Results from subgroup analyses raise concerns on the effect of pembrolizumab in EGFR mutant (in all stratum), East Asian patients and never smokers. The information on the reduced survival benefit of pembrolizumab compared to docetaxel in patients who were never-smokers or patients with tumours harbouring EGFR activating mutations who received at least platinum-based chemotherapy and a tyrosine kinase inhibitor is reported in section 5.1 of the SmPC.

Risks

Unfavourable effects

Overall, the safety profile of pembrolizumab in the NSCLC population was quite similar to that in melanoma patients, although it should be noted the drug exposure is reduced compared to melanoma patients. In NSCLC patients the most common AEs were Fatigue (30.4%), Decreased Appetite (25.2%), Dyspnoea (23.2%), Cough (20.8%) and Nausea (20 %). An increased frequency of drug-related Pneumonitis and respiratory fatalities (pneumonia, pneumonitis, and respiratory failure), some of which resulting in deaths, was reported. However, the information on the possible fatal outcome of Pneumonitis has been added to the Keytruda SmPC (Section 4.4) in the context of variation EMEA/H/C/003820/II/0002 (positive CHMP opinion adopted on 1 April 2016).

Uncertainty in the knowledge about the unfavourable effects

N/A

Effects Table

Table 77: Effects Table for Keytruda for the treatment of advanced NSCLC in adults whose tumors express PD-L1 and who have disease progression on or after prior chemotherapy.

Effect	Short Description	Unit	Treatment Pembrolizumab 2 mg/kg Q3W	Control docetaxel	Uncertainties/ Strength of evidence
Favourable Effects*					
PD-L1 TPS≥50%					
OS	median 95%CI	months	14.9 (10.4,..)	8.2 (6.4, 10.7)	Clinally meaningful improvement in all efficacy parameters
			0.54 (0.38,0.77) P=0.00024		

Effect	Short Description	Unit	Treatment Pembrolizumab 2 mg/kg Q3W	Control docetaxel	Uncertainties / Strength of evidence
PFS	median 95%CI	months	5.2 (4.0,6.5) 0.58 (0.43,0.77) P=0.00009	4.1 (3.6, 4.3)	
ORR	% 95%CI	%	30.2 (22.7, 38.6)	7.9 (4.1, 13.4)	
Response duration	median Range	days	NR (20+-512+)	246 (63+-268+)	
PD-L1 TPS≥1%					
OS	median 95%CI	months	10.4 (9.4,11.9) 0.71 (0.58,0.88) P=0.00076	8.5 (7.5, 9.8)	Not statistically significant difference in PFS. However, there is a trend to an increase over time in the difference in the rate of event-free patients between the experimental and the control arms.
PFS	median 95%CI	months	3.9 (3.1,4.1) 0.88 (0.73,1.04) P=0.06758	4.0 (3.1, 4.2)	
ORR	% 95%CI	%	18.0 (14.1, 22.5)	9.3 (6.5, 12.9)	
Response duration	median Range	months	NR (20+-610+)	189 (43+-268+)	
Unfavourable Effects* (PD-L1 TPS≥1%)					
Tolerability	drug related AEs	%	63.4	81.2	Overall, a lower rate of drug-related, drug-related Grade ⩾3, and treatment discontinuation in the pembrolizumab arms. Well different safety profile among docetaxel and pembrolizumab. No new pembrolizumab safety concerns arise from the NSCLC population.
	drug related Gr≥3 AE	%	12.7	35.3	
	drug related SAEs	%	9.4	13.6	
	death drug related	%	0.9	1.6	
	discontinuation drug related AEs	%	4.4	10.0	
	discontinuation drug related SAEs	%	3.2	3.6	
Drug-related AEs	Fatigue	%	13.6	24.6	
	Decreased appetite	%	13.6	15.9	
	Rash	%	8.6	4.5	
	Diarrhea	%	7.1	18.1	
	Hypothyroidism	%	7.4	0.3	
	Pneumonitis	%	4.1	1.0	

*Pivotal study P010 (data cut-off: 30 Sep 2015) NR: Not Reached

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Treatment with pembrolizumab resulted in a clinically significant benefit in OS compared to standard therapy with docetaxel in adult patients with advanced PD-L1-positive NSCLC who were on disease progression or after prior chemotherapy. The superiority of treatment with pembrolizumab over docetaxel was further supported by PFS, ORR and response duration results, even though PFS was statistically significant in the >50% PD-L1 positive stratum only. Indeed, although the OS results observed in the overall population are clearly driven by the effect observed in the strongly positive PD-L1 subgroup, exploratory analyses, in the weakly positive subgroup, indicated a trend to a time-dependent increase in the difference in survival rates favouring pembrolizumab over docetaxel, and albeit the Kaplan Meier analysis of PFS did not show any benefit for pembrolizumab over docetaxel, the duration of response observed with pembrolizumab was much longer than what observed with docetaxel. The benefit of pembrolizumab treatment is thus not considered limited to only the NSCLC patient population expressing high levels of PD-1.

The safety profile in patients with advanced NSCLC does not differ significantly from what already

known in the advanced melanoma setting and overall seems to compare favourably to that of docetaxel.

Benefit-risk balance

The observed clinically relevant survival benefit obtained with pembrolizumab treatment compared to standard therapy with docetaxel, and the favourable safety profile outweigh the risks, hence the B/R balance of pembrolizumab in the second-line or greater treatment of PD-L1 positive NSCLC is considered positive.

Discussion on the Benefit-Risk Balance

The benefit of treatment with pembrolizumab compared to standard therapy with docetaxel in the second line of PD-L1 positive NSCLC is clearly evident in terms of OS, PFS and ORRs. The safety profile in the new indication almost overlaps with that already known for the melanoma indication and favourably compares with that of docetaxel.

There are no meaningful differences among the two pembrolizumab doses, supporting the proposed 2mg/kg Q3W dose, already recommended in the melanoma indication. Further support comes from the observation that statistical significance for PROs was achieved for the pembrolizumab 2 mg/kg dose only.
The CHMP considers the following measures necessary to address issues related to efficacy:

- The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically:

Although PD-L1 status is predictive of response in NSCLC patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD L1 obtained in the ongoing NSCLC studies (P001, P010, P024, and P042):

- Data on the Nanostring RNA gene signature
- IHC staining for PD-L2
- Data on RNA and proteomic serum profiling

Due date: 2Q 2020

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, II and IIIB

Extension of Indication to include a new indication for Keytruda in second line Non-Small Cell Lung Cancer (NSCLC); as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. Annex II is updated in order to include NSCLC on-going studies among the study designed to explore value of the biomarkers to predict efficacy of pembrolizumab. The Package Leaflet and the RMP (final version 3.3) is updated in accordance.

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

This CHMP recommendation is subject to the following amended condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Obligation to conduct post-authorisation measures**

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

Description	**Due date**
4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically:	
Although PD-L1 status is predictive of response in advanced melanoma and NSCLC patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD L1 obtained in the ongoing melanoma (P001, P002 and P006) and	1Q 2017
NSCLC studies (P001, P010, P024, and P042):	2Q 2020
• Comparison between PD-L1 IHC staining in archival tissue vs newly obtained (melanoma studies only) • Comparison of PD-L1 IHC between pre and post treatment tumour tissues (melanoma studies only) • Data on the Nanostring RNA gene signature • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling • Data on Immune cell profiling (peripheral blood) (melanoma studies only)	

5. EPAR changes

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

Scope

Extension of Indication to include a new indication for Keytruda in second line Non-Small Cell Lung Cancer (NSCLC); as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. Annex II is updated in order to include NSCLC on-going studies among the study designed to explore value of the biomarkers to predict efficacy of pembrolizumab. The Package Leaflet and the RMP (final version 3.3) is updated in accordance.

Summary

For further information please refer to the published Assessment Report: Keytruda H-C-3820-II-07-AR.