14 September 2017
EMA/687095/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0027

Note

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

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Assessment Timetable

Timetable	Planned dates	Actual dates
Start of procedure	25 March 2017	25 March 2017
CHMP Rapporteur Assessment Report	19 May 2017	22 May 2017
CHMP Co-Rapporteur Assessment Report	19 May 2017	23 May 2017
PRAC Rapporteur Assessment Report	26 May 2017	26 May 2017
PRAC members comments	31 May 2017	n/a
Updated PRAC Rapporteur Assessment Report	1 June 2017	n/a
PRAC Outcome	9 June 2017	9 June 2017
CHMP members comments	12 June 2017	12 June 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2017	14 June 2017
Request for Supplementary Information (RSI)	22 June 2017	22 June 2017
Submission of responses	14 July 2017	17 July 2017
CHMP Rapporteurs Joint response Assessment Report	21 August 2017	21 August 2017
Comments from CHMP	4 September 2017	4 September 2017
Updated CHMP Rapporteurs Joint response Assessment Report	7 September 2017	7 September 2017
2nd RSI	14 September 2017	14 September 2017
Restart	20 September 2017	20 September 2017
CHMP Rapporteurs Joint response Assessment Report	27 September 2017	29 September 2017
Comments from CHMP	2 October 2017	2 October 2017
Updated CHMP Rapporteurs Joint response Assessment Report	5 October 2017	5 October 2017
Oral Explanation	Oct CHMP 2017	10 October 2017
Opinion	12 October 2017	Withdrawn by the Applicant on 11 October 2017

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List of abbreviations

AE	Adverse Event
AEOSI	Adverse Event of Special Interest
ALB	Albumin
ADA	Anti-drug antibody
ALK	Anaplastic lymphoma kinase
APT	All Patients Treated
ASaT/APat	All Subject as Treated/ All Patient as Treated
AUC	Area under the concentration-time curve
AUCss	Area under the concentration-time curve at steady state
BICR	Blinded independent central review
CI	Confidence interval
CV	Coefficient of variation
CL	Clearance
CMAX	Peak serum concentration
Cmin	Trough serum concentration
CONC	Concentration
CR	Complete Response
CT	Computed tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4
CWRES	Conditional weighted residuals
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eDMC	external Data Monitoring Committee
DOR	Duration of Response
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
ePROs	electronically collected Patient-Reported Outcomes
FAS	Full Analysis Set
FWER	family-wise type I error rate
GCP	Good Clinical Practice
HR	Hazard Ratio
HL	Hodgkin lymphoma
HNSCC	Head and neck squamous cell carcinoma
IA2	Second Interim Analysis
IPRED	Individual predicted concentration
irAE	Immune-related Adverse Event
ISS	Integrated Summary of Safety
ITT	Intention To Treat
IIV	Interindividual variability
IV	intravenous
IWRES	Individual weighted residual
LS	least squares
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSI-H	microsatellite instability-high

Nab	Neutralizing antibody
NONMEM	Nonlinear mixed-effects modeling software
NSCLC	Non Small Cell Lung Cancer
OFV	Objective function value
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed cell death 1 (receptor)
PD-L1	Programmed cell death 1 receptor ligand 1
PD-L2	Programmed cell death 1 receptor ligand 2
PFS	Progression Free Survival
PK	Pharmacokinetic
Pop PK	Population Pharmacokinetic
PRED	Population predicted concentration
PS	Performance Status
PR	Partial Response
PRO	Patien-Reported Outcome
Q	Inter-compartmental flow rate
Q3W	every 3 weeks
QoL	Quality of Life
RECIST 1.1	Response Evaluation Criteria on Solid Tumors Version 1.1
RSE	Percent relative standard error = [standard error/population mean estimate] x 100
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SD	Standard Deviation
SOC	System Organ Class
t1/2	Terminal elimination half-life
TKI	Tyrosine kinase inhibitor
TPS	Tumor Proportion Score
ULN	Upper limit of normal
WRES	Weighted residuals
WT	Body weight

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 3 March 2017 an application for a variation.

The following variation was requested:

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

Extension of Indication to include 1st line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with platinum-pemetrexed chemotherapy based on the results from study KEYNOTE-021 (cohort G); a Phase 1/2, open-label trial of pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC.
As a consequence sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly.
An updated RMP version 9.0 was provided as part of the application.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0059/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Keytruda (pembrolizumab, MK-3475) is a humanized monoclonal antibody that binds to human programmed cell death 1 (PD 1) and blocks the interaction between the PD-1 pathway receptor and its

ligands, programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2) on antigen presenting tumor cells.

Lung cancer is the second most common malignancy, with a mortality that exceed those from any other malignancy worldwide. Based on the estimated number of cancer deaths expected to occur in 2016 in the USA, lung cancer is still the leading cause of death in both genders, despite declines in incidence from the mid-1980s in men and in the mid-2000s in women (Siegel RL, CA Cancer J Clin 2016).

Around 85%-90% of all lung cancers are Non Small Cell Lung Cancer (NSCLC), that include non-squamous (i.e, adenocarcinoma, large-cell carcinoma, and other cell types) and squamous (epidermoid) cell carcinoma (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011). During the last 25 years, the distribution of NSCLC histological types changed in Europe, with a decrease of squamous cell carcinoma and an increase of adenocarcinoma in men, while in women there was an increase of both histologies.

More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival, as expressed by an untreated median OS of 4 months and a metastatic 5-year survival rate of <5% (Lindsey A. et al, 2016).

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

In the absence of driver mutations (i.e, EGFR and ALK negative disease), platinum-doublets regimens (four with a maximum of six cycles) should be considered for metastatic NSCLC in patients without major comorbidities and PS0-2 (Novello S. et al, 2016). A comparable efficacy has been observed with several regimens including cisplatin and carboplatin combinations with gemcitabine, paclitaxel and docetaxel (Schiller JH. et al, 2002). No survival benefit was seen for three agent over two-agent regimens, with the exception of bevacizumab that when added to platinum-based backbone regimen improved OS in non-squamous NSCLC patients with ECOG PS 0-1 (Sandler A. et al, 2006).

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

For long time, lung cancer had been thought non immunogenic. However, in NSCLC elevated levels of CTLA-4, PD1/PD-L1, B7-H3 and B7/H4 on CD8+ tumor-infiltrating lymphocytes have been shown (Pardoll DM, 2012). At present, pembrolizumab is considered a treatment option in the first-line setting for PD-L1 strongly positive (≥50%) tumors based on results from the phase III, randomized, pivotal study (KEYNOTE-024) comparing pembrolizumab to a SOC platinum-based doublet (i.e PFS HR: 0.50, p<0.001; OS HR: 0.60, p=0.005).

Emerging evidence suggest that chemotherapy could enhance the efficacy of immunotherapy, not only improving anti-tumour effects by overcoming parts of immunosuppression, but also by enhancing cross-presentation of antitumor antigens and by supporting better penetration of immune cells in tumour core Apetoh L, 2015).

In EU, Keytruda received a MA on 17 July 2015 as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, and was approved as monotherapy on 29 July 2016 for

the treatment of previously treated PD-L1 TPS ≥1% locally advanced or metastatic NSCLC patients and on 27 January 2017 for the first-line treatment of metastatic PD-L1 TPS ≥50% NSCLC. In addition, on 2 May 2017 Keytruda has been approved as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

The current application is a type II variation to extend the indication in combination with platinum-pemetrexed chemotherapy for the first line treatment of metastatic non-squamous NSCLC, based on results from Cohort G1 of the multi-cohorts, open-label study KEYNOTE-021 ("*A Phase I/II Study of MK-3475 in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma*").

The MAH applied for the following change of indication:

"KEYTRUDA, in combination with platinum-pemetrexed chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC."

Following the CHMP request, the wording of the indication was changed as follows:

"KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC and no EGFR or ALK positive tumour mutations."

This sought indication has been recently (May 2017) granted by FDA ("*in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC*") under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

The clinical development program for Keytruda in NSCLC is ongoing and includes the following clinical trials:

Table: Clinical Development Program for pembrolizumab in NSCLC

Study	Design	Subject Population	Primary Endpoint(s)	Status
KEYNOTE-001	Phase 1, open-label trial 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; treatment ongoing
KEYNOTE-010	Phase 2/3, randomized, open-label trial of 2 doses of pembrolizumab vs docetaxel	NSCLC with PD-L1 TPS ≥1%; experienced disease progression after platinum-containing systemic therapy	OS, PFS	Enrollment complete; treatment ongoing
KEYNOTE-021	Phase 1/2, open-label trial of 2 dose schedules of pembrolizumab in combination with chemotherapy or immunotherapy (multiple cohorts; 2 parts)	Locally advanced or metastatic NSCLC	ORR	Enrollment complete; treatment ongoing
KEYNOTE-024	Phase 3, randomized, open-label trial 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; treatment ongoing
KEYNOTE-042	Phase 3, randomized, open-label trial 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, double-blind, placebo-controlled trial of pembrolizumab for 1 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, double-blind, placebo-controlled trial of platinum plus pemetrexed chemotherapy with or without pembrolizumab	Metastatic nonsquamous NSCLC eligible for first-line therapy	PFS	Enrollment ongoing
KEYNOTE-407	Phase 3, randomized, double-blind trial of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab	Metastatic squamous NSCLC eligible for first-line therapy	PFS, OS	Enrollment ongoing

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; vs = versus.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

The rationale for not submitting an environmental risk assessment was provided.

According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not 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 MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

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

2.3.2. Pharmacokinetics

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

The focus of this clinical pharmacology summary will be on presenting the updated results in support of such new clinical indication in which pembrolizumab was combined with platinum-pemetrexed chemotherapy.

The updated clinical pharmacology results new in this submission include:

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

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

Pharmacokinetic in target population

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

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

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

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

2.3.4. PK/PD modelling

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

The structure of the definitive population PK model for pembrolizumab has a two-compartment model structure with a linear clearance from the central compartment, parameterized in terms of clearance (CL), inter-compartmental clearance (Q), central compartment volume of distribution (Vc), and peripheral

compartment volume of distribution (Vp). All PK parameters were allometrically scaled based on body weight with separate exponents estimated for the clearance (CL, Q) and volume (Vc, Vp) parameters, as follows:

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

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

WT is the median body weight across the analysis population.

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

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

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

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

Specifically, the following covariates were included in the model:

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

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

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

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

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

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

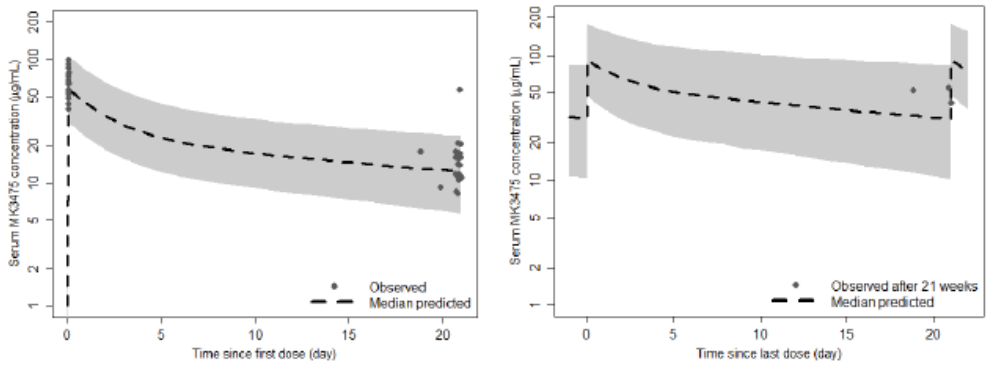
Numbers of Subjects and Observations by Dose and Dosing Regimen in the Pooled Analysis Dataset (KN001, KN002, KN006, KN021)

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

Note: some subjects received more than one dose levels under dose escalation cohorts
Reviewed per SOP-QP2-005

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

Consistency of Observed Concentrations in NSCLC Subjects Concomitantly Treated with Pemetrexed and Platinum Therapy with Predictions Confirmed Based Simulations From the Population PK Model of the Reference Monotherapy Dataset KN001,-002,-006: Pembrolizumab (MK-3475) Concentration-Time Profiles during the First Dose (left panel) and at Steady State (right panel) at 200 mg Q3W

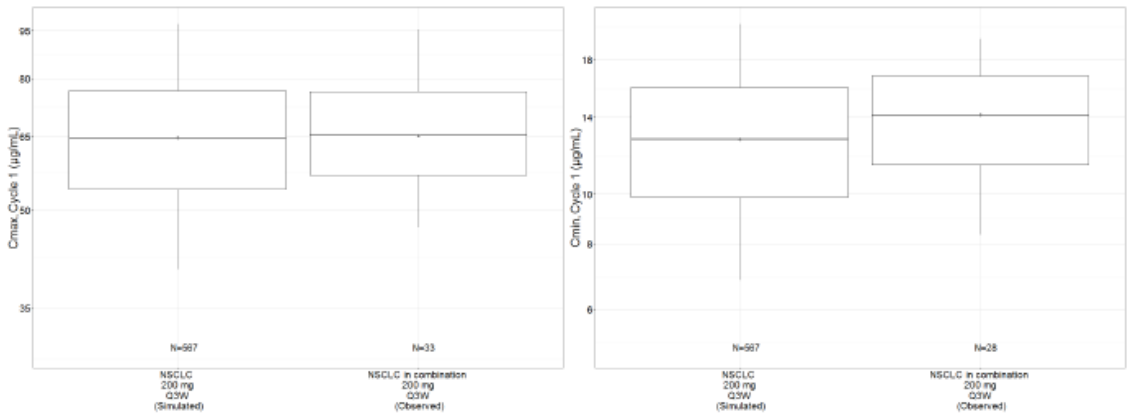


Dots are individual data from NSCLC patients from KN021; Solid line is median prediction from the model for a regimen of 200 mg Q3W and the shaded area represents the 90% prediction interval.
Reviewed per SOP-QP2-005.Data source: [04JYRX: analysis-p1p2p6p21poppk02]

To further establish the similarity in pembrolizumab exposures across indications, several comparisons have been made of peak and trough concentrations between indications. Observed peak and trough concentrations at 200 mg Q3W in NSCLC patients concomitantly treated with pemetrexed and platinum

therapy are compared to predicted peak and trough concentrations in NSCLC patients at this dose regimen (in monotherapy) in the figure and table below.

Similar Distributions of Observed Peak and Trough Concentrations (Cycle 1) in NSCLC at 200 mg Q3W With Concomitant Pemetrexed and Platinum Therapy Compared to Predicted Concentrations in NSCLC at 200 mg Q3W Monotherapy



Reviewed per SOP-QP2-005

Descriptive Statistics of Observed Peak and Trough Concentrations (Cycle 1) in NSCLC at 200 mg Q3W With Concomitant Pemetrexed and Platinum Therapy Compared to Predicted Concentrations in NSCLC 200 mg Q3W Monotherapy

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

[a] Cmax is concentration at time of peak sample in Cycle 1
[b] Cmin is trough concentration following Cycle 1
Reviewed per SOP-QP2-005

CHMP comment

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

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

According to the study protocols, PK sampling of study KN021 included several pre- dose trough samples beyond cycle 1. In particular, as reported in the final protocol of the study, "trough (pre-dose) and peak

(post-dose) samples will be collected at Cycles 1 and 2. A trough sample will be collected at Cycle 3, 6, 9, 13 and 17. All trough samples should be drawn within 24 hours before infusion of pembrolizumab and the peak samples in cycle 1 and 2 should be drown within 30 minutes after the end of the infusion".

The PK report and the evaluation presented by the MAH included descriptive statistics for Cmin and Cmax from cycle 1 only and the observed data at steady-state were very limited (only few patients). The MAH updated the evaluation of all PK results from KN021 (cutoff 23-JUN-2017) as requested.

2.3.5. Discussion and Conclusions on clinical pharmacology

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

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

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

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

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

The PK report and the evaluation presented by the MAH included descriptive statistics for Cmin and Cmax from cycle 1 only and the observed data at steady-state were very limited (only few patients). The MAH updated the evaluation of all PK results from KN021 (cutoff 23-JUN-2017) as requested.

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

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

2.4. Clinical efficacy

This application is based on data derived from KEYNOTE-021 (KN021), a multi-cohorts phase I/II study investigating the activity of pembrolizumab-based combination regimens in unresectable or metastatic NSCLC. In particular, KN021 study was aimed in the Part 1 to determine the recommended Phase 2 dose for pembrolizumab in combination with chemotherapy (paclitaxel/carboplatin in Cohort A; paclitaxel/carboplatin/bevacizumab in Cohort B; pemetrexed/carboplatin in Cohort C), with immunotherapy (ipilimumab in Cohort D) or with EGFR tyrosine kinase inhibitors (erlotinib in Cohort E; gefitinib in Cohort F).

Based on preliminary analysis, the pembrolizumab/pemetrexed/carboplatin combination in advanced NSCLC regardless of PD-L1 status and in the absence of sensitizing EGFR mutations or ALK translocations (Cohort C) resulted to be tolerable with the highest ORR among the 3 chemotherapy regimens investigated. To further evaluate the efficacy and safety of the combination, the KN021 study continued with a Phase 2 design (Part II) to randomly compare pemetrexed/carboplatin with or without pembrolizumab (Cohort G1). In addition, an expansion cohort of the pembrolizumab/ipilimumab combination (Cohort H) was included in Part 2.

To support the sought extension of indication in combination with platinum-pemetrexed chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC, the MAH submitted results from cohort G1 (pembrolizumab/chemotherapy combination versus chemotherapy alone) as pivotal, while the Cohort C, dose-finding for the pembrolizumab/pemetrexed/carboplatin combination, was considered to provide supportive data.

Study ID / centres / locations	**Study design**	**Cohort G1**				
		Treatment	**No of pts planned / random / treated**	**Demographics**	**Primary endpoint**	**Secondary endpoints**
KEYNOTE-021 Cohort G1 22 enrolling centers in 2 countries: United States (23), Taiwan (3)	Multi-center, randomized, multi-cohort, open-label, Phase 1/2 study in subjects with locally advanced or metastatic NSCLC	**pembrolizumab** 200 mg IV Q3W + **pemetrexed** 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	54/60/59	Sex: 22M/38F Median age (min/max): 62.5 years (40-77)	**ORR** (RECIST 1.1) by BICR	**PFS** (key secondary) **DOR** **OS**
		pemetrexed 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	54/63/62	Sex: 26M/37F Median age (min/max): 66 years (37-80)		
		Cohort C				
		pembrolizumab 2 mg/kg IV Q3W + **pemetrexed** 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	12	Sex: 6M/6F Median age (min/max): 59.5 years (36-75)	RP2D pembro/chemo	**ORR** (RECIST 1.1) **PFS** **DOR** **OS**
		pembrolizumab 10 mg/kg IV Q3W + **pemetrexed** 500 mg/m^2 IV Q3W + **carboplatin** AUC 5 mg/mL/min IV Q3W	12	Sex: 6M/6F Median age (min/max): 62 years (53-75)		

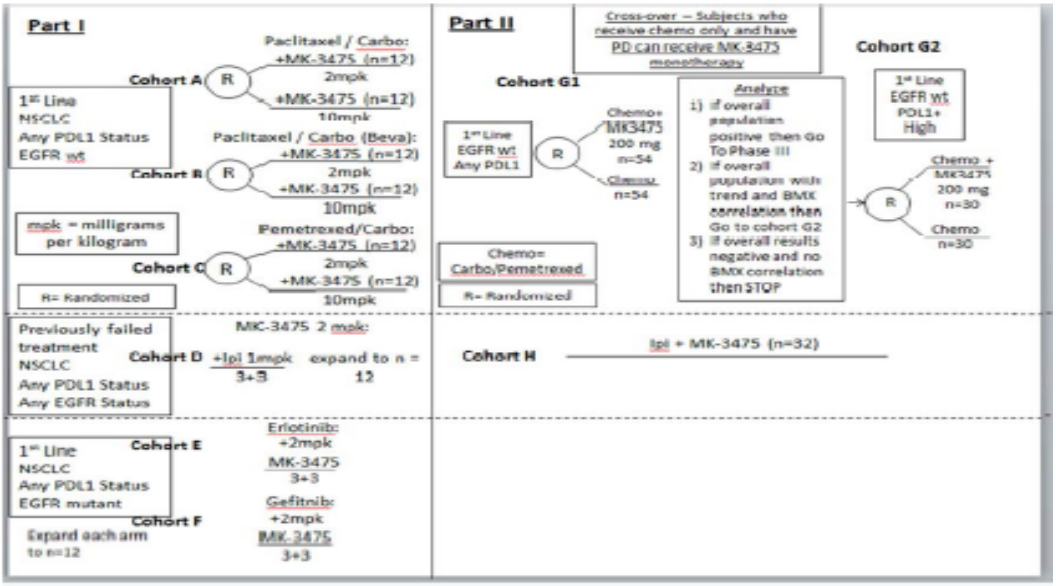
RP2D: recommended phase 2 dose

2.4.1. Dose response study(ies)

The recommended dose of pembrolizumab in combination with pemetrexed/carboplatin is 200 mg Q3W, which is also the approved dose of pembrolizumab as monotherapy for previously-untreated PD-L1 strongly positive NSCLC patients. The use of approved 200 mg Q3W monotherapy dose in combination with pemetrexed/carboplatin is supported by consistency in pembrolizumab PK between combination and monotherapy administration (see Section 2.3.4).

2.4.2. Main study(ies)

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



Beva = bevacizumab; BMX = biomarker correlation with efficacy; Carbo = carboplatin; Chemo = chemotherapy; EGFR = epidermal growth factor receptor; Ipi = ipilimumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; wt = wild type.

CHMP comment

The pivotal efficacy data to support the sought extension of indication are related to the randomized comparison of chemotherapy (pemetrexed/carboplatin) with or without pembrolizumab 200 mg investigated in the Cohort G1 of KN021 study. Switch to pembrolizumab monotherapy was allowed in patients progressing in the chemotherapy arm.

The original Part II study design also included the option, at the Sponsor's discretion, to have an additional cohort (Cohort G2) with the enrollment restricted to subjects with positive PD-L1 status, if the pre-specified target HR in Cohort G1 was not achieved but a strong correlation between PD-L1 expression levels and anti-tumor activity was suggested. However, the investigation in Cohort G2 never started.

Methods

Study participants

Main inclusion criteria

- Histologically or cytologically confirmed non-squamous NSCLC with no prior systemic treatment for Stage IIIb/IV NSCLC.
- Subjects who had disease progression >1yr after completing adjuvant therapy for Stage I-IIIA

disease were eligible, as long as no systemic therapy was given for the recurrent disease.

- At least one radiographically measurable lesion as per RECIST 1.1, defined as a lesion ≥10 mm in longest diameter or lymph node ≥15 mm in short axis imaged by CT scan or MRI.
- Age ≥18 years.
- A life expectancy of at least 3 months.
- ECOG Performance Status of 0 or 1.
- Resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). In case of major surgery or radiation therapy of > 30 Gy, the toxicity and/or complications from the intervention must have recovered.

Main exclusion criteria

- Current or previous participation in a study of an investigational agent, with study therapy received or investigation device used within 4 weeks of the first dose of treatment.
- Prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (eg, cetuximab) or major surgery within 3 weeks of the first dose of trial treatment.
- Radiation therapy >30 Gy to the lung within 6 months of the first dose of trial treatment.
- Prior TKI therapy or completed palliative radiotherapy within 7 days of the first dose of trial treatment.
- Requirement of any other form of antineoplastic therapy while on study.
- Administration of live-virus vaccination within 30 days of planned treatment start.
- Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal (GI) obstruction, abdominal carcinomatosis.
- Known history of prior malignancy, except if the patient has undergone potentially curative therapy with no evidence of disease recurrence within 5 years. This 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, in situ cervical cancer, or other in situ cancers.
- Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication.
- Previously severe hypersensitivity reaction to treatment with another mAb.
- Active autoimmune disease requiring systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Chronic treatment with systemic steroids.
- Prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Prior participation in any other pembrolizumab trial and previous treatment with pembrolizumab.
- Active infection requiring therapy; Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies); Known active Hepatitis B or C.

CHMP comment

According to inclusion criteria, a good prognosis patient population with non squamous NSCLC with no prior systemic therapy for metastatic or recurrent disease was expected to be enrolled.

Treatments

- Pembrolizumab 200 mg, as a 30 minute (-5 min/+10 min) IV infusion Q3W, followed

by pemetrexed 500 mg/m^2, as a IV infusion over 10 minutes, and carboplatin AUC 5 mg/mL/min, as an IV infusion over 15 to 60 minutes, for 4 cycles every 3 weeks. Thereafter, pembrolizumab for 24 months and optional indefinite pemetrexed maintenance therapy were administered.

- Pemetrexed 500 mg/m^2, as a IV infusion over 10 minutes, and carboplatin AUC 5 mg/mL/min, as an IV infusion over 15 to 60 minutes, for 4 cycles every 3 weeks. Thereafter, optional indefinite pemetrexed maintenance therapy was administered.

Premedication with folic acid, vitamin B12 and corticosteroid was administered according to local guidelines.

Treatment with pembrolizumab continued for 2 years from the date the first dose was administered or until documented PD (even if Investigators could elect to continue treatment beyond progression in specific circumstances), unacceptable AE(s), intercurrent illness that prevented further administration of treatment, Investigator's decision to withdraw the subject, subject's decision to withdraw consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons.

CHMP comment

Platinum-based doublets is a well recognized standard of care for the first-line treatment of NSCLC and cisplatin/pemetrexed is recommended as first line treatment of non-squamous NSCLC. Over time, carboplatin largely replaced cisplatin as the platinum-containing drug due to the more favorable safety profile, and was the most preferred treatment option in US, while cisplatin-containing combinations were the reference standard in Europe.

Considering that KN021 was mostly conducted in US (the remaining 2 sites were in Taiwan), the selection of platinum-doublets including carboplatin as backbone chemotherapy regimen can be acknowledged, even though a higher RR and slightly longer OS were reported with cisplatin-combinations compared to carboplatin-doublets (Ardizzoni A, 2007), and, according to Cohort G1 inclusion criteria, patients were eligible to receive cisplatin. Therefore, the cisplatin-based chemotherapy could has also been a suitable backbone. Nevertheless, the study design of Cohort G1 allows to evaluate pembrolizumab as add on to backbone pemetrexed/carboplatin chemotherapy, thus limiting the possible difference in efficacy across arms.

Objectives

The primary objective of Cohort G1 was to evaluate the anti-tumour activity of pembrolizumab in combination with pemetrexed/carboplatin. In addition, the efficacy, the duration of response, the pharmacokinetic profile of pembrolizumab when given in combination with chemotherapy and the correlation between PD-L1 expression levels and anti-tumor activity were assessed as secondary objectives.

Outcomes/endpoints

The primary efficacy endpoint was ORR per RECIST 1.1 based on BICR. The key secondary efficacy endpoint was PFS per RECIST 1.1 based on BICR. The ORR and PFS analyses were conducted using a step down procedure, in which the Type I error rate (alpha=2.5%, one-sided) over the multiple endpoints was controlled by a fixed-sequence, closed-testing procedure that tested for a treatment difference for ORR first, followed by a test for a treatment difference for PFS.

As secondary endpoints, OS and duration of response (DOR) were also considered.

Response to treatment was assessed every 6 weeks for the first 18 weeks, followed by every 9 weeks in Year 1 and every 12 weeks in Year 2 based on radiographic imaging reviewed by BICR per RECIST 1.1 for determination of ORR and PFS. Confirmatory scans were to be performed 4 to 6 weeks after the first

documentation of PD (if the subject was clinically stable) or response per RECIST 1.1. Pembrolizumab-treated subjects who attained an Investigator-determined confirmed complete response (CR) per RECIST 1.1 had the option of stopping trial treatment. These subjects with a CR, as well as subjects assigned to the pembrolizumab arm who stopped trial therapy after 24 months of treatments for reasons other than disease progression or intolerability, could be evaluated at the discretion of the Investigator for re-treatment with pembrolizumab for up to 12 months after they experienced radiographic PD. Retreatment with pembrolizumab was called the Second Course Phase. Response or progression in the Second Course Phase did not count towards the ORR and PFS of the primary endpoint in this trial.

The primary analysis was pre-specified in the study protocol to occur at 6 months after last patient enrolment. For the primary analysis of PFS, subjects without documented PD/death were censored at the last disease assessment date. For Cohort G1, more censoring rules for sensitivity analyses were considered.

The ORR and PFS analyses were conducted using a step down procedure, in which the Type I error rate (alpha=2.5%, one-sided) over the multiple endpoints was controlled by a fixed-sequence, closed-testing procedure that tested for a treatment difference for ORR first followed by a test for a treatment difference for PFS.

CHMP comment

The primary analysis of efficacy was planned to occur with at least 6 months of treatment or follow up for all patients enrolled, which is considered adequate. This pre-specified analysis was conducted at the data cutoff date of 08-AUG-2016. An updated analysis with 5 additional months of follow-up was also conducted (cutoff date 31-DEC-2016) and results have been submitted.

In line with the phase II study design, the selected primary endpoint is ORR. The step down procedure used to conduct the PFS analysis as key secondary endpoint is acknowledged.

Sample size

Cohort G1 was designed to randomize approximately 108 subjects. The sample size would result in at least 89% power to detect a 30% difference in ORR (30% in the control arm vs 60% in the pembrolizumab combination arm) at α=2.5% (one-sided). An observed ORR difference of approximately 18.4% was needed to achieve a positive ORR outcome.

Randomisation

Patients were centrally randomized (1:1 ratio) to receive pemetrexed and carboplatin with or without pembrolizumab, using an interactive voice response system (IVRS)/ integrated web response system. Randomized patients were stratified based on negative or positive PD-L1 tumor expression (TPS <1% or TPS ≥1%). A block randomization with blocks of 4 was used within each stratum.

Blinding (masking)

This was an open-label trial.

The subject-level PD-L1 biomarker results were masked to the Investigator and site personnel. Imaging data for the primary analysis was centrally reviewed by independent radiologists without knowledge of subject treatment assignment.

Statistical methods

The ITT population, including all randomized subjects, served as the primary population for the analyses of efficacy data.

The Type-I error rate alpha=2.5% (one-sided) over the multiple endpoints (primary ORR and key secondary PFS) was controlled by a fixed-sequence, closed-testing procedure, stepping down from ORR to PFS.

An outline of the analysis strategy for key efficacy endpoints is in the table below:

Table: Summary of analysis strategy for key efficacy endpoints in Cohort G1

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
ORR (RECIST 1.1) by blinded independent central review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered as non-responders
PFS (RECIST 1.1) by blinded independent central review	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie-handling method Kaplan-Meier method for PFS curve estimation in each treatment group	ITT	Censored according to rules for primary and sensitivity analyses of PFS[1]

ITT = intent-to-treat; ORR = objective response rate; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

[1] See Table 10 in Section 8.2.5.1.2 of the protocol [Ref. 5.3.5.1: P021V01MK3475: 16.1.1]

No interim analysis was planned for this study.

Primary endpoint (ORR) analysis:

ORR was estimated based on the number of responders as a percent of participants in the ITT population, with 95% CI according to the Clopper-Pearson method. To estimate the treatment difference and its 95% CI with strata weighting by sample size, the stratified Miettinen and Nurminen's method was used. The stratification factor used for randomization (i.e. PD-L1 expression positive vs. negative) was applied to the analysis.

Key secondary endpoint (PFS) analysis:

The non-parametric Kaplan-Meier method was used to estimate the PFS curve in each treatment group. The stratified log-rank test was used to test for treatment difference in PFS at one-sided alpha level of 2.5%. Stratified Cox proportional hazard model with Efron's tie handling method was used to estimate the hazard ratio and its 95% confidence interval between the two arms. The same stratification factor used for randomization (i.e. PD-L1 expression positive vs. negative) was applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression was assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. For the primary analysis, for the subjects who had PD, the true date of disease progression was approximated by the date of the first assessment at which PD is objectively documented

per RECIST 1.1, regardless of discontinuation of study drug. Death was always considered as a confirmed PD event. In order to evaluate the robustness of the PFS endpoint, three sensitivity analyses were performed with a different set of censoring rules.

Table: Censoring Rules for Primary and Sensitivity Analyses of PFS

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
No PD and no death; ≥ 2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment	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 consecutive missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 consecutive missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death

Secondary endpoint (OS) analysis:

The Kaplan-Meier method was used to estimate the survival curves. The treatment difference in survival was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate was reported. The same stratification factors used for randomization (i.e. PD-L1 expression positive vs. negative) was applied to both the stratified log-rank test and the stratified Cox model.

Secondary endpoint (DOR) analysis:

The non-parametric Kaplan-Meier plots/estimates and descriptive statistics were provided. Subjects who are alive, have not yet progressed, have not initiated new anti-cancer treatment, have not had ≥ 2 consecutive missed disease assessments and have not been determined to be lost to follow-up were considered ongoing responders at the time of analysis. Censoring rules for DOR are summarized in the Table below:

Table: Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
≥ 2 consecutive missed disease assessments at any time prior to progression or death	Last adequate disease assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed disease assessments	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy, have not had ≥ 2 consecutive missed disease assessments, and have not been determined to be lost to follow-up.		

Methods for dealing with treatment switching:

Since subjects in the control arm are expected to discontinue from the study earlier compared to subjects

in the pembrolizumab plus chemotherapy arm because of earlier onset of PD and they may switch to the pembrolizumab treatment after the progressive disease, adjustment for the effect of crossover on OS may be performed based on recognized methods, e.g., the Rank Preserving Structural Failure Time (RPSFT) model, two stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

PFS and OS after Crossover:

The same approaches as previously described for the primary PFS and primary OS analyses will be applied to subjects who crossover to pembrolizumab after disease progression on the control arm (chemotherapy) in this study. The reference start time of PFS and OS is the time of first dose crossover therapy. Time to progression while on the control arm will be compared to the time to progression following crossover, where the time to progression following crossover is defined as the time from time of crossover to the earliest documented disease progression. The last available tumor assessment before crossover will serve as the baseline for disease assessment post crossover. If the number of events permits, time to progression before and after crossover will be summarized descriptively using the Kaplan-Meier method.

PFS2

The same approach as previously described for the primary PFS will be applied to compare PFS in subjects randomized to the MK-3475 in combination with chemotherapy arm and PFS2 in subjects randomized to chemotherapy alone arm.

Subgroup Analyses and Effect of Baseline Factors:

The treatment effect within each of the following classification variables was explored for: Age ($\leqslant$ 65 vs. > 65 years), Sex (female vs. male), Race (white, non-white), and ECOG status (0 vs. 1). The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above.

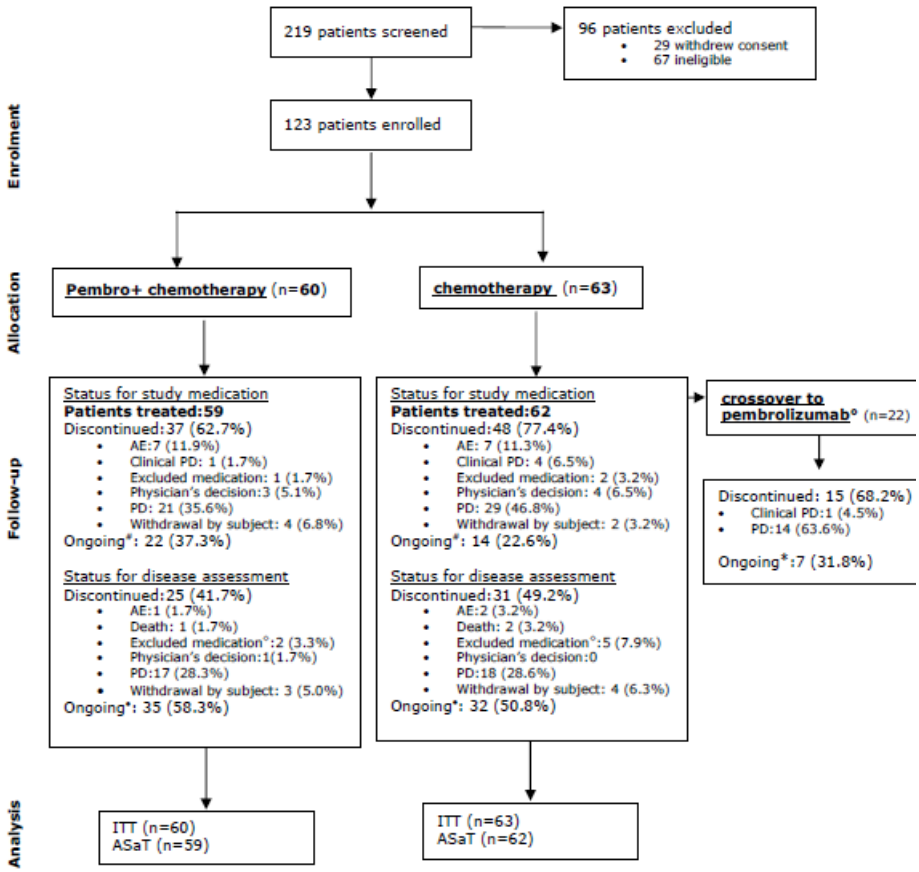
CHMP comment

The Statistical Methods are adequate in relation to the type of variables defined for each endpoint. The censoring rules and sensitivity analyses for PFS and DOR are considered extensive and valid. Some supportive analyses related to the methods for dealing with treatment switching (i.e. Rank Preserving Structural Failure Time [RPSFT] model, two stage model, analysis of PFS and OS after Crossover and PFS2) were not been carried out, even if pre-specified, due to the insufficient follow up and low numbers at the time of this analysis. From a regulatory perspective, being KN021 study a Single Pivotal, a more compelling significance threshold than $p<0.025$ one sided should have been considered. However, in light of the results this is not a concern at this time of the assessment.

Results

Participant flow

KN021 Cohort G1 (data cut-off date 31-DEC-2016)



Database Cutoff Date: 31DEC2016
°Subjects on the chemotherapy arm were considered for crossover to pembrolizumab after documented, progressive disease per RECIST 1.1 by the Investigator followed by confirmation with the Sponsor, and met eligibility criteria. An additional 14 subjects received anti PD-1/anti PD-L1 therapy after primary therapy discontinuation during survival follow up; ᶠ status was not reported as of the cutoff date. Subjects could be ongoing with study treatment; °Excluded Medication: this discontinuation reason indicates that a subject entered the Survival Follow-up period because new anti-cancer therapy was started or planned to start; * status was not reported as of the cutoff date. Subjects could be undergoing disease assessment; *status was not reported as of the cutoff date. Subjects could be ongoing with pembrolizumab monotherapy treatment; ITT: Intention to treat; ASaT: All Subject as Treated.

Recruitment

Randomization in Cohort G1 started on 31 December 2014, with the last subject included on 25 January 2016. Overall, 26 centers (23 in US and 3 in Taiwan) were involved. One site in US did not screen any subjects, while 2 additional sites screened but did not randomize subjects.

Conduct of the study

A total of 3 global amendments to the original study protocol (dated 08 Oct 2013) were implemented during the study.

The key changes introduced by these Amendments for Cohort G1 are reported below:

Protocol Amendment	Most relevant changes
#01 (15 October 2014)	Defined the study drugs and doses; Added a crossover study design; Added several objectives and inclusion/exclusion criteria to be consistent with the pembrolizumab clinical development program; Added details to further define various aspects of the statistical analysis plan.

#2 (16 April 2015)	Added detail to the description of post-treatment safety follow-up to be consistent with the pembrolizumab clinical development program; Added detail and clarification regarding the conduct of the study to reflect changes in standard of care and the pembrolizumab clinical development program requirements, the statistical analysis plan, and eligibility for the Second Course Phase of the study.
# 3 (18 April 2016)	Reordered endpoints and objectives to make ORR the primary endpoint, PFS the key secondary endpoint, and DOR a secondary endpoint based on data from Cohort C; Added a multiplicity adjustment with an alpha level of 2.5% (one-sided) to the statistical analysis, applied first to the primary endpoint, ORR, and then to the key secondary endpoint, PFS; Added details and clarifications related to analysis of endpoints, definitions of analysis populations and subgroups, and various aspects of the conduct of the study; Broadened list of acceptable contraceptive methods; Added requirement for permanent discontinuation of subjects who had a recurrence of Grade 2 pneumonitis.

In addition, changes made in the imaging review process to accommodate the need for additional review were reported as a note to file. On 25-Apr-2016, during a routine quality assessment comparing site and BICR CT/MRI evaluations, discordant best overall response results for 17 subjects were identified. Of those, 4 were attributed to central reader error by MSD and the imaging vendor (Median Technologies) that was contracted to perform the BICR. The high percentage of errors (4/17 [23%]) due to central readers posed a risk to the quality of trial efficacy endpoints based on imaging. Therefore, the assignment of 4 different radiologists with greater experience was requested by the Sponsor. The new reviewers repeated the BICR for all study cohorts imaging data that had been collected up to that point in the trial and continued to review all trial imaging data collected going forward. In addition, Median revised the Independent Imaging Review Charter to describe additional quality assurance measures implemented for all study cohorts. At a follow-up quality assessment on 25-Jul-2016 no central reviewer errors were noted. On 14-15 September 2016, an onsite audit was conducted at the central imaging vendor to ensure proper oversight and GCP compliance.

In total, there were 40 major protocol deviations documented for 27 patients in Cohort G1. No subjects were excluded from the analysis as none of the protocol deviations were deemed medically important.

CHMP comment

It is not specified if discordant best overall response was initially observed in patients treated in cohort G1. However, the MAH maintains that initial BCIR assessments were not included in any efficacy analyses.

The changes to the statistical plan introduced during the study are not expected to impact on the reliability of the trial. Indeed, adequate supportive analyses taking into account the possibility of switching from chemotherapy to pembrolizumab were pre-specified by the MAH following the introduction through Amendment #1 of the crossover study design with a potential underestimation of the effect in the OS analysis. Although they have not been carried out due to the insufficient follow up and low numbers, this Amendment is conservative because produces a dilution of the effect in the OS endpoint. With Amendment #3, a mutual exchange among endpoints, leading to definition of ORR as primary

endpoint and PFS as key secondary endpoint, and the upgrade of DOR from exploratory to secondary endpoint were implemented. Multiplicity was controlled by a fixed-sequence, closed-testing procedure. These changes were justified post-hoc by the MAH based on data from Cohort C of KN021 study. However, no concerns are raised by this modified study conduction considering the overall magnitude of reported ORR and PFS results.

Baseline data

Table: Subjects Characteristics
Cohort G1
(ITT Population)

	Pembro 200mg Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	60		63		123	
Gender						
Male	22	(36.7)	26	(41.3)	48	(39.0)
Female	38	(63.3)	37	(58.7)	75	(61.0)
Age (Years)						
< 65	36	(60.0)	28	(44.4)	64	(52.0)
>= 65	24	(40.0)	35	(55.6)	59	(48.0)
Mean	61.8		63.2		62.5	
SD	9.2		9.6		9.4	
Median	62.5		66.0		64.0	
Range	40 to 77		37 to 80		37 to 80	
Race						
American Indian Or Alaska Native	1	(1.7)	0	(0.0)	1	(0.8)
Asian	5	(8.3)	5	(7.9)	10	(8.1)
Black Or African American	4	(6.7)	0	(0.0)	4	(3.3)
White	49	(81.7)	58	(92.1)	107	(87.0)
Missing	1	(1.7)	0	(0.0)	1	(0.8)
Ethnicity						
Hispanic Or Latino	0	(0.0)	1	(1.6)	1	(0.8)
Not Hispanic Or Latino	56	(93.3)	56	(88.9)	112	(91.1)
Not Reported	0	(0.0)	2	(3.2)	2	(1.6)
Unknown	4	(6.7)	4	(6.3)	8	(6.5)
Region						
US	56	(93.3)	61	(96.8)	117	(95.1)
Ex US	4	(6.7)	2	(3.2)	6	(4.9)
Smoking Status						
Never Smoker	15	(25.0)	9	(14.3)	24	(19.5)
Ex Smoker	36	(60.0)	44	(69.8)	80	(65.0)
Current Smoker	9	(15.0)	10	(15.9)	19	(15.4)
ECOG						
0	24	(40.0)	29	(46.0)	53	(43.1)
1	35	(58.3)	34	(54.0)	69	(56.1)
2	1	(1.7)	0	(0.0)	1	(0.8)
Histology						
Adenocarcinoma	58	(96.7)	55	(87.3)	113	(91.9)

	Pembro 200mg Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Histology						
NSCLC NOS	2	(3.3)	7	(11.1)	9	(7.3)
Other	0	(0.0)	1	(1.6)	1	(0.8)
Metastatic Stage						
MX	1	(1.7)	3	(4.8)	4	(3.3)
M0	1	(1.7)	6	(9.5)	7	(5.7)
M1	13	(21.7)	10	(15.9)	23	(18.7)
M1A	14	(23.3)	13	(20.6)	27	(22.0)
M1B	31	(51.7)	31	(49.2)	62	(50.4)
Cancer Stage						
IIIA	0	(0.0)	1	(1.6)	1	(0.8)
IIIB	1	(1.7)	2	(3.2)	3	(2.4)
IV	59	(98.3)	60	(95.2)	119	(96.7)
Brain Metastasis Status at Baseline						
Yes	9	(15.0)	6	(9.5)	15	(12.2)
No	51	(85.0)	57	(90.5)	108	(87.8)
Baseline Tumor Size						
Subjects with data	59		59		118	
Mean	71.6		79.5		75.5	
SD	43.8		45.4		44.6	
Median	67.0		66.0		66.5	
Range	13.0 to 185.0		15.0 to 179.0		13.0 to 185.0	
PD-L1 Status						
TPS<1%	21	(35.0)	23	(36.5)	44	(35.8)
TPS 1-49%	19	(31.7)	23	(36.5)	42	(34.1)
TPS>=50%	20	(33.3)	17	(27.0)	37	(30.1)
Prior Systemic Adjuvant/Neo-adjuvant Therapy						
Yes	4	(6.7)	5	(7.9)	9	(7.3)
No	56	(93.3)	58	(92.1)	114	(92.7)
(Database Cutoff Date: 08AUG2016).						

Source: [P021V01MK3475: analysis-adsl]

Seven (11.1%) patients in the chemotherapy arm and 2 (3.3%) in the experimental arm were reported to have NSCLC not otherwise specified (NOS).

Listing of Clinical Outcomes for Subjects with NSCLC Not Otherwise Specified (NOS)
Cohort G1 Subjects
(ITT Population)

Subject ID	Best Response	PFS Event Flag	PFS Duration (Months)	OS Event Flag	OS Duration (Months)	Reason for Treatment Discontinuation
Control						
Site Number=PPD Subject ID=PPD Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance‡=398						
PPD	PD	Y	1.35	Y	19.0	PROGRESSIVE DISEASE
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=						
PPD	NE	N	0.03	N	0.30	
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=117						
PPD	SD	Y	2.79	Y	7.85	PROGRESSIVE DISEASE
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=1						
PPD	NE	Y	0.79	Y	0.79	ADVERSE EVENT
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=152						
PPD	PD	Y	1.18	Y	7.66	PROGRESSIVE DISEASE
Site Number=PPD Subject ID=PPD Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=45						
PPD	SD	Y	1.91	Y	2.37	PROGRESSIVE DISEASE

Subject ID	Best Response	PFS Event Flag	PFS Duration (Months)	OS Event Flag	OS Duration (Months)	Reason for Treatment Discontinuation
Site Number=PPD Subject ID=PPD, Gender=M, Race=PPD, Age=PPD Years, Rel Day of Study Medication Discontinuance†=232						
PPD	SD	Y	9.33	Y	9.33	PROGRESSIVE DISEASE
Pembro 200mg Combo						
Site Number=PPD Subject ID=PPD, Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=						
PPD	SD	Y	2.76	N	23.2	
Site Number=PPD Subject ID=PPD, Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=148						
PPD	PD	Y	1.28	Y	11.9	PROGRESSIVE DISEASE

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
Database Cutoff Date: 31MAY2017.

Source: [P021V01MK3475: analysis-adsl; adtte;adorr]

CHMP comment

Baseline characteristics were overall balanced across arms, with the exception of age <65 years (60% vs 44.4%) and never smoker status (25% vs 14%) that were more frequent in the pembrolizumab/chemotherapy arm. However, due to the overall limited patient population, this difference is sustained by a minimal numerical gap in the subgroups across arms.

Unlike most studies of NSCLC, more females participated in KN021 Cohort G1 than males (63.3% vs. 36.7% in the pembrolizumab-containing arm and 58.7% and 41.3% in the chemotherapy alone arm).

The majority of patients were naïve to prior systemic therapy. It is noted that among the 6 subjects with NOS histology treated with chemotherapy (one subject was not treated), the best response was SD and PFS duration was far shorter than the median PFS observed in the control arm for all patients except for one subject A similar finding is observed also in the 2 patients with NOS histology in the experimental arm. All patients treated in the control arm died with OS duration usually far shorter than the median OS.

The MAH is requested to provide a sensitivity analysis excluding patients with NOS histology for ORR, PFS and OS.

Numbers analysed

The ITT population, including subjects in the treatment group to which they were randomized, regardless of whether or not they received study therapy (60 patients in the pembrolizumab combination arm and 63 patients in the control arm), served as the primary population for the analysis of efficacy data.

The All Subject as Treated (ASaT) population, defined as all subjects who were allocated and received at least one dose of study treatment (59 patients in the pembrolizumab combination arm and 62 patients in the control arm) was used as the primary analysis population for safety.

Outcomes and estimation

Results from the pre-specified efficacy analysis (cutoff date: 08-Aug-2016), conducted at the median follow up of 10.6 months with a minimum of 6 months from last patient randomized, have been submitted, along with an updated 5-months follow up analysis (cutoff date: 31-Dec-2016), conducted in response to a regulatory request. The median follow-up for subjects in the updated analysis of Cohort G1 was 14.5 months with a minimum of 11 months from the last patient randomized to data cut-off.
Results from the lastly updated analysis are shown in details, and in some cases differences with results of the pre-specified efficacy analysis are discussed.

Primary endpoint

Objective Response Rate (ORR) based on BICR assessment per RECIST 1.1

Table: Analysis of Objective Response (confirmed)
Based on BICR assessment per RECIST 1.1
Cohort G1
(ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Standard Treatment	
				Estimate (95% CI)[†]	p-Value[††]
Pembro 200mg Combo	60	34	56.7 (43.2,69.4)	26.4 (8.9,42.3)	0.0016
Control	63	19	30.2 (19.2,43.0)		

[†] Based on Miettinen & Nurminen method stratified by PD-L1 status (positive vs. negative).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 31DEC2016.

Source: [P021V01MK3475: analysis-adsl; adorr]

CHMP comment

One additional confirmed response was observed in both arms at the updated analysis compared to pre-defined analysis. The ORR in the control arm was consistent with historical data. An estimated ORR difference of 26.4%, slightly smaller than that pre-defined (30%), was observed in terms of ORR in the ITT population. Based on subgroup analysis by PD-L1 expression a higher difference was observed in both PD-L1 negative (TPS <1%) and PD-L1 strongly positive (TPS≥50%). See below further comments.

As published (Langer CJ et al, 2016), pemetrexed maintenance was received by 50 (85%) of 59 treated patients in the pembrolizumab plus chemotherapy group and 43 (69%) of 62 patients in the chemotherapy alone group. This is in line with the different rate of patients with CR/PR/SD reported in each arm.

Secondary endpoints

Progression Free Survival (PFS)

PFS was considered a key secondary endpoint. Because the analysis of ORR was statistically significant, the test for significance of PFS was conducted.

Table: Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1
(ITT Population)

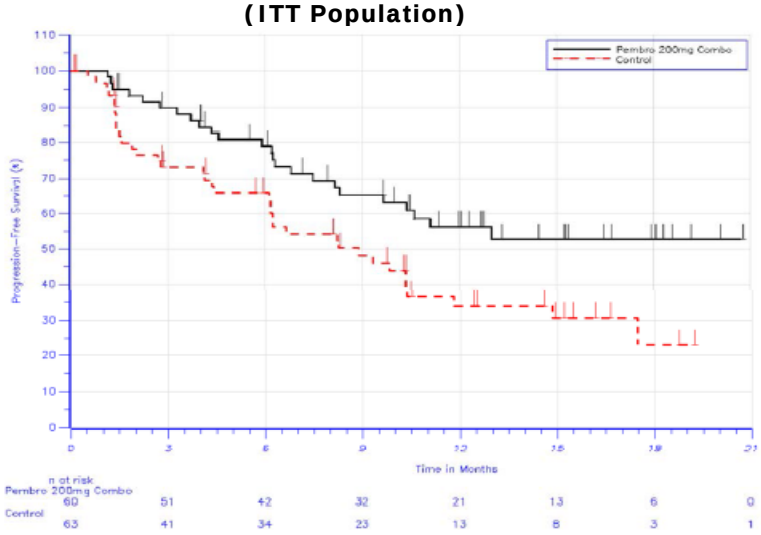
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro 200mg Combo	60	24 (40.0)	575.6	4.2	Not Reached (9.7, .)	78.9 (65.9, 87.5)	0.49 (0.29, 0.83)	0.00352
Control	63	37 (58.7)	458.5	8.1	8.9 (6.2, 10.3)	65.8 (52.1, 76.4)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (positive vs. negative).
[§] One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 31DEC2016.

Source: [P021V01MK3475: analysis-adsl; adorr]

The PFS rate at 12 months was 56.2% (95% CI 41.5-68.6) for the pembrolizumab combination arm and 33.9% (95% CI 21.0-47.3) for the control arm.

Figure: Kaplan-Meier estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1
(ITT Population)



Database Cutoff Date: 31DEC2016.
Source: [P021V01MK3475: analysis-adsl; adorr]

Due to the insufficient follow up, the analysis of PFS2 was not conducted.

CHMP comment

The benefit in PFS was even slightly increased in the updated (HR 0.49, 95% CI 0.29-0.83, p=0.00352) compared to the pre-specified analysis (HR 0.53, 95% CI 0.31-0.91, p=0.01024). Moreover, with 5 additional months of follow up, the median PFS of the pembrolizumab combination arm became not reached, while it was 13 (8.3,...) months at pre-specified analysis. No change was observed in the median PFS of the control arm that was 8.9 months, consistently across the two analyses. It is pointed out that the median PFS of 8.9 months reported in the chemotherapy alone arm is higher compared to historical data reported with platinum doublets in first-line NSCLC.

Duration of Response (DOR)

At the time of data cut-off (31DEC2016), more subjects had an ongoing response in the pembrolizumab combination arm (58.8%) than in the control arm (47.4%).

Table: Summary of Time to Response and Duration of Response
for Subjects with Confirmed Response
Based on BICR Assessment per RECIST 1.1
Cohort G1
(ITT Population)

	Pembro 200mg Combo (N=60)	Control (N=63)
Number of subjects with response†	34	19
Time to Response† (months)		
Mean (SD)	2.8 (2.5)	2.6 (1.3)
Median (Range)	1.6 (1.2-12.3)	2.7 (1.1-6.0)
Response Duration‡ (months)		
Median (Range)	Not reached (1.4+ - 18.6+)	16.2 (2.8 - 20.7+)
Number (%‡) of Subjects with Extended Response Duration:		
≥3 months	30 (96.9)	17 (94.7)
≥6 months	26 (90.1)	10 (76.3)
≥9 months	16 (81.1)	10 (76.3)

† Response: Best objective response as confirmed complete response or partial response.
‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 31DEC2016.
Source: [P021V01MK3475: analysis-adsl; adorr]

Table: Summary of Response Outcome in Subjects with Confirmed Response Based on BICR Assessment per RECIST 1.1 Cohort G1 (ITT Population)

	Pembro 200mg Combo (N=60)	Control (N=63)
Number of Subjects with Response[†]	34	19
Subjects who progressed or died[‡] (%)	**5 (14.7)**	**5 (26.3)**
Range of DoR (months)	2.8 - 8.9	2.8 - 16.2
Censored subjects (%)	**29 (85.3)**	**14 (73.7)**
Subjects who progressed or died after 2 or more missed visits	0 (0.0)	0 (0.0)
Subjects started new anti-cancer treatment	8 (23.5)	4 (21.1)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	1 (2.9)	1 (5.3)
Ongoing response[§]	20 (58.8)	9 (47.4)
≥3 months	20 (58.8)	9 (47.4)
≥6 months	20 (58.8)	7 (36.8)
≥9 months	16 (47.1)	7 (36.8)
Range of DoR (months)	6.2+ - 18.6+	4.2+ - 20.7+

[†] Response: Best overall response as confirmed complete response or partial response.
[‡] Include subjects who progressed or died either prior to or without missing 2 or more consecutive disease assessments.
[§] Ongoing response: subjects who are alive, have not progressed, have not initiated new anti-cancer treatment,have not been determined to be lost to follow-up and whose last adequate assessment was <5 months prior to the data cutoff date.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded Independent Central Review
Database Cutoff Date: 31DEC2016.

Source: [P021V01MK3475: analysis-adsl; adtte]

CHMP comment

An earlier and longer response was obtained by the addition of pembrolizumab to chemotherapy. The advantage with the pembrolizumab/chemotherapy combination is also expressed by the higher rate of patients with extended response duration (at ≥6 months and ≥9 months) which is maintained at the updated analysis.

Overall Survival (OS)

Table: Analysis of Overall Survival Cohort G1 (ITT Population)

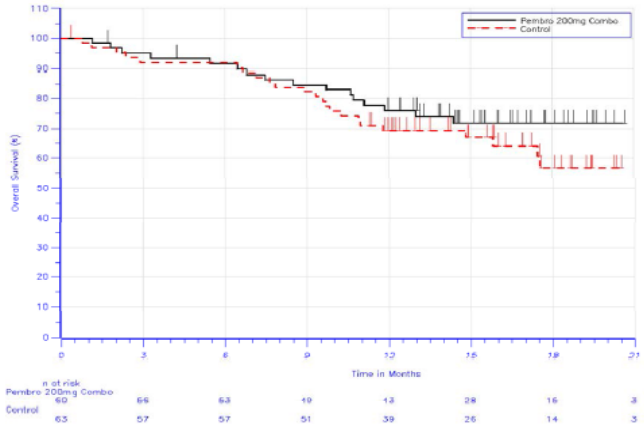
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro 200mg Combo	60	16 (26.7)	828.6	1.9	Not Reached (., .)	91.5 (80.8, 96.4)	0.69 (0.36, 1.31)	0.12674
Control	63	23 (36.5)	833.3	2.8	Not Reached (15.8, .)	91.9 (81.7, 96.6)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (positive vs. negative).
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 31DEC2016.

Source: [P021V01MK3475: analysis-adsl; adorr]

At 12 months, 76.0% (95% CI 62.8-85.0) and 69.3% (95% CI 56.2-79.2) of subjects were still alive in the pembro/combo and control arms, respectively.

Figure: Kaplan-Meier estimates of Overall Survival
Cohort G1
(ITT Population)



Database Cutoff Date: 31DEC2016.
Source: [P021V01MK3475: analysis-adsl; adorr]

In the control arm, 36 of 62 subjects (58.1%) received subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab, or durvalumab), including 22 patients who received pembrolizumab as part of the study crossover. Among of the 48 patients who discontinued treatment in the control arm, the crossover rate was 75.0% (36/48).

Due to the insufficient follow-up, the analysis of PFS and OS after crossover were not conducted.

Updated results (data cutoff date: 31 May 2017) submitted with responses to RSI

The median follow-up for subjects in the updated analysis 2 of Cohort G1 was 18.7 months (range 0.8-29.0), with a minimum of 16 months from the last patient randomized until the data cut-off [Table 20].

Objective Response Rate

Analysis of Objective Response (Confirmed)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

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

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

Source: [P021V01MK3475: analysis-adsl; adorr]

With the added follow-up, 2 additional responses were observed in the chemo alone arm and 1 additional response was observed in the pembrolizumab combo arm. The between arm difference was similar to the pre-specified analysis. Additionally, 1 CR developed in each arm.

Objective Response Rate for Pre-Specified and Updated Analysis 2 in Cohort G1

	Study Treatment	
Endpoint	**Pembro Combo**	**Control**
ORR (pre-specified analysis)	55.0% (55.0% PR, 0% CR)	28.6% (28.6% PR, 0% CR)
ORR (updated analysis 2)	56.7% (55.0% PR, 1.7% CR)	31.7% (30.2% PR, 1.6% CR)

Duration of Response

The median DOR was not reached in either the pembrolizumab combo arm (range 1.4+ to 22.7+ months) or the chemo alone arm (range 2.8 to 23.7+ months).

Summary of Time to Response and Duration of Response for Subjects with Confirmed Response
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

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

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

Source: [P021V01MK3475: analysis-adsl; adtte; adorr]

More subjects had an ongoing response in the pembrolizumab combo arm (17/34 [50.0%]) than in the chemo alone arm (8/20 [40.0%]) at the time of the data cut-off.

Progression-Free Survival

Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro 200mg Combo	60	26 (43.3)	681.4	3.8	19.0 (8.5, .)	79.0 (65.9, 87.5)	0.54 (0.33, 0.88)	0.00673
Control	63	40 (63.5)	537.0	7.4	8.9 (6.2, 11.8)	66.3 (52.7, 76.8)	---	---

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

Source: [P021V01MK3475: analysis-adsl; adtte]

The median PFS of the pembrolizumab combo arm increased from 13.0 months in the pre-specified analysis to 19.0 months in updated analysis 2.

Summary of PFS Rate Over Time Based on BICR per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

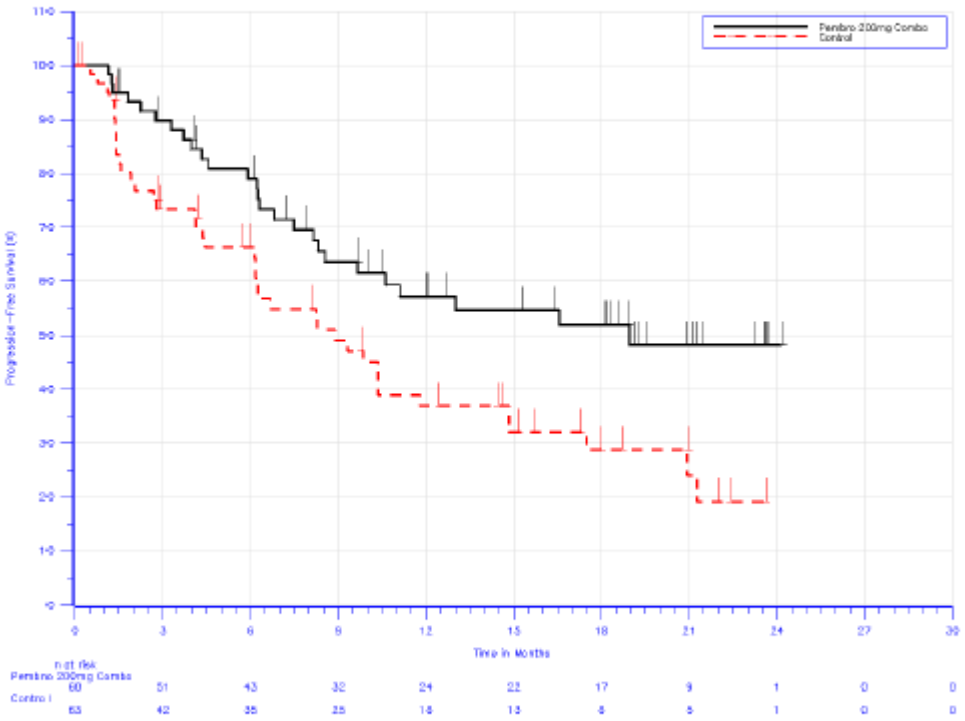
	Pembro 200mg Combo (N=60)	Control (N=63)
PFS rate at 6 Months in (95% CI)[†]	79.0 (65.9, 87.5)	66.3 (52.7, 76.8)
PFS rate at 12 Months in (95% CI)[†]	57.1 (42.6, 69.2)	36.8 (24.1, 49.6)
PFS rate at 18 Months in (95% CI)[†]	51.9 (37.1, 64.8)	28.7 (16.6, 42.1)
PFS rate at 24 Months in (95% CI)[†]	48.2 (32.9, 61.9)	19.2 (7.7, 34.5)

[†] From the product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded Independent Central Review
Database Cutoff Date: 31MAY2017.

Source: [P021V01MK3475: analysis-adsl; adtte]

The Kaplan-Meier plot demonstrated early separation of the curves, sustained from the first assessment through the remainder of the evaluation period, and the PFS curve for the pembrolizumab combo arm plateaued just above the 50% mark after approximately 12 months and declined gradually thereafter:

Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)



(Database Cutoff Date: 31May2017).
Source: [P021V01MK3475: analysis-adsl; adtte]

Overall Survival

In the updated analysis, a definite trend in OS was observed favoring the pembrolizumab combo arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436).

Analysis of Overall Survival
Cohort G1 Subjects
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro 200mg Combo	60	20 (33.3)	1055.6	1.9	Not Reached (22.8, .)	91.7 (81.1, 96.4)	0.59 (0.34, 1.05)	0.03436
Control	63	31 (49.2)	1007.1	3.1	20.9 (14.9, .)	91.9 (81.7, 96.6)	---	---

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

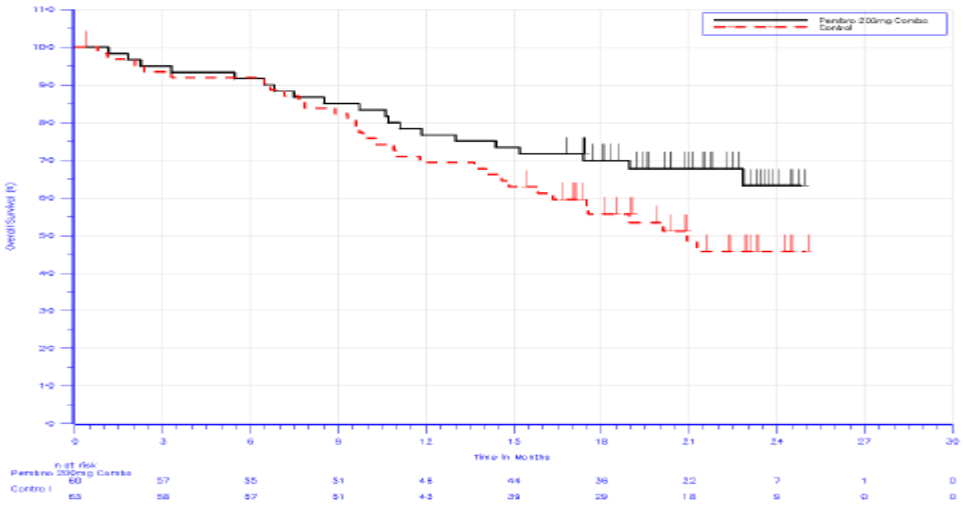
Source: [P021V01MK3475: analysis-adsl; adtte]

Overall Survival Rate
Cohort G1 Subjects
(ITT Population)

	Pembro 200mg Combo (N=60)	Control (N=63)
OS rate at 6 Months in (95% CI)†	91.7 (81.1, 96.4)	91.9 (81.7, 96.6)
OS rate at 12 Months in (95% CI)†	76.7 (63.8, 85.5)	69.4 (56.3, 79.2)
OS rate at 18 Months in (95% CI)†	69.8 (56.5, 79.8)	55.7 (42.4, 67.2)
OS rate at 24 Months in (95% CI)†	63.2 (47.4, 75.4)	45.8 (31.9, 58.7)
†From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 31MAY2017.		

Source: [P021V01MK3475: analysis-adsl; adtte]

Kaplan-Meier Estimates of Overall Survival
Cohort G1 Subjects
(ITT Population)



(Database Cutoff Date: 31May2017).
Source: [P021V01MK3475: analysis-adsl; adtte]

Overall, 40 of 63 subjects (63.5%) in the chemo alone arm received subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab or durvalumab), including 25 who received pembrolizumab as part of the study crossover. The crossover rate was 75.5% (40/53) for subjects who discontinued treatment in the chemo alone arm in this updated analysis, similar to the rate in the pre-specified analysis (74.4% [32/43]).

The high rate of subsequent PD-1/PD-L1 inhibitor therapy may have an influence on OS results and the shape of the Kaplan-Meier curves, resulting in the extremely favorable survival observed in the chemo alone arm. Despite the excellent survival observed in the chemo alone arm, a notable OS trend favoring the pembrolizumab combo arm has emerged supporting the importance of up front combination therapy initially shown with ORR and PFS results compared to giving chemotherapy followed by a PD-1/PD-L1 inhibitor at the time of progression.

With each analysis, an improvement in the OS HR is seen. In the pre-specified analysis, OS was not significantly different between treatment arms (HR 0.90, 95% CI 0.42-1.91) and the survival curves on the Kaplan-Meier plot were overlapping. In updated analysis 1 (data cutoff date:31 Dec 2016), a trend for survival favoring the pembrolizumab combo arm (HR 0.69, 95% CI 0.36-1.31) with separation of the survival curves was observed. Updated analysis 2 now showed a definitive OS trend favoring the pembrolizumab combo arm with further separation of the Kaplan-Meier curves.

Progression-Free Survival 2

Progression-free survival 2 (PFS2) was defined as the time from randomization to progression after next line therapy (as determined by investigator) or death from any cause. If no data on progression or death were available, the date of discontinuation of next-line therapy was used as a surrogate.

A benefit in PFS2 was observed for the pembrolizumab combo arm (HR 0.56, 95% CI 0.35-0.92, p=0.00960).

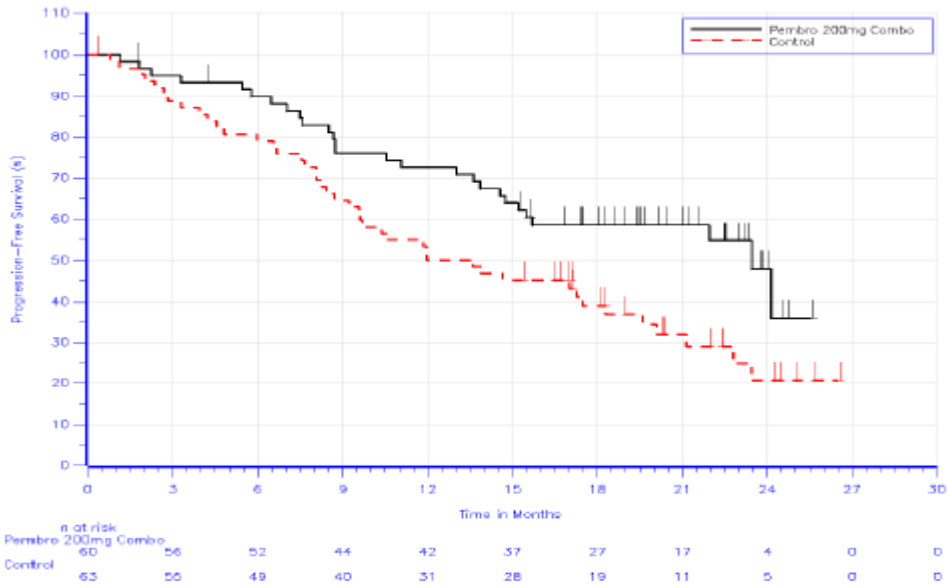
Analysis of PFS2
Based on Investigator Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro 200mg Combo	60	27 (45.0)	933.1	2.9	23.5 (15.2, .)	89.8 (78.7, 95.3)	0.56 (0.35, 0.92)	0.00960
Control	63	43 (68.3)	812.1	5.3	12.8 (9.2, 18.3)	79.0 (66.6, 87.2)	---	---

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

Source: [P021V01MK3475: analysis-adsl; adtte]

Kaplan-Meier Estimates of PFS2
Based on Investigator Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)



Database Cutoff Date: 31MAY2017.
Source: [P021V01MK3475: analysis-adsl; adtte]

Overall, with an updated follow-up the benefit in terms of ORR and PFS is confirmed. A trend in OS favouring the experimental arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05,

p=0.03436) is reported despite a not negligible rate of patients in the control arm (40/63, 63.5%) receiving subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab or durvalumab). A benefit in PFS2 was also reported (HR 0.56, 95% CI 0.35-0.92, p=0.00960).

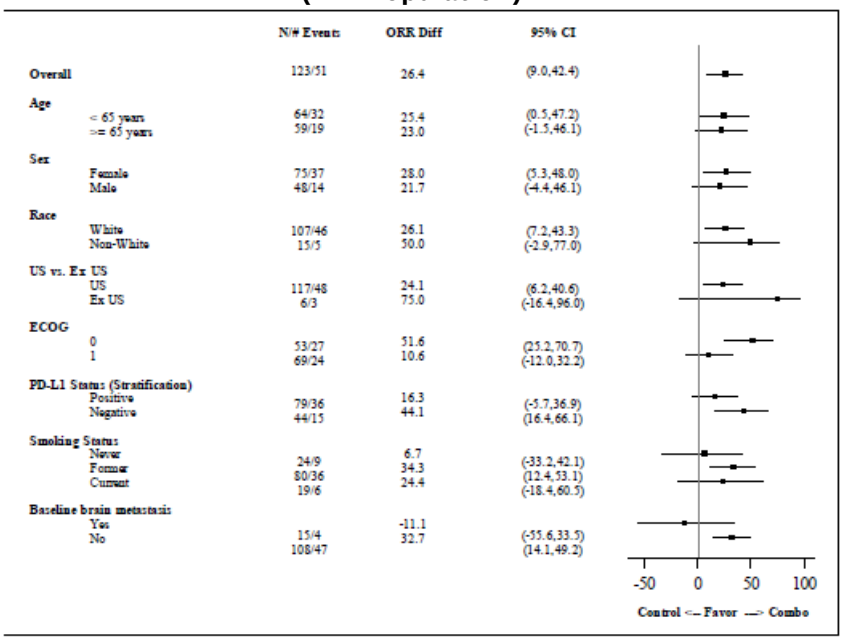
Ancillary analyses

Ancillary analyses were only performed at the time of pre-specified analysis (cut-off date: 08-Aug-2016).

ORR and PFS were presented by subgroup based on selected baseline factors including PD-L1 status (TPS≥1% vs TPS<1%).

Objective Response Rate (ORR)

Figure: Forest Plot of ORR difference by subgroup factors
Based on BICR Assessment per RECIST 1.1
Cohort G1
(ITT Population)

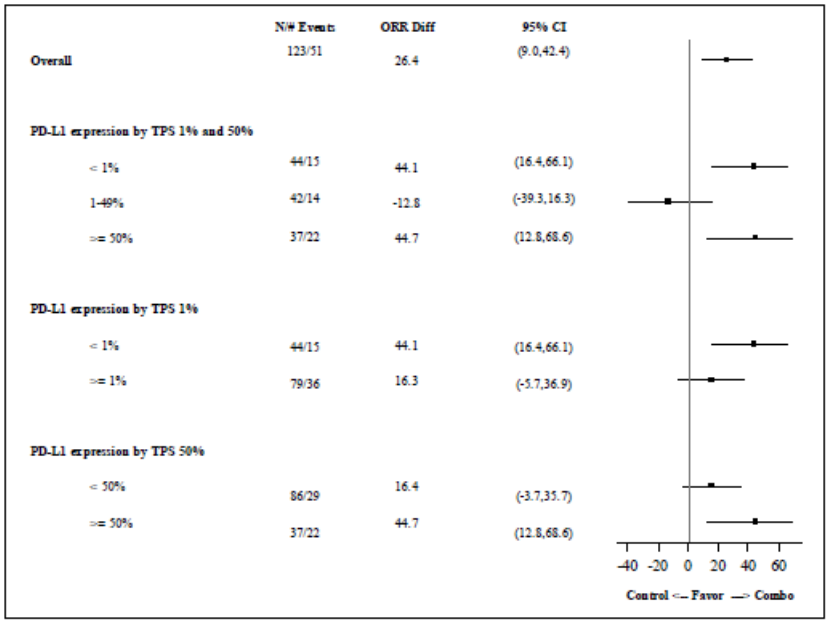


Database Cutoff Date: 08AUG2016.
Source: [P021V01MK3475: analysis-adsl; adorr];

CHMP comment

As already reported with pembrolizumab monotherapy in both first-line and previously treated NSCLC (KN024 and KN010 studies), a reduced difference in ORR was reported with pembrolizumab combination compared to chemotherapy alone in never smoker patients. The Forest Plot of PFS by subgroup factors should be provided.

Figure: Forest Plot of ORR difference by PD-L1 expression
Based on BICR Assessment per RECIST 1.1
Cohort G1
(ITT Population)



Database Cutoff Date: 08AUG2016.
Source: [P021V01MK3475: analysis-adsl; adorr]

The ORR observed in subgroups based on PD-L1 expression is shown in the following Table:

Table: Analysis of Objective Response (Confirmed)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with PD-L1 TPS ≥ 1% and TPS<1%
(ITT Population)

	PD-L1 TPS ≥1%					PD-L1 TPS <1%				
Treat.	N	N responses	ORR (%) (95% CI)	Diff vs Control estimate (95% CI)†	Diff vs Control p-value††	N	N responses	ORR (%) (95% CI)	Diff vs Control estimate (95% CI)†	Diff vs Control p-value††
pembro combo	39	21	53.8 (37.2,69.9)	16.3 (-5.7, 36.9)	0. 073	21	12	57.1 (34.0,78.2)	44.1 (16.4, 66.1)	0.001
Control	40	15	37.5 (22.7,54.2)			23	3	13.0 (2.8,33.6)		

Table made by the assessor from Table 14.2-5 and Table 14.2-6 of KN021 CSR; †based on Miettinen & Nurminen method; ††one-sided p-value for testing. H0: difference in %=0 versus H1:difference in % >0.
Database Cutoff Date:08AUG2016

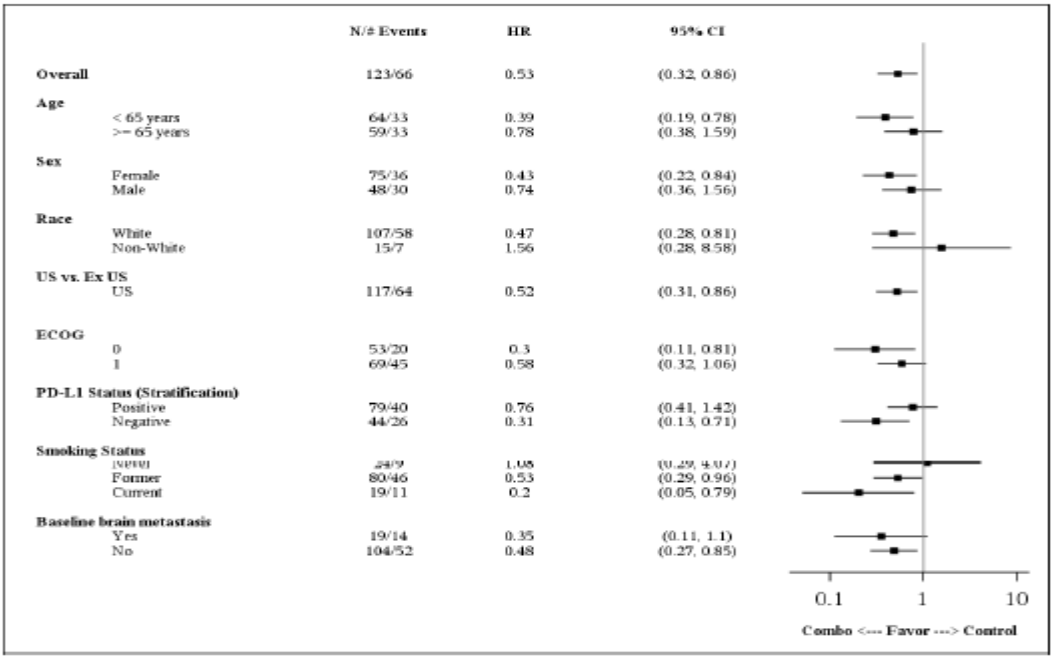
Table: Analysis of Objective Response (Confirmed)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with PD-L1 TPS ≥ 50% and TPS<50%
(ITT Population)

	PD-L1 TPS ≥50%					PD-L1 TPS <50%				
Treat.	N	N responses	ORR (%) (95% CI)	Diff vs Control estimate (95% CI)†	Diff vs Control p-value††	N	N responses	ORR (%) (95% CI)	Diff vs Control estimate (95% CI)†	Diff vs Control p-value††
pembro combo	20	16	80.0 (56.3, 94.3)	44.7 (12.8, 68.6)	0. 003	40	17	42.5 (27.0,59.1)	16.4 (-3.7, 35.7)	0.055
Control	17	6	35.3 (14.2,61.7)			46	12	26.1 (14.3,41.1)		

Table made by the assessor from Table 14.2-7 and Table 14.2-8 of KN021 CSR; †based on Miettinen & Nurminen method; ††one-sided p-value for testing. H0: difference in %=0 versus H1:difference in % >0.
Database Cutoff Date:08AUG2016

Progression Free Survival (PFS)

Forest Plot of PFS Hazard Ratio by Subgroup Factors
Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule)
Cohort G1 Subjects
(ITT Population)



Database Cutoff Date: 31MAY2017.
Source: [P021V01MK3475: analysis-adsl; adtte];

Although it is acknowledged that the numbers are too small to draw conclusions, the finding in never smoker patients is in line with those reported in Study KN024 and KN010.
Information on the reduced benefit observed in the combo arm compared to chemotherapy in this subgroup of patients should be added in the SmPC Section 5.1.

Table: Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with PD-L1 TPS ≥ 1% and TPS<1%
(ITT Population)

	PD-L1 TPS ≥1%						PD-L1 TPS <1%					
Treatment	N	N Events (%)	mPFS† (months) (95% CI)	PFS Rate Month 6† (%) (95% CI)	vs Control HR (95% CI)	vs Control p-value§	N	N Events (%)	m PFS (months) (95% CI)	PFS Rate Month 6† (%) (95% CI)	vs Control HR‡ (95% CI)	vs Control p-value§
pembro combo	39	16 (41.0)	8.3 (6.2,.)	69.2 (51.1,81.7)	0.76 (0.39, 1.48)	0.209	21	7 (33.3)	13 (9.7,13.0)	90.5 (67.0,97.5)	0.28 (0.11, 0.71)	0.002
Control	40	19 (47.5)	8.9 (4.4,.)	67.3 (49.5,80.0)			23	14 (60.9)	6.2 (2.0,10.3)	54.5 (30.5,73.2)		

Table made by the assessor from Table 14.2-17 and Table 14.2-18 of KN021 CSR; †From product-limit (Kaplan-Meier)method for censored data; ‡based on Cox regression model with treatment as covariate; § One-sided p-value based on log-rank test.
Database Cutoff Date:08AUG2016

Table: Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with PD-L1 TPS ≥ 50% and TPS<50%
(ITT Population)

	PD-L1 TPS ≥50%						PD-L1 TPS <50%					
Treatment	N	N Events (%)	mPFS† (months) (95% CI)	PFS Rate Month 6† (%) (95% CI)	vs Control HR (95% CI)	vs Control p-value§	N	N Events (%)	m PFS (months) (95% CI)	PFS Rate Month 6† (%) (95% CI)	vs Control HR‡ (95% CI)	vs Control p-value§
pembro combo	20	6 (30.0)	NR (6.3,.)	79.4 (54.0,91.7)	0.26 (0.09, 0.76)	0.004	40	17 (42.5)	11.1 (8.1,13.0)	76.0 (58.9,86.8)	0.70 (0.37, 1.31)	0.131
Control	17	9 (52.9)	6.2 (1.9,12.0)	73.1 (42.9,89.0)			46	24 (52.2)	9.3 (4.1,.)	59.8 (43.5,72.8)		

Table made by the assessor from Table 14.2-19 and Table 14.2-20 of KN021 CSR; NR: Not reached; †From product-limit (Kaplan-Meier)method for censored data; ‡based on Cox regression model with treatment as covariate; § One-sided p-value based on log-rank test.
Database Cutoff Date:08AUG2016

Updated analysis (Data cutoff date: 31 May 2017)

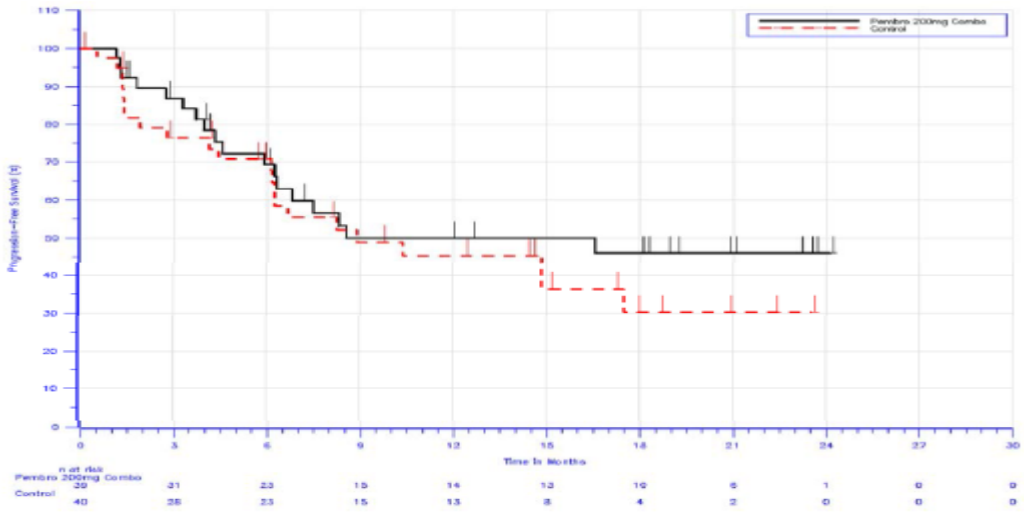
Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with TPS >= 1%
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡	vs. Control p-Value§
Pembro 200mg Combo	39	18 (46.2)	397.3	4.5	8.5 (6.2, .)	69.3 (51.3, 81.8)	0.76 (0.41, 1.42)	0.19511
Control	40	22 (55.0)	342.2	6.4	8.9 (6.2, 17.5)	70.8 (53.4, 82.6)	---	---

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

Source: [P021V01MK3475: analysis-adsl; adtte]

Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with TPS >= 1%
(ITT Population)



(Database Cutoff Date: 31May2017).
Source: [P021V01MK3475: analysis-adsl; adtte]

Responses were observed regardless of PD-L1 status (although more pronounced in strongly positive). A benefit in terms of ORR and PFS is observed in PD-L1 TPS <1%; interestingly, a very poor response rate to chemotherapy is observed in PD-L1 negative patients. This is somewhat unexpected, and likely a chance finding. In terms of baseline characteristics, the main category exhibiting a difference between

treatment arms in the TPS <1% subgroup was age. The majority (76.2%) of subjects in the pembro combo arm were less than 65 years of age, whereas the majority (60.9%) of subjects in the chemo alone arm were over 65 years of age, with median ages of 58 years and 67 years, respectively. There is no clear benefit of the combination over chemotherapy in PD-L1 TPS ⩾1%, with a similar PFS rate at 6 months (69.3% with pembro combo and 70.8% with chemo); there is a concern in granting an indication for a combination treatment based on a borderline clinical effect while the results of Study KN-042, comparing pembrolizumab monotherapy to platinum based chemotherapy as first-line treatment in PD-L1 positive (TPS ⩾1%) patients, are still pending. If available, top-line results of Study KN042 should be provided

PFS sensitivity analyses using alternate sets of censoring rules were also performed.

Table: Analysis of Progression-Free Survival based on BICR assessment per RECIST 1.1 Sensitivity Analyses 1,2 and 3 All Subjects (ITT Population)

	N. events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS* (months) (95% CI)	PFS Rate 6 months (%)* (95% CI)	Pembro vs control	
						HR (95%CI)°	p-value§
Sensitivity Analysis 1							
Pembro combo	21 (35.0)	442.8	4.7	Not reached (8.3,..)	76.6 (63.1, 85.7)	0.52 (0.30, 0.90)	0.009
Control	32 (50.8)	357.2	9.0	8.9 (4.4, 10.32)	62.4 (48.2, 73.8)		
Sensitivity Analysis 2							
Pembro combo	37 (61.7)	460.1	8.0	9.2 (6.3,11.1)	68.3 (55.0, 78.5)	0.58 (0.38, 0.90)	0.007
Control	48 (76.2)	361.4	13.3	5.3 (3.4, 6.6)	50.0 (37.1, 61.6)		
Sensitivity Analysis 3							
Pembro combo	23 (38.3)	461.4	5.0	13.0 (8.3,..)	77.2 (63.9, 86.1)	0.53 (0.31, 0.91)	0.010
Control	33 (52.4)	363.8	9.1	8.9 (4.4, 10.3)	62.7 (48.6, 74.0)		
Sensitivity Analysis (Time to Scheduled Analysis)							
Pembro combo	23 (38.3)	475.0	4.8	13.0 (10.3,..)	79.3 (66.3, 87.7)	0.52 (0.30, 0.90)	0.008
Control	33 (52.4)	369.1	8.9	9.3 (4.1, 10.3)	63.5 (49.6, 74.6)		

Table made by Assessor from Table 14.2-12, Table 14.2-13, Table 14.2-14 and Table 14.2-15.
Sensitivity analysis 1 censors a subject's data at the last disease assessment without PD when there are 2 or more consecutive missed disease assessments.
Sensitivity analysis 2 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.
Sensitivity analysis 3 censors a subject's data at the last disease assessment for subjects without documented PD or death, regardless of initiation of new anticancer treatment.
*From product-limit (Kaplan-Meier) method for censored data.
°Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (positive vs negative).
§One-sided p-value based on log-rank test.
Pembro combo: pembrolizumab/pemetrexed/carboplatin. Control arm: pemetrexed/carboplatin
Database Cutoff Date: 08AUG2016

The PFS analysis based on Investigator assessment was generally consistent with the result by central review (HR 0.62, 95% CI 0.37-1.04, p=0.03607; median PFS: 11.9 months in the pembrolizumab combination arm and 7.5 months in the control arm).

CHMP comment

PFS sensitivity analyses confirmed the primary analysis results.

Summary of main study(ies)

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

Table 1. Summary of Efficacy for trial KEYNOTE-021 (Cohort G1)

Title: A Phase I/II Study of MK-3475 (SCH900475) in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma			
Study identifier	KEYNOTE-021; NCT02039674		
Design	Multi-center, randomized, multi-cohort, open-label, Phase 1/2 study of IV pembrolizumab at 3 doses in combination with chemotherapy, immunotherapy, or tyrosine kinase inhibitor (TKI) therapy in subjects with locally advanced or metastatic non-small cell lung carcinoma (NSCLC). Cohort G1 pertains to the combination of pembrolizumab with pemetrexed/carboplatin as a first-line treatment.		
Hypothesis	Superiority		
Treatments groups	Pembro+ chemotherapy		pembrolizumab 200 mg IV Day 1 Q3W for up to 24 months + pemetrexed 500 mg/m^2 IV Day 1 Q3W for up to 24 months with pembrolizumab + carboplatin AUC 5mg/mL/min IV Day 1 Q3W for 4 cycles 60 patients randomized
	chemotherapy		pemetrexed 500 mg/m^2 IV Day 1 Q3W for up to 24 months + carboplatin AUC 5mg/mL/min IV Day 1 Q3W for 4 cycles 63 patients randomized
Endpoints and definitions	Primary endpoint	ORR	Complete response plus partial response based on BICR assessment of tumor imaging using RECIST 1.1 criteria
	Key Secondary endpoint	PFS	Time from randomization to PD, based upon RECIST 1.1 by BICR, or death, whichever occurred earlier
	Secondary endpoint	DOR	Time from first documented evidence of complete response or partial response until disease progression or death due to any cause, whichever occurs first
	Secondary endpoint	OS	Time from randomization to death due to any cause
Data cut-off	31 December 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	pembrolizumab combination	chemotherapy
	Number of subject	60	63
	Primary endpoint		
	ORR (BICR-RECIST 1.1) N (%) (95% CI)	34 (56.7) (43.2, 69.4)	19 (30.2) (19.2, 43.0)
	Difference % vs chemotherapy (95% CI)	26.4 (8.9, 42.3)	
	p-value (one sided)	0.0016	
	Key secondary endpoint		
	PFS (BICR RECIST 1.1) N. with events (%)	24 (40.0)	37 (58.7)
	Median PFS months (95% CI)	Not Reached (9.7,..)	8.9 (6.2,10.3)
	Hazard Ratio pembro combination vs chemotherapy (95% CI)	0.49 (0.29, 0.83)	

	p-value (one sided log-rank test)	0.0035	
	Secondary endpoints		
	Response duration (months) Median (range)	Not Reached (1.4+-18.6+)	16.2 (2.8-20.7+)
	OS N. with events (%)	16 (26.7)	23 (36.5)
	Median OS months (95% CI)	Not Reached (..,..)	Not Reached (15.8,..)
	Hazard Ratio pembro combination vs chemotherapy (95% CI)	0.69 (0.36, 1.31)	
	p-value (one sided log-rank test)	0.1267	
Notes			

Supportive study(ies)

The MAH submitted as supportive to this application data from the 24 non-squamous metastatic NSCLC patients, eligible for 1L systemic chemotherapy and with no sensitizing mutations of EGFR or ALK translocations, who were enrolled in Cohort C of KN021 study. A randomized dose finding design was used, with 12 subjects assigned to each of the 2 dose levels of pembrolizumab (2 and 10 mg/kg) combined with pemetrexed/carboplatin therapy every 3 weeks for 4 cycles. In addition, subjects were to receive maintenance pemetrexed (at the Investigator's discretion) with pembrolizumab until progression, protocol-defined unacceptable toxicity, or up to 24 months, whichever occurred first.

The enrolment started on 20 March 2014, and the last patients was randomized on 14 October 2014. The ITT population (identical to the All Subjects as Treated population) was the primary population for the analysis of efficacy data.

The primary study objective in this cohort was to determine the recommended Phase 2 dose for pembrolizumab in combination with chemotherapy in subjects with unresectable or metastatic NSCLC.

As in Cohort G1, all patients were evaluated every 6 weeks for the first 18 weeks, followed by every 9 weeks in Year 1 and every 12 weeks in Year 2, based on radiographic imaging reviewed by BICR per RECIST 1.1 to assess response to treatment.

The majority of subjects in Cohort C had Stage IV NSCLC (95.8%), adenocarcinoma histology (79.2%), no prior systemic adjuvant or neo-adjuvant chemotherapy (95.8%), and an ECOG performance status of 1 at baseline (70.8%). About one-third of subjects were in each PD-L1 TPS category (TPS<1%, TPS 1-49%, TPS≥50%).

The majority of subjects discontinued study medication due to progressive disease (58.3%), adverse events (16.7%) and clinical progression (8.3%). One subject in the pembrolizumab 2 mg/kg combination arm completed 2 years of therapy and stopped treatment, and one subject in the pembrolizumab 10 mg/kg combination arm remains on study treatment.

Descriptive analyses were planned and conducted for the primary endpoint ORR and secondary endpoints PFS, DOR and OS. The data cut-off for the submitted analyses was 8 August 2016, with a median follow up of 17.4 months.

Table: Summary of Objective Response (confirmed)
Based on BICR assessment per RECIST 1.1
Cohort C
(ITT Population)

	Pembro 10mg/kg Combo			Pembro 2mg/kg Combo			Total		
	n	(%)	(95% CI)	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	12			12			24		
Complete Response (CR)	0	(0.0)	(0.0, 26.5)	1	(8.3)	(0.2, 38.5)	1	(4.2)	(0.1, 21.1)
Partial Response (PR)	10	(83.3)	(51.6, 97.9)	7	(58.3)	(27.7, 84.8)	17	(70.8)	(48.9, 87.4)
Overall Response (CR+PR)	**10**	**(83.3)**	**(51.6, 97.9)**	**8**	**(66.7)**	**(34.9, 90.1)**	**18**	**(75.0)**	**(53.3, 90.2)**
Stable Disease (SD)	2	(16.7)	(2.1, 48.4)	3	(25.0)	(5.5, 57.2)	5	(20.8)	(7.1, 42.2)
Disease Control (CR+PR+SD)	**12**	**(100.0)**	**(73.5, 100.0)**	**11**	**(91.7)**	**(61.5, 99.8)**	**23**	**(95.8)**	**(78.9, 99.9)**
Progressive Disease	0	(0.0)	(0.0, 26.5)	1	(8.3)	(0.2, 38.5)	1	(4.2)	(0.1, 21.1)
Non-evaluable	0	(0.0)	(0.0, 26.5)	0	(0.0)	(0.0, 26.5)	0	(0.0)	(0.0, 14.2)
No Assessment	0	(0.0)	(0.0, 26.5)	0	(0.0)	(0.0, 26.5)	0	(0.0)	(0.0, 14.2)

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
(Database Cutoff Date: 08AUG2016).

Source: [P021V01MK3475: analysis-adsl; adorr]

The confirmed ORR based on Investigator assessment for all 24 subjects was 70.8% (95% CI 48.9-87.4).

Table: Summary of Objective Response (confirmed) by PD-L1 expression
Based on BICR assessment per RECIST 1.1
Cohort C
(ITT Population)

	Pembro 10mg/kg Combo		Pembro 2mg/kg Combo		Total	
	< 1% n (%)	>=1% n (%)	< 1% n (%)	>=1% n (%)	< 1% n (%)	>=1% n (%)
Number of Subjects in Population	4	8	4	8	8	16
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.3)
Partial Response (PR)	3 (75.0)	7 (87.5)	4 (100.0)	3 (37.5)	7 (87.5)	10 (62.5)
Overall Response (CR+PR)	**3 (75.0)**	**7 (87.5)**	**4 (100.0)**	**4 (50.0)**	**7 (87.5)**	**11 (68.8)**
Stable Disease (SD)	1 (25.0)	1 (12.5)	0 (0.0)	3 (37.5)	1 (12.5)	4 (25.0)
Disease Control (CR+PR+SD)	**4 (100.0)**	**8 (100.0)**	**4 (100.0)**	**7 (87.5)**	**8 (100.0)**	**15 (93.8)**
Progressive Disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.3)
Not Evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No Assessment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Responses are based on BICR assessments per RECIST 1.1.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08AUG2016

Source: [P021V01MK3475: analysis-adsl; adorr]

Table: Summary of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort C
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)
Pembro 10mg/kg Combo	12	10 (83.3)	110.9	9.0	8.3 (4.6, 14.3)	72.7 (37.1, 90.3)
Pembro 2mg/kg Combo	12	9 (75.0)	149.7	6.0	11.8 (3.4, .)	83.3 (48.2, 95.6)
Total	24	19 (79.2)	260.7	7.3	10.2 (6.5, 13.9)	78.4 (55.6, 90.4)

† From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08AUG2016.

Source: [P021V01MK3475: analysis-adsl; adtte]

Results of PFS analyses by Investigator assessment were similar to those from the primary analysis, with a median PFS of 8.9 months and a PFS rate at 6 months of 77.3%.

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

	Pembro 10mg/kg Combo (N=12)	Pembro 2mg/kg Combo (N=12)	Total (N=24)
Number of subjects with response†	10	8	18
Time to Response† (months)			
Mean (SD)	2.4 (1.0)	2.6 (1.8)	2.5 (1.3)
Median (Range)	2.8 (1.4-4.2)	1.8 (1.3-6.2)	2.4 (1.3-6.2)
Response Duration‡ (months)			
Median (Range)	6.6 (2.7 - 21.5+)	10.0 (4.8 - 22.1+)	8.3 (2.7 - 22.1+)
Number (%‡) of Subjects with Extended Response Duration:			
≥3 months	9 (90.0)	8 (100.0)	17 (94.4)
≥6 months	5 (50.0)	7 (87.5)	12 (66.7)
≥9 months	4 (40.0)	4 (50.0)	8 (44.4)

† Response: Best objective response as confirmed complete response or partial response.
‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 08AUG2016.

Source: [P021V01MK3475: analysis-adsl; adtte; adorr]

Table: Summary of Overall Survival
Cohort C
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)
Pembro 10mg/kg Combo	12	8 (66.7)	194.9	4.1	17.4 (4.7, .)	83.3 (48.2, 95.6)
Pembro 2mg/kg Combo	12	7 (58.3)	209.3	3.3	16.6 (11.4, .)	91.7 (53.9, 98.8)
Total	24	15 (62.5)	404.2	3.7	16.7 (13.9, .)	87.5 (66.1, 95.8)

† From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 08AUG2016.

Source: [P021V01MK3475: analysis-adsl; adtte]

By Kaplan-Meier estimation, 75.0% (95% CI 52.6-87.9) of subjects were alive at 12 months.

CHMP comment

A quite similar patient population was enrolled in Cohort C compared to Cohort G1. In this dose-finding part of KN021 study including 24 patients, a confirmed ORR was reported in 75% of enrolled patients, with disease stabilization in 96% of them. No major contribution to the definition of the PD-L1 expression role as response predictive factor can be derived from Cohort C, considering the very low number of patients in each subgroup. A median PFS of 10.2 months and a median OS of 16.7 months were registered.

2.4.3. Discussion on clinical efficacy

Pembrolizumab as monotherapy is already part of the NSCLC treatment landscape, being approved for the first-line treatment of metastatic PD-L1 strongly positive (TPS≥50%) NSCLC in the absence of EGFR or ALK positive tumour mutations, and for the treatment of locally advanced or metastatic PD-L1 positive (TPS≥1%) patients who have received at least one prior chemotherapy regimen, including approved target therapy for EGFR and ALK aberrations in case of positive tumor mutations.

This application has been submitted to extend the indication as first-line treatment besides PD-L1 expression in non-squamous metastatic NSCLC patients when pembrolizumab is administered with pemetrexed/carboplatin as a combined chemotherapy regimen.

Design and conduct of clinical studies

KN021 is an ongoing multi-cohorts phase I/II study, conducted in US and Taiwan, investigating the activity of pembrolizumab-based combination regimens in unresectable or metastatic NSCLC. To support the efficacy of pembrolizumab added to platinum-doublet chemotherapy, results from the randomized Cohort G1 of KEYNOTE-021, comparing the combination of pembrolizumab 200 mg plus pemetrexed/carboplatin versus chemotherapy alone, have been submitted. Data from the dose-finding Cohort C (pembrolizumab 2 mg/kg plus pemetrexed/carboplatin or pembrolizumab 10 mg/kg plus pemetrexed/carboplatin) were submitted by the MAH as supportive.

Patients with chemotherapy-naïve Stage IIIB or IV, non-squamous NSCLC in the absence of targetable EGFR or ALK genetic aberrations were randomized. Further details on the randomization method should be provided.

Platinum-based doublets are a well-recognized standard of care for the first-line treatment of NSCLC and cisplatin/pemetrexed is recommended as first line treatment of non-squamous NSCLC. Over time, carboplatin largely replaced cisplatin as the platinum-containing drug due to the more favorable safety profile, and was the most preferred treatment option in US, while cisplatin-containing combinations were the reference standard in Europe. Considering that KN021 was mostly conducted in US, with the remaining 2 sites in Taiwan, the selection of platinum-doublets including carboplatin as backbone chemotherapy regimen can be acknowledged, even though a higher RR and slightly longer OS were reported with cisplatin-combinations compared to carboplatin-doublets (Ardizzoni A, 2007). Based on

inclusion criteria, cisplatin-eligible patients could have been enrolled in Cohort G1. Therefore, the cisplatin-based chemotherapy could has also been a suitable backbone. Nevertheless, the study design of Cohort G1 allows to evaluate pembrolizumab as add on to backbone chemotherapy, thus limiting the possible difference in efficacy across arms.

The primary efficacy endpoint was ORR per RECIST 1.1 based on BICR, while PFS per RECIST 1.1 based on BICR was considered a key secondary endpoint. These two endpoints were analyzed using a step down procedure, in which the Type I error rate (alpha=2.5%, one-sided) over the multiple endpoints was controlled by a fixed-sequence, closed-testing procedure that tested for a treatment difference for ORR first, followed by a test for a treatment difference for PFS. As additional secondary endpoints, OS and duration of response (DOR) were also evaluated.

The primary efficacy analysis of efficacy was planned to occur with at least 6 months of treatment or follow up for all patients enrolled, which is considered adequate. This pre-specified analysis was conducted at the data cutoff date of 08-AUG-2016. An updated analysis with 5 additional months of follow-up was also conducted (cutoff date 31-DEC-2016) and results were provided at the time of the initial submission. An updated analysis after an additional 10 months of follow-up beyond the pre-specified analysis (data cutoff date: 31 May 2017) was conducted as response to the CHMP 1st RSI.

Efficacy data and additional analyses

Overall, 123 patients were randomized (1:1) to receive pemetrexed and carboplatin alone for 4 cycles (63 patients), or to receive pemetrexed and carboplatin plus pembrolizumab 200 mg for 4 cycles followed by pembrolizumab 200 mg (60 patients). In both arms maintenance pemetrexed was administered at the Investigator's discretion. The option to receive up to 24 months of pembrolizumab monotherapy was offered to subjects in the control arm experiencing investigator-assessed PD defined by RECIST 1.1 and additional specified criteria. In total, 22 patients in the control shifted to pembrolizumab single agent and additional 14 patients received antiPD-1/anti PD-L1.

Baseline characteristics were overall balanced across arms, with the exception of age <65 years (60% vs 44.4%) and never smoker status (25% vs 14%) that were more frequent in the pembrolizumab/chemotherapy arm.

At the data cut-off date:31-Dec-2016, around one third of patients were still on treatment, and for more than 50% the disease assessment was ongoing. The confirmed ORR was 56.7% in the pembrolizumab combination arm and 30.2% in the control group. An estimated ORR difference slightly smaller than that pre-defined (30%), was observed in terms of ORR in the ITT population.

A benefit in PFS was reported with the pembrolizumab/chemotherapy combination (HR 0.49, 95% CI 0.29-0.83, p=0.00352). The median time to response was shorter with the combination (1.6 months) than with chemotherapy alone (2.7 months), with a median duration of response not reached and 16.2 months (16.2 months (2.8-20.7+), respectively. OS data are still immature.

At the most updated analysis, the benefit in terms of ORR and PFS is confirmed. A trend in OS favouring the experimental arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436) is reported despite a not negligible rate of patients in the control arm (40/63, 63.5%) receiving subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab or durvalumab). A benefit in PFS2 was also reported (HR 0.56, 95% CI 0.35-0.92, p=0.00960).

As already shown with pembrolizumab monotherapy in both first-line and previously treated NSCLC (KN024 and KN010 studies), a reduced difference in ORR and PFS was reported with pembrolizumab combination compared to chemotherapy alone in never smoker patients. Information on the reduced benefit observed in the combo arm compared to chemotherapy in this subgroup of patients should be added in the SmPC Section 5.1.

Results according to PD-L1 expression were provided, showing responses regardless of PD-L1 status (although more pronounced in strongly positive). A benefit in terms of PFS is observed for PD-L1 strongly positive patients.

Pembrolizumab as single-agent is approved in EU for the first-line treatment of PD-L1 ≥50% metastatic NSCLC based on results from study KN024, showing a clear benefit over platinum-containing chemotherapy in terms of both PFS (HR 0.50; 95% CI 0.37, 0.68) and OS (HR 0.60; 95%CI 0.41, 0.89), and a more favourable safety profile.

As the MAH pointed out, the clinical development of Keytruda for NSCLC was biomarker-based for monotherapy and non-biomarker-based for combination treatments. This is not questioned, in principle. It is also acknowledged that, due to the parallel development of different therapeutic approaches it is not possible to generate data of direct comparisons for all of them. On the other hand, it is essential to put results of studies supporting a new indication in the context of available therapeutic treatment options.

Study KN021 was not designed to address the efficacy of pembro combo in PD-L1 strongly-positive patients, and a very limited number of patients in this subgroup were treated with pembro combination in cohort G1(20 patients in total). Taking into account the relatively limited data, and the intrinsic limitations of cross-trial comparison, it cannot be firmly concluded that pembrolizumab in combination is more efficacious than pembrolizumab monotherapy, although a higher response rate has been reported in study KN021 compared to KN024.

There is no clear benefit of the combination over chemotherapy in PD-L1 TPS ⩾1%, with a similar PFS rate at 6 months that still persist at the longer follow-up (69.3% with pembro combo and 70.8% with chemo alone). The late separation of the K-M curves is acknowledged. In order to explain the poor outcome observed with chemotherapy in PD-L1<1% subjects, the MAH presented the patient baseline characteristics showing a meaningful imbalance essentially with regard to age, with 23.8% of subjects older than 65 years in the experimental arm vs 60.9% in the control arm. The compliance by age to chemotherapy in the PD-L1<1% group should be discussed by the MAH.

2.4.4. Conclusions on the clinical efficacy

It is acknowledged that data from Study KN021 suggest a benefit of the pembro combination over chemotherapy. However, based on available data not allowing to draw firm conclusion with regard to many relevant aspects, it would seem wise to wait for the top-line results from studies KN189 and KN042. Interim analyses for these studies are planned , and the MAH is therefore asked to provide these data as available, in order to allow a more informed evaluation of the B/R (Study KN189), and a better contextualization (Study KN042), of the sought indication.

2.5. Clinical safety

Introduction

The known pembrolizumab safety profile is mainly associated with immune-related adverse reactions and characterized by general (fatigue), gastrointestinal (diarrhoea and nausea), and skin (rash and pruritus) 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.

In order to evaluate the safety of pembrolizumab, in combination with pemetrexed and carboplatin, for the treatment of advanced non-squamous NSCLC patients, safety data from Cohort C and G1 of KEYNOTE-021 study were pooled. Both Cohorts enrolled patients with previously untreated advanced or metastatic NSCLC of any PD-L1 status, and without EGFR sensitizing mutations or ALK translocations. In Cohort G1, patients randomized to the control arm (pemetrexed/carboplatin) had the opportunity to

receive up to 24 months of pembrolizumab monotherapy in case of progressive disease by RECIST 1.1 and specific criteria were met. No safety data related to these 25 patients who switched to second-line pembrolizumab as monotherapy were submitted with this application.

Safety data are displayed in a tabular format, including data from subjects treated with chemotherapy alone in the control arm of Cohort G1 KEYNOTE-021 study, data from subjects treated with pembrolizumab/pemetrexed/carboplatin (pembro-chemo combination) in both Cohort C and G1 of KEYNOTE-021, and the Reference Safety Dataset, comprising a pooled population (2799 melanoma and NSCLC patients) from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 studies, treated with pembrolizumab as monotherapy.

CHMP comment

To evaluate the safety profile of the combined regimen including pembrolizumab/pemetrexed/carboplatin in the first-line treatment of metastatic non-squamous NSCLC, pooled data registered in a total of 83 patients treated in Cohorts G1 and C of KN021 study have been submitted. Considering the similar baseline characteristics of patients in the two Cohorts, the proposed approach is agreed. In addition, as reference for the pembrolizumab safety profile when administered as monotherapy, a safety dataset of 2799 patients, also including 154 first-line metastatic NSCLC patients treated in KN024, was provided. Due to the partial overlapping of the sought indication ("in combination with platinum-pemetrexed chemotherapy as first-line treatment of metastatic non-squamous NSCLC") with that already granted ("as monotherapy, for the first-line treatment of metastatic NSCLC with PD-L1 TPS⩾50%"), a direct comparison with safety data from first-line metastatic NSCLC patients (KN024 study) was performed by the MAH.

The comparison has been conducted considering 3 patients populations, including subjects who received pembro combination (KN021 Cohorts C and G1 pooled), pembrolizumab monotherapy (KN024) and chemotherapy alone (KN021 Cohort G1). Limitations of cross-trials comparison are acknowledged, as well as the fact that KN024 included about 18% of patients with squamous histology. However, patients' characteristics were broadly similar in terms of cancer stage, prior systemic adjuvant/neo-adjuvant treatments, age, ECOG PS, brain metastases at baseline, while female and never smokers were more represented in KN-021.

Patient exposure

Overall, 83 patients received at least one dose of pembrolizumab in combination with pemetrexed/carboplatin in the Cohort C and G1 of KEYNOTE-021 study.

Demographic and other baseline characteristics were generally similar between the pembrolizumab/chemotherapy combination group and the chemotherapy alone group. The observed differences (i.e, 60% vs 45.2% of patients ≤65 years in the pembrolizumab combination group compared to chemotherapy.) are not expected to impact on the safety evaluation of the pembrolizumab/chemotherapy combination.

Table: Subjects Characteristics
KN021 (Cohorts C and G1) and
Monotherapy Reference Dataset (KN001, KN002, KN006, KN010)
(ASaT)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
Gender						
Male	26	(41.9)	33	(39.8)	1,659	(59.3)
Female	36	(58.1)	50	(60.2)	1,140	(40.7)
Age (Years)						
<65	28	(45.2)	50	(60.2)	1,587	(56.7)
>=65	34	(54.8)	33	(39.8)	1,212	(43.3)
Mean	63.1		61.6		61.0	
SD	9.7		9.3		12.5	
Median	66.0		62.0		62.0	
Range	37 to 80		36 to 77		15 to 94	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(1.2)	7	(0.3)
Asian	5	(8.1)	5	(6.0)	233	(8.3)
Black Or African American	0	(0.0)	12	(14.5)	48	(1.7)
Multiple	0	(0.0)	0	(0.0)	11	(0.4)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	4	(0.1)
White	57	(91.9)	64	(77.1)	2,474	(88.4)
Missing	0	(0.0)	1	(1.2)	22	(0.8)
Ethnicity						
Hispanic Or Latino	1	(1.6)	0	(0.0)	128	(4.6)
Not Hispanic Or Latino	55	(88.7)	78	(94.0)	2,582	(92.2)
Not Reported	2	(3.2)	0	(0.0)	47	(1.7)
Unknown	4	(6.5)	5	(6.0)	37	(1.3)
Missing	0	(0.0)	0	(0.0)	5	(0.2)
Geographic Region						
US	60	(96.8)	79	(95.2)	1,250	(44.7)
Ex US	2	(3.2)	4	(4.8)	1,549	(55.3)
ECOG						
0	28	(45.2)	31	(37.3)	1,452	(51.9)
1	34	(54.8)	52	(62.7)	1,345	(48.1)
ECOG						
2	0	(0.0)	0	(0.0)	2	(0.1)

KN021 Cohort C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.

Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.

MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.

MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.

MK-3475 KN002 Database Cutoff Date: 28FEB2015.

MK-3475 KN006 Database Cutoff Date: 03MAR2015.

MK-3475 KN010 Database Cutoff Date: 30SEP2015.

MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl]

In cohort G1, a longer exposure to study regimen was registered in the pembrolizumab combination arm compared to chemotherapy alone, in terms of median number of months on therapy (8 versus 4.9 months) and median number of administrations (12 versus 8 doses). In addition, the number of subjects receiving the pembrolizumab combination was greater than that treated with chemotherapy at each time interval (≥1, ≥3, ≥6, and ≥12 months).

Table: Exposure by Duration
Cohort G1
(ASaT Population)

Duration of Exposure	Pembro 200mg Combo (N=59)		Control (N=62)	
	n	Person-years	n	Person-years
> 0 m	59	39.4	62	28.6
≥ 1 m	55	39.2	51	28.2
≥ 3 m	51	38.6	41	26.4
≥ 6 m	40	34.5	26	20.8
≥ 12 m	11	12.8	6	6.9

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4375 (months).
For subjects who crossed over to pembrolizumab, doses administrated after crossover are excluded.
Database Cutoff Date: 08AUG2016.

Source: [P021V01MK3475: analysis-adsl] [P021V01MK3475: tabulations-explus]

A summary of drug administration by dose regimen is shown in the Table below:

Table: Summary of Drug Administration by Dose Regimen
Cohort G1
(ASaT Population)

Number of Administrations	Pembro 200mg Combo (N = 59)			Control (N = 62)	
	Pembrolizumab n (%)	Pemetrexed n (%)	Carboplatin n (%)	Pemetrexed n (%)	Carboplatin n (%)
1	1 (1.69)	1 (1.69)	1 (1.69)	3 (4.84)	3 (4.84)
2	4 (6.78)	4 (6.78)	4 (6.78)	8 (12.90)	11 (17.74)
3	1 (1.69)	1 (1.69)	2 (3.39)	2 (3.23)	4 (6.45)
4	0 (0.00)	3 (5.08)	52 (88.14)	7 (11.29)	44 (70.97)
>=5	53 (89.83)	50 (84.75)	0 (0.00)	42 (67.74)	0 (0.00)
Mean	11.9	11.1	3.8	8.6	3.4
SD	5.9	6.1	0.6	5.9	1.0
Median	12.0	11.0	4.0	8.0	4.0
Range	1 to 24	1 to 24	1 to 4	1 to 23	1 to 4

For subjects who crossed over to pembrolizumab, doses administered after crossover are excluded.
Database Cutoff Date: 08AUG2016.

Source: [P021V01MK3475: analysis-adsl; adex]

In Cohort C, the median number of months on therapy was 9 (range: 0-27) and the median number of doses was 12.5 (range: 1-33). Duration of exposure was ≥6 months for 15 of 24 subjects (62.5%). The number of administration by dose regimen was similar to what observed in Cohort G1, with on average patients completing 3.8 cycles (SD 0.7) of carboplatin, 9.1 cycles (SD 7.4) of pemetrexed, and 13.8 cycles (SD 9.8) of pembrolizumab.

CHMP comment

The addition of pembrolizumab does not seem to compromise the standard chemotherapy program. On the contrary, more patients treated with pembro-chemo combination received the planned 4 cycles of carboplatin (88% vs 71%) and a higher rate received pemetrexed as maintenance (84.7% vs 67.7%) and for longer (median administration 11 vs 8 doses).

Adverse events

The safety profile of pembrolizumab combined with pemetrexed and carboplatin has been evaluated during the treatment period up to the cutoff of 31 May 2017 for both Cohorts C and G1. The median follow-up for subjects in Cohort G1 was 18.7 months (range 0.8-29.0), with a minimum of 16months from last patient randomized until data cutoff. The median follow-up for the 24 subjects enrolled in Cohort C was 17.4 months. Adverse events, occurred from the first dose up to 30 days after the last dose of study drug, were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Table: Adverse Event Summary
KN021 (Cohorts C and G1) and
Monotherapy Reference Dataset (KN001, KN002, KN006, KN010)
(ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	61	(98.4)	83	(100.0)	2,727	(97.4)
with no adverse event	1	(1.6)	0	(0.0)	72	(2.6)
with drug-related† adverse events	56	(90.3)	79	(95.2)	2,062	(73.7)
with toxicity grade 3-5 adverse events	32	(51.6)	48	(57.8)	1,273	(45.5)
with toxicity grade 3-5 drug-related adverse events	16	(25.8)	33	(39.8)	386	(13.8)
with serious adverse events	17	(27.4)	36	(43.4)	1,041	(37.2)
with serious drug-related adverse events	6	(9.7)	22	(26.5)	281	(10.0)
who died	2	(3.2)	3	(3.6)	110	(3.9)
who died due to a drug-related adverse event	2	(3.2)	1	(1.2)	10	(0.4)
discontinued‡ due to an adverse event	8	(12.9)	14	(16.9)	334	(11.9)
discontinued due to a drug-related adverse event	8	(12.9)	11	(13.3)	146	(5.2)
discontinued due to a serious adverse event	3	(4.8)	9	(10.8)	253	(9.0)
discontinued due to a serious drug-related adverse event	3	(4.8)	6	(7.2)	101	(3.6)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
KN021 Cohort C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
MedDRA version used is 19.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

Adverse Event Summary
Cohort G1 Subjects
(ASaT Population)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	59	(100.0)	61	(98.4)
with no adverse event	0	(0.0)	1	(1.6)
with drug-related† adverse events	55	(93.2)	57	(91.9)
with toxicity grade 3-5 adverse events	35	(59.3)	34	(54.8)
with toxicity grade 3-5 drug-related adverse events	24	(40.7)	18	(29.0)
with serious adverse events	29	(49.2)	20	(32.3)
with serious drug-related adverse events	16	(27.1)	7	(11.3)
who died	1	(1.7)	2	(3.2)
who died due to a drug-related adverse event	1	(1.7)	2	(3.2)
discontinued‡ due to an adverse event	10	(16.9)	9	(14.5)
discontinued due to a drug-related adverse event	9	(15.3)	9	(14.5)
discontinued due to a serious adverse event	7	(11.9)	3	(4.8)
discontinued due to a serious drug-related adverse event	6	(10.2)	3	(4.8)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Adverse Event Summary
Cohort C Subjects
(ASaT Population)

	Pembro 10mg/kg Combo		Pembro 2mg/kg Combo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	12		12		24	
with one or more adverse events	12	(100.0)	12	(100.0)	24	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	12	(100.0)	12	(100.0)	24	(100.0)
with toxicity grade 3-5 adverse events	9	(75.0)	7	(58.3)	16	(66.7)
with toxicity grade 3-5 drug-related adverse events	7	(58.3)	4	(33.3)	11	(45.8)
with serious adverse events	7	(58.3)	6	(50.0)	13	(54.2)
with serious drug-related adverse events	3	(25.0)	4	(33.3)	7	(29.2)
who died	2	(16.7)	0	(0.0)	2	(8.3)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	3	(25.0)	4	(33.3)	7	(29.2)
discontinued due to a drug-related adverse event	3	(25.0)	3	(25.0)	6	(25.0)
discontinued due to a serious adverse event	1	(8.3)	2	(16.7)	3	(12.5)
discontinued due to a serious drug-related adverse event	1	(8.3)	1	(8.3)	2	(8.3)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

For every SOC, except *Blood and Lymphatic System Disorders*, more AEs were reported in the pembro-chemo combination compared to chemotherapy alone. The SOCs with the largest between groups differences were *Skin and subcutaneous tissue disorders* (69% vs 42%), *Infections and infestations* (62.7% vs 37.1%), *Eye disorders* (45.8% vs 25.8%), *Nervous system disorders* (70% vs 50%), *Metabolism and nutrition disorders* (64% vs 47%), *General disorders and administration site conditions* (84.3% vs 67.7%), and *Respiratory, thoracic, and mediastinal disorders* (72.3% vs 56.5%). A similar pattern with smaller differences was seen with other SOCs.

The frequency of the most common AEs, with the exception of anaemia, was generally higher in the pembrolizumab combination arm. The comparison between treatment in AEs sorted by risk difference (Cohort G1) is displayed in the following Figure:

Figure: Between-Treatment Comparison in AEs
Selected AEs (≥15% incidence) and sorted by Risk Difference
KN021 Cohort G1
(ASaT Population)
Pembro 200mg Combo (N=59) vs Control (N=62)

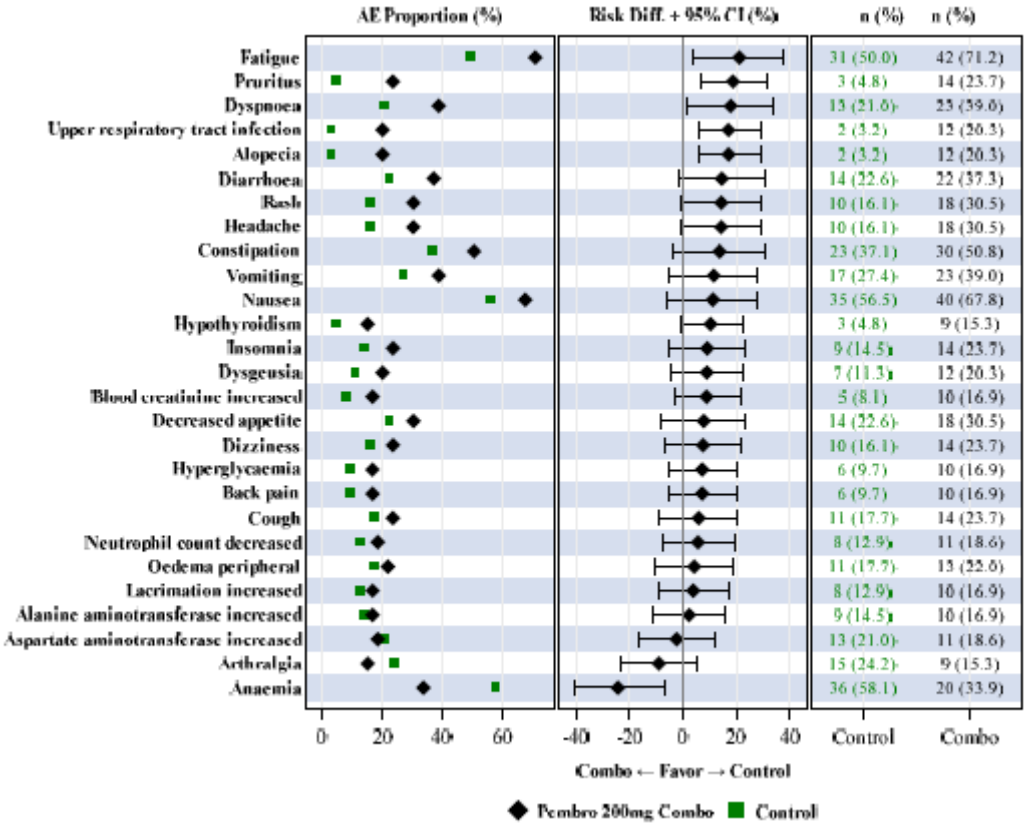


Table: Subjects with AEs (Incidence ≥10% in One or More Treatment Groups) KN021 (Cohorts C and G1) and monotherapy Reference Dataset (KN001, KN002, KN006, KN010) Adverse Events with at Least One Incidence in KN021 (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	61	(98.4)	83	(100.0)	2,692	(96.2)
with no adverse events	1	(1.6)	0	(0.0)	107	(3.8)
Fatigue	31	(50.0)	59	(71.1)	1,044	(37.3)
Nausea	35	(56.5)	52	(62.7)	685	(24.5)
Constipation	23	(37.1)	45	(54.2)	498	(17.8)
Anaemia	36	(58.1)	31	(37.3)	347	(12.4)
Diarrhoea	14	(22.6)	30	(36.1)	625	(22.3)
Dyspnoea	13	(21.0)	29	(34.9)	534	(19.1)
Decreased appetite	14	(22.6)	27	(32.5)	630	(22.5)
Rash	10	(16.1)	25	(30.1)	499	(17.8)
Vomiting	17	(27.4)	25	(30.1)	387	(13.8)
Headache	10	(16.1)	23	(27.7)	400	(14.3)
Cough	11	(17.7)	22	(26.5)	615	(22.0)
Dizziness	10	(16.1)	21	(25.3)	244	(8.7)
Pruritus	3	(4.8)	21	(25.3)	562	(20.1)
Oedema peripheral	11	(17.7)	19	(22.9)	285	(10.2)
Alanine aminotransferase increased	9	(14.5)	18	(21.7)	172	(6.1)
Upper respiratory tract infection	2	(3.2)	18	(21.7)	182	(6.5)
Aspartate aminotransferase increased	13	(21.0)	17	(20.5)	168	(6.0)
Arthralgia	15	(24.2)	16	(19.3)	504	(18.0)
Insomnia	9	(14.5)	16	(19.3)	219	(7.8)
Back pain	6	(9.7)	15	(18.1)	349	(12.5)
Blood creatinine increased	5	(8.1)	15	(18.1)	108	(3.9)
Alopecia	2	(3.2)	14	(16.9)	52	(1.9)
Dysgeusia	7	(11.3)	14	(16.9)	70	(2.5)
Neuropathy peripheral	3	(4.8)	14	(16.9)	76	(2.7)
Lacrimation increased	8	(12.9)	13	(15.7)	21	(0.8)
Pain in extremity	2	(3.2)	13	(15.7)	237	(8.5)
Hypothyroidism	3	(4.8)	12	(14.5)	236	(8.4)
Rash maculo-papular	2	(3.2)	12	(14.5)	100	(3.6)
Rhinorrhoea	3	(4.8)	12	(14.5)	53	(1.9)
Anxiety	2	(3.2)	11	(13.3)	142	(5.1)
Dehydration	4	(6.5)	11	(13.3)	106	(3.8)
Dry eye	1	(1.6)	11	(13.3)	49	(1.8)
Hyperglycaemia	6	(9.7)	11	(13.3)	130	(4.6)
Neutrophil count decreased	8	(12.9)	11	(13.3)	21	(0.8)
Urinary tract infection	2	(3.2)	11	(13.3)	162	(5.8)
Abdominal pain	2	(3.2)	10	(12.0)	274	(9.8)
Hypertension	3	(4.8)	10	(12.0)	106	(3.8)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Hypokalaemia	7	(11.3)	10	(12.0)	124	(4.4)
Dry skin	4	(6.5)	9	(10.8)	165	(5.9)
Pyrexia	3	(4.8)	9	(10.8)	357	(12.8)
Weight decreased	8	(12.9)	9	(10.8)	219	(7.8)
Neutropenia	8	(12.9)	8	(9.6)	17	(0.6)
White blood cell count decreased	8	(12.9)	7	(8.4)	28	(1.0)
Depression	7	(11.3)	5	(6.0)	102	(3.6)
Platelet count decreased	8	(12.9)	3	(3.6)	29	(1.0)
Asthenia	4	(6.5)	2	(2.4)	362	(12.9)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

At an analysis adjusted for exposure to study medication in Cohort G1, a smaller difference in the event rates by PT or by SOC was observed between groups compared to unadjusted AE rates. In both treatment arms, the majority of AEs occurred in the first 3 months, the period during which carboplatin was administered.

CHMP comment

The higher and longer exposure to chemotherapy achieved in patients treated with the pembro-chemo combination could account for the not negligible increase in the rates of AEs reported compared to chemotherapy alone, as shown by the reduced difference among groups at the analysis adjusted for exposure to study medication.

Grade ≥3 Adverse Events

In patients treated with pembrolizumab/chemotherapy combination, Grade ≥3 AEs, except for anemia, were reported at a frequency lower than 5%. The most common Grade≥ 3 AEs were anemia (13.3%), cellulitis (4.8%), dehydration (4.8%), decreased neutrophil count (4.8%), and pneumonia (4.8%).

Table: Subjects with Grade 3-5 Adverse Events (incidence ≥1% in One or More Groups) KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) (APaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	32	(51.6)	48	(57.8)	1,273	(45.5)
with no adverse events	30	(48.4)	35	(42.2)	1,526	(54.5)
Blood and lymphatic system disorders	**12**	**(19.4)**	**14**	**(16.9)**	**123**	**(4.4)**
Anaemia	9	(14.5)	11	(13.3)	90	(3.2)
Leukopenia	0	(0.0)	1	(1.2)	4	(0.1)
Neutropenia	2	(3.2)	2	(2.4)	5	(0.2)
Pancytopenia	2	(3.2)	0	(0.0)	1	(0.0)
Thrombocytopenia	2	(3.2)	2	(2.4)	10	(0.4)

Cardiac disorders	**1**	**(1.6)**	**4**	**(4.8)**	**84**	**(3.0)**
Aortic valve disease	0	(0.0)	1	(1.2)	0	(0.0)
Myocardial infarction	0	(0.0)	2	(2.4)	5	(0.2)
Tachycardia	0	(0.0)	1	(1.2)	1	(0.0)
Gastrointestinal disorders	**5**	**(8.1)**	**5**	**(6.0)**	**231**	**(8.3)**
Autoimmune colitis	0	(0.0)	1	(1.2)	0	(0.0)
Colitis	0	(0.0)	1	(1.2)	32	(1.1)
Diarrhoea	1	(1.6)	3	(3.6)	36	(1.3)
Nausea	0	(0.0)	1	(1.2)	33	(1.2)
Vomiting	0	(0.0)	1	(1.2)	32	(1.1)
General disorders and administration site conditions	**1**	**(1.6)**	**4**	**(4.8)**	**213**	**(7.6)**
Asthenia	0	(0.0)	1	(1.2)	34	(1.2)
Fatigue	0	(0.0)	3	(3.6)	69	(2.5)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(1.2)**	**43**	**(1.5)**
Cholecystitis	0	(0.0)	1	(1.2)	5	(0.2)
Immune system disorders	**0**	**(0.0)**	**1**	**(1.2)**	**7**	**(0.3)**
Anaphylactic reaction	0	(0.0)	1	(1.2)	2	(0.1)
Infections and infestations	**3**	**(4.8)**	**14**	**(16.9)**	**220**	**(7.9)**
Cellulitis	0	(0.0)	4	(4.8)	14	(0.5)
Pneumonia	0	(0.0)	4	(4.8)	75	(2.7)
Sepsis	1	(1.6)	2	(2.4)	13	(0.5)
Urinary tract infection	0	(0.0)	2	(2.4)	14	(0.5)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**3**	**(3.6)**	**38**	**(1.4)**
Investigations	**8**	**(12.9)**	**9**	**(10.8)**	**130**	**(4.6)**
Alanine aminotransferase increased	1	(1.6)	3	(3.6)	25	(0.9)
Aspartate aminotransferase increased	1	(1.6)	3	(3.6)	24	(0.9)
Lymphocyte count decreased	1	(1.6)	3	(3.6)	12	(0.4)
Neutrophil count decreased	2	(3.2)	4	(4.8)	3	(0.1)
Platelet count decreased	2	(3.2)	2	(2.4)	3	(0.1)
White blood cell count decreased	1	(1.6)	2	(2.4)	2	(0.1)
Metabolism and nutrition disorders	**4**	**(6.5)**	**12**	**(14.5)**	**233**	**(8.3)**
Dehydration	1	(1.6)	4	(4.8)	28	(1.0)
Hyperglycaemia	1	(1.6)	1	(1.2)	29	(1.0)
Hyponatraemia	1	(1.6)	2	(2.4)	62	(2.2)
Hypophosphataemia	0	(0.0)	3	(3.6)	14	(0.5)
Musculoskeletal and connective tissue disorders	**5**	**(8.1)**	**2**	**(2.4)**	**126**	**(4.5)**
Arthralgia	1	(1.6)	0	(0.0)	17	(0.6)
Back pain	1	(1.6)	1	(1.2)	38	(1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(1.2)**	**79**	**(2.8)**
Nervous system disorders	**3**	**(4.8)**	**6**	**(7.2)**	**108**	**(3.9)**
Syncope	1	(1.6)	3	(3.6)	15	(0.5)
Psychiatric disorders	**0**	**(0.0)**	**2**	**(2.4)**	**27**	**(1.0)**
Renal and urinary disorders	**1**	**(1.6)**	**3**	**(3.6)**	**38**	**(1.4)**
Acute kidney injury	1	(1.6)	3	(3.6)	17	(0.6)
Respiratory, thoracic and mediastinal disorders	**4**	**(6.5)**	**11**	**(13.3)**	**244**	**(8.7)**
Chronic obstructive pulmonary disease	1	(1.6)	3	(3.6)	14	(0.5)
Dyspnoea	0	(0.0)	3	(3.6)	78	(2.8)
Pleural effusion	0	(0.0)	2	(2.4)	37	(1.3)
Pneumonitis	0	(0.0)	2	(2.4)	34	(1.2)
Pulmonary embolism	2	(3.2)	1	(1.2)	46	(1.6)
Skin and subcutaneous tissue disorders	**1**	**(1.6)**	**2**	**(2.4)**	**40**	**(1.4)**
Rash	0	(0.0)	2	(2.4)	9	(0.3)
Vascular disorders	**1**	**(1.6)**	**4**	**(4.8)**	**84**	**(3.0)**
Hypertension	1	(1.6)	3	(3.6)	32	(1.1)

Table made by the assessor from Table 5.3.5.3.3-nsclc:5 (ISS)

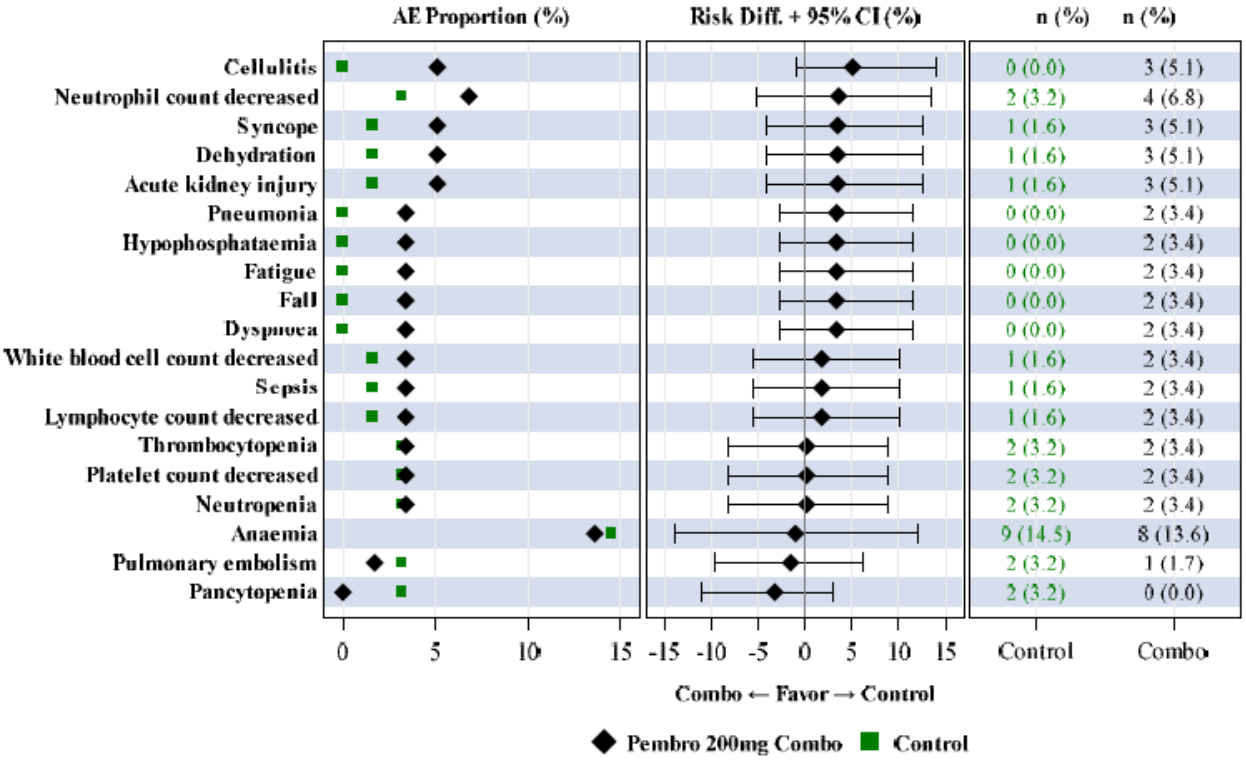
Every subject is counted a single time for each applicable specific AE. A subjects with multiple AEs within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
KN021 C+G1 Combo Pooled group includes all subjects who received at least one dose of pembrolizumab combination treatment in KN021 Cohort C and Cohort G1
Reference dataset includes includes all subjects who received at least one dose of pembrolizumab in KN001, KN002, KN006 and KN010.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MedDRA version used is 19.0.
Grades are based on NCI CTCAE version4.0

(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).
(KN021 Database Cutoff Date: 08 AUG2016).

The comparison between pembrolizumab combination and chemotherapy alone in Grade≥3 AEs in Cohort G1, sorted by risk difference is displayed in the following Figure:

Figure: Between-Treatment Comparison in Grade≥3 AEs
Selected AEs (≥2% incidence) and sorted by Risk Difference
(ASaT Population) Pembro 200mg Combo (N=59) vs Control (N=62)



Among subjects who reported a Grade ≥3 AE, the median time to onset was 57.5 days (range 3-347) in the pembrolizumab combination arm and 22.0 days (range 2-232) in the control arm.

In Cohort G1, when the incidence of Grade ≥3 AEs was adjusted for exposure to study medication, the difference between pembrolizumab combination and chemotherapy alone was generally smaller, and appeared to be driven by the difference in events per 100 person/months observed during the first 3 months of study treatment (53 out of 91 events with pembrolizumab combination, and 45 out of 63 events with chemotherapy).

Table: Exposure-Adjusted Grade≥ 3 AEs by Observation Period (Multiple Occurrences of Events); (Incidence > 0% in One or More Treatment Groups) Cohort G1 Subjects (ASaT Population) (Excerpt from Table 14.3-23)

Observation period of drug exposure	Event Count and Rate (Events/100 person-months)[†]							
	Pembro 200mg Combo				Control			
	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of Subjects exposed[‡]	59	53	42	15	62	49	31	9
Total exposure[§] person-months	167.49	145.74	172.81	29.60	166.67	116.83	96.43	16.16
Total events (rate)	53 (31.64)	15 (10.29)	21 (12.15)	2 (6.76)	45 (27.00)	11 (9.42)	5 (5.19)	2 (12.37)

CHMP comment

No major difference is observed overall in the rate of Grade ≥3 AEs between chemotherapy and pembrolizumab/chemotherapy combination (51.6% and 57.8%). The majority of the most common AEs (fatigue, nausea, constipation and diarrhea) were Grade 1-2 in severity. As expected, the safety profile of pembrolizumab in combination with chemotherapy was less favourable compared to pembrolizumab monotherapy due to the added contribution of pemetrexed/carboplatin in terms of Grade≥3 AEs. However, there are SOCs for which the rate of Grade≥3 AEs was markedly higher than that with chemotherapy alone, thus suggesting a major contribution due to the addition of pembrolizumab. This is the case of *Infections and Infestations* (16.9% vs 4.8%), *Metabolism and nutrition disorders* (14.5% vs 6.5%), *Respiratory, thoracic and mediastinal disorders* (13.3% vs 6.5%).

The Applicant argues that the prolonged exposure to chemotherapy may contribute to the higher frequency of specific Grade ⩾3 AEs observed in subjects in the pembro-chemo combination arm. Although this can be agreed on, higher Grade ⩾3 AEs event rates were reported for the pembro-chemo combination despite exposure adjustments. This is especially notable for the SOC Infections and infestations in which the exposure adjusted Grade≥3 AEs were 12 (2.3%) with the combination versus 3 (0.8%) in the control arm.

The conclusion of the MAH that the difference between pembrolizumab combination and chemotherapy in the exposure-adjusted analyses appeared to be driven by the difference in event rates during the first 3 months of study treatment cannot be followed, since the largest difference in exposure-adjusted grade ≥ 3 events between both treatment arms was observed between 6 and 12 months (pembro-chemo combination 21, chemotherapy control 5 events, see table above).

Drug-related Adverse Events

The overall incidence of drug-related AEs was 95.2% with pembrolizumab/chemotherapy combination and 90.3% with chemotherapy alone. With the exception of anaemia, the incidence of common drug-related AEs, was higher in the pembrolizumab/chemotherapy combination group compared to that observed in the chemotherapy alone.

Table: Subjects With Drug-Related Adverse Events (Incidence ⩾5% in One or More Treatment Groups) KN021 (Cohorts C and G1) and monotherapy Reference Dataset (KN001, KN002, KN006, KN010) - Adverse Events with at Least One Incidence in KN021 (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	56	(90.3)	79	(95.2)	2,005	(71.6)
with no adverse events	6	(9.7)	4	(4.8)	794	(28.4)
Fatigue	25	(40.3)	49	(59.0)	678	(24.2)
Nausea	27	(43.5)	40	(48.2)	304	(10.9)
Anaemia	33	(53.2)	27	(32.5)	94	(3.4)
Rash	9	(14.5)	21	(25.3)	386	(13.8)
Diarrhoea	7	(11.3)	18	(21.7)	343	(12.3)
Alanine aminotransferase increased	7	(11.3)	17	(20.5)	97	(3.5)
Aspartate aminotransferase increased	7	(11.3)	17	(20.5)	94	(3.4)
Vomiting	11	(17.7)	17	(20.5)	107	(3.8)
Constipation	6	(9.7)	15	(18.1)	90	(3.2)
Decreased appetite	11	(17.7)	15	(18.1)	255	(9.1)
Dysgeusia	6	(9.7)	11	(13.3)	45	(1.6)
Oedema peripheral	2	(3.2)	11	(13.3)	54	(1.9)
Pruritus	2	(3.2)	11	(13.3)	467	(16.7)
Alopecia	2	(3.2)	10	(12.0)	24	(0.9)
Neutrophil count decreased	8	(12.9)	10	(12.0)	15	(0.5)
Rash maculo-papular	2	(3.2)	10	(12.0)	76	(2.7)
Blood creatinine increased	4	(6.5)	9	(10.8)	35	(1.3)
Hypothyroidism	1	(1.6)	9	(10.8)	213	(7.6)
Lacrimation increased	6	(9.7)	9	(10.8)	9	(0.3)
Dizziness	4	(6.5)	8	(9.6)	46	(1.6)
Dry eye	1	(1.6)	7	(8.4)	31	(1.1)
Hypokalaemia	2	(3.2)	7	(8.4)	18	(0.6)
Cough	0	(0.0)	6	(7.2)	112	(4.0)
Dyspepsia	2	(3.2)	6	(7.2)	9	(0.3)
Lymphocyte count decreased	3	(4.8)	6	(7.2)	24	(0.9)
Neutropenia	5	(8.1)	6	(7.2)	8	(0.3)
Pain in extremity	0	(0.0)	6	(7.2)	44	(1.6)
Pyrexia	1	(1.6)	6	(7.2)	126	(4.5)
Rhinorrhoea	1	(1.6)	6	(7.2)	4	(0.1)
White blood cell count decreased	5	(8.1)	6	(7.2)	14	(0.5)
Dry mouth	3	(4.8)	5	(6.0)	77	(2.8)
Dry skin	2	(3.2)	5	(6.0)	90	(3.2)
Hypomagnesaemia	1	(1.6)	5	(6.0)	19	(0.7)
Mucosal inflammation	1	(1.6)	5	(6.0)	23	(0.8)
Stomatitis	3	(4.8)	5	(6.0)	33	(1.2)
Weight decreased	3	(4.8)	5	(6.0)	60	(2.1)
Arthralgia	3	(4.8)	4	(4.8)	281	(10.0)
Dyspnoea	4	(6.5)	3	(3.6)	109	(3.9)
Myalgia	0	(0.0)	3	(3.6)	146	(5.2)
Thrombocytopenia	4	(6.5)	3	(3.6)	23	(0.8)
Platelet count decreased	7	(11.3)	2	(2.4)	12	(0.4)
Asthenia	2	(3.2)	1	(1.2)	218	(7.8)

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

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

KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.

Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.

For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.

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

MedDRA version used is 19.0

MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.

MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.

MK-3475 KN002 Database Cutoff Date: 28FEB2015.

MK-3475 KN006 Database Cutoff Date: 03MAR2015.

MK-3475 KN010 Database Cutoff Date: 30SEP2015.

MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

The incidence of treatment interruption due to drug-related AEs was 31.3% for pembrolizumab/chemotherapy combination, 25.8% for chemotherapy alone, and 12.5% for pembrolizumab monotherapy in the reference safety dataset. The most common drug-related AEs leading to treatment interruption in the pembrolizumab combined group were fatigue (7.2%) and neutropenia (7.2%, including 5 subjects with neutrophil count decreased and 1 subject with neutropenia). In the chemotherapy alone control group, 5 patients (8.1%) interrupted treatment due to anemia and 6 patients (9.7%) due to neutropenia (3 subjects with neutrophil counts decreased and 3 subjects with neutropenia).

Drug-related Grade ≥3 Adverse Events

Table: Subjects With Drug-Related Grade ≥3 Adverse Events (Incidence ⩾1% in One or More Treatment Groups)
KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) - Adverse Events with at Least One Incidence in KN021 (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	16	(25.8)	33	(39.8)	248	(8.9)
with no adverse events	46	(74.2)	50	(60.2)	2,551	(91.1)
Anaemia	9	(14.5)	9	(10.8)	13	(0.5)
Alanine aminotransferase increased	1	(1.6)	3	(3.6)	14	(0.5)
Aspartate aminotransferase increased	1	(1.6)	3	(3.6)	11	(0.4)
Lymphocyte count decreased	1	(1.6)	3	(3.6)	4	(0.1)
Neutrophil count decreased	2	(3.2)	3	(3.6)	2	(0.1)
Acute kidney injury	0	(0.0)	2	(2.4)	3	(0.1)
Cellulitis	0	(0.0)	2	(2.4)	0	(0.0)
Diarrhoea	1	(1.6)	2	(2.4)	25	(0.9)
Fatigue	0	(0.0)	2	(2.4)	30	(1.1)
Neutropenia	1	(1.6)	2	(2.4)	3	(0.1)
Rash	0	(0.0)	2	(2.4)	6	(0.2)
Sepsis	1	(1.6)	2	(2.4)	0	(0.0)
Thrombocytopenia	2	(3.2)	2	(2.4)	3	(0.1)
Anaphylactic reaction	0	(0.0)	1	(1.2)	1	(0.0)
Atrial fibrillation	0	(0.0)	1	(1.2)	1	(0.0)
Autoimmune colitis	0	(0.0)	1	(1.2)	0	(0.0)
Colitis	0	(0.0)	1	(1.2)	27	(1.0)
Decreased appetite	0	(0.0)	1	(1.2)	8	(0.3)
Dehydration	1	(1.6)	1	(1.2)	3	(0.1)
Febrile neutropenia	0	(0.0)	1	(1.2)	0	(0.0)
Hypocalcaemia	0	(0.0)	1	(1.2)	0	(0.0)
Hypokalaemia	0	(0.0)	1	(1.2)	7	(0.3)
Hyponatraemia	0	(0.0)	1	(1.2)	11	(0.4)
Leukopenia	0	(0.0)	1	(1.2)	3	(0.1)
Myocardial infarction	0	(0.0)	1	(1.2)	1	(0.0)
Nausea	0	(0.0)	1	(1.2)	10	(0.4)
Platelet count decreased	1	(1.6)	1	(1.2)	1	(0.0)
Pneumonia	0	(0.0)	1	(1.2)	8	(0.3)
Pneumonitis	0	(0.0)	1	(1.2)	32	(1.1)
Pyelonephritis acute	0	(0.0)	1	(1.2)	0	(0.0)
Transaminases increased	0	(0.0)	1	(1.2)	2	(0.1)
Vomiting	0	(0.0)	1	(1.2)	9	(0.3)
White blood cell count decreased	1	(1.6)	1	(1.2)	0	(0.0)
Pancytopenia	2	(3.2)	0	(0.0)	1	(0.0)
Rash macular	1	(1.6)	0	(0.0)	0	(0.0)
Stomatitis	1	(1.6)	0	(0.0)	1	(0.0)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

CHMP comment

Overall, drug-related AEs and drug-related Grade≥3 AEs were most frequent in patients treated with pembrolizumab combined with chemotherapy compared to those who received chemotherapy alone or pembrolizumab monotherapy in the Reference dataset. The safety profile in the chemotherapy alone group was as expected, with *Anaemia* (53.2%), *Nausea* (43.5%), *Fatigue* (40.3%), and *Vomiting* (17.7%) as the most common drug-related AEs. A notably higher rate of *Hypothyroidism* was reported with pembro-chemo combination compared to chemotherapy alone (10.8% vs 1.6%).

Although the higher rate of drug-related AEs, the type of the most common events reported with the combined regimen was consistent with the known safety profile of any single agent individually. No new safety issues were identified with the addition of pembrolizumab to pemetrexed/carboplatin regimen.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs), occurred from the first dose up to 90 days after the last dose of study drug, were reported.

Table: Subjects With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ⩾1% in One or More Treatment Groups) KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) Adverse Events with at Least One Incidence in KN021 (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	17	(27.4)	36	(43.4)	1,041	(37.2)
with no adverse events	45	(72.6)	47	(56.6)	1,758	(62.8)
Blood and lymphatic system disorders	**5**	**(8.1)**	**5**	**(6.0)**	**52**	**(1.9)**
Anaemia	1	(1.6)	3	(3.6)	31	(1.1)
Febrile neutropenia	1	(1.6)	1	(1.2)	2	(0.1)
Neutropenia	1	(1.6)	0	(0.0)	1	(0.0)
Pancytopenia	2	(3.2)	0	(0.0)	1	(0.0)
Thrombocytopenia	1	(1.6)	1	(1.2)	5	(0.2)
Cardiac disorders	**2**	**(3.2)**	**4**	**(4.8)**	**90**	**(3.2)**
Aortic valve disease	0	(0.0)	1	(1.2)	0	(0.0)
Atrial fibrillation	1	(1.6)	1	(1.2)	13	(0.5)
Cardiac ventricular thrombosis	1	(1.6)	0	(0.0)	0	(0.0)
Myocardial infarction	0	(0.0)	2	(2.4)	5	(0.2)
Tachycardia	0	(0.0)	1	(1.2)	2	(0.1)
Gastrointestinal disorders	**7**	**(11.3)**	**4**	**(4.8)**	**184**	**(6.6)**
Abdominal pain	0	(0.0)	1	(1.2)	22	(0.8)
Autoimmune colitis	0	(0.0)	1	(1.2)	0	(0.0)
Colitis	0	(0.0)	1	(1.2)	31	(1.1)
Diarrhoea	1	(1.6)	0	(0.0)	26	(0.9)
Diverticular perforation	1	(1.6)	0	(0.0)	0	(0.0)
Dysphagia	1	(1.6)	0	(0.0)	5	(0.2)
Haematochezia	1	(1.6)	0	(0.0)	6	(0.2)
Nausea	2	(3.2)	1	(1.2)	18	(0.6)
Small intestinal obstruction	2	(3.2)	0	(0.0)	6	(0.2)
Vomiting	0	(0.0)	1	(1.2)	18	(0.6)
General disorders and administration site conditions	**1**	**(1.6)**	**6**	**(7.2)**	**133**	**(4.8)**
Asthenia	0	(0.0)	1	(1.2)	12	(0.4)
Death	0	(0.0)	1	(1.2)	17	(0.6)
Fatigue	0	(0.0)	2	(2.4)	12	(0.4)
Non-cardiac chest pain	0	(0.0)	1	(1.2)	2	(0.1)
Pyrexia	1	(1.6)	2	(2.4)	35	(1.3)
Immune system disorders	**0**	**(0.0)**	**1**	**(1.2)**	**6**	**(0.2)**
Anaphylactic reaction	0	(0.0)	1	(1.2)	1	(0.0)
Infections and infestations	**3**	**(4.8)**	**12**	**(14.5)**	**233**	**(8.3)**

Cellulitis	0	(0.0)	4	(4.8)	15	(0.5)
Diverticulitis	1	(1.6)	0	(0.0)	3	(0.1)
Periorbital cellulitis	1	(1.6)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	4	(4.8)	85	(3.0)
Pyelonephritis acute	0	(0.0)	1	(1.2)	1	(0.0)
Sepsis	1	(1.6)	2	(2.4)	14	(0.5)
Upper respiratory tract infection	0	(0.0)	1	(1.2)	2	(0.1)
Urinary tract infection	0	(0.0)	2	(2.4)	14	(0.5)
Urosepsis	0	(0.0)	1	(1.2)	2	(0.1)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**1**	**(1.2)**	**39**	**(1.4)**
Investigations	**0**	**(0.0)**	**1**	**(1.2)**	**24**	**(0.9)**
Transaminase increased	0	(0.0)	1	(1.2)	0	(0.0)
Metabolism and nutrition disorders	**1**	**(1.6)**	**3**	**(3.6)**	**99**	**(3.5)**
Dehydration	1	(1.6)	3	(3.6)	24	(0.9)
Musculoskeletal and connective tissue disorders	**3**	**(4.8)**	**1**	**(1.2)**	**75**	**(2.7)**
Back pain	1	(1.6)	0	(0.0)	15	(0.5)
Flank pain	1	(1.6)	0	(0.0)	2	(0.1)
Musculoskeletal pain	1	(1.6)	0	(0.0)	8	(0.3)
Neck pain	0	(0.0)	1	(1.2)	3	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(1.2)**	**96**	**(3.4)**
Malignant pleural effusion	0	(0.0)	1	(1.2)	4	(0.1)
Nervous system disorders	**2**	**(3.2)**	**3**	**(3.6)**	**106**	**(3.8)**
Cerebrovascular accident	1	(1.6)	0	(0.0)	10	(0.4)
Cerebrovascular disorder	0	(0.0)	1	(1.2)	0	(0.0)
Encephalopaty	0	(0.0)	1	(1.2)	2	(0.1)
Haemorrhage intracranial	0	(0.0)	1	(1.2)	4	(0.1)
Syncope	1	(1.60)	0	(0.0)	10	(0.4)
Psychiatric disorders	**0**	**(0.0)**	**2**	**(2.4)**	**27**	**(1.0)**
Depression	0	(0.0)	1	(1.2)	1	(0.0)
Mental status changes	0	(0.0)	1	(1.2)	3	(0.1)
Renal and urinary disorders	**1**	**(1.6)**	**4**	**(4.8)**	**54**	**(1.9)**
Acute kidney injury	1	(1.6)	4	(4.8)	22	(0.8)
Respiratory, thoracic and mediastinal disorders	**3**	**(4.8)**	**11**	**(13.3)**	**247**	**(8.8)**
Acute respiratory failure	0	(0.0)	1	(1.2)	7	(0.3)
Chronic obstructive pulmonary disease	1	(1.6)	2	(2.4)	16	(0.6)
Dyspnoea	0	(0.0)	2	(2.4)	45	(1.6)
Pleural effusion	0	(0.0)	2	(2.4)	48	(1.7)
Pneumonitis	0	(0.0)	2	(2.4)	46	(1.6)
Pulmonary embolism	1	(1.6)	1	(1.2)	41	(1.5)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**2**	**(2.4)**	**19**	**(0.7)**
Rash	0	(0.0)	2	(2.4)	6	(0.2)
Vascular disorders	**0**	**(0.0)**	**1**	**(1.2)**	**53**	**(1.9)**
Embolism	0	(0.0)	1	(1.2)	9	(0.3)

Table made by the assessor from Table 5.3.5.3.3-nsclc:10 (ISS)

Every subject is counted a single time for each applicable specific AE. A subjects with multiple AEs within a system organ class is counted a single time for that system organ class.

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

KN021 C+G1 Combo Pooled group includes all subjects who received at least one dose of pembrolizumab combination treatment in KN021 Cohort C and Cohort G1

Reference dataset includes includes all subjects who received at least one dose of pembrolizumab in KN001, KN002, KN006 and KN010.

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

MedDRA version used is 19.0.

Grades are based on NCI CTCAE version4.0

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

(KN021 Database Cutoff Date: 08 AUG2016).

Drug-related Serious Adverse Events

More subjects in the pembrolizumab/chemotharpy combination group reported drug-related SAEs compared to the chemotherapy alone control group (26.5% vs 9.7%).

Table: Subjects With Drug-Related Serious Adverse Events Up to 90 Days of Last Dose (Incidence ⩾1% in One or More Treatment Groups)
KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010)
Adverse Events with at Least One Incidence in KN021
(ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	6	(9.7)	22	(26.5)	196	(7.0)
with no adverse events	56	(90.3)	61	(73.5)	2,603	(93.0)
Acute kidney injury	0	(0.0)	2	(2.4)	5	(0.2)
Cellulitis	0	(0.0)	2	(2.4)	0	(0.0)
Fatigue	0	(0.0)	2	(2.4)	3	(0.1)
Pyrexia	0	(0.0)	2	(2.4)	10	(0.4)
Rash	0	(0.0)	2	(2.4)	2	(0.1)
Sepsis	1	(1.6)	2	(2.4)	0	(0.0)
Anaemia	1	(1.6)	1	(1.2)	4	(0.1)
Anaphylactic reaction	0	(0.0)	1	(1.2)	1	(0.0)
Atrial fibrillation	0	(0.0)	1	(1.2)	0	(0.0)
Autoimmune colitis	0	(0.0)	1	(1.2)	0	(0.0)
Colitis	0	(0.0)	1	(1.2)	25	(0.9)
Dehydration	1	(1.6)	1	(1.2)	3	(0.1)
Febrile neutropenia	0	(0.0)	1	(1.2)	0	(0.0)
Myocardial infarction	0	(0.0)	1	(1.2)	1	(0.0)
Nausea	2	(3.2)	1	(1.2)	6	(0.2)
Pneumonia	0	(0.0)	1	(1.2)	8	(0.3)
Pneumonitis	0	(0.0)	1	(1.2)	44	(1.6)
Pyelonephritis acute	0	(0.0)	1	(1.2)	0	(0.0)
Thrombocytopenia	1	(1.6)	1	(1.2)	2	(0.1)
Transaminases increased	0	(0.0)	1	(1.2)	0	(0.0)
Vomiting	0	(0.0)	1	(1.2)	5	(0.2)
Diarrhoea	1	(1.6)	0	(0.0)	17	(0.6)
Pancytopenia	2	(3.2)	0	(0.0)	1	(0.0)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
MedDRA version used is 19.0
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

CHMP comment

Drug-related SAEs were much more frequent in the combination arm compared to chemotherapy alone (26.5% vs 9.7%). In the pembrolizumab combination group, SAEs were mostly in the SOCs *Infections and Infestations* (14.5%), and *Respiratory, thoracic and mediastinal disorders* (13.3%), while the most common SAEs reported with chemotherapy alone were in the SOC *Gastrointestinal disorders* (11.3%).

However, the incidence of specific PTs considered drug-related to pembro-chemo combination was low, with the most common events (i.e *Acute kidney injury*, *Cellulitis*, *Fatigue*, *Pyrexia*, Rash, and *Sepsis*) registered in no more than 2 patients (2.4%).

Deaths

Overall, in NSCLC patients treated with pembrolizumab/chemotherapy combination, 3 deaths (3.6%) due to an AE (2 in Cohort C: due to unknown cause or pneumonitis; 1 in Cohort G1: due to sepsis) were registered.

A subject (Cohort G1) received the last dose of carboplatin on Cycle 4, Day 62, and the last dose of pembrolizumab and pemetrexed on Cycle 5, Day 83. On Day 91 the subject experienced sepsis , and was hospitalized and treated with antibiotics on Day 92. On Day 94 the subject developed worsening hypoxemic respiratory failure, worsening shock, and multi-organ failure. After discussion with the family, the subject was transitioned to comfort measures and died on Day 99. No autopsy was performed. This case was considered drug-related by the Investigator.

A subject (Cohort C) received 4 cycles of carboplatin and 7 cycles each of pemetrexed and pembrolizumab. On Day 140, the subject experienced increased dyspnea on exertion and weakness requiring oxygen and was hospitalized and treated for a diagnosis of acute respiratory failure (Grade 4) due to a possible lung infection versus interstitial lung disease versus exacerbation of chronic obstructive pulmonary disease (Grade 3). On Day 146, a chest X-ray indicated decreased interstitial prominence and the subject was discharged from hospital on a prednisone taper. The event of acute respiratory failure (Grade 4) was considered resolved and chronic obstructive pulmonary disease (Grade 3) was ongoing. The Investigator considered the acute respiratory failure (Grade 4) to be not related to study medication. On Day 169, a CT-scan showed progression of disease and the subject discontinued from the study. On Day 198, the subject died due to unknown cause. No autopsy was performed.

A subject (Cohort C) received 4 cycles of carboplatin and 8 cycles each of pemetrexed and pembrolizumab. Dose of pembrolizumab was delayed for cycles 3,5, 7 and 8 (dyspnea) and cycles 7 and 8 (AST increased), and on an unspecified day dose frequency was changed from Q3W to Q4W. On Day 264, study treatment was interrupted in response to ongoing tachycardia (Grade 1), and on Day 299, the subject was discontinued from study treatment due to malignant neoplasm disease progression and continued as a participant in Survival Follow-up. On Day 316, the subject was admitted to the hospital with a diagnosis of pneumonitis based on clinical assessment with unknown etiology and discharged on Day 325 continuing treatment with oral steroids. At discharge, the patients had not fully recovered from pneumonitis and tachycardia, and the events continued until the subject' s death on Day 348. After the data cutoff date, the Investigator changed the event term of "pneumonitis" to "malignant neoplasm progression".

None of the fatal cases occurred in patients treated with pembrolizumab in combination with pemetrexed/carboplatin was deemed related to study medication, but sepsis was considered by the Investigator to be related to pemetrexed.

Two (3.2%) deaths due to an AE (1 sepsis and 1 pancytopenia), both considered drug-related by the Investigator, were registered in the chemotherapy control arm of KN021 study Cohort G1.

CHMP comment

A similar rate of fatal cases due to AE was registered in patients treated with chemotherapy compared to those who received pembrolizumab added to chemotherapy (3.6% vs 3.2%). One drug-related fatal case (*Sepsis*) was reported with the pembro-chemo combination.

Adverse Events of Special Interest (AEOSI)

The AEOSI, including immune-mediated AEs and infusion-related reactions considered to be identified or potential risk for pembrolizumab, are characterized in an ongoing manner as part of the pembrolizumab development program. A pre-specified list of PTs was developed for assessing AEOSI and the current list, including 17 AEOSI categories, applied to this dataset is shown in the Table below:

Table: Adverse Events of Special Interest Preferred Terms (Version 10.2 RMST 02-May-2016)

Important Identified Risks
Pneumonitis Acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and idiopathic pneumonia syndrome
Colitis Colitis, colitis microscopic, enterocolitis, enterocolitis haemorrhagic, necrotising colitis, colitis erosive
Hepatitis Hepatitis, Autoimmune hepatitis, hepatitis acute, hepatitis fulminant, drug-induced liver injury
Nephritis Nephritis, autoimmune nephritis, chronic autoimmune glomerulonephritis, fibrillary glomerulonephritis, focal segmental glomerulosclerosis, glomerulonephritis, glomerulonephritis acute, glomerulonephritis membranoproliferative, glomerulonephritis membranous, glomerulonephritis minimal lesion, glomerulonephritis proliferative, glomerulonephritis rapidly progressive, mesangioproliferative glomerulonephritis, nephritis haemorrhagic, tubulointerstitial nephritis, nephrotic syndrome
Adrenal Insufficiency Adrenal insufficiency, adrenocortical insufficiency acute, secondary adrenocortical insufficiency
Hypophysitis Hypophysitis, hypopituitarism, lymphocytic hypophysitis
Hyperthyroidism Hyperthyroidism, Basedow's disease, thyrotoxic crisis
Hypothyroidism Hypothyroidism, hypothyroidic goitre, myxoedema, myxoedema coma, primary hypothyroidism
Thyroiditis Thyroid disorder, thyroiditis, autoimmune thyroiditis, thyroiditis acute
Type 1 Diabetes Mellitus Diabetic ketoacidosis, diabetic ketoacidotic hyperglycaemic coma, fulminant type 1 diabetes mellitus, latent autoimmune diabetes in adults, type 1 diabetes mellitus

Other Immune-mediated Events
Uveitis Iritis, uveitis, cyclitis, autoimmune uveitis, iridocyclitis
Pancreatitis Pancreatitis, autoimmune pancreatitis, pancreatitis acute, pancreatitis haemorrhagic, pancreatitis necrotising
Myositis Myositis, necrotising myositis, polymyositis, immune-mediated necrotising myopathy, rhabdomyolysis, myopathy
Guillain-Barre Syndrome Demyelinating polyneuropathy, Guillain-Barre syndrome, axonal neuropathy, multifocal motor neuropathy, polyneuropathy idiopathic progressive, Miller Fisher syndrome
Severe Skin Reactions *Any grade from Severe cutaneous reactions SMQ narrow*: Acute generalised exanthematous pustulosis, cutaneous vasculitis, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, drug reaction with eosinophilia and systemic symptoms, epidermal necrosis, erythema multiforme, exfoliative rash, oculomucocutaneous syndrome, skin necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis and toxic skin eruption *If >Grade 3:* Any event from the epidermal and dermal conditions HLGT of the skin and subcutaneous tissue disorders system organ classes
Infusion Reactions Hypersensitivity, drug hypersensitivity, anaphylactic reaction, cytokine release syndrome, serum sickness, serum sickness-like reaction, infusion related reaction
Important Potential Risks
Myasthenic Syndrome Myasthenic syndrome, myasthenia gravis, myasthenia gravis crisis, ocular myasthenia

AEOSI = adverse events of special interest; HLGT = high level group terms; MedDRA = Medical Dictionary of Regulatory Activities; RMST = Risk Management Safety Team; SMQ = standardized MedDRA query.

The incidence of AEOSI including all risk categories, both identified and potential, among patients treated with pembrolizumab in combination with chemotherapy is reported below in comparison with chemotherapy alone control arm in KN021 and pembrolizumab monotherapy in reference safety dataset:

Table: Adverse Event Summary KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) AEOSI Including All Risk Categories (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	7	(11.3)	23	(27.7)	598	(21.4)
with no adverse event	55	(88.7)	60	(72.3)	2,201	(78.6)
with drug-related† adverse events	4	(6.5)	16	(19.3)	509	(18.2)
with toxicity grade 3-5 adverse events	1	(1.6)	5	(6.0)	159	(5.7)
with toxicity grade 3-5 drug-related adverse events	1	(1.6)	4	(4.8)	129	(4.6)
with serious adverse events	0	(0.0)	5	(6.0)	159	(5.7)
with serious drug-related adverse events	0	(0.0)	4	(4.8)	135	(4.8)
who died	0	(0.0)	1	(1.2)	4	(0.1)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	4	(0.1)
discontinued‡ due to an adverse event	1	(1.6)	4	(4.8)	83	(3.0)
discontinued due to a drug-related adverse event	1	(1.6)	3	(3.6)	81	(2.9)
discontinued due to a serious adverse event	0	(0.0)	3	(3.6)	64	(2.3)
discontinued due to a serious drug-related adverse event	0	(0.0)	2	(2.4)	63	(2.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
KN021 Cohort C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
MedDRA version used is 19.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aephis]

Table: Subjects with Important Identified AEOSI KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) AEOSI Including All Risk Categories (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	7	(11.3)	23	(27.7)	596	(21.3)
with no adverse events	55	(88.7)	60	(72.3)	2,203	(78.7)
Adrenal Insufficiency	**0**	**(0.0)**	**1**	**(1.2)**	**22**	**(0.8)**
Adrenal insufficiency	0	(0.0)	1	(1.2)	20	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	1	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(0.0)
Colitis	**0**	**(0.0)**	**3**	**(3.6)**	**49**	**(1.8)**
Colitis	0	(0.0)	3	(3.6)	46	(1.6)
Colitis microscopic	0	(0.0)	0	(0.0)	2	(0.1)
Enterocolitis	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	1	(0.0)
Hepatitis	**0**	**(0.0)**	**0**	**(0.0)**	**19**	**(0.7)**
Autoimmune hepatitis	0	(0.0)	0	(0.0)	12	(0.4)
Drug-induced liver injury	0	(0.0)	0	(0.0)	2	(0.1)
Hepatitis	0	(0.0)	0	(0.0)	6	(0.2)
Hyperthyroidism	**1**	**(1.6)**	**6**	**(7.2)**	**96**	**(3.4)**
Hyperthyroidism	1	(1.6)	6	(7.2)	96	(3.4)
Hypophysitis	**0**	**(0.0)**	**0**	**(0.0)**	**17**	**(0.6)**
Hypophysitis	0	(0.0)	0	(0.0)	9	(0.3)
Hypopituitarism	0	(0.0)	0	(0.0)	8	(0.3)
Hypothyroidism	**3**	**(4.8)**	**12**	**(14.5)**	**237**	**(8.5)**
Hypothyroidism	3	(4.8)	12	(14.5)	236	(8.4)
Myxoedema	0	(0.0)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**2**	**(3.2)**	**3**	**(3.6)**	**70**	**(2.5)**
Anaphylactic reaction	0	(0.0)	1	(1.2)	3	(0.1)
Cytokine release syndrome	0	(0.0)	0	(0.0)	2	(0.1)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Infusion Reactions	**2**	**(3.2)**	**3**	**(3.6)**	**70**	**(2.5)**
Drug hypersensitivity	0	(0.0)	1	(1.2)	13	(0.5)
Hypersensitivity	1	(1.6)	2	(2.4)	22	(0.8)
Infusion related reaction	1	(1.6)	0	(0.0)	29	(1.0)
Serum sickness	0	(0.0)	0	(0.0)	1	(0.0)
Myositis	**0**	**(0.0)**	**0**	**(0.0)**	**11**	**(0.4)**
Myopathy	0	(0.0)	0	(0.0)	3	(0.1)
Myositis	0	(0.0)	0	(0.0)	7	(0.3)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	4	(0.1)
Pancreatitis	**0**	**(0.0)**	**0**	**(0.0)**	**9**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	7	(0.3)
Pancreatitis acute	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonitis	**0**	**(0.0)**	**4**	**(4.8)**	**94**	**(3.4)**
Interstitial lung disease	0	(0.0)	0	(0.0)	7	(0.3)
Pneumonitis	0	(0.0)	4	(4.8)	87	(3.1)
Severe Skin Reactions	**1**	**(1.6)**	**2**	**(2.4)**	**46**	**(1.6)**
Confusion	0	(0.0)	0	(0.0)	1	(0.0)
Dermatitis	0	(0.0)	0	(0.0)	1	(0.0)
Dermatitis bullous	0	(0.0)	0	(0.0)	2	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	2	(0.1)
Drug eruption	0	(0.0)	0	(0.0)	1	(0.0)
Erythema	0	(0.0)	0	(0.0)	1	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	3	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	2	(0.1)
Jaundice	0	(0.0)	0	(0.0)	1	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	2	(0.1)
Pemphigoid	0	(0.0)	0	(0.0)	2	(0.1)
Pruritus	0	(0.0)	0	(0.0)	4	(0.1)
Pruritus genital	0	(0.0)	0	(0.0)	1	(0.0)
Psoriasis	0	(0.0)	0	(0.0)	2	(0.1)
Rash	0	(0.0)	2	(2.4)	9	(0.3)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	0	(0.0)	2	(0.1)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Severe Skin Reactions	**1**	**(1.6)**	**2**	**(2.4)**	**46**	**(1.6)**
Rash macular	1	(1.6)	0	(0.0)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	7	(0.3)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.0)
Rash pustular	0	(0.0)	0	(0.0)	1	(0.0)
Skin lesion	0	(0.0)	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	1	(0.0)
Toxic skin eruption	0	(0.0)	0	(0.0)	1	(0.0)
Thyroiditis	**0**	**(0.0)**	**0**	**(0.0)**	**16**	**(0.6)**
Autoimmune thyroiditis	0	(0.0)	0	(0.0)	5	(0.2)
Thyroiditis	0	(0.0)	0	(0.0)	11	(0.4)
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(0.2)**
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	2	(0.1)
Type 1 diabetes mellitus	0	(0.0)	0	(0.0)	5	(0.2)
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**14**	**(0.5)**
Iridocyclitis	0	(0.0)	0	(0.0)	2	(0.1)
Iritis	0	(0.0)	0	(0.0)	2	(0.1)
Uveitis	0	(0.0)	0	(0.0)	10	(0.4)

Every subject is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

For a small subset of terms, not all relevant events have been included in the reference safety dataset as a result of coding issues and differing database locks. In particular, five additional cases of Nephritis were observed but not reported in the above Table due to changes in the database and subsequent PT encoding (in total 9 events, 0.3%); one case of colitis was included due to data entry error (in total 48 events, 1.7%); one event of anaphylactoid reaction was not counted as an infusion-related reaction since this term was not part of the AEOSI list at the time of reporting (in total 71 events, 2.5%).

There were no reports of Mysthenic syndrome in the pembrolizumab/chemotherapy combination group.

CHMP comment

The overall incidence of AEOSI was not influenced by the addition of chemotherapy to pembrolizumab, even though some events, such as *Hypothyroidism,* occurred more frequently in patients treated with pembrolizumab/chemotherapy combination compared to those who received chemotherapy alone (14.5% vs 4.8%). A similar findings was observed in HL patients treated with pembrolizumab, but in that case it was possible to justify the higher number of events based on the rate of prior radiation therapy to neck and/or mediastinum. However based on updated data radiotherapy does not appear to be the cause of the apparent higher increase in the incidences of hypothyroidism and hyperthyroidism in Study KEYNOTE-021.

Based on the currently available data, it remains unclear whether the combination increases the risk of thyroid dysfunction. Data from Study KN189 will help to clarify on this issue. In the meanwhile information on the higher risk of adverse reaction with pembro combo compared to pembro monotherapy should be reported in Section 4.4

Laboratory findings

Laboratory abnormalities were analyzed based on the highest CTCAE grade reported in the ASaT population.

The most frequently reported laboratory abnormalities with pembrolizumab chemotherapy combination are listed in the following Table:

Table: Summary of subjects with increases in laboratory test toxicity Grades from baseline KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) (ASaT Population)

Laboratory test	KN021 G1 Chemo Alone (N=62)		KN021 C+G1 Combo Pooled (N=83)		Reference Data (N=2,799)	
	All Grades n(%)	Grade 3-4 n(%)	All Grades n(%)	Grade 3-4 n(%)	All Grades n(%)	Grade 3-4 n(%)
Haemoglobin decreased	52 (83.9)	12 (19.4)	70 (86.4)	12 (14.8)	1,324 (49.9)	121 (4.6)
Glucose increased	36 (61.0)	3 (5.1)	61 (74.4)	7 (8.5)	1,418 (54.7)	121 (4.7)
Leukocytes decreased	35 (57.4)	5 (8.2)	42 (51.9)	8 (9.9)	331 (12.5)	13 (0.5)
Lymphocytes decreased	34 (59.6)	16 (28.1)	48 (59.3)	19 (23.5)	848 (33.5)	213 (8.4)
Neutophils decreased	26 (43.3)	5 (8.3)	30 (37.0)	8 (9.9)	178 (6.9)	39 (1.5)
Platelet decreased	21 (36.2)	6 (10.3)	18 (22.2)	5 (6.2)	312 (11.8)	35 (1.3)
Aspartate Aminotransferase Increased	27(45.8)	1 (1.7)	45 (55.6)	5 (6.2)	721 (27.3)	53 (2.0)
Alanine Aminotransferase Increased	19 (32.2)	1 (1.7)	36 (45.0)	4 (5.0)	624 (23.6)	56 (2.1)
Triglycerides increased	3 (42.9)	0 (0.0)	3 (33.3)	0 (0.0)	726 (32.5)	27 (1.2)
Creatinine increased	11 (19.0)	1 (1.7)	28 (34.6)	3 (3.7)	425 (16.0)	18 (0.7)
Albumin decreased	18 (30.5)	0 (0.0)	32 (39.5)	0 (0.0)	913 (34.8)	38 (1.5)
Calcium decreased	11 (18.6)	1 (1.7)	20 (25.0)	3 (3.8)	616 (23.3)	32 (1.2)
Calcium increased	7 (12.3)	0 (0.0)	15 (18.8)	1 (1.3)	214 (8.1)	28 (1.1)
Phosphate decreased	13 (23.6)	6 (10.9)	22 (27.8)	5 (6.3)	498 (19.8)	121 (4.8)
Potassium decreased	13 (22.4)	1 (1.7)	26 (32.5)	6 (7.5)	332 (12.5)	49 (1.9)
Sodium decreased	20 (35.1)	2 (3.5)	30 (38.0)	6 (7.6)	970 (36.5)	188 (7.1)

Table made by the Assessor from Table 5.3.5.3.3-nsclc:142 (ISS)

No patients in either treatment arms of Cohort G1 met the criteria for Hy's Law. However, a higher rate of patients treated with pembrolizumab/chemotherapy combination compared to chemotherapy alone experienced aminotransferases increase ≥3 X ULN (8.5% vs 6.5%) and ≥5 X ULN (3.4% vs 1.6%). In 2 patients treated with pembrolizumab combined to chemotherapy an increase in aminotransferases ≥10 X ULN was registered. No patients in both arms reported bilirubin elevation.

In Cohort C, 1 patient treated with pembrolizumab 2 mg/kg combined with chemotherapy was initially

reported to have laboratory abnormalities consistent with Hy's Law. However, on closer inspection it was noted that an erroneous manual entry of the upper limit of normal for bilirubin on 2 occasions led to the classification despite normal bilirubin levels.

CHMP comment

As expected, a higher rate of laboratory abnormalities was registered with the pembrolizumab combination compared to monotherapy. In addition, for some laboratory findings (i.e, increase of glucose, AST, ALT, creatinine and potassium decreased) an enlarged rate and severity were registered with the pembrolizumab/chemotherapy combination compared to both chemotherapy alone and pembrolizumab monotherapy. However numbers are too small to draw reliable conclusions.

Safety in special populations

Age

There were no patients older than 85 years in KEYNOTE-021 study.

Table: Adverse Event Summary by Age Category (<65, 65-74, 75-84, ≥85 Years) KN021 (Cohorts C and G1) (ASaT Population)

	KN021 G1 Chemo Alone			KN021 C+G1 Combo Pooled		
	<65	65-74	75-84	<65	65-74	75-84
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects in population	28	31	3	50	26	7
with one or more adverse events	28 (100)	31 (100)	2 (66.7)	50 (100)	26 (100)	7 (100)
with no adverse event	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
with drug-related† adverse events	24 (85.7)	30 (96.8)	2 (66.7)	48 (96.0)	25 (96.2)	6 (85.7)
with toxicity grade ≥3 AEs	13 (46.4)	18 (58.1)	1 (33.3)	27 (54.0)	18 (69.2)	3 (42.9)
with toxicity grade ≥3 drug-related AEs	6 (21.4)	10 (32.3)	0 (0.0)	18 (36.0)	14 (53.8)	1 (14.3)
with serious adverse events	6 (21.4)	10 (32.3)	1 (33.3)	19 (38.0)	14 (53.8)	3 (42.9)
with serious drug-related AEs	1 (3.6)	5 (16.1)	0 (0.0)	11 (22.0)	10 (38.5)	1 (14.3)
who died	0 (0.0)	2 (6.5)	0 (0.0)	2 (4.0)	1 (3.8)	0 (0.0)
who died due to a drug-related AE	0 (0.0)	2 (6.5)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
discontinued‡ due to an adverse event	3 (10.7)	5 (16.1)	0 (0.0)	11 (22.0)	2 (7.7)	1 (14.3)
discontinued due to a drug-related AE	3 (10.7)	5 (16.1)	0 (0.0)	9 (18.0)	1 (3.8)	1 (14.3)
discontinued due to a serious AE	0 (0.0)	3 (9.7)	0 (0.0)	8 (16.0)	1 (3.8)	0 (0.0)
discontinued due to a serious drug-related AE	0 (0.0)	3 (9.7)	0 (0.0)	6 (12.0)	0 (0.0)	0 (0.0)
CNS (confusion/extrapyramidal)	5 (17.9)	3 (9.7)	0 (0.0)	7 (14.0)	3 (11.5)	1 (14.3)
AE related to falling	0 (0.0)	4 (12.9)	0 (0.0)	8 (16.0)	5 (19.2)	2 (28.6)
CV events	6 (21.4)	9 (29.0)	0 (0.0)	16 (32.0)	11 (42.3)	1 (14.3)
Cerebrovascular events	1 (3.6)	0 (0.0)	0 (0.0)	1 (2.0)	1 (3.8)	0 (0.0)
Infections	8 (28.6)	14 (45.2)	1 (33.3)	33 (66.0)	17 (65.4)	2 (28.6)

Table made by the Assessor from Appendix 2.7.4:1 and Appendix 2.7.4:2 (SCS)
† 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.
AEs were followed up to 30 days after last dose of study treatment, SAEs were followed up to 90 days after last dose of study treatment
KN021 Database Cutoff Date: 08AUG2016

Table: Adverse Event Summary by Age Category (<65, ≥65 Years) KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) (ASaT Population)

	KN021 G1 Chemo Alone				KN021 C+G1 Combo Pooled				Reference Data			
	<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	28		34		50		33		1,587		1,212	
with one or more adverse events	28	(100.0)	33	(97.1)	50	(100.0)	33	(100.0)	1,547	(97.5)	1,180	(97.4)
with no adverse event	0	(0.0)	1	(2.9)	0	(0.0)	0	(0.0)	40	(2.5)	32	(2.6)
with drug-related[†] adverse events	24	(85.7)	32	(94.1)	48	(96.0)	31	(93.9)	1,164	(73.3)	898	(74.1)
with toxicity grade 3-5 adverse events	13	(46.4)	19	(55.9)	27	(54.0)	21	(63.6)	695	(43.8)	578	(47.7)
with toxicity grade 3-5 drug-related adverse events	6	(21.4)	10	(29.4)	18	(36.0)	15	(45.5)	202	(12.7)	184	(15.2)
with serious adverse events	6	(21.4)	11	(32.4)	19	(38.0)	17	(51.5)	553	(34.8)	488	(40.3)
with serious drug-related adverse events	1	(3.6)	5	(14.7)	11	(22.0)	11	(33.3)	145	(9.1)	136	(11.2)
who died	0	(0.0)	2	(5.9)	2	(4.0)	1	(3.0)	46	(2.9)	64	(5.3)
who died due to a drug-related adverse event	0	(0.0)	2	(5.9)	1	(2.0)	0	(0.0)	4	(0.3)	6	(0.5)
discontinued[‡] due to an adverse event	3	(10.7)	5	(14.7)	11	(22.0)	3	(9.1)	164	(10.3)	170	(14.0)
discontinued due to a drug-related adverse event	3	(10.7)	5	(14.7)	9	(18.0)	2	(6.1)	66	(4.2)	80	(6.6)
discontinued due to a serious adverse event	0	(0.0)	3	(8.8)	8	(16.0)	1	(3.0)	123	(7.8)	130	(10.7)
discontinued due to a serious drug-related adverse event	0	(0.0)	3	(8.8)	6	(12.0)	0	(0.0)	47	(3.0)	54	(4.5)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

CHMP comment

Based on submitted data, the combined regimen of pembrolizumab and chemotherapy was less favourably tolerated than chemotherapy alone in patients older than 65 years, in particular in terms of Grade≥3 drug-related AEs (45.5% vs 29.4%) and serious drug-related AEs A higher rate of Grade ≥3 drug-related AE (33.3% vs14.7%).

An additional table displaying safety by age group for specific AEs in the elderly population (Table 2.5.19) reported 42.3% cardiovascular events in subjects 65-74 years treated in the in the pembro-chemo combination group compared to 29% events in the same age group of the chemotherapy group. Infections were reported in 65.4% of subjects 65-74 years in the pembro-chemo combination group compared to 45.2% events in the same age group of the chemotherapy group (incidence for < 65 years were 66% in the pembro combo vs. 28.5% in the chemo alone group).

However, no firm conclusions can be drawn on the overall safety of pembrolizumab combined with chemotherapy by age categories due to the limited size of the subgroups. With only 3 respectively 7 subjects in the age group of 75-84 years and the oldest subject in the pembro-chemo combination group being 77 years of age, the age distribution in Study KN021 appears not representative of a generally older NSCLC population. Moreover imbalances between treatment arms in Study KNO21 with a lower proportion of elderly patients in the pembro-chemo combination group compared to the chemotherapy control arm (40% vs. 55% subjects ⩾ 65 years) might further impact the safety evaluation in the elderly.

Gender

Table: Adverse Event Summary by Gender (Male, Female)
KN021 (Cohorts C and G1) and
Monotherapy Reference Dataset (KN001, KN002, KN006, KN010)
(ASaT Population)

	KN021 G1 Chemo Alone				KN021 C+G1 Combo Pooled				Reference Data			
	Male		Female		Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	26		36		33		50		1,659		1,140	
with one or more adverse events	25	(96.2)	36	(100.0)	33	(100.0)	50	(100.0)	1,616	(97.4)	1,111	(97.5)
with no adverse event	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	43	(2.6)	29	(2.5)
with drug-related† adverse events	21	(80.8)	35	(97.2)	31	(93.9)	48	(96.0)	1,239	(74.7)	823	(72.2)
with toxicity grade 3-5 adverse events	12	(46.2)	20	(55.6)	18	(54.5)	30	(60.0)	759	(45.8)	514	(45.1)
with toxicity grade 3-5 drug-related adverse events	5	(19.2)	11	(30.6)	13	(39.4)	20	(40.0)	251	(15.1)	135	(11.8)
with serious adverse events	6	(23.1)	11	(30.6)	13	(39.4)	23	(46.0)	636	(38.3)	405	(35.5)
with serious drug-related adverse events	0	(0.0)	6	(16.7)	10	(30.3)	12	(24.0)	184	(11.1)	97	(8.5)
who died	0	(0.0)	2	(5.6)	2	(6.1)	1	(2.0)	69	(4.2)	41	(3.6)
who died due to a drug-related adverse event	0	(0.0)	2	(5.6)	1	(3.0)	0	(0.0)	9	(0.5)	1	(0.1)
discontinued‡ due to an adverse event	3	(11.5)	5	(13.9)	5	(15.2)	9	(18.0)	197	(11.9)	137	(12.0)
discontinued due to a drug-related adverse event	3	(11.5)	5	(13.9)	5	(15.2)	6	(12.0)	98	(5.9)	48	(4.2)
discontinued due to a serious adverse event	0	(0.0)	3	(8.3)	3	(9.1)	6	(12.0)	155	(9.3)	98	(8.6)
discontinued due to a serious drug-related adverse event	0	(0.0)	3	(8.3)	3	(9.1)	3	(6.0)	72	(4.3)	29	(2.5)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

ECOG status

Table: Adverse Event Summary by ECOG Status Category (0, 1)
KN021 (Cohorts C and G1) and
Monotherapy Reference Dataset (KN001, KN002, KN006, KN010)
(ASaT Population)

	KN021 G1 Chemo Alone				KN021 C+G1 Combo Pooled				Reference Data			
	0		1		0		1		0		1	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	28		34		31		52		1,452		1,345	
with one or more adverse events	28	(100.0)	33	(97.1)	31	(100.0)	52	(100.0)	1,422	(97.9)	1,303	(96.9)
with no adverse event	0	(0.0)	1	(2.9)	0	(0.0)	0	(0.0)	30	(2.1)	42	(3.1)
with drug-related† adverse events	26	(92.9)	30	(88.2)	31	(100.0)	48	(92.3)	1,153	(79.4)	909	(67.6)
with toxicity grade 3-5 adverse events	14	(50.0)	18	(52.9)	20	(64.5)	28	(53.8)	588	(40.5)	684	(50.9)
with toxicity grade 3-5 drug-related adverse events	9	(32.1)	7	(20.6)	16	(51.6)	17	(32.7)	203	(14.0)	183	(13.6)
with serious adverse events	8	(28.6)	9	(26.5)	15	(48.4)	21	(40.4)	466	(32.1)	575	(42.8)
with serious drug-related adverse events	3	(10.7)	3	(8.8)	11	(35.5)	11	(21.2)	150	(10.3)	131	(9.7)
who died	2	(7.1)	0	(0.0)	2	(6.5)	1	(1.9)	37	(2.5)	73	(5.4)
who died due to a drug-related adverse event	2	(7.1)	0	(0.0)	1	(3.2)	0	(0.0)	4	(0.3)	6	(0.4)
discontinued‡ due to an adverse event	3	(10.7)	5	(14.7)	6	(19.4)	8	(15.4)	147	(10.1)	187	(13.9)
discontinued due to a drug-related adverse event	3	(10.7)	5	(14.7)	5	(16.1)	6	(11.5)	82	(5.6)	64	(4.8)
discontinued due to a serious adverse event	3	(10.7)	0	(0.0)	4	(12.9)	5	(9.6)	103	(7.1)	150	(11.2)

discontinued due to a serious drug-related adverse event	3	(10.7)	0	(0.0)	3	(9.7)	3	(5.8)	52	(3.6)	49	(3.6)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN001 Database Cutoff Date for Melanoma: 18APR2014.
MK-3475 KN001 Database Cutoff Date for Lung Cancer: 23JAN2015.
MK-3475 KN002 Database Cutoff Date: 28FEB2015.
MK-3475 KN006 Database Cutoff Date: 03MAR2015.
MK-3475 KN010 Database Cutoff Date: 30SEP2015.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.

Source: [ISS: analysis-adsl; adae; aeplus]

Region

The majority of subjects in Cohorts C and G1 in KEYNOTE-021 were from the United States. Only six subjects were enrolled from Taiwan.

CHMP comment

The pembrolizumab/chemotherapy regimen was overall more toxic than chemotherapy alone or pembrolizumab monotherapy. The small sample size does not allow drawing conclusions on the contribution of specific factors such as gender and ECOG PS. No subject with ECOG PS 2 was enrolled in Study KN021.

Discontinuation due to adverse events

A total of 14 subjects (16.9%) in the pembrolizumab/chemotherapy combination group discontinued treatment due to an AE compared to 8 subjects (12.9%) in the chemotherapy alone control group.

The number and percent of subjects with treatment discontinuation because of drug-related AEs (at least one incidence in KN021) are shown in the following Table:

Table: Subjects With Drug-related AEs resulting in treatment discontinuation (Incidence ⩾1% in One or More Treatment Groups) KN021 (Cohorts C and G1) and Monotherapy Reference Dataset (KN001, KN002, KN006, KN010) Adverse Events with at Least One Incidence in KN021 (ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		2,799	
with one or more adverse events	8	(12.9)	11	(13.3)	146	(5.2)
with no adverse events	54	(87.1)	72	(86.7)	2,653	(94.8)
Rash	0	(0.0)	3	(3.6)	1	(0.0)
Acute kidney injury	1	(1.6)	2	(2.4)	2	(0.1)
Pneumonitis	0	(0.0)	1	(1.2)	34	(1.2)
Blood creatinine increase	1	(1.6)	1	(1.2)	0	(0.0)
Colitis	0	(0.0)	1	(1.2)	14	(0.5)
Febrile neutropenia	0	(0.0)	1	(1.2)	0	(0.0)
Renal disorder	0	(0.0)	1	(1.2)	0	(0.0)
Sepsis	1	(1.6)	1	(1.2)	0	(0.0)
Alanine aminotransferase increased	1	(1.6)	0	(0.0)	2	(0.1)
Anaemia	1	(1.6)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	1	(1.6)	0	(0.0)	0	(0.0)
Fatigue	1	(1.6)	0	(0.0)	5	(0.2)
Infusion related reaction	1	(1.6)	0	(0.0)	0	(0.0)

Pancytopenia	1	(1.6)	0	(0.0)	0	(0.0)
Thrombocytopenia	1	(1.6)	0	(0.0)	1	(0.0)

Table made by the assessor from Table 5.3.5.3.3-nsclc:13 (ISS)

Every subject is counted a single time for each applicable specific AE.

KN021 C+G1 Combo Pooled group includes all subjects who received at least one dose of pembrolizumab combination treatment in KN021 Cohort C and Cohort G1

Reference dataset includes includes all subjects who received at least one dose of pembrolizumab in KN001, KN002, KN006 and KN010.

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

MedDRA version used is 19.0.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

(KN021 Database Cutoff Date: 08 AUG2016).

Post marketing experience

No post-marketing data have been submitted. The PSUR (covered period 04 March 2016 to 03 September 2016) has been just reviewed by the PRAC (EMEA/H/C/PSUSA/00010403/201609).

2.5.1. Discussion on clinical safety

To evaluate the safety profile of the combined pembrolizumab/pemetrexed/carboplatin regimen as first-line treatment of metastatic non-squamous NSCLC, a limited safety database including a total of 83 patients treated in Cohorts G1 and C of KN021 study have been submitted. A comparative safety analysis has been conducted versus the 62 patients treated with chemotherapy alone in the control arm of Cohort G1, and the reference safety dataset of pembrolizumab monotherapy including 2799 melanoma and NSCLC patients.

The median exposure to treatment in Cohort G1 was longer in the pembrolizumab combination arm compared to chemotherapy alone (i.e, median number on therapy: 8 vs 4.9 months; median number of administrations: 12 vs 8 doses). The rate of patients with an exposure duration ≥6 months was higher in the pembrolizumab combination arm than in the chemotherapy group (68% vs 42%). Indeed, the addition of pembrolizumab does not seem to compromise the standard chemotherapy program. On the contrary, more patients treated with pembro-chemo combination received the planned 4 cycles of carboplatin (88% vs 71%) and a higher rate received pemetrexed as maintenance (84.7% vs 67.7%) and for longer (median administration 11 vs 8 doses). A slightly higher exposure to pembro-chemo combination was reported in Cohort C compared to Cohort G1 (i.e, median number on therapy: 8 months; median number of administrations: 12.5 doses).

With regard to baseline characteristics a higher proportion of younger subjects was enrolled in the pembro-chemo combination group: 60% of subjects were younger than age of 65 years compared to 45% in the chemotherapy alone group and more never smokers were present in the pembro combo arm (25.0%) than in the control arm (14.3%); both points might have an impact on the safety evaluation (with a favourable impact on the combination arm).

Overall, the safety profile of pembrolizumab in combination with chemotherapy was characterised by higher rate of AEs in comparison to chemotherapy alone as well as versus pembrolizumab monotherapy. At the data cutoff date (08-Aug-2016), the addition of pembrolizumab to backbone pemetrexed/carboplatin resulted in a not negligible increase of ≥3 drug-related AEs (39.8% vs 25.8%), SAEs (43.4% vs 27.4%) and serious drug-related AEs (26.5% vs 9.7%). The safety profile of the combination regimen was even worse when compared to pembrolizumab monotherapy, in particular considering drug-related AEs (95.2% vs 73.7%), Grade ≥3 drug-related AEs (39.8% vs 13.8%), serious drug-related AEs (26.5% vs 10%), discontinuation due to drug-related AEs (13.3% vs 5.2%). It is

pointed out that the safety profile of the pembro-chemo combination was even worse in the 24 patients from Cohort C of KN021 study (66.7% Grade≥3 AEs; 41.7% Grade≥3 drug-related AEs; 29.2% discontinuation due to AEs). Even acknowledging that the small number of patients could compromise the value of these findings, the contribution of the longer drug-exposure in Cohort C to the higher rate of AEs cannot be excluded. Updated safety results from both Cohorts G1 and C of KN021 study have been provided with the responses with additional 10 months follow-up. No new safety signs emerged, and the differences are mainly characterized by a slight increase in some AEs, likely due to the longer follow-up. Not surprisingly, the combination of pembrolizumab and chemotherapy has a clear worse safety profile compared to pembrolizumab as single agent.

For every SOC, except *Blood and Lymphatic System Disorders*, more AEs were reported in the pembro-chemo combination compared to chemotherapy alone. In terms of PT, with the exception of *Anaemia*, the most common AEs and drug-related AEs were generally more frequent with the pembro-chemo combination. In patients treated with pembrolizumab/chemotherapy combination the AEs most commonly reported were *Fatigue* (71.1%), *Nausea* (62.7%), *Constipation* (54.2%), *Anaemia* (37.3%), *Diarrhoea* (36.1%), *Dyspnoea* (34.9%), *Decreased appetite* (32.5%), *Rash* (30.1%) and *Vomiting* (30.1%). In the group of patients treated with chemotherapy alone the most frequent AEs were *Anaemia* (58.1%), *Nausea* (56.5%), *Fatigue* (50%), *Constipation* (37.1%) and *Vomiting* (27.4%). The higher and longer exposure to chemotherapy achieved in patients treated with the pembro-chemo combination could partly account for the not negligible increase in the rates of AEs reported compared to chemotherapy alone, as shown by the reduced difference among groups at the analysis adjusted for exposure to study medication in Cohort G1.

Although the not negligible rate of AEs reported with the combined regimen, there is no major difference in the rate of Grade≥3 AEs between chemotherapy and pembrolizumab/chemotherapy combination (51.6% and 57.8%). With the exception of *Anaemia*, the frequency of Grade≥3 AEs was lower than 5% in both groups. As expected, the safety profile of pembrolizumab in combination with chemotherapy was less favourable compared to pembrolizumab monotherapy. However, there are SOCs for which the rate of reported Grade≥3 AEs was markedly higher than that with chemotherapy alone, thus suggesting a major contribution due to the addition of pembrolizumab. This is the case of *Infections and Infestations* (16.9% vs 4.8%), *Metabolism and nutrition disorders* (14.5% vs 6.5%), *Respiratory, thoracic and mediastinal disorders* (13.3% vs 6.5%).

Drug-related AEs were much more frequently reported in the pembro combo population when compared to the pembrolizumab monotherapy population (95.2% vs 73.4%). A higher rate of grade 3-5 drug-related AEs was also observed with the pembro combo than in the pembrolizumab monotherapy population (39.8% vs 26.6%). Fatigue, nausea, constipation, anemia, and diarrhea were much more frequently reported in the pembro combo population when compared to the pembrolizumab monotherapy population: fatigue (71.1% vs 20.8%), nausea (62.7% vs 19.5%), constipation (54.2% vs 20.8%), anemia (37.3% vs 13.0%), and diarrhea (36.1% vs 20.8%). Discontinuations due to AEs were more frequently observed with the combination compared to pembrolizumab monotherapy (16.9 % vs 9.1%).

No new safety issues were identified with the addition of pembrolizumab to pemetrexed/carboplatin regimen.

In the pembrolizumab combination group, SAEs were mostly in the SOCs *Infections and Infestations* (14.5%), and *Respiratory, thoracic and mediastinal disorders* (13.3%), while the most common SAEs reported with chemotherapy alone were in the SOC *Gastrointestinal disorders* (11.3%). However, the incidence of specific PTs considered drug-related to pembro-chemo combination was low, with the most common events (i.e *Acute kidney injury*, *Cellulitis*, *Fatigue*, *Pyrexia*, Rash, and *Sepsis*) registered in no more than 2 patients (2.4%).

In terms of AEOSI, no new findings emerged.

The overall incidence of AEOSI was not influenced by the addition of chemotherapy to pembrolizumab, even though some events, such as *Hypothyroidism,* occurred more frequently in patients treated with pembrolizumab/chemotherapy combination compared to those who received chemotherapy alone (14.5% vs 4.8%). A similar findings was observed in HL patients treated with pembrolizumab, but in that case it was possible to justify the higher number of events based on the rate of prior radiation therapy to neck and/or mediastinum. However based on updated data radiotherapy does not appear to be the cause of the apparent higher increase in the incidences of hypothyroidism and hyperthyroidism in Study KEYNOTE-021.

Based on the currently available data, it remains unclear whether the combination increases the risk of thyroid dysfunction. Data from Study KN189 will help to clarify on this issue. In the meanwhile information on the higher risk of adverse reaction with pembro combo compared to pembro monotherapy should be reported in Section 4.4.

A similar rate of fatal cases due to AE was registered in patients treated with chemotherapy compared to those who received pembrolizumab added to chemotherapy (3.6% vs 3.2%). One drug-related fatal case (*Sepsis*) was reported with the pembro-chemo combination.

As expected, a higher rate of laboratory abnormalities was registered with the pembrolizumab combination compared to monotherapy. For some laboratory findings (i.e, increase of glucose, AST, ALT, creatinine and potassium decreased) an increased rate and severity were registered in comparison to both chemotherapy alone and pembrolizumab monotherapy.

Overall, as first line treatment of NSCLC the combination of pembrolizumab and chemotherapy is more toxic than pembrolizumab as single agent. However, it is acknowledged that safety data reflects the individual profiles of the components, and that the worst tolerability is the results of the sum of very well known and characterized adverse effect of pembrolizumab, pemetrexed and carboplatin.

The lack of comparative data of the combination and pembrolizumab monotherapy, the limited safety dataset of the combination, and the higher risk of adverse reaction of the combination compared to single agent pembrolizumab should be clearly stated in section 4.4 together with a recommendation to carefully consider the benefit of the combination in NSCLC patients whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS).

2.5.2. Conclusions on clinical safety

A limited database has been submitted to evaluate the safety profile of the combined pembrolizumab/pemetrexed/carboplatin regimen as first-line treatment of metastatic non-squamous NSCLC.

The pembrolizumab/chemotherapy regimen was overall more toxic than chemotherapy alone or pembrolizumab monotherapy. However, no new safety issues were identified and the safety profile of the combined regimen was as expected based on the known tolerability of the backbone chemotherapy and pembrolizumab monotherapy.

Single toxicities (e.g. some infection events) were reported with higher incidences for the combination therapy as compared to both, pembrolizumab monotherapy and chemotherapy alone. However given the small numbers it is not possible to draw meaningful conclusions. Overall the safety database of the combination therapy appears to be too limited to assess definitely whether there may be single toxicities with higher incidences than what would be expected by the addition of both individual components.

2.5.3. PSUR cycle

2.6. Risk management plan

Summary of safety concerns

There have been no new safety concerns identified for pembrolizumab as part of this extension of indication.
At this stage, the list of safety concerns as approved in the previous version of the RMP is still considered valid for the extension of indication.

Table 1: summary of safety concerns

Summary of safety concerns	
Important identified risks	**Immune-Related Adverse Reactions** - Immune-related pneumonitis - Immune-related colitis - Immune-related hepatitis - Immune-related nephritis - Immune-related endocrinopathies • Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) • Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) • Type 1 diabetes mellitus - Severe skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) - Other immune-related adverse reactions • Uveitis • Myositis • Pancreatitis • Severe Skin Reactions • Guillain-Barre Syndrome • Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients **Infusion-Related Reactions**
Important potential risks	**Immune-Related Adverse Events** • Gastrointestinal perforation secondary to colitis • For Hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab **Immunogenicity**
Missing information	- Safety in patients with moderate or severe hepatic impairment - Safety in patients with severe renal impairment

Summary of safety concerns	
	- 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

No new additional pharmacovigilance activities for the new indication are proposed by the MAH, which is considered acceptable at this stage. However, pending assessment of the requested data, additional pharmacovigilance activities could be requested.

Table 2: Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / activity Type, title and category	Objectives *	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports
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- GI perforation secondary to colitis, Immunogenicity) -Long term safety	Started	Final Study Report Aug 2019
Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-	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- GI perforation secondary to colitis, Immunogenicity) -Long term safety	Started	Final Study Report Sep 2018

Table 2: Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / activity Type, title and category	**Objectives ***	**Safety concerns addressed**	**Status (planned / started)**	**Date for submission of interim or final reports**
Small Cell Lung Cancer (P024) (Category 3)				
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- GI perforation secondary to colitis, Immunogenicity) -Long term safety	Started	Final Study Report Dec 2019

Table 2: Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / activity Type, title and category	Objectives *	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports
Clinical Trial A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies (P013) (Category 3)	To determine the safety and tolerability of pembrolizumab in subjects with relapsed/refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma, relapsed/refractory mediastinal large B cell lymphoma (MLBCL), and relapsed/refractory non-Hodgkin lymphoma (NHL), that have failed, are ineligible for, or refused a stem cell transplant.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; Immunogenicity)	Started	Final Study Report Mar 2019
Clinical Trial A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (P087) (Category 3)	To determine the safety and tolerability of pembrolizumab.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; Immunogenicity)	Started	Final Study Report Aug 2021
Clinical Trial A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (P204) (Category 3)	To compare PFS as assessed by blinded independent central review according to the IWG response criteria between treatment arms.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab;	Started	Final Study Report Apr 2021

Table 2: Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / activity Type, title and category	Objectives *	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports
		Immunogenicity)		

Table 2: Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / activity Type, title and category	Objectives *	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports
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- GI perforation secondary to colitis) -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

No changes to the risk minimisation measures were proposed which is considered acceptable at this stage.

Table 3: Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related Pneumonitis	The risk of the immune-related adverse reaction of pneumonitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Colitis	The risk of the immune-related adverse reaction of colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Hepatitis	The risk of the immune-related adverse reaction of hepatitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials

Table 3: Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Immune-related Nephritis	The risk of the immune-related adverse reaction of nephritis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Immune-related Endocrinopathies -Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis) - Type 1 Diabetes Mellitus	The risk of the immune-related endocrinopathies [Hypophysitis (including hypopituitarism and secondary adrenal insufficiency); Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis); Type 1 Diabetes Mellitus] associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4 and 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Severe Skin Reactions including SJS and TEN	The risk of severe skin reactions including SJS and TEN associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Other Immune-related adverse reactions -Uveitis, Myositis, Pancreatitis, Myocarditis, Guillain-Barre Syndrome, Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients	The risk of other immune-related adverse reactions (uveitis, myositis, pancreatitis, myocarditis Guillain-Barre syndrome, Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients) associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 (myocarditis is also described in Section 4.2) and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Important Identified Risks: Infusion-Related Reactions		
Infusion-Related Reactions	The risk of infusion-related reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Important Potential Risks: Immune-Related Adverse Events		

Table 3: Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Gastrointestinal perforation secondary to colitis	The risk of the immune-related adverse event of gastrointestinal perforation secondary to colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	None
For Hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Educational materials
Important Potential Risks: Immunogenicity		
Immunogenicity	The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 4.8.	None
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	The missing information of safety in these patients is described in the SmPC, Section 4.2, 4.4.	None
Safety in patients with active systemic autoimmune disease	The missing information of safety in patients with active systemic autoimmune disease is described in the SmPC, Section 4.4, 5.1.	None
Safety in patients with HIV or Hepatitis B or Hepatitis C	The missing information of safety in patients with patients with HIV or Hepatitis B or Hepatitis C is described in the SmPC, Section 4.4, 5.1.	None
Safety in Pediatric patients	The missing information of safety in pediatric patients is described in the SmPC, Section 4.2.	None
Reproductive and lactation data	Use during pregnancy and use in nursing mothers is described in the SmPC, Section 4.6, 5.3.	None
Long term safety	None	None
Safety in various ethnic groups	None	None
Potential pharmacodynamic interaction with systemic immunosuppressants	The missing information of potential pharmacodynamic interaction with systemic immunosuppressants is described in the SmPC, Section 4.4, 4.5.	None

Table 3: Summary of Safety Concerns and Risk Minimization Activities

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

2.7. Update of the Product information

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

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. The justification can be considered in principle acceptable due to the limited changes to the package leaflet. However, a request to provide an overview of all changes of the SmPC affecting the package leaflet since the last consultation with target patients groups was carried out through the ongoing Var II/23 (extension of indication in Urothelial Cancer), considering that several modification have been implemented based on variations since the readability test was performed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication application is, in combination with pemetrexed/carboplatin chemotherapy, for the first-line treatment of patients with metastatic non-squamous NSCLC.

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

3.1.2. Available therapies and unmet medical need

The prognosis of advanced NSCLC is poor, with an untreated median OS of 4 months and a metastatic 5-year survival rate of <5%.

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

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

Pembrolizumab as monotherapy is a treatment option for first line treatment in patients with metastatic PD-L1 strongly positive (TPS≥50%) NSCLC. A clinically significant improvement was reported with pembrolizumab compared to platinum-doublets chemotherapy, with a PFS gain of 4.3 months and 40% decreased risk of death.

3.1.3. Main clinical studies

The efficacy of pembrolizumab 200 mg every 3 weeks, combined to chemotherapy (pemetrexed/carboplatin) as first line treatment of metastatic non-squamous NSCLC, has been evaluated based on comparative data versus chemotherapy alone, in a total of 123 patients randomized in Cohort G1 of a multi-cohorts phase I/II study KN021. The study primary endpoint was ORR and PFS was considered as a key secondary endpoint.

Data from the 24 non-squamous, previously untreated, metastatic NSCLC patients, enrolled in the dose-finding Cohort C of KN021 study, were submitted as supportive.

3.2. Favourable effects

A confirmed ORR of 56.7% was reported in the pembrolizumab combination arm compared to 30.2% in the control group, with an estimated ORR difference slightly smaller than that pre-defined (30%). The median time to response was shorter with the combination (1.6 months) than with chemotherapy alone (2.7 months), and responses were longer in the pembrolizumab combined arm, with a median duration not reached (1.4+, 18.6+) compared to 16.2 months (2.8, 20.7+). In addition, the rate of patients with response duration lasting ≥6 Months was 90% vs 73% in the combination regimen and in the chemotherapy alone arm, respectively.

A benefit in PFS was reported with the pembrolizumab/chemotherapy combination (HR 0.49, 95% CI 0.29-0.83, p=0.00352) in the ITT population.

An updated analysis (data cutoff date: 31 May 2017) confirmed the benefit in terms of ORR (56.7% vs 31.7%) and PFS (HR 0.54, 95% CI 0.33-0.88, p=0.00673). A trend in OS favouring the experimental arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436) is reported despite a not negligible rate of patients in the control arm (40/63, 63.5%) receiving subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab or durvalumab). A benefit in PFS2 was also reported (HR 0.56, 95% CI 0.35-0.92, p=0.00960).

Results according to PD-L1 expression were provided, showing responses regardless of PD-L1 status (although more pronounced in strongly positive). A statistically significant gain in terms of PFS was observed for PD-L1 strongly positive (TPS≥50%) and PD-L1 negative (TPS<1%) patients.

3.3. Uncertainty in the knowledge about the beneficial effects

Even though data from Study KN021 seem to suggest a benefit of the pembro combination over chemotherapy in the overall study population, available data do not allow drawing firm conclusions regarding a possible association between tumour PD-L1 expression levels and efficacy. In particular, no clear benefit of the combination over chemotherapy was observed in PD-L1 TPS ≥1% patients, with a

similar PFS rate at 6 months (69.3% vs 70.8%, respectively). Interim analyses for studies KN189 and KN042, currently planned , should be provided by the MAH.

Even acknowledging the clinical relevance of the benefit observed in PD-L1 TPS <1% patients, the unexpected poor outcome in the chemotherapy arm needs to be further evaluated and the compliance by age to chemotherapy in this subgroup should be discussed by the MAH.

3.4. Unfavourable effects

The addition of pembrolizumab to backbone pemetrexed/carboplatin resulted in a higher rate of Grade ≥3 drug-related AEs (39.8% vs 25.8%), SAEs (43.4% vs 27.4%) and serious drug-related AEs (26.5% vs 9.7%). However, a similar rate of patients discontinued treatment due to drug-related AEs in the two subgroups (13.3% with the combination and 12.9% with chemotherapy alone).

Compared to the reference dataset of pembrolizumab monotherapy, the combination regimen was characterized by an increased rate of AEs, in particular considering drug-related AEs (95.2% vs 73.7%), Grade ≥3 drug-related AEs (39.8% vs 13.8%), serious drug-related AEs (26.5% vs 10%), discontinuation due to drug-related AEs (13.3% vs 5.2%).

The most frequently reported drug-related AEs were *Fatigue* (59%), *Nausea* (48.2%), *Anaemia* (32.5%), *Rash* (25.3%) and *Diarrhea* (21.7%) with pembrolizumab combined to pemetrexed/carboplatin, while in the chemotherapy alone group *Anaemia* (53.2%), *Nausea* (43.5%), *Fatigue* (40.3%), and *Vomiting* (17.7%) were more commonly observed.

Drug-related SAEs most common with the pembro-chemo combination were *Acute kidney injury*, *Cellulitis*, *Fatigue*, *Pyrexia*, Rash, and *Sepsis*, each registered in no more than 2 patients (2.4%).

3.5. Uncertainty in the knowledge about the unfavourable effects

A limited safety database, including a total of 83 patients treated in Cohorts G1 and C of KN021 study, has been submitted.

Single toxicities (e.g. some infection events) were reported with higher incidences for the combination therapy as compared to both, pembrolizumab monotherapy and chemotherapy alone. However given the small numbers it is not possible to draw meaningful conclusions. Overall the safety database appears too limited to finally assess whether there may be toxicities with higher incidences than what would be expected by the addition of both individual components.

3.6. Effects Table

Table: Effects Table for Keytruda in combination with pemetrexed and carboplatin for the of first-line treatment of patients with metastatic non-squamous NSCLC.

Study KEYNOTE-021 Cohort G1 (data cut-off: 31 May 2017)

Effect	Short Description	Unit	pembro 200 mg pemetrexed/ carboplatin	pemetrexed/ carboplatin	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
ORR (primary	Confirmed CR + PR	% (95% CI)	56.7 (43.2, 69.4)	31.7 (20.6, 44.7)	Even if submitted data	

endpoint)	BIRC per RECIST 1.1				are promising, the benefit of adding pembrolizumab to pemetrexed /carboplatin is not clearly demonstrated. Results from studies KN189 and KN042 should be provided. 58% of patients in the chemotherapy arm received anti PD-1/anti PD-L1 after progression.	CSE
PFS	survival without progression from randomization to PD or death whichever occurred first BIRC per RECIST 1.1	months (95% CI)	19.0 (8.5,...)	8.9 (6.2, 11.8)		
			HR(95% CI) 0.54 (0.33, 0.88) p-value: 0.00673			
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	Not Reached (22.8,...)	20.9 (14.9,...)		
Response duration	Duration of CR/PR until documented PD BIRC per RECIST 1.1	months (range)	Not Reached (1.4+-22.7+)	Not Reached (2.8-23.7+)		

Unfavourable Effects

Tolerability			KN021 C+G1 pembro/chemo	KN021 G1 Chemo alone		(1)
	drug related AEs	%	95.2	90.3		
	drug related Gr≥3 AE	%	39.8	25.8		
	drug related SAEs	%	26.5	9.7		
	death drug related	%	1.2	3.2		
	discontinuation drug related AEs	%	13.3	12.9		
	discontinuation drug related SAEs	%	7.2	4.8	A limited safety database (83 patients) has been submitted. With the exception of Anaemia, the incidence of most common AEs was higher in the pembro/chemo combination group. No new safety concerns	
Drug-related AEs	Incidence of Fatigue	%	59.0	40.3		
	Incidence of Nausea	%	48.2	43.5		
	Incidence of Anaemia	%	32.5	53.2		
	Incidence of Rash	%	25.3	14.5		
	Incidence of Diarrhoea	%	21.7	11.3		
	Incidence of Vomiting	%	20.5	17.7		
	Incidence of ALT/AST increased	%	20.5	11.3		
	Incidence of Constipation	%	18.1	9.7		
	Incidence of Oedema peripheral	%	13.3	3.2		
	Incidence of Pruritus	%	13.3	3.2		
	Incidence of Alopecia	%	12.0	3.2		

CSE: Clinical Summary of Efficacy; Pooled data from Cohort G1 and Cohort C of KN021 study

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An improvement of anticancer activity is expected based on immunotherapy and chemotherapy combination. Indeed, besides cytotoxic effects, chemotherapy also acts through immunological effects, including reduction of T-regulatory cell activity and enhancement of cross presentation of tumour antigens.

An increased ORR and a statistically significant improvement in PFS were reported with the addition of pembrolizumab to backbone chemotherapy in first line metastatic non-squamous NSCLC, supported by OS data favouring the pembro combo arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436) despite 63.5% of patients in the control arm receiving subsequent therapy with a PD-1/PD-L1 inhibitor. The combined regimen was overall more toxic than chemotherapy alone and pembrolizumab monotherapy, even though the addition of pembrolizumab does not seem to compromise the standard chemotherapy program. Indeed, although the higher rate, the type of the most common drug-related AEs reported with the combined regimen was consistent with the known safety profile of any single agent individually, and no new safety issues were identified.

As the MAH pointed out, the clinical development of Keytruda for NSCLC was biomarker-based for monotherapy and non-biomarker-based for combination treatments. This is not questioned, in principle. It is also acknowledged that, due to the parallel development of different therapeutic approaches it is not possible to generate data of direct comparisons for all of them. On the other hand, it is essential to put results of studies supporting a new indication in the context of available therapeutic treatment options, especially when a worst tolerability appears evident, and data are available only from an exploratory study with the results from the confirmatory trial still pending, as it is in this case.

Pembrolizumab as single-agent is approved in EU for the first-line treatment of PD-L1 ≥50% metastatic NSCLC based on results from study KN024, showing a clear benefit over platinum-containing chemotherapy in terms of both PFS (HR 0.50; 95% CI 0.37, 0.68) and OS (HR 0.60; 95%CI 0.41, 0.89), and a more favourable safety profile.

Study KN021 was not designed to address the efficacy of pembro combo in this subset of patients, and a very limited number of PD-L1 strongly-positive patients were included in the trial (all cohorts), of whom only 45 were treated with combination (20 in cohort G1). Taking into account the relatively limited data, and the intrinsic limitations of cross-trial comparison, it cannot be firmly concluded that the combination is more efficacious than the monotherapy, although a higher response rate has been reported with the combination.

3.7.2. Balance of benefits and risks

These are the first data related to the combined association of pembrolizumab and chemotherapy that have been submitted. The safety profile of the combined regimen is worse compared to both pembrolizumab monotherapy and chemotherapy alone, even if toxicity was as expected and no new safety signal was reported.

Overall, the combination of pembrolizumab and chemotherapy appears more efficacious than chemotherapy. However, the concerns expressed regarding the lack of an outstanding benefit of the combination over chemotherapy in subjects PD-L1 TPS ⩾1% still remain, since at the updated analysis the median PFS, and the PFS rate at 6 months is quite similar.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7.4. Conclusions

Overall, data from Study KN021 suggest a benefit of the pembro combination over chemotherapy. However, based on available data that do not allow drawing firm conclusion with regard to many relevant aspects, it would seem wise to wait for the top-line results from studies KN189 and KN042. Interim analyses for these studies are currently planned , and the MAH is therefore asked to provide these data as available, in order to allow a more informed evaluation of the B/R (Study KN189), and a better contextualization (Study KN042), of the sought indication.

4. Recommendations

The application for:
Extension of Indication to include 1st line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with platinum-pemetrexed chemotherapy based on the results from study KEYNOTE-021 (cohort G); a Phase 1/2, open-label trial of pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC.
As a consequence sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly.
An updated RMP version 9.0 was provided as part of the application.

☒ is not approvable since major objection and other concerns have been identified, which preclude a recommendation at the present time.

Annex 1: 2nd Request for Supplementary Information

Benefit risk

Major Objection

1. Available data do not allow drawing firm conclusion on the benefit risk of pembrolizumab combined to chemotherapy in the treatment as first line treatment of metastatic non-squamous NSCLC. Interim analyses for studies KN189 and KN042 are currently planned and the MAH is therefore asked to provide these data as available, in order to allow a more informed evaluation of the B/R (Study KN189), and a better contextualization (Study KN042), of the sought indication.

Clinical efficacy aspects

Other concerns

2. The MAH is requested to provide a sensitivity analysis excluding patients with NOS histology for ORR, PFS and OS.
3. The compliance by age to chemotherapy in the PD-L1<1% group should be discussed by the MAH.

Clinical safety aspects

Other concerns

4. Updated results from KN021 (data cut-off date: 31 May 2017) should be provided in a tabular format including data from subjects treated with chemotherapy alone (control arm of Cohort G1), pooled pembro combo data (Cohort C+ Cohort G1) and the Reference Safety Dataset. In particular, the MAH should submit Tables on AE Summary, AEs with incidence ≥10%, Grade ≥3 AEs with incidence ≥1%, Drug-related AEs with incidence ≥5%, Drug-related Grade≥3 AEs with incidence ≥1%, SAE with incidence ≥1%, Drug-related SAE with incidence ≥1%, AEOSI Summary, Important Identified AEOSI and Drug-related AEs resulting in treatment discontinuation with incidence ≥1%.

Annex 2: Joint Rapporteurs preliminary assessment report of the MAH responses to the 1st Request for Supplementary Information

Clinical Pharmacology Aspects

Other Concerns

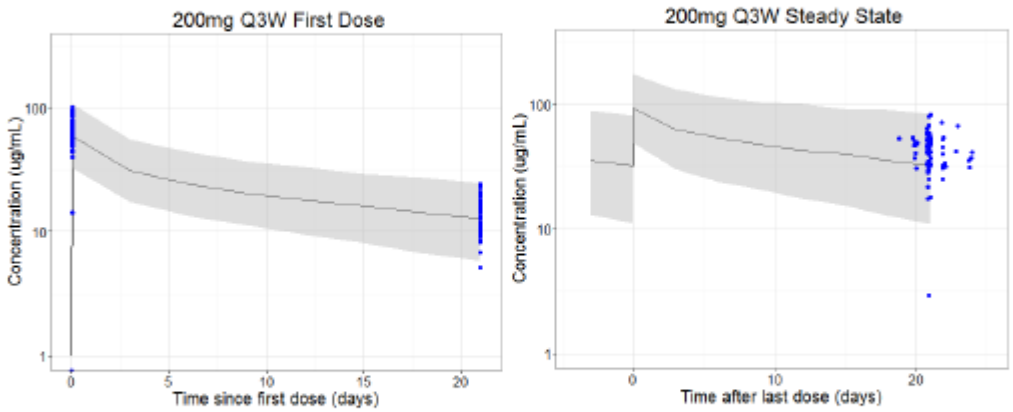
Question 1

The PK report and the evaluation presented by the MAH includes descriptive statistics for Cmin and Cmax from cycle 1 only and the observed data at steady-state are very limited (only few patients). The MAH is requested to justify this lack of information and to provide a complete evaluation of all PK results from KN021. This should include descriptive statistics of all later PK sampling time points and a comprehensive PK evaluation at steady state from KN021.

Summary of MAH's response

The PK report focused on KEYNOTE-021 Cohort G1, in which subjects received the pembrolizumab 200 mg dose. A limited number of steady state PK data points were available at the time of the pre-specified analysis. As requested, the PK analysis has been updated to include additional PK data with a cutoff of 23-JUN-2017. An updated PK overlay plot for Cohort G1 (200 mg Q3W) is provided in the following Figure 1, along with descriptive statistics of later PK sampling time points in Table below.

Overlay of Observed Pembrolizumab Concentrations in NSCLC With Pembrolizumab Dose of 200 mg Q3W and Concomitant Pemetrexed and Platinum Therapy (KN021G) at First Dose (left panel) and Steady State (right panel)



Solid points represent observed pembrolizumab serum concentrations from KN021G patients receiving 200mg Q3W pembrolizumab with concomitant pemetrexed and platinum therapy. Solid lines represent median predicted concentration time profile, based on the previously developed population PK model of monotherapy pembrolizumab. Shaded areas represent 90% prediction interval for the prediction. The left panel shows predicted concentrations at first dose, and the right panel shows predicted and observed concentrations at steady state.

Descriptive Statistics of Pembrolizumab Observed Peak and Trough Concentrations in NSCLC at 200 mg Q3W With Concomitant Pemetrexed and Platinum Therapy (KN021G)

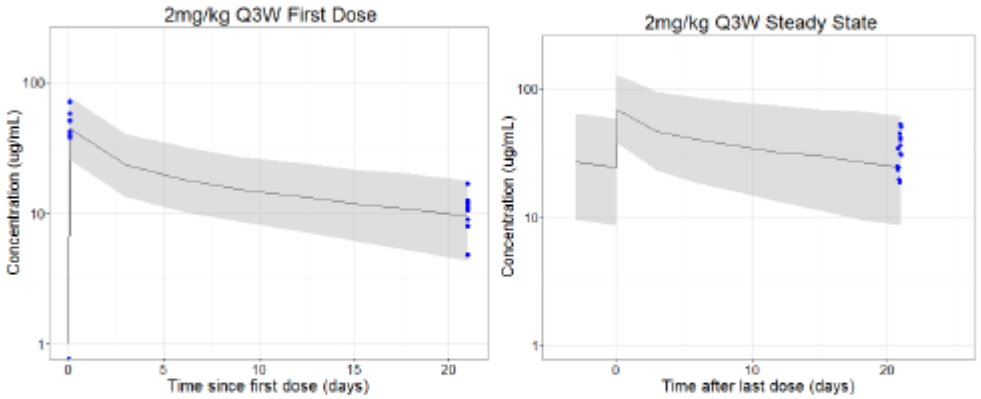
Parameter	Cycle	NSCLC Pembrolizumab 200 mg Q3W + pemetrexed + platinum therapy			
		N	Mean	Median	SD
Cmax [a] (µg/mL)	Cycle 1 (Week0)	54	65.1	64.4	16.2
	Cycle 2 (Week3)	52	80.6	77.3	18.7
Cmin [b] (µg/mL)	Cycle 2 (Week3)	53	14.8	14.7	4.7
	Cycle 3 (Week6)	45	23.9	22.9	7.1
	Cycle 6 (Week15)	48	37.1	34.8	12.3
	Cycle 9 (Week24)	38	40.6	39.8	12.8
	Cycle 13 (Week36)	31	43.1	45.0	12.3
	Cycle 17 (Week48)	17	46.6	47.5	12.8
	Cycle 25 (Week72)	10	49.5	47.5	15.2

[a] Cmax is concentration at time of peak sample
[b] Cmin is trough concentration

A prediction interval for pembrolizumab serum concentrations after the first dose and at steady state were generated for pembrolizumab 200 mg Q3W dosing using the established monotherapy population PK model. Overlay of observed pembrolizumab serum concentrations from KEYNOTE-021 indicate similarity of pembrolizumab concentrations when administered as monotherapy and when coadministered with platinum chemotherapy.

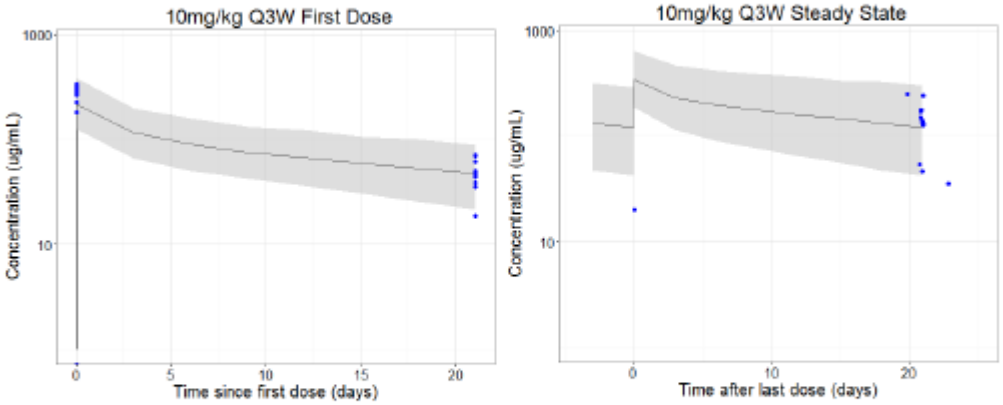
For completeness, PK overlay plots of data from patients dosed with pembrolizumab 2 mg/kg and 10 mg/kg Q3W in combination with platinum chemotherapy from KEYNOTE-021 Cohort C are presented below together with a summary statistics.

Overlay of Observed Pembrolizumab Concentrations in NSCLC With Pembrolizumab Dose of 2 mg/kg Q3W and Concomitant Pemetrexed and Platinum Therapy (KN021C) at First Dose (left panel) and Steady State (right panel)



Solid points represent observed pembrolizumab serum concentrations from KN021C patients receiving 2mg/kg Q3W pembrolizumab with concomitant pemetrexed and platinum therapy. Solid lines represent median predicted concentration time profile, based on the previously developed population PK model of monotherapy pembrolizumab. Shaded areas represent 90% prediction interval for the prediction. The left panel shows predicted concentrations at first dose, and the right panel shows predicted and observed concentrations at steady state.

Overlay of Observed Pembrolizumab Concentrations in NSCLC With Pembrolizumab Dose of 10 mg/kg Q3W and Concomitant Pemetrexed and Platinum Therapy (KN021C) at First Dose (left panel) and Steady State (right panel)



Solid points represent observed pembrolizumab serum concentrations from KN021C patients receiving 10mg/kg Q3W pembrolizumab with concomitant pemetrexed and platinum therapy. Solid lines represent median predicted concentration time profile, based on the previously developed population PK model of monotherapy pembrolizumab. Shaded areas represent 90% prediction interval for the prediction. The left panel shows predicted concentrations at first dose, and the right panel shows predicted and observed concentrations at steady state.

Descriptive Statistics of Pembrolizumab Observed Peak and Trough Concentrations in NSCLC at 2 mg/kg Q3W or 10 mg/kg Q3W in NSCLC (KN021C)

Parameter	Cycle	NSCLC MK-3475 2 mg/kg (Part I)				NSCLC MK-3475 10 mg/kg (Part I)			
		N	Mean	Median	SD	N	Mean	Median	SD
Cmax [a] (µg/mL)	Cycle 1 (Week0)	9	52.7	51.1	12.3	12	277	278	47.5
	Cycle 2 (Week3)	11	67.8	53.1	26.8	10	308	306	49.0
Cmin [b] (µg/mL)	Cycle 2 (Week3)	11	10.7	10.7	3.0	11	48.4	48.7	15.0
	Cycle 3 (Week6)	10	15.9	15.9	3.8	11	79.7	84.7	28.5
	Cycle 6 (Week15)	9	25.6	26.1	9.6	9	143	145	51.1
	Cycle 9 (Week24)	7	24.0	24.6	12.8	7	141	140	62.3
	Cycle 13 (Week36)	6	22.6	20.9	13.7	6	115	132	65.6

[a] Cmax is concentration at time of peak sample
[b] Cmin is trough concentration

CHMP Assessment

The PK report has been updated and the requested data have been provided.

Issue solved.

Benefit / Risk

Major Objections

Question 2

Overall, the combination of pembrolizumab and chemotherapy appears more efficacious than chemotherapy. However, data are only available from an open label phase II study, and the combined regimen appears to be quite more toxic than pembrolizumab as single agent. In addition, it is noted that there is no clear benefit of the combination over chemotherapy in PD-L1 TPS ≥1%, with a similar PFS rate at 6 months.

These issues raises concerns, and results need to be put in the context of available scientific evidence (including phase 3 KN-189 study) and current treatment landscape. Therefore, the MAH is asked to:

i. discuss the results from study KN-021 in the context of the demonstrated OS benefit of single agent pembrolizumab over chemotherapy in previously untreated strongly PD-L1 positive (TPS ≥50%) NSCLC (already approved indication) providing all available data across trials in previously untreated PD-L1 strongly positive non-squamous NSCLC patients;

ii. provide top-line results of phase 3 study KN-042 comparing pembrolizumab monotherapy to platinum based chemotherapy as first-line treatment in PD-L1 positive (TPS ≥1%) patients, with OS as the primary endpoint, and discuss the results in patients with non-squamous histology in comparison to those from study KN-021.

iii. acknowledging the clinical relevance of the benefit observed in PD-L1 TPS <1% patients, discuss the somewhat unexpected poor outcome in the chemotherapy arm in the context of all available data (even from literature), and present baseline characteristics of these patients, and discuss the potential impact on the observed treatment effect in this subgroup.

Summary of MAH's response

The first-line treatment of advanced NSCLC is rapidly changing with multiple new therapeutic choices becoming available for physicians and patients to consider in formulating treatment plans.

The NSCLC pembrolizumab development program has evolved from initial clinical observations evaluating pembrolizumab as monotherapy to more recently clinical observations in combinations with chemotherapies, targeted therapies, and other non-PD-1 immunotherapies.

The monotherapy studies have focused on a biomarker selected PD-L1 positive population (TPS ≥1% and TPS ≥50%) population and have used existing treatment standards as controls:

• previously treated subjects: KEYNOTE-001 and KEYNOTE-010 (TPS ≥1% selection cutpoint)

• previously untreated subjects: KEYNOTE 001 Cohort F1, KEYNOTE-024 (TPS ≥50% selection cutpoint), and KEYNOTE-042 (TPS ≥1% selection cutpoint).

In contrast to monotherapy, the combination studies involving chemotherapy, IDO-1 inhibitors, and others are focused on patients who are not selected by PD-L1 status. This approach is based on initial data generated in unselected populations in which the efficacy signal was present in both the PD-L1 negative and positive populations.

The MAH considers this dual approach to be valuable in offering each physician and patient choices when deciding on treatment, taking into consideration the specific circumstances that may apply at the level of the individual patient. At this stage in the development of pembrolizumab in NSCLC, the biomarker-based monotherapy program and the non-biomarker-based chemotherapy combination program are proceeding on parallel development paths with no head to head comparisons planned. In addition there are a number of other PD-1 and PD-L1 development programs that in the near term may produce positive studies using other combination approaches (eg, PD-1/-L1 plus CTLA-4 and PD-L1 plus other chemotherapy combinations). These programs will not necessarily have direct comparisons to monotherapy or other combinations and likely will not seek to demonstrate a contribution from each component of the combination. The results of these studies will culminate in multiple potential treatment options for physicians and patients, including monotherapy and differing combinations; the data from KEYNOTE-021 representing one such option.

The MAH agrees that the combination of pembrolizumab and chemotherapy is more efficacious than chemotherapy alone based on the findings from KEYNOTE-021 (Cohort G1), a randomized study that demonstrated a large, statistically significant, clinically meaningful benefit in both ORR and PFS with the addition of pembrolizumab to standard chemotherapy. In updated analysis 2 submitted with this response, the OS benefit has further improved with a more prominent late separation of the survival curves and a HR of 0.59 (95% CI 0.34-1.05). KEYNOTE-021 Cohort G1 was designed to detect a difference in ORR and PFS between pembrolizumab/pemetrexed/carboplatin (pembro combo) and pemetrexed/carboplatin (chemo alone) administered to previously untreated subjects with advanced non-squamous NSCLC, irrespective of tumor PD-L1 status.

In keeping with the development strategy in NSCLC the study was not designed and therefore not powered to analyze biomarker-defined subgroups; any such data can only be considered exploratory in nature. Subgroup data from the TPS ≥1% and <1% subgroups were only provided as the 1% cutpoint was a stratification factor. In response to the specific comment that the PFS in the PD-L1 positive group at 6 months is no different than in the chemo alone arm, it should be noted that for the overall evaluation of the treatment effect in updated analysis 2, the HR for this subgroup was 0.76 (95% CI 0.41-1.42) favoring the pembro combo arm.

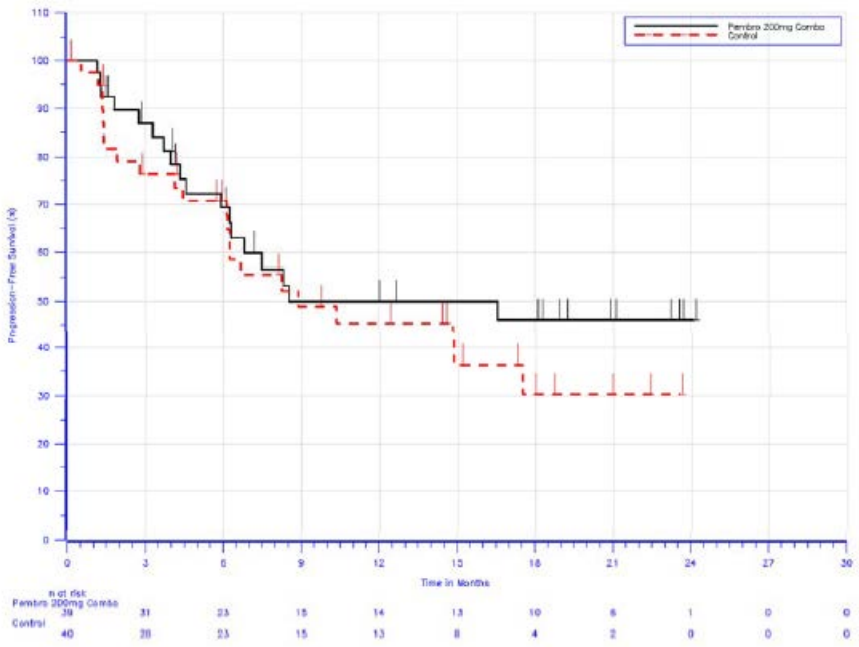
Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with TPS >= 1%
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro 200mg Combo	39	18 (46.2)	397.3	4.5	8.5 (6.2, .)	69.3 (51.3, 81.8)	0.76 (0.41, 1.42)	0.19511
Control	40	22 (55.0)	342.2	6.4	8.9 (6.2, 17.5)	70.8 (53.4, 82.6)	---	---

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

Source: [P021V01MK3475: analysis-adsl; adtte]

Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects with TPS >= 1%
(ITT Population)



Specifically addressing the concerns:

Discuss the results from study KN-021 in the context of the demonstrated OS benefit of single agent pembrolizumab over chemotherapy in previously untreated strongly PD-L1 positive (TPS ≥50%) NSCLC (already approved indication) providing all available data across trials in previously untreated PD-L1 strongly positive non-squamous NSCLC patients.

In patients with non-squamous NSCLC with a PD-L1 TPS ≥50%, the benefit of the addition of pembrolizumab to pemetrexed/carboplatin compared with pembrolizumab monotherapy remains undetermined. The following Table summarizes data across trials in previously untreated subjects with PD-L1 strongly positive, non-squamous NSCLC.

Summary of Efficacy Results by Study
(Subjects with Non-squamous NSCLC and TPS ≥50%)

	KEYNOTE-021 Cohort G1[1]	KEYNOTE-021 Cohort A[2,3] [1]	KEYNOTE-021 Cohort B[2] [1]	KEYNOTE-021 Cohort C[2] [1]	KEYNOTE-024[4]	KEYNOTE-001 Cohort F1[5]
Endpoint Study Treatment	**Endpoint (95% CI) (n)**					
ORR Pembro combo	80.0% (56.3-94.3) (n = 20)	56% (21-86) (n = 9)	50% (16-84) (n = 8)	75% (35-97) (n = 8)	44.0% (35.1-53.2) (n = 125)	52.0% (31.3-72.2) (n = 25)
ORR Chemo alone	41.2% (18.4-67.1) (n = 17)	NA	NA	NA	29.8 (22.0-38.7) (n=124)	NA
PFS hazard ratio	0.28 (0.10-0.78)	NA	NA	NA	0.55 (0.39-0.76)	NA
OS hazard ratio	0.40 (0.13-1.19)	NA	NA	NA	0.56 (0.36-0.87)	NA

NA = not available
[1]Updated Analysis 2 (data cut off 31-MAY-2017)
[2]Data cut off 16-DEC-2015
[3]Includes 3 subjects with squamous NSCLC
[4]In KEYNOTE-024, the study treatments were pembro monotherapy and chemo alone
[5]Includes all previously untreated subjects, pembro monotherapy

Clearly, in KEYNOTE-024 the outcomes of previously untreated subjects with NSCLC and a TPS ≥50% treated with pembrolizumab monotherapy are significantly better than those treated with chemotherapy alone; the KEYNOTE-021 Cohort G1 data in the TPS ≥50% subgroup remain exploratory.

Taken together, the results from KEYNOTE-024 and Cohort G1 of KEYNOTE-021 indicate that PD-L1 testing should be performed on all patients with previously untreated NSCLC as the first step in determining the course of treatment. Based on the benefit-risk profile of pembrolizumab monotherapy seen in KEYNOTE-024, patients with both squamous and non-squamous NSCLC tumors expressing PD-L1 with a TPS ≥50% would be most appropriately treated with monotherapy pembrolizumab.

For patients with non-squamous NSCLC, the combination of pembrolizumab with pemetrexed/carboplatin offers another alternative treatment option to standard chemotherapy, irrespective of PD-L1 expression. Both options have yielded far better outcomes than previously reported with standard chemotherapy and are clinically relevant choices.

Provide top-line results of phase 3 study KN-042 comparing pembrolizumab monotherapy to platinum based chemotherapy as first-line treatment in PD-L1 positive (TPS ≥1%) patients, with OS as the primary endpoint, and discuss the results in patients with non-squamous histology in comparison to those from study KN-021.

The results of KEYNOTE-042 are not available as the study has not yet reached any of the event-driven analysis thresholds. The study commenced recruiting in December 2014 and completed enrollment in March 2017.

Acknowledging the clinical relevance of the benefit observed in PD-L1 TPS <1% patients, discuss the somewhat unexpected poor outcome in the chemotherapy arm in the context of all available data (even from literature), and present baseline characteristics of these patients, and discuss the potential impact on the observed treatment effect in this subgroup.

The baseline characteristics of subjects with PD-L1 TPS <1% are presented in the following Table 15:

Subject Characteristics
Cohort G1 Subjects with TPS < 1%
(ITT Population)

	Pembro 200mg Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	21		23		44	
Gender						
Male	8	(38.1)	7	(30.4)	15	(34.1)
Female	13	(61.9)	16	(69.6)	29	(65.9)
Age (Years)						
< 65	16	(76.2)	9	(39.1)	25	(56.8)
>= 65	5	(23.8)	14	(60.9)	19	(43.2)
Mean	60.4		64.3		62.5	
SD	7.4		10.9		9.5	
Median	58.0		67.0		61.0	
Range	50 to 76		37 to 80		37 to 80	
Race						
American Indian Or Alaska Native	1	(4.8)	0	(0.0)	1	(2.3)
Asian	1	(4.8)	2	(8.7)	3	(6.8)
Black Or African American	2	(9.5)	0	(0.0)	2	(4.5)
White	17	(81.0)	21	(91.3)	38	(86.4)
Ethnicity						
Not Hispanic Or Latino	21	(100.0)	21	(91.3)	42	(95.5)
Not Reported	0	(0.0)	2	(8.7)	2	(4.5)
Region						
US	20	(95.2)	22	(95.7)	42	(95.5)
Ex US	1	(4.8)	1	(4.3)	2	(4.5)
Smoking Status						
Never Smoker	2	(9.5)	2	(8.7)	4	(9.1)
Ex Smoker	14	(66.7)	18	(78.3)	32	(72.7)
Current Smoker	5	(23.8)	3	(13.0)	8	(18.2)
ECOG						
0	11	(52.4)	13	(56.5)	24	(54.5)
1	10	(47.6)	10	(43.5)	20	(45.5)
Histology						
Adenocarcinoma	21	(100.0)	19	(82.6)	40	(90.9)
NSCLC NOS	0	(0.0)	3	(13.0)	3	(6.8)
Other	0	(0.0)	1	(4.3)	1	(2.3)
Metastatic Stage						

	Pembro 200mg Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Metastatic Stage						
MX	1	(4.8)	1	(4.3)	2	(4.5)
M0	0	(0.0)	3	(13.0)	3	(6.8)
M1	3	(14.3)	2	(8.7)	5	(11.4)
M1A	6	(28.6)	5	(21.7)	11	(25.0)
M1B	11	(52.4)	12	(52.2)	23	(52.3)
Cancer Stage						
IV	21	(100.0)	23	(100.0)	44	(100.0)
Brain Metastasis Status at Baseline						
Yes	4	(19.0)	1	(4.3)	5	(11.4)
No	17	(81.0)	22	(95.7)	39	(88.6)
Baseline Tumor Size						
Subjects with data	21		21		42	
Mean	72.5		94.0		83.2	
SD	49.4		51.7		51.1	
Median	58.0		87.0		78.5	
Range	13.0 to 185.0		17.0 to 179.0		13.0 to 185.0	
PD-L1 Status						
TPS<1%	21	(100.0)	23	(100.0)	44	(100.0)
Prior Systemic Adjuvant/Neo-adjuvant Therapy						
Yes	1	(4.8)	2	(8.7)	3	(6.8)
No	20	(95.2)	21	(91.3)	41	(93.2)
(Database Cutoff Date: 31MAY2017).						

Source: [P021V01MK3475: analysis-adsl]

The main characteristic exhibiting a difference between treatment arms in the TPS <1% subgroup was age. The majority (76.2%) of subjects in the pembro combo arm were less than 65 years of age, whereas the majority (60.9%) of subjects in the chemo alone arm were over 65 years of age, with median ages of 58 years and 67 years, respectively. In a comprehensive review of lung cancer in the elderly, Hurria and Kris (Ca Cancer J Clin, 2003) discuss age as a prognostic factor in NSCLC outcomes and conclude that age is not a significant prognostic factor for OS or response to treatment for patients with NSCLC. In fact, in their review, some studies indicated that increased age was associated with an enhanced response to chemotherapy.

Supporting the conclusion that PD-L1 expression is not a predictive marker for survival among patients with advanced NSCLC treated with chemotherapy is an analysis by Sorensen et al (Transl Oncol 2016), who presented data from 204 advanced NSCLC patients with PD-L1 expression determined by a prototype 22C3 assay. All patients were treated with chemotherapy alone and no differences in survival were demonstrated between PD-L1 subgroups.

With regard to KEYNOTE-021, the study was not designed and therefore not powered to analyze efficacy by subgroups in either the experimental or the control arm and any such analysis is exploratory. The outcome differences between TPS subgroups apparent in the pre-specified analysis have narrowed in updated analysis 2; additional responses were observed after the pre-specified analysis (1 in the pembro combo arm and 2 in the chemo alone arm) and data from updated analysis 2 are discussed here.

The ORR for the entire pembro combo arm (56.7% [95% CI 43.2-69.4]) and for the PD-L1 TPS <1% subgroup of the pembro combo arm (61.9% [95% CI 38.4-81.9]) were similar.

The ORR for the entire chemo alone arm (31.7% [95% CI 20.6-44.7]) appeared numerically higher than the ORR observed for the PD-L1 TPS<1% subgroup of the chemo alone arm (17.4% [95% CI 5.0-38.8]). However, the confidence intervals substantially overlap and the apparent difference may be due to the small number of subjects in each subgroup. In addition, the median PFS observed in the PD-L1 TPS <1%

subgroup of the chemo alone arm (8.3 months [95% CI 2.0-10.3]) was similar to the overall chemo alone arm result and was better than the median PFS observed in multiple studies of pemetrexed/platinum treatment for advanced, nonsquamous NSCLC and the shape of the PFS curve in the Kaplan-Meier plot was consistent with prior studies.

In conclusion, KEYNOTE-021 Cohort G1 demonstrated a large, statistically significant, clinically meaningful benefit in both ORR and PFS with the addition of pembrolizumab to standard chemotherapy in a PD-L1 unselected population. Subset analyses in this study remain exploratory.

Rapporteur assessment

Pembrolizumab as single-agent is approved in EU for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. The approval was based on the results of KN024 that showed:

- a clear benefit of pembrolizumab over platinum-containing chemotherapy in terms of both PFS (HR 0.50; 95% CI 0.37, 0.68) and OS (HR 0.60; 95%CI 0.41, 0.89), that was undisputable even considering the non-squamous subgroup;

- a more favourable safety profile of pembrolizumab as single agent over chemotherapy.

Taking this into account, the MAH was requested to discuss the results in PD-L1 strongly-positive non-squamous patients from Study KN021 in comparison with those observed in Study KN024, and across the various trials that included a similar patient population.

The MAH pointed out their approach to the clinical development of Keytruda for NSCLC, which is biomarker-based for monotherapy and non-biomarker-based for combination treatments. This is not questioned, in principle. It is also acknowledged that, due to the parallel development of different therapeutic approaches it is not possible to generate data of direct comparisons for all of them. On the other hand, it is essential to put results of studies supporting a new indication in the context of available therapeutic treatment options, especially when a worse tolerability appears evident, and data are available only from an exploratory study with the results from the confirmatory trial still pending, as it is in this case.

The MAH discussed the results from Study KN-021 in the context of the already approved indication in PD-L1 strongly positive.

Study KN021 was not designed to address the efficacy of pembro combo in this subset of patients, and a very limited number of PD-L1 strongly-positive patients were included in the trial (all cohorts), of whom only 45 were treated with combination (20 in cohort G1). Taking into account the relatively limited data, and the intrinsic limitations of cross-trial comparison, it cannot be firmly concluded that the combination is more efficacious than the monotherapy, although a higher response rate has been reported with the combination.

The MAH itself admits that "*patients with both squamous and non-squamous NSCLC tumors expressing PD-L1 with a TPS≥50% would be most appropriately treated with monotherapy pembrolizumab*".

Overall, the combination of pembrolizumab and chemotherapy appears more efficacious than chemotherapy. However, the concerns expressed regarding the lack of an outstanding benefit of the combination over chemotherapy in subjects PD-L1 TPS ≥1% persist, since at the updated analysis the median PFS, and the PFS rate at 6 months is quite similar (69.3% with pembro combo and 70.8% with chemo alone). The late separation of the K-M curves is acknowledged.

With regard to the possible explanation for the poor outcome observed with chemotherapy in PD-L1<1% subjects, the MAH presented and discussed the baseline characteristics showing a meaningful imbalance

essentially with regard to age, with 23.8% of subjects older than 65 years in the experimental arm vs 60.9 in the control arm. Whether this have influenced the observed result is unclear, and the MAH did not discuss the compliance to chemotherapy by age. It is acknowledged, that available data from external sources do not suggest that PD-L1 is predictive of outcome on chemotherapy for NSCLC patients, and therefore the potential role of chance imbalances in age could have been better examined, and more thoroughly discussed.

In conclusion, it is acknowledged that data from Study KN021 suggest a benefit of the pembro combination over chemotherapy. However, based on available data not allowing to draw firm conclusion with regard to many relevant aspects, it would seem wise to wait for the top-line results from studies KN189 and KN042. Interim analyses for these studies are currently planned and the MAH is therefore asked to provide these data as available, in order to allow a more informed evaluation of the B/R (Study KN189), and a better contextualization (Study KN042), of the sought indication.

Co-Rapp assessment:

For the overall population the combination of pembrolizumab and chemotherapy appears more efficacious than chemotherapy. The updated analysis provided by the MAH strongly support this assessment. With the updated follow-up the benefit in terms of ORR and PFS is confirmed. A trend in OS favoring the experimental arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436) is reported despite a not negligible rate of cross-over from patients in the control arm (63.5%) to subsequent therapy with a PD-1/PD-L1 inhibitor. With these outstanding results one could discuss the approval of the chemo/combo treatment for the overall population considering the time lag for the approval and the implication for patients, if the request for first Phase III data persists. Nevertheless there remain questions regarding the efficacy and the benefit /risk balance in the different subgroups according to PD-L1 expression in view of the existing data for pembrolizumab monotherapy for subjects with TPS ≥50% (and the awaited monotherapy data for TPS>1%). The differences in the HRs of TPS PD-L1<1, PD-L1 >1, PDL1>50% are somehow unexpected and inconsistent. From our point of view this is most likely based on the limited sample size. With this limited dataset it is impossible to draw conclusions for relevant aspects like the benefit/risk assessment for the PD-L1 strong positive subpopulation. As already pointed out, the prevalence of NSCLC is relatively high and a large number of patients are supposed to be treated in the first-line setting with this pembrolizumab/chemotherapy combination, therefore approval with data from a the limited number of patients (n=60) treated with this combination in only one phase II study remains questionable. The MAH is therefore asked to submit the requested data in their responses to the outstanding questions in the next round.

CHMP conclusion: Issue not solved. The MAH should provide top-line results of Study KN189 as available. If available, top-line results of Study KN042 should be provided as well.

Question 3

The sought indication refers to Keytruda administered in combination with platinum-pemetrexed chemotherapy. If not otherwise justified by the MAH, the wording of indication should be revised to reflect that the pembrolizumab/chemotherapy combination in KN-021 included carboplatin as part of the platinum doublet.

Summary of MAH's response

The MAH acknowledges the comment and has revised the wording of the indication to reflect that carboplatin was included as part of the platinum doublet.

CHMP assessment

The MAH revised the wording as requested.

Issue solved.

Question 4

Based on inclusion criteria in the provided study protocol, the provision of a tumor biopsy sample for assessment of PD-L1 was not required for eligibility, as on the contrary reported in the paper (Langer CJ, Lancet Oncol 2016). On the other hands, in Cohort G1 patients were stratified according to PD-L1 status. The MAH is asked to clarify.

Summary of MAH's response

The MAH would like to clarify that the provision of tumor tissue was required according to the protocol. This requirement was not stated in the inclusion criteria, but was detailed in the study design section of the protocol [P021V01MK3475: 16.1.1.4 sect. 2.1].

"Participation in this trial will be dependent upon supplying tumor tissue from either a newly obtained formalin-fixed specimen, or an older formalin-fixed, paraffin-embedded specimen from locations not radiated prior to biopsy. Newly obtained formalin-fixed specimens are strongly encouraged. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, only new biopsies will be acceptable for determination of PD-L1 status. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner."

CHMP assessment

The MAH provided the requested clarification

Issue solved.

Question 5

The MAH should clarify the applied randomization scheme providing further details on method applied (i.e. if a block randomization was used within each stratum). If this is the case, the MAH should provide details on size of blocks and on how they were generated (i.e, through a permuted block design). In addition, the list of randomization by chronological inclusion in the two arms should be provided.

Summary of MAH's response

The randomization and stratification scheme was described completely in Sections 5.3 and 5.4 of the protocol and in Section 9.4.5 of the study report .

Randomization occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Four cohorts were randomized: A, B, C, and G. Subjects in Cohorts A, B, and C were assigned randomly in a 1:1 ratio to receive chemotherapy plus pembrolizumab 2 mg/kg or chemotherapy plus pembrolizumab 10 mg/kg. Subjects in Cohort G1 were assigned randomly in a 1:1 ratio to receive carboplatin and pemetrexed with or without pembrolizumab 200 mg. Cohort G2 was not initiated.

Randomization of subjects in Cohort G1 was stratified based on negative or positive tumor expression of PD-L1. Positive tumor expression of PD-L1 was defined as a Tumor Proportion Score (TPS) ≥1%. The negative stratum included subjects with a TPS <1% and subjects with tumor tissue inevaluable for PD-L1. A block randomization with blocks of 4 was used within each stratum.

The list of subjects randomized within each stratum by chronological inclusion in the 2 treatment arms has been provided.

Please note that a testing block allocation schema was inadvertently used to randomize the first 2 subjects in each stratum by the IVRS vendor, ALMAC. ALMAC quickly identified the issue, generated a formal block allocation schema, and applied it to the subsequent 119 randomized subjects in Cohort G1.

In the TPS negative stratum, subjects randomized from 31-MAR-2015 through 20-JAN-2016 maintained balanced randomization in blocks of 4. In the TPS positive stratum, subjects randomized from 31-MAR-2015 through 25-JAN-2016 likewise maintained balanced randomization in blocks of 4. Four subjects, despite allocation using a testing randomization schema, maintained the balance across the 2 strata.

The MAH remained blinded to the randomization schedule throughout the trial.

CHMP assessment

The MAH provided the requested clarifications. A block randomization with blocks of 4 was used within each stratum, with the exception of the first 2 patients in each stratum that were erroneously randomized based on a testing block allocation schema: this is however not deemed to be a relevant issue.

Issue solved.

Question 6

The MAH is asked to clarify the number of major protocol deviations and patients affected in Cohorts G1 and provide an overview of all major deviations.

Summary of MAH's response

The MAH maintains a strict definition of major deviations including any issues regarding consent forms and safety reporting as major deviations, even if the incidents were administrative in nature. Importantly, no subjects in Cohort G1 or C were excluded from the analyses as none of the protocol deviations were considered to have the potential to negatively impact the integrity of the analyses. The rights and safety of the subjects were not compromised. There were 58 major protocol deviations documented for 36 randomized subjects and 4 subjects who were screened but not eligible for randomization.

Although all subjects provided prospective consent prior to study procedures, the most common protocol deviations in Cohorts G1 or C were related to documentation of the ICF process (eg, missing or late Investigator signature on the ICF, missing documentation of the IC process in source documents, missing signed updated ICFs) and timely reporting of SAEs/ECIs to the Sponsor (ICF documentation: 21 subjects at 7 sites; SAE/ECI reporting: 21 subjects at 8 sites). Other deviations included EGFR/ALK results not being available at time of randomization (subsequently shown to be negative) or a CT of the pelvis not obtained for some time points with no change in subsequent imaging. A listing with detail of each issue has been submitted.

CHMP assessment

The MAH did not provide the number of major deviations specifically for part G1 of the Study, as requested. However, details were provided on the type of deviations and, based on such information, it is considered that they are not expected to have impacted the results.

Issue solved.

Question 7

For 8 (12.7%) patients in the chemotherapy arm reported to have NSCLC not otherwise specified (NOS)/other (these were only 2 in the experimental arm), the squamous histology cannot be excluded. Details on the clinical outcome of these patients should be provided by the MAH.

Summary of MAH's response

The individual clinical outcomes for the 9 subjects (2 pembro combo, 7 chemo alone) reported to have NSCLC NOS are detailed in the following Table. No treatment discontinuation is specified for one subject (randomized and not treated) and for another subject (ongoing).

One additional subject randomized to chemo alone and whose histology was designated as "other" was a subject with large cell carcinoma and is not included in Table.

Listing of Clinical Outcomes for Subjects with NSCLC Not Otherwise Specified (NOS)
Cohort G1 Subjects
(ITT Population)

Subject ID	Best Response	PFS Event Flag	PFS Duration (Months)	OS Event Flag	OS Duration (Months)	Reason for Treatment Discontinuation
Control						
Site Number=PPD Subject ID=PPD Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=398						
PPD	PD	Y	1.35	Y	19.0	PROGRESSIVE DISEASE
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=						
PPD	NE	N	0.03	N	0.30	
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=117						
PPD	SD	Y	2.79	Y	7.85	PROGRESSIVE DISEASE
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=1						
PPD	NE	Y	0.79	Y	0.79	ADVERSE EVENT
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=152						
PPD	PD	Y	1.18	Y	7.66	PROGRESSIVE DISEASE
Site Number=PPD Subject ID=PPD Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=45						
PPD	SD	Y	1.91	Y	2.37	PROGRESSIVE DISEASE

Subject ID	Best Response	PFS Event Flag	PFS Duration (Months)	OS Event Flag	OS Duration (Months)	Reason for Treatment Discontinuation
Site Number=PPD Subject ID=PPD Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=232						
PPD	SD	Y	9.33	Y	9.33	PROGRESSIVE DISEASE
Pembro 200mg Combo						
Site Number=PPD Subject ID=PPD Gender=M, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=						
PPD	SD	Y	2.76	N	23.2	
Site Number=PPD Subject ID=PPD Gender=F, Race=PPD Age=PPD Years, Rel Day of Study Medication Discontinuance†=148						
PPD	PD	Y	1.28	Y	11.9	PROGRESSIVE DISEASE

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
Database Cutoff Date: 31MAY2017.

Source: [P021V01MK3475: analysis-adsl; adtte;adorr]

CHMP assessment

The MAH provided the requested data. It is noted that among the 6 subjects with NOS histology treated with chemotherapy (one subject was not treated), the best response was SD and PFS duration was far shorter than the median PFS observed in the control arm for all patients except for one subject. A similar finding is observed also in the 2 patients with NOS histology in the experimental arm. All patients treated in the control arm died with OS duration usually far shorter than the median OS reported in the updated analysis (see Q9).

To what extent the inclusion of such patients showing poor response to chemotherapy, unfortunately much more represented in the control arm (7/63 vs 2/60) might have influenced the study results is hard to establish.

The MAH is requested to provide a sensitivity analysis excluding patients with NOS histology for ORR, PFS and OS.

Issue not solved.

Question 8

The MAH should provide a summary of Objective Response, including for each treatment group information on CR/PR.

Summary of MAH's response

Objective Response Rate for Pre-Specified and Updated Analysis 2 in Cohort G1

	Study Treatment	
Endpoint	**Pembro Combo**	**Control**
ORR (pre-specified analysis)	55.0% (55.0% PR, 0% CR)	28.6% (28.6% PR, 0% CR)
ORR (updated analysis 2)	56.7% (55.0% PR, 1.7% CR)	31.7% (30.2% PR, 1.6% CR)

Please refer to Question 9 for further details on the updated efficacy information.

CHMP assessment

The MAH provided the requested data. Only at the updated analysis CR were reported (1 in each arm).

Issue solved.

Question 9

Updated efficacy results from cohort G1, also including PFS2 data, should be provided.

Summary of MAH's response

After an additional 10 months of follow-up beyond the pre-specified analysis, a high level summary of the updated efficacy analysis 2 (data cut off of 31 May 2017) of Cohort G1 for ORR, PFS, DOR, and OS and a brief comparison to the pre-specified analysis has been submitted.

Cohort G1

The median follow-up for subjects in the updated analysis 2 of Cohort G1 was 18.7 months (range 0.8-29.0), with a minimum of 16 months from the last patient randomized until the data cut-off [Table 20].

Objective Response Rate

Analysis of Objective Response (Confirmed)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

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

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

Source: [P021V01MK3475: analysis-adsl; adorr]

With the added follow-up, 2 additional responses were observed in the chemo alone arm and 1 additional response was observed in the pembro combo arm. The between arm difference was similar to the pre-specified analysis. Additionally, 1 CR developed in each arm.

Progression-Free Survival

Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro 200mg Combo	60	26 (43.3)	681.4	3.8	19.0 (8.5, .)	79.0 (65.9, 87.5)	0.54 (0.33, 0.88)	0.00673
Control	63	40 (63.5)	537.0	7.4	8.9 (6.2, 11.8)	66.3 (52.7, 76.8)	---	---

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

Source: [P021V01MK3475: analysis-adsl; adtte]

The median PFS of the pembro combo arm increased from 13.0 months in the pre-specified analysis to 19.0 months in updated analysis 2.

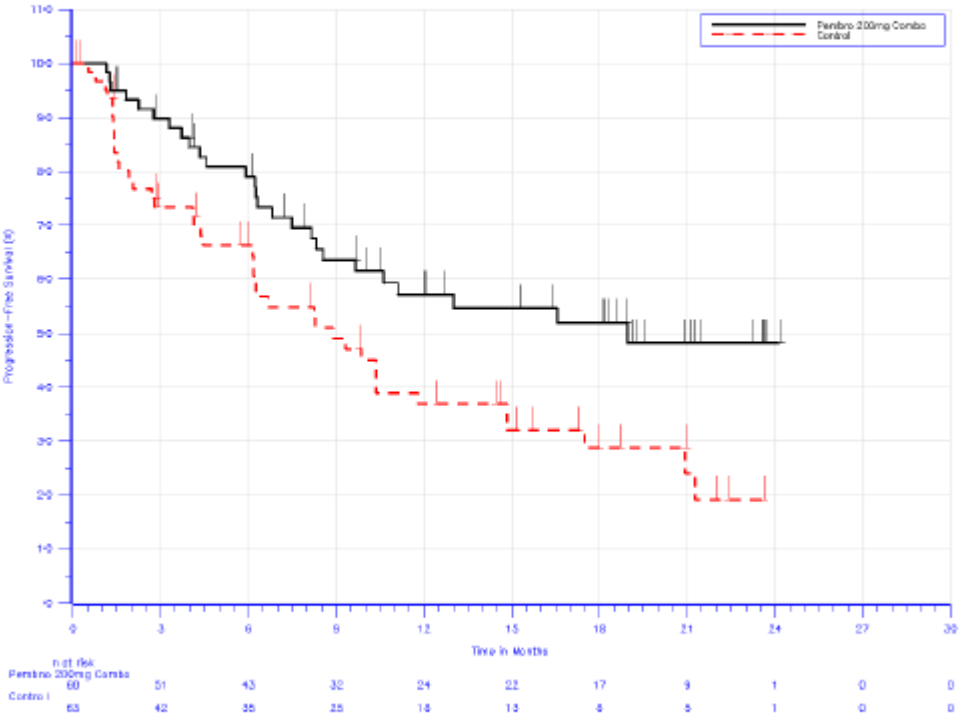
Summary of PFS Rate Over Time Based on BICR per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

	Pembro 200mg Combo (N=60)	Control (N=63)
PFS rate at 6 Months in (95% CI)†	79.0 (65.9, 87.5)	66.3 (52.7, 76.8)
PFS rate at 12 Months in (95% CI)†	57.1 (42.6, 69.2)	36.8 (24.1, 49.6)
PFS rate at 18 Months in (95% CI)†	51.9 (37.1, 64.8)	28.7 (16.6, 42.1)
PFS rate at 24 Months in (95% CI)†	48.2 (32.9, 61.9)	19.2 (7.7, 34.5)
†From the product-limit (Kaplan-Meier) method for censored data. BICR = Blinded Independent Central Review Database Cutoff Date: 31MAY2017.		

Source: [P021V01MK3475: analysis-adsl; adtte]

The Kaplan-Meier plot demonstrated early separation of the curves, sustained from the first assessment through the remainder of the evaluation period, and the PFS curve for the pembro combo arm plateaued just above the 50% mark after approximately 12 months and declined gradually thereafter:

Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)



(Database Cutoff Date: 31May2017).
Source: [P021V01MK3475: analysis-adsl; adtte]

Duration of Response

The median DOR was not reached in either the pembro combo arm (range 1.4+ to 22.7+ months) or the chemo alone arm (range 2.8 to 23.7+ months).

Summary of Time to Response and Duration of Response for Subjects with Confirmed Response
Based on BICR Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

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

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

Source: [P021V01MK3475: analysis-adsl; adtte; adorr]

More subjects had an ongoing response in the pembro combo arm (17/34 [50.0%]) than in the chemo alone arm (8/20 [40.0%]) at the time of the data cut-off.

Overall Survival

In the updated analysis, a definite trend in OS was observed favoring the pembro combo arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436).

Analysis of Overall Survival
Cohort G1 Subjects
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro 200mg Combo	60	20 (33.3)	1055.6	1.9	Not Reached (22.8, .)	91.7 (81.1, 96.4)	0.59 (0.34, 1.05)	0.03436
Control	63	31 (49.2)	1007.1	3.1	20.9 (14.9, .)	91.9 (81.7, 96.6)	---	---

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

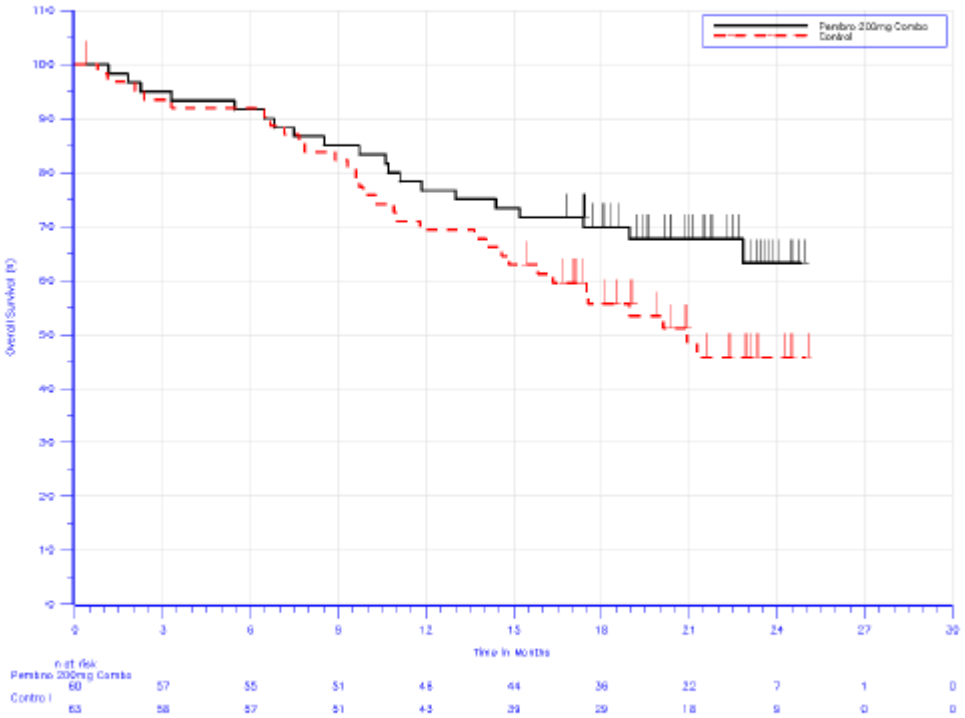
Source: [P021V01MK3475: analysis-adsl; adtte]

Overall Survival Rate
Cohort G1 Subjects
(ITT Population)

	Pembro 200mg Combo (N=60)	Control (N=63)
OS rate at 6 Months in (95% CI)†	91.7 (81.1, 96.4)	91.9 (81.7, 96.6)
OS rate at 12 Months in (95% CI)†	76.7 (63.8, 85.5)	69.4 (56.3, 79.2)
OS rate at 18 Months in (95% CI)†	69.8 (56.5, 79.8)	55.7 (42.4, 67.2)
OS rate at 24 Months in (95% CI)†	63.2 (47.4, 75.4)	45.8 (31.9, 58.7)
†From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 31MAY2017.		

Source: [P021V01MK3475: analysis-adsl; adtte]

Kaplan-Meier Estimates of Overall Survival
Cohort G1 Subjects
(ITT Population)



(Database Cutoff Date: 31May2017).
Source: [P021V01MK3475: analysis-adsl; adtte]

Overall, 40 of 63 subjects (63.5%) in the chemo alone arm received subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab or durvalumab), including 25 who received pembrolizumab as part of the study crossover. The crossover rate was 75.5% (40/53) for subjects who discontinued treatment in the chemo alone arm in this updated analysis, similar to the rate in the pre-specified analysis (74.4% [32/43]).

The high rate of subsequent PD-1/PD-L1 inhibitor therapy may have an influence on OS results and the shape of the Kaplan-Meier curves, resulting in the extremely favorable survival observed in the chemo alone arm. Despite the excellent survival observed in the chemo alone arm, a notable OS trend favoring the pembro combo arm has emerged supporting the importance of up front combination therapy initially shown with ORR and PFS results compared to giving chemotherapy followed by a PD-1/PD-L1 inhibitor at the time of progression.

With each analysis, an improvement in the OS HR is seen. In the pre-specified analysis, OS was not significantly different between treatment arms (HR 0.90, 95% CI 0.42-1.91) and the survival curves on the Kaplan-Meier plot were overlapping. In updated analysis 1 (data cutoff date:31 Dec 2016), a trend for survival favoring the pembro combo arm (HR 0.69, 95% CI 0.36-1.31) with separation of the survival curves was observed. Updated analysis 2 now showed a definitive OS trend favoring the pembro combo arm with further separation of the Kaplan-Meier curves.

Progression-Free Survival 2

Progression-free survival 2 (PFS2) was defined as the time from randomization to progression after nextline therapy (as determined by investigator) or death from any cause. If no data on progression or death were available, the date of discontinuation of next-line therapy was used as a surrogate.

A benefit in PFS2 was observed for the pembro combo arm (HR 0.56, 95% CI 0.35-0.92, p=0.00960).

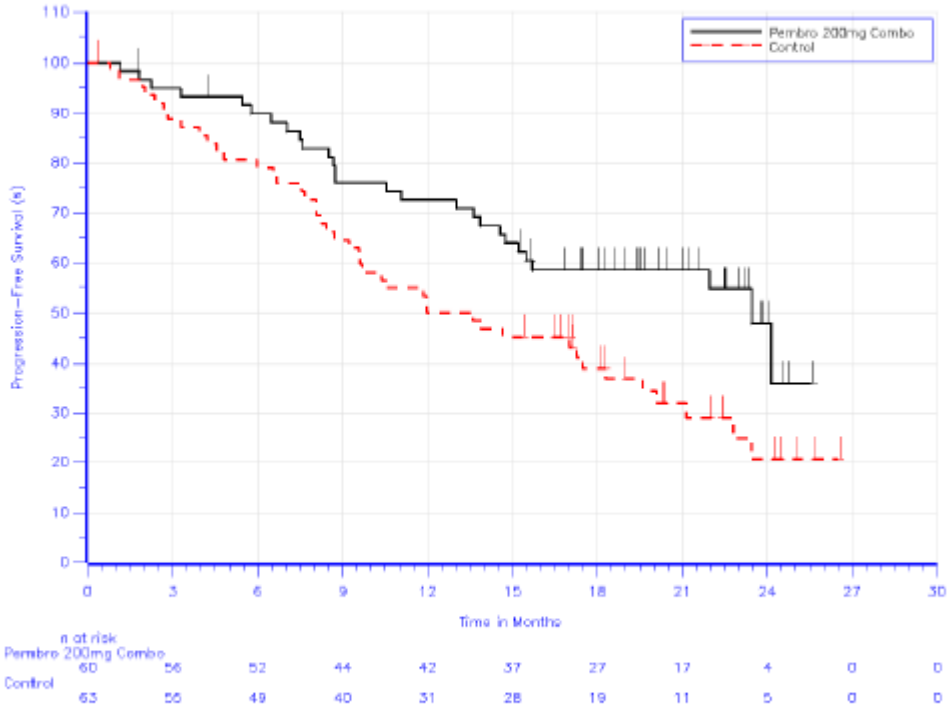
Analysis of PFS2
Based on Investigator Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembro 200mg Combo	60	27 (45.0)	933.1	2.9	23.5 (15.2, .)	89.8 (78.7, 95.3)	0.56 (0.35, 0.92)	0.00960
Control	63	43 (68.3)	812.1	5.3	12.8 (9.2, 18.3)	79.0 (66.6, 87.2)	---	---

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

Source: [P021V01MK3475: analysis-adsl; adtte]

Kaplan-Meier Estimates of PFS2
Based on Investigator Assessment per RECIST 1.1
Cohort G1 Subjects
(ITT Population)



Database Cutoff Date: 31MAY2017.
Source: [P021V01MK3475: analysis-adsl; adtte]

CHMP assessment

The MAH provided updated results. Overall, with an updated follow-up the benefit in terms of ORR and PFS is confirmed. A trend in OS favouring the experimental arm compared to the chemo alone arm (HR 0.59, 95% CI 0.34-1.05, p=0.03436) is reported despite a not negligible rate of patients in the control arm (40/63, 63.5%) receiving subsequent therapy with a PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab or durvalumab). A benefit in PFS2 was also reported (HR 0.56, 95% CI 0.35-0.92, p=0.00960).

Please, see the assessment of the response to Q2.

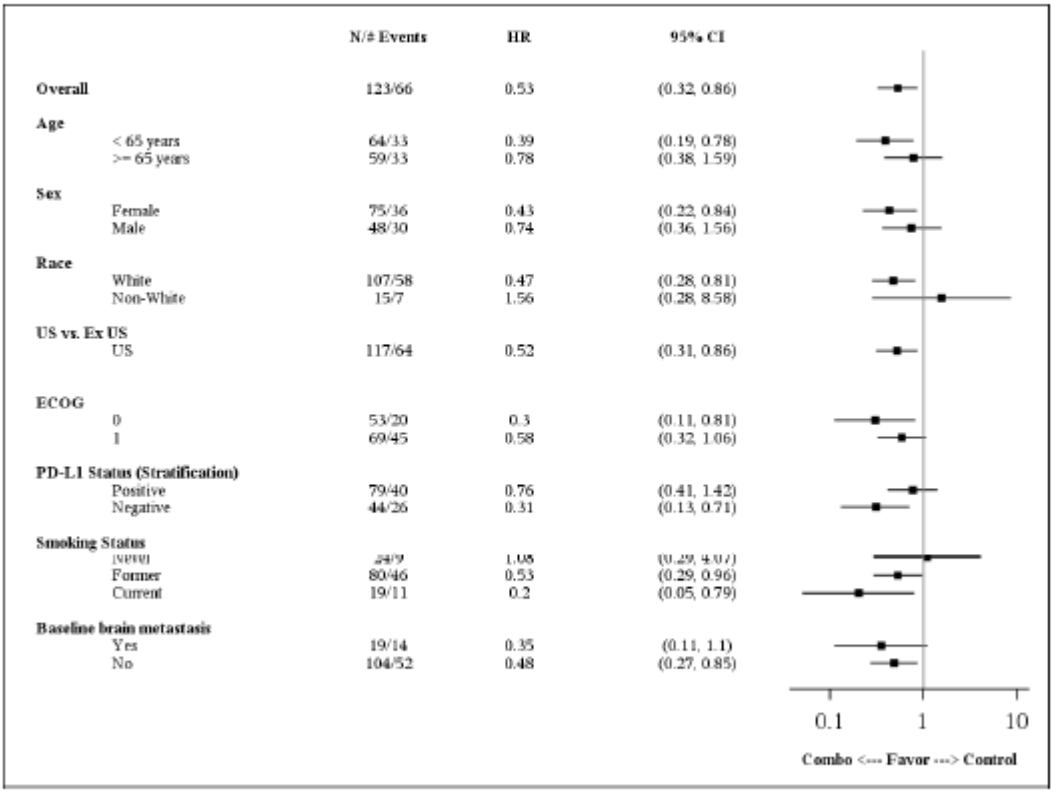
Issue solved.

Question 10

A reduced difference in ORR was reported with pembrolizumab combination compared to chemotherapy alone in never smoker patients. The Forest Plot of PFS by subgroup factors should be provided.

Summary of MAH's response

Forest Plot of PFS Hazard Ratio by Subgroup Factors
Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule)
Cohort G1 Subjects
(ITT Population)



Database Cutoff Date: 31MAY2017.
Source: [P021V01MK3475: analysis-adsl; adtte];

Of note, any apparent differences are likely due to random variation given the small subsets and wide confidence intervals, all of which overlap the overall population HR estimate. Specifically, in the never smokers subgroup (pembro combo 15 subjects, chemo alone 9 subjects), the PFS HR is 1.08 (95% CI 0.29, 4.07) and despite a HR slightly greater than 1.0, the wide confidence interval indicates this outcome is consistent with the outcomes of the entire population.

CHMP assessment

The MAH provided the requested data. Although it is acknowledged that the numbers are too small to draw conclusions, the finding is in line with those reported in Study KN024 and KN010.

The MAH is requested to include information in the SmPC Section 5.1 on the reduced benefit observed in the combo arm compared to chemotherapy in this subgroup of patients

Issue solved provided that the MAH will include the requested information in Section 5.1. of the SmPC.

Question 11

A randomized, open label, placebo-controlled trial of platinum plus pemetrexed chemotherapy with or without pembrolizumab (KEYNOTE-189) is at present ongoing. The MAH should provide an update of enrollment and estimated timelines for the submission of results.

Summary of MAH's response

KEYNOTE-189 enrollment was completed as of March 2017; analysis timing is event-driven

CHMP assessment

The MAH provided the requested information.

Please, see the assessment of the response to Q2. The MAH is requested to provide data from the interim PFS analysis .

Issue solved

Question 12

The inclusion criteria of Study KN021 accepted all NSCLC histologies for inclusion in the study. Nevertheless only Non-squamous NSCLC patients were included in Cohort G1. The MAH is asked to comment on this.

Summary of MAH's response

KEYNOTE-021 was a multi-cohort study designed to evaluate pembrolizumab combinations in NSCLC. The inclusion criteria indicated acceptance of all histologies; however, in the protocol trial design further requirements for each cohort were detailed:

"Cohorts G1 and G2 – First Line subjects who are EGFR wild type non-squamous histology"

CHMP assessment

Issue resolved

Clinical safety aspects

Other concerns

Question 13

A direct comparison of safety data among KN021, KN024 study, and, if available, KN042 should be provided and discussed by the MAH.

Summary of MAH's response

A direct comparison of safety data from studies KEYNOTE-021 and KEYNOTE-024 is provided below. Data from KEYNOTE-042 are not yet available. It is worth pointing out that cross trial comparisons have limitations and can be considered directional only.

Overall, the incidence of known AEOSIs for pembrolizumab as well as the incidence of individual AEOSIs was comparable between the pembro combo population from KEYNOTE-021 and the pembrolizumab monotherapy population from KEYNOTE-024.

Although the observed rates of other events in the pembro combo population were generally higher than those in the pembrolizumab monotherapy population from KEYNOTE-024, this would be anticipated given that similar rates for these events were also observed in the chemo alone arm of KEYNOTE-021, indicating a contribution from chemotherapy.

In order to compare data collected over similar follow-up periods, safety data from the pre-specified analysis of KEYNOTE 021 are compared with the safety data from KEYNOTE-024. The median and minimum follow-up times for the 2 studies using these analyses were similar (KEYNOTE-021 Cohort G1: 10.6 months and 6 months, respectively; KEYNOTE-024: 11.2 months and 6 months, respectively).

<u>Overall Adverse Events</u>

Adverse Event Summary
Subjects from KN021 Cohorts C and G1 and Reference Data Comprising Subjects Treated with MK-3475 from KN024
(ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		154	
with one or more adverse events	61	(98.4)	83	(100.0)	148	(96.1)
with no adverse event	1	(1.6)	0	(0.0)	6	(3.9)
with drug-related† adverse events	56	(90.3)	79	(95.2)	113	(73.4)
with toxicity grade 3-5 adverse events	32	(51.6)	48	(57.8)	82	(53.2)
with toxicity grade 3-5 drug-related adverse events	16	(25.8)	33	(39.8)	41	(26.6)
with serious adverse events	17	(27.4)	36	(43.4)	68	(44.2)
with serious drug-related adverse events	6	(9.7)	22	(26.5)	33	(21.4)
who died	2	(3.2)	3	(3.6)	9	(5.8)
who died due to a drug-related adverse event	2	(3.2)	1	(1.2)	1	(0.6)
discontinued‡ due to an adverse event	8	(12.9)	14	(16.9)	14	(9.1)
discontinued due to a drug-related adverse event	8	(12.9)	11	(13.3)	11	(7.1)
discontinued due to a serious adverse event	3	(4.8)	9	(10.8)	13	(8.4)
discontinued due to a serious drug-related adverse event	3	(4.8)	6	(7.2)	10	(6.5)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN024.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.
MK-3475 KN024 Database Cutoff Date: 09MAY2016.

Source: [ISS: analysis-adsl; adae; aeplus]

Subjects With Adverse Events
(Incidence ≥10% in One or More Treatment Groups)
Subjects from KN021 Cohorts C and G1 and Reference Data Comprising Subjects Treated with MK-3475 from KN024
(ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		154	
with one or more adverse events	61	(98.4)	83	(100.0)	146	(94.8)
with no adverse events	1	(1.6)	0	(0.0)	8	(5.2)
Fatigue	31	(50.0)	59	(71.1)	32	(20.8)
Nausea	35	(56.5)	52	(62.7)	30	(19.5)
Constipation	23	(37.1)	45	(54.2)	32	(20.8)
Anaemia	36	(58.1)	31	(37.3)	20	(13.0)
Diarrhoea	14	(22.6)	30	(36.1)	32	(20.8)
Dyspnoea	13	(21.0)	29	(34.9)	34	(22.1)
Decreased appetite	14	(22.6)	27	(32.5)	31	(20.1)
Rash	10	(16.1)	25	(30.1)	22	(14.3)
Vomiting	17	(27.4)	25	(30.1)	12	(7.8)
Headache	10	(16.1)	23	(27.7)	9	(5.8)
Cough	11	(17.7)	22	(26.5)	26	(16.9)
Dizziness	10	(16.1)	21	(25.3)	16	(10.4)
Pruritus	3	(4.8)	21	(25.3)	23	(14.9)
Oedema peripheral	11	(17.7)	19	(22.9)	16	(10.4)
Alanine aminotransferase increased	9	(14.5)	18	(21.7)	17	(11.0)
Upper respiratory tract infection	2	(3.2)	18	(21.7)	9	(5.8)
Aspartate aminotransferase increased	13	(21.0)	17	(20.5)	13	(8.4)
Arthralgia	15	(24.2)	16	(19.3)	24	(15.6)
Insomnia	9	(14.5)	16	(19.3)	13	(8.4)
Back pain	6	(9.7)	15	(18.1)	20	(13.0)
Blood creatinine increased	5	(8.1)	15	(18.1)	10	(6.5)
Alopecia	2	(3.2)	14	(16.9)	2	(1.3)
Dysgeusia	7	(11.3)	14	(16.9)	3	(1.9)
Neuropathy peripheral	3	(4.8)	14	(16.9)	2	(1.3)
Lacrimation increased	8	(12.9)	13	(15.7)	0	(0.0)
Pain in extremity	2	(3.2)	13	(15.7)	6	(3.9)
Hypothyroidism	3	(4.8)	12	(14.5)	14	(9.1)
Rash maculo-papular	2	(3.2)	12	(14.5)	6	(3.9)
Rhinorrhoea	3	(4.8)	12	(14.5)	2	(1.3)
Anxiety	2	(3.2)	11	(13.3)	4	(2.6)
Dehydration	4	(6.5)	11	(13.3)	4	(2.6)
Dry eye	1	(1.6)	11	(13.3)	2	(1.3)
Hyperglycaemia	6	(9.7)	11	(13.3)	11	(7.1)
Neutrophil count decreased	8	(12.9)	11	(13.3)	1	(0.6)
Urinary tract infection	2	(3.2)	11	(13.3)	8	(5.2)
Abdominal pain	2	(3.2)	10	(12.0)	10	(6.5)
Hypertension	3	(4.8)	10	(12.0)	6	(3.9)
Hypokalaemia	7	(11.3)	10	(12.0)	4	(2.6)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Dry skin	4	(6.5)	9	(10.8)	13	(8.4)
Pyrexia	3	(4.8)	9	(10.8)	24	(15.6)
Weight decreased	8	(12.9)	9	(10.8)	13	(8.4)
Neutropenia	8	(12.9)	8	(9.6)	2	(1.3)
White blood cell count decreased	8	(12.9)	7	(8.4)	1	(0.6)
Depression	7	(11.3)	5	(6.0)	2	(1.3)
Platelet count decreased	8	(12.9)	3	(3.6)	1	(0.6)
Nasopharyngitis	2	(3.2)	2	(2.4)	16	(10.4)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN024.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.
MK-3475 KN024 Database Cutoff Date: 09MAY2016.

Source: [ISS: analysis-adsl; adae; aeplus]

It is anticipated that the addition of chemotherapy to pembrolizumab would result in higher rates of AEs known to be associated with chemotherapy in the pembro combo group compared with subjects administered pembrolizumab monotherapy given the contribution from chemotherapy.

The overall incidence of Grade 3-5 AEs in the pembro combo population was similar to that observed in the pembrolizumab monotherapy population from KEYNOTE-024 (57.8% vs 53.2%). The incidence of Grade 3-5 anaemia was higher in the pembro combo population as compared to the pembrolizumab monotherapy population from KEYNOTE-024 (13.3% vs. 4.5%); however the incidence was no different from that in the chemo alone arm (14.5%). The incidence of Grade 3-5 cellulitis and pneumonia were also higher in the pembro combo population compared with the pembrolizumab monotherapy population from KEYNOTE-024 (cellulitis: 4.8% v. 0.6%, pneumonia: 4.8% vs 1.9%). Given the small numbers, as these rates represent 4 subjects or fewer, it is difficult to draw a meaningful conclusion from this observed difference.

The overall incidence of SAEs in the pembro combo population was similar to that observed in the pembrolizumab monotherapy population from KEYNOTE-024 (43.4% vs 44.2%). The incidences of SAEs of cellulitis, acute kidney injury, and pneumonia were higher in the pembro combo population compared with the pembrolizumab monotherapy population from KEYNOTE-024 (cellulitis: 4.8% vs 0.6%, acute kidney injury: 4.8% vs 0.0%, and pneumonia 4.8% vs 1.9%). As noted for Grade 3-5 events, given the small numbers it is difficult to draw a meaningful conclusion from this observed difference.

The overall incidence of AEs resulting in treatment discontinuation was higher in the pembro combo population compared with the pembrolizumab monotherapy population from KEYNOTE-024 (16.9% vs 9.1%).

Subjects With Adverse Events Resulting in Treatment Discontinuation
(Incidence ≥1 Subjects in One or More Treatment Groups)
Subjects from KN021 Cohorts C and G1 and Reference Data Comprising Subjects Treated with MK-3475 from KN024
(ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		154	
with one or more adverse events	8	(12.9)	14	(16.9)	14	(9.1)
with no adverse events	54	(87.1)	69	(83.1)	140	(90.9)
Rash	0	(0.0)	3	(3.6)	0	(0.0)
Acute kidney injury	1	(1.6)	2	(2.4)	0	(0.0)
Pneumonitis	0	(0.0)	2	(2.4)	6	(3.9)
Blood creatinine increased	1	(1.6)	1	(1.2)	0	(0.0)
Colitis	0	(0.0)	1	(1.2)	0	(0.0)
Febrile neutropenia	0	(0.0)	1	(1.2)	0	(0.0)
Haemorrhage intracranial	0	(0.0)	1	(1.2)	0	(0.0)
Myocardial infarction	0	(0.0)	1	(1.2)	0	(0.0)
Renal disorder	0	(0.0)	1	(1.2)	0	(0.0)
Sepsis	1	(1.6)	1	(1.2)	0	(0.0)
Alanine aminotransferase increased	1	(1.6)	0	(0.0)	1	(0.6)
Anaemia	1	(1.6)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	1	(1.6)	0	(0.0)	0	(0.0)
Cardiac arrest	0	(0.0)	0	(0.0)	1	(0.6)
Fatigue	1	(1.6)	0	(0.0)	1	(0.6)
Haemorrhagic stroke	0	(0.0)	0	(0.0)	1	(0.6)
Infusion related reaction	1	(1.6)	0	(0.0)	0	(0.0)
Pancytopenia	1	(1.6)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	1	(0.6)
Sudden death	0	(0.0)	0	(0.0)	1	(0.6)
Thrombocytopenia	1	(1.6)	0	(0.0)	0	(0.0)
Transaminases increased	0	(0.0)	0	(0.0)	1	(0.6)
Vomiting	0	(0.0)	0	(0.0)	1	(0.6)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN024.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.
MK-3475 KN024 Database Cutoff Date: 09MAY2016.

Source: [ISS: analysis-adsl; adae; aeplus]

However when comparing SAEs resulting in treatment discontinuation as shown in above Table 26, the incidence was similar between the 2 groups (pembro combo: 10.8%, pembrolizumab monotherapy: 8.4%) as were discontinuations due to death (pembro combo: 3.6%, pembrolizumab monotherapy: 5.8%).

Additionally, the numbers of the individual AEs in the pembro combo population resulting in treatment discontinuations were small with only 3 AE terms having greater than 1 event (rash 3, acute kidney injury 2, and pneumonitis 2).

Adverse Events of Special Interest (AEOSIs)

The overall incidence of AEOSIs in the pembro combo population was similar to that observed in the pembrolizumab monotherapy population from KEYNOTE-024 (27.7% vs 29.2%).

Adverse Event Summary
AEOSI Including All Risk Categories
Subjects from KN021 Cohorts C and G1 and Reference Data Comprising Subjects Treated with MK-3475 from KN024
(ASaT Population)

	KN021 G1 Chemo Alone		KN021 C+G1 Combo Pooled		Reference Data	
	n	(%)	n	(%)	n	(%)
Subjects in population	62		83		154	
with one or more adverse events	7	(11.3)	23	(27.7)	45	(29.2)
with no adverse event	55	(88.7)	60	(72.3)	109	(70.8)
with drug-related† adverse events	4	(6.5)	16	(19.3)	39	(25.3)
with toxicity grade 3-5 adverse events	1	(1.6)	5	(6.0)	15	(9.7)
with toxicity grade 3-5 drug-related adverse events	1	(1.6)	4	(4.8)	13	(8.4)
with serious adverse events	0	(0.0)	5	(6.0)	17	(11.0)
with serious drug-related adverse events	0	(0.0)	4	(4.8)	16	(10.4)
who died	0	(0.0)	1	(1.2)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	1	(1.6)	4	(4.8)	6	(3.9)
discontinued due to a drug-related adverse event	1	(1.6)	3	(3.6)	6	(3.9)
discontinued due to a serious adverse event	0	(0.0)	3	(3.6)	5	(3.2)
discontinued due to a serious drug-related adverse event	0	(0.0)	2	(2.4)	5	(3.2)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
KN021 C + G1 Combo Pooled group includes all subjects who received at least one dose of MK-3475 Combo treatment in KN021 Cohort C and Cohort G1.
Reference Dataset group includes all subjects who received at least one dose of MK-3475 in KN024.
For subjects who was treated with KN021 chemotherapy alone and crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 19.0
Grades are based on NCI CTCAE version 4.0.
MK-3475 KN021 Database Cutoff Date: 08AUG2016.
MK-3475 KN024 Database Cutoff Date: 09MAY2016.
Source: [ISS: analysis-adsl; adae; aeplus]

The incidence of individual AEOSIs was similar when comparing the pembro combo population from KEYNOTE-021 to the pembrolizumab monotherapy population from KEYNOTE-024: colitis (3.6% vs 1.3%), hypothyroidism (14.5% vs 9.1%), myositis (0.0% vs 1.9%) and pneumonitis (4.8% vs 5.8%).

Discussion

The incidence of overall AEs in the pembro combo population from KEYNOTE-021 is similar to that observed for the pembrolizumab monotherapy population from KEYNOTE-024. The rates of drug-related AEs and discontinuations due to a drug-related AE are higher in the pembro combo population from KEYNOTE-021 compared with the pembrolizumab monotherapy population from KEYNOTE-024. This contribution from chemotherapy is anticipated, given that the rates of drug-related AEs and discontinuations due to a drug-related AE in subjects receiving chemo alone in KEYNOTE-021 Cohort G1 were similar to those observed in the pembro combo population from KEYNOTE-021.

The overall incidences of Grade 3-5 AEs and SAEs in the pembro combo population were similar to those observed in the pembrolizumab monotherapy population from KEYNOTE-024. The incidences of Grade 3-5 anaemia, cellulitis, and pneumonia, as well as SAEs of acute kidney injury, cellulitis, and pneumonia, are higher in the pembro combo population as compared to the pembrolizumab monotherapy population from KEYNOTE- 024. Anaemia (due to myelosuppression) and acute kidney injury are known adverse reactions to the chemotherapy components. Given the small numbers of events of cellulitis and pneumonia, it is difficult to draw a meaningful conclusion from the observed difference between the groups though it is possible that myelosuppression from the chemotherapy components may be a contributory factor.

With regard to the AEOSIs for pembrolizumab, the overall incidence of AEOSIs in the pembro combo population from KEYNOTE-021 is similar to that previously observed in the pembrolizumab monotherapy population from KEYNOTE-024. Furthermore, the incidences of individual AEOSIs were similar between the 2 groups. It would appear that the addition of platinum doublet chemotherapy to pembrolizumab did not result in a change in the rates of known AEOSIs for pembrolizumab.

In conclusion, the overall incidence of known AEOSIs for pembrolizumab as well as the incidence of individual AEOSIs was comparable between the pembro combo population from KEYNOTE-021 and the pembrolizumab monotherapy population from KEYNOTE-024. The observed higher rates of other events in the pembro combo population was anticipated given that similar rates for these events were also observed in the chemo alone arm of KEYNOTE-021.

Oncologists are familiar with the long-established toxicity from chemotherapy and are proficient in managing these AEs appropriately. Given the intended indication of the pembrolizumab combination as treatment for a potentially fatal medical condition, as well as the substantial benefit in PFS provided by the combination, these observed higher rates of AEs in the combination population from KEYNOTE-021 as compared to the pembrolizumab monotherapy population from KEYNOTE-024 do not alter the positive benefit-risk assessment of the combination.

CHMP assessment

Taking into account the first-line indication of pembrolizumab as single-agent in patients whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS), the MAH was requested to discuss the safety of the combination in comparison with those observed in Study KN024 that included a similar patient population.

The MAH provided the requested data. The comparison has been conducted considering 3 patients populations, including subjects who received pembro combination (KN021 Cohorts C and G1 pooled), pembrolizumab monotherapy (KN024) and chemotherapy alone (KN021 Cohort G1).

Limitations of cross-trials comparison are acknowledged, as well as the fact that KN024 included about 18% of patients with squamous histology. However, patients' characteristics were broadly similar in terms of cancer stage, prior systemic adjuvant/neo-adjuvant treatments, age, ECOG PS, brain metastases at baseline, while female and never smokers were more represented in KN-021.

Not surprisingly, the combination of pembrolizumab and chemotherapy has a clear worse safety profile compared to pembrolizumab as single agent.

Drug-related AEs were much more frequently reported in the pembro combo population when compared to the pembrolizumab monotherapy population (95.2% vs 73.4%) including a higher rate of grade 3-5 drug-related AEs (39.8% vs 26.6%)

Fatigue, nausea, constipation, anemia, and diarrhea were much more frequently reported in the pembro combo population when compared to the pembrolizumab monotherapy population: fatigue (71.1% vs 20.8%), nausea (62.7% vs 19.5%), constipation (54.2% vs 20.8%), anemia (37.3% vs 13.0%), and diarrhea (36.1% vs 20.8%).

Discontinuations due to AEs were more frequently observed with the combination compared to pembrolizumab monotherapy (16.9 % vs 9.1%).

In terms of AEOSI, no new findings emerged.

The incidences of Grade 3-5 cellulitis, and pneumonia, as well as SAEs of acute kidney injury, cellulitis, and pneumonia, are higher in the pembro combo population as compared to the pembrolizumab monotherapy population from KEYNOTE- 024 and also higher as compared to the chemotherapy alone arm. However it is acknowledged that given the small numbers, as these rates represent 4 subjects or

fewer, it is not possible to draw meaningful conclusions from these observed differences. Overall the safety data base of the combination therapy appears to be too limited to assess definitely whether there may be single toxicities with higher incidences than what would be expected by the addition of both individual components.

In conclusion, even acknowledging the limitations of cross trial comparison, it appears that the combination of pembrolizumab and chemotherapy is more toxic than pembrolizumab as single agent. This is relevant for the subset of patients already covered by the approved indication of pembrolizumab as monotherapy.

It is however acknowledged that the safety profile reflects the individual profiles of the components, and that the worse tolerability is overallthe result of the sum of very well known and characterized adverse effect of pembrolizumab, pemetrexed and carboplatin.

The lack of comparative data of the combination and pembrolizumab monotherapy, the limited safety dataset of the combination, and the higher risk of adverse reaction of the combination compared to single agent pembrolizumab should be clearly stated in section 4.4 together with a recommendation to carefully consider the benefit of the combination in NSCLC patients whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS).

Issue solved provided that requested change in Section 4.4 is implemented.

Question 14

Updated safety results from both Cohorts G1 and C of KN021 study should be provided.

Summary of MAH's response

Updated safety data are similar to and consistent with results previously reported. No new safety concerns were identified. Small increases in rates in both arms for some AE categories were observed commensurate with the additional 10 months of follow-up. The discontinuation rate due to adverse events remains low and similar in both arms of Cohort G1 (16.9% pembro combo, 14.5% chemo alone). The updated safety profile for subjects treated with pembrolizumab/pemetrexed/carboplatin in Cohorts C and G1 is consistent with the previous characterization of the safety profile of the combination.

<u>Cohort G1</u>

Adverse Event Summary
Cohort G1 Subjects
(ASaT Population)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	59	(100.0)	61	(98.4)
with no adverse event	0	(0.0)	1	(1.6)
with drug-related† adverse events	55	(93.2)	57	(91.9)
with toxicity grade 3-5 adverse events	35	(59.3)	34	(54.8)
with toxicity grade 3-5 drug-related adverse events	24	(40.7)	18	(29.0)
with serious adverse events	29	(49.2)	20	(32.3)
with serious drug-related adverse events	16	(27.1)	7	(11.3)
who died	1	(1.7)	2	(3.2)
who died due to a drug-related adverse event	1	(1.7)	2	(3.2)
discontinued‡ due to an adverse event	10	(16.9)	9	(14.5)
discontinued due to a drug-related adverse event	9	(15.3)	9	(14.5)
discontinued due to a serious adverse event	7	(11.9)	3	(4.8)
discontinued due to a serious drug-related adverse event	6	(10.2)	3	(4.8)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Cohort G1 Subjects
(ASaT Population)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	59	(100.0)	61	(98.4)
with no adverse events	0	(0.0)	1	(1.6)
Nausea	44	(74.6)	36	(58.1)
Fatigue	43	(72.9)	34	(54.8)
Constipation	32	(54.2)	24	(38.7)
Vomiting	27	(45.8)	18	(29.0)
Diarrhoea	26	(44.1)	17	(27.4)
Dyspnoea	25	(42.4)	13	(21.0)
Anaemia	21	(35.6)	36	(58.1)
Decreased appetite	21	(35.6)	16	(25.8)
Headache	19	(32.2)	14	(22.6)
Rash	19	(32.2)	10	(16.1)
Cough	16	(27.1)	16	(25.8)
Blood creatinine increased	15	(25.4)	6	(9.7)
Dizziness	15	(25.4)	12	(19.4)
Insomnia	15	(25.4)	9	(14.5)
Oedema peripheral	15	(25.4)	13	(21.0)
Pruritus	15	(25.4)	4	(6.5)
Upper respiratory tract infection	14	(23.7)	4	(6.5)
Arthralgia	13	(22.0)	16	(25.8)
Alopecia	12	(20.3)	2	(3.2)
Aspartate aminotransferase increased	12	(20.3)	14	(22.6)
Back pain	12	(20.3)	9	(14.5)
Dysgeusia	12	(20.3)	8	(12.9)
Hyperglycaemia	12	(20.3)	5	(8.1)
Alanine aminotransferase increased	11	(18.6)	11	(17.7)
Hypokalaemia	11	(18.6)	7	(11.3)
Lacrimation increased	11	(18.6)	8	(12.9)
Neutrophil count decreased	11	(18.6)	8	(12.9)
Urinary tract infection	11	(18.6)	3	(4.8)
Abdominal pain	9	(15.3)	4	(6.5)
Dry eye	9	(15.3)	2	(3.2)
Fall	9	(15.3)	2	(3.2)
Musculoskeletal pain	9	(15.3)	6	(9.7)
Hypothyroidism	8	(13.6)	2	(3.2)
Neuropathy peripheral	8	(13.6)	4	(6.5)
Pain in extremity	8	(13.6)	5	(8.1)
Pyrexia	8	(13.6)	3	(4.8)
Weight decreased	8	(13.6)	8	(12.9)
Acute kidney injury	7	(11.9)	2	(3.2)
Cellulitis	7	(11.9)	1	(1.6)
Conjunctivitis	7	(11.9)	2	(3.2)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Dyspepsia	7	(11.9)	2	(3.2)
Dysphonia	7	(11.9)	6	(9.7)
Hypertension	7	(11.9)	3	(4.8)
Mucosal inflammation	7	(11.9)	1	(1.6)
Myalgia	7	(11.9)	3	(4.8)
Nasal congestion	7	(11.9)	2	(3.2)
Rhinorrhoea	7	(11.9)	5	(8.1)
Sinusitis	7	(11.9)	2	(3.2)
Abdominal pain upper	6	(10.2)	0	(0.0)
Anxiety	6	(10.2)	3	(4.8)
Hypocalcaemia	6	(10.2)	1	(1.6)
Hypophosphataemia	6	(10.2)	3	(4.8)
Lymphocyte count decreased	6	(10.2)	3	(4.8)
Non-cardiac chest pain	6	(10.2)	0	(0.0)
Rash maculo-papular	6	(10.2)	2	(3.2)
Weight increased	6	(10.2)	3	(4.8)
White blood cell count decreased	6	(10.2)	8	(12.9)
Bronchitis	5	(8.5)	0	(0.0)
Dehydration	5	(8.5)	5	(8.1)
Flushing	5	(8.5)	2	(3.2)
Gastrooesophageal reflux disease	5	(8.5)	2	(3.2)
Hyperthyroidism	5	(8.5)	1	(1.6)
Neutropenia	5	(8.5)	8	(12.9)
Pleural effusion	5	(8.5)	0	(0.0)
Vertigo	5	(8.5)	0	(0.0)
Vision blurred	5	(8.5)	5	(8.1)
Chills	4	(6.8)	3	(4.8)
Contusion	4	(6.8)	3	(4.8)
Dry mouth	4	(6.8)	4	(6.5)
Eye discharge	4	(6.8)	0	(0.0)
Hypomagnesaemia	4	(6.8)	3	(4.8)
Hypotension	4	(6.8)	2	(3.2)
Malaise	4	(6.8)	2	(3.2)
Musculoskeletal chest pain	4	(6.8)	4	(6.5)
Neck pain	4	(6.8)	5	(8.1)
Oedema	4	(6.8)	0	(0.0)
Pneumonitis	4	(6.8)	0	(0.0)
Pollakiuria	4	(6.8)	0	(0.0)
Rhinitis	4	(6.8)	6	(9.7)
Stomatitis	4	(6.8)	6	(9.7)
Syncope	4	(6.8)	1	(1.6)
Upper-airway cough syndrome	4	(6.8)	2	(3.2)
Abdominal distension	3	(5.1)	5	(8.1)
Blood alkaline phosphatase increased	3	(5.1)	7	(11.3)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Blood thyroid stimulating hormone increased	3	(5.1)	0	(0.0)
Chronic kidney disease	3	(5.1)	0	(0.0)
Depression	3	(5.1)	8	(12.9)
Dry skin	3	(5.1)	4	(6.5)
Dysuria	3	(5.1)	0	(0.0)
Epistaxis	3	(5.1)	4	(6.5)
Eye swelling	3	(5.1)	2	(3.2)
Haematuria	3	(5.1)	0	(0.0)
Haemoglobin decreased	3	(5.1)	0	(0.0)
Haemoptysis	3	(5.1)	1	(1.6)
Hyperhidrosis	3	(5.1)	0	(0.0)
Hypernatraemia	3	(5.1)	1	(1.6)
Hypoalbuminaemia	3	(5.1)	2	(3.2)
Hyponatraemia	3	(5.1)	4	(6.5)
Laceration	3	(5.1)	1	(1.6)
Limb discomfort	3	(5.1)	0	(0.0)
Localised oedema	3	(5.1)	1	(1.6)
Memory impairment	3	(5.1)	1	(1.6)
Otitis media	3	(5.1)	0	(0.0)
Palpitations	3	(5.1)	2	(3.2)
Paraesthesia	3	(5.1)	2	(3.2)
Platelet count decreased	3	(5.1)	8	(12.9)
Pneumonia	3	(5.1)	0	(0.0)
Rhinitis allergic	3	(5.1)	3	(4.8)
Sinus tachycardia	3	(5.1)	0	(0.0)
Tachycardia	3	(5.1)	1	(1.6)
Temperature intolerance	3	(5.1)	0	(0.0)
Thrombocytopenia	3	(5.1)	4	(6.5)
Wheezing	3	(5.1)	1	(1.6)
Asthenia	2	(3.4)	4	(6.5)
Peripheral sensory neuropathy	2	(3.4)	4	(6.5)
Chest pain	1	(1.7)	5	(8.1)
Dysphagia	1	(1.7)	5	(8.1)
Dyspnoea exertional	1	(1.7)	4	(6.5)
Hypercalcaemia	1	(1.7)	4	(6.5)
Oropharyngeal pain	1	(1.7)	5	(8.1)

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For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Subjects With Serious Adverse Events up to 90 Days of Last Dose
(Incidence >0% in One or More Treatment Groups)
Cohort G1 Subjects
(ASaT Population)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	29	(49.2)	20	(32.3)
with no adverse events	30	(50.8)	42	(67.7)
Acute kidney injury	6	(10.2)	1	(1.6)
Cellulitis	4	(6.8)	0	(0.0)
Pleural effusion	3	(5.1)	0	(0.0)
Dyspnoea	2	(3.4)	0	(0.0)
Fatigue	2	(3.4)	0	(0.0)
Pneumonia	2	(3.4)	0	(0.0)
Pyrexia	2	(3.4)	1	(1.6)
Sepsis	2	(3.4)	1	(1.6)
Abdominal pain	1	(1.7)	1	(1.6)
Anaemia	1	(1.7)	2	(3.2)
Anaphylactic reaction	1	(1.7)	0	(0.0)
Asthenia	1	(1.7)	0	(0.0)
Basal cell carcinoma	1	(1.7)	0	(0.0)
Cardiac tamponade	1	(1.7)	0	(0.0)
Cerebrovascular disorder	1	(1.7)	0	(0.0)
Dehydration	1	(1.7)	1	(1.6)
Depression	1	(1.7)	0	(0.0)
Embolism	1	(1.7)	0	(0.0)
Encephalopathy	1	(1.7)	0	(0.0)
Febrile neutropenia	1	(1.7)	1	(1.6)
Femur fracture	1	(1.7)	0	(0.0)
Haemoptysis	1	(1.7)	0	(0.0)
Haemorrhage intracranial	1	(1.7)	0	(0.0)
Hypokalaemia	1	(1.7)	0	(0.0)
Lung infiltration	1	(1.7)	0	(0.0)
Mental status changes	1	(1.7)	0	(0.0)
Myocardial infarction	1	(1.7)	0	(0.0)
Nausea	1	(1.7)	1	(1.6)
Non-cardiac chest pain	1	(1.7)	0	(0.0)
Pancytopenia	1	(1.7)	2	(3.2)
Pathological fracture	1	(1.7)	0	(0.0)
Pneumonitis	1	(1.7)	0	(0.0)
Pulmonary embolism	1	(1.7)	1	(1.6)
Rash	1	(1.7)	0	(0.0)
Small intestinal obstruction	1	(1.7)	2	(3.2)
Thrombocytopenia	1	(1.7)	1	(1.6)
Transaminases increased	1	(1.7)	0	(0.0)
Upper respiratory tract infection	1	(1.7)	0	(0.0)
Urinary tract infection	1	(1.7)	0	(0.0)
Urosepsis	1	(1.7)	0	(0.0)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Vomiting	1	(1.7)	0	(0.0)
Atrial fibrillation	0	(0.0)	1	(1.6)
Back pain	0	(0.0)	1	(1.6)
Cardiac ventricular thrombosis	0	(0.0)	1	(1.6)
Cerebrovascular accident	0	(0.0)	2	(3.2)
Chronic obstructive pulmonary disease	0	(0.0)	1	(1.6)
Diarrhoea	0	(0.0)	1	(1.6)
Diverticular perforation	0	(0.0)	1	(1.6)
Diverticulitis	0	(0.0)	1	(1.6)
Dysphagia	0	(0.0)	1	(1.6)
Flank pain	0	(0.0)	1	(1.6)
Gastroenteritis	0	(0.0)	1	(1.6)
Haematochezia	0	(0.0)	1	(1.6)
Musculoskeletal pain	0	(0.0)	1	(1.6)
Neutropenia	0	(0.0)	1	(1.6)
Periorbital cellulitis	0	(0.0)	1	(1.6)
Pneumothorax	0	(0.0)	1	(1.6)
Salivary gland calculus	0	(0.0)	1	(1.6)
Spinal fracture	0	(0.0)	1	(1.6)
Syncope	0	(0.0)	1	(1.6)
Transient ischaemic attack	0	(0.0)	1	(1.6)

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For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Adverse Event Summary
AEOSI Including All Risk Categories
Cohort G1 Subjects
(ASaT Population)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	15	(25.4)	7	(11.3)
with no adverse event	44	(74.6)	55	(88.7)
with drug-related† adverse events	13	(22.0)	3	(4.8)
with toxicity grade 3-5 adverse events	2	(3.4)	1	(1.6)
with toxicity grade 3-5 drug-related adverse events	2	(3.4)	1	(1.6)
with serious adverse events	2	(3.4)	0	(0.0)
with serious drug-related adverse events	2	(3.4)	0	(0.0)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	1	(1.7)	1	(1.6)
discontinued due to a drug-related adverse event	1	(1.7)	1	(1.6)
discontinued due to a serious adverse event	1	(1.7)	0	(0.0)
discontinued due to a serious drug-related adverse event	1	(1.7)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Subjects With Adverse Events of Special Interest (AEOSI)
(Incidence > 0% in One or More Treatment Groups)
Cohort G1 Subjects
(ASaT Population)

	Pembro 200mg Combo		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	15	(25.4)	7	(11.3)
with no adverse events	44	(74.6)	55	(88.7)
Colitis	**1**	**(1.7)**	**0**	**(0.0)**
Colitis	1	(1.7)	0	(0.0)
Hyperthyroidism	**5**	**(8.5)**	**1**	**(1.6)**
Hyperthyroidism	5	(8.5)	1	(1.6)
Hypothyroidism	**8**	**(13.6)**	**2**	**(3.2)**
Hypothyroidism	8	(13.6)	2	(3.2)
Infusion Reactions	**1**	**(1.7)**	**3**	**(4.8)**
Anaphylactic reaction	1	(1.7)	0	(0.0)
Hypersensitivity	0	(0.0)	2	(3.2)
Infusion related reaction	0	(0.0)	1	(1.6)
Pneumonitis	**4**	**(6.8)**	**0**	**(0.0)**
Pneumonitis	4	(6.8)	0	(0.0)
Severe Skin Reactions	**1**	**(1.7)**	**1**	**(1.6)**
Rash	1	(1.7)	0	(0.0)
Rash macular	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Cohort C

Adverse Event Summary
Cohort C Subjects
(ASaT Population)

	Pembro 10mg/kg Combo		Pembro 2mg/kg Combo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	12		12		24	
with one or more adverse events	12	(100.0)	12	(100.0)	24	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related† adverse events	12	(100.0)	12	(100.0)	24	(100.0)
with toxicity grade 3-5 adverse events	9	(75.0)	7	(58.3)	16	(66.7)
with toxicity grade 3-5 drug-related adverse events	7	(58.3)	4	(33.3)	11	(45.8)
with serious adverse events	7	(58.3)	6	(50.0)	13	(54.2)
with serious drug-related adverse events	3	(25.0)	4	(33.3)	7	(29.2)
who died	2	(16.7)	0	(0.0)	2	(8.3)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	3	(25.0)	4	(33.3)	7	(29.2)
discontinued due to a drug-related adverse event	3	(25.0)	3	(25.0)	6	(25.0)
discontinued due to a serious adverse event	1	(8.3)	2	(16.7)	3	(12.5)
discontinued due to a serious drug-related adverse event	1	(8.3)	1	(8.3)	2	(8.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Adverse Event Summary
AEOSI Including All Risk Categories
Cohort C Subjects
(ASaT Population)

	Pembro 10mg/kg Combo		Pembro 2mg/kg Combo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	12		12		24	
with one or more adverse events	4	(33.3)	4	(33.3)	8	(33.3)
with no adverse event	8	(66.7)	8	(66.7)	16	(66.7)
with drug-related† adverse events	3	(25.0)	2	(16.7)	5	(20.8)
with toxicity grade 3-5 adverse events	1	(8.3)	0	(0.0)	1	(4.2)
with toxicity grade 3-5 drug-related adverse events	1	(8.3)	0	(0.0)	1	(4.2)
with serious adverse events	1	(8.3)	1	(8.3)	2	(8.3)
with serious drug-related adverse events	1	(8.3)	1	(8.3)	2	(8.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	1	(8.3)	1	(8.3)	2	(8.3)
discontinued due to a drug-related adverse event	1	(8.3)	1	(8.3)	2	(8.3)
discontinued due to a serious adverse event	1	(8.3)	0	(0.0)	1	(4.2)
discontinued due to a serious drug-related adverse event	1	(8.3)	0	(0.0)	1	(4.2)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

Subjects With Adverse Events of Special Interest (AEOSI)
(Incidence > 0% in One or More Treatment Groups)
Cohort C Subjects
(ASaT Population)

	Pembro 10mg/kg Combo		Pembro 2mg/kg Combo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	12		12		24	
with one or more adverse events	4	(33.3)	4	(33.3)	8	(33.3)
with no adverse events	8	(66.7)	8	(66.7)	16	(66.7)
Adrenal Insufficiency	**1**	**(8.3)**	**0**	**(0.0)**	**1**	**(4.2)**
Adrenal insufficiency	1	(8.3)	0	(0.0)	1	(4.2)
Colitis	**1**	**(8.3)**	**1**	**(8.3)**	**2**	**(8.3)**
Colitis	1	(8.3)	1	(8.3)	2	(8.3)
Hypothyroidism	**2**	**(16.7)**	**2**	**(16.7)**	**4**	**(16.7)**
Hypothyroidism	2	(16.7)	2	(16.7)	4	(16.7)
Infusion Reactions	**0**	**(0.0)**	**1**	**(8.3)**	**1**	**(4.2)**
Drug hypersensitivity	0	(0.0)	1	(8.3)	1	(4.2)
Severe Skin Reactions	**1**	**(8.3)**	**0**	**(0.0)**	**1**	**(4.2)**
Rash	1	(8.3)	0	(0.0)	1	(4.2)

Every subject is counted a single time for each applicable row and column.
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Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

CHMP assessment

Updated safety data were provided as requested with additional 10 months follow-up. No new safety signs emerged, and the differences are mainly characterized by a slight increase in some AEs, likely due to the longer follow-up.

Issue solved

Question 15

The MAH is asked to clarify the different numbers for subjects with SAEs in the pembrolizumab monotherapy reference data (n=2,799) in Table 5.3.5.3.3-nsclc: 10 (SAEs n=1,041, 37.2%) and Table 2.7.4: 8 (SAEs n=739, 26.4%).

Summary of MAH's response

In order to provide a summary without lengthy tables containing multiple zero entries, data in [Table 2.7.4: 8-nsclc] were filtered to include only events reported in at least one subject in either the pembrolizumab combination arm or the chemo alone arm of Cohort G1. The number of SAEs in the monotherapy reference data column (n=739) represents the filtered subset of the total monotherapy reference SAEs (n=1,041).

CHMP assessment

The MAH clarified the discrepancy as requested.

Issue solved

Question 16

No information on previous radiotherapy received by patients in KN-021 study seem to be available in the submitted CSR. The MAH should discuss and provide a justification for the higher rates of hypothyroidism (in 14.5% of subjects) and hyperthyroidism (7.2%) among subjects treated with the pembro-chemo

combination group compared to those reported from the pembrolizumab monotherapy reference safety dataset (hypothyroidism 8.5%, hyperthyroidism 3.4%).

Summary of MAH's response

As indicated, previous radiotherapy information was not included in the KEYNOTE-021 CSR. In order to enhance the information, a listing of Cohort G1 subjects who received prior radiation has been provided. In the 59 subjects comprising the ASaT population of the pembro combo arm in Cohort G1, there were 15 subjects who received prior radiation.

On review of the 11 subjects on the pembro combo arm who developed hypothyroidism or hyperthyroidism, 2 subjects had received any prior radiation and 9 subjects had not received any prior radiation. Prior radiation in this population does not appear to play a role in the rates of thyroid dysfunction observed, despite reports in the literature of prior radiation contributing to thyroid dysfunction in tumors other than NSCLC (Carter Y et al, The Oncologist 2014; Kanyilmaz G et al, Med Dosim 2017). Newer antineoplastic agents including targeted therapies and immunotherapies are associated with thyroid dysfunction in approximately 20%–50% of patients (Hamnvik O-PR et al, J Natl Cancer Inst 2011).

In Cohort G1, updated safety results (Question 14) indicate rates of hypothyroidism of 13.6% in the pembro combo arm compared to 3.2% in the chemo alone arm and hyperthyroidism of 8.5% in the pembro combo arm vs 1.6% in the chemo alone arm. In the pembro combo arm, these represent 8 events of hypothyroidism and 5 events of hyperthyroidism, occurring in 11 subjects since 2 subjects developed hypothyroidism after experiencing hyperthyroidism.

All the events were low grade (Grade 1 or 2) and easily managed with appropriate clinical care. These rates of thyroid disorders appear numerically higher than those in the reference dataset, however, the small number of events in Cohort G1 and the comparison across trials preclude definitive conclusions; these observations are exploratory.

In conclusion the rates of hypothyroidism and hyperthyroidism observed in Cohort G1 are likely no different from the rates observed with pembrolizumab monotherapy when the small number of events and the background rates in the chemo alone subjects are considered. Prior radiation does not appear to be a predisposing factor for thyroid dysfunction in this population. All the events were low grade (Grade 1 or 2) and easily managed with appropriate clinical care.

CHMP assessment

The MAH provided the requested information regarding prior radiotherapy. Based on the data provided radiotherapy does not appear to be the cause of the apparent higher incidences of hypothyroidism and hyperthyroidism.

Based on the currently available data, it remains unclear whether the combination increases the risk of thyroid dysfunction. Data from Study KN189 will help to clarify on this issue. In the meanwhile information on the higher risk of adverse reaction with pembro combo compared to pembro monotherapy should be reported in Section 4.4 (see the answer to Q13)

Issue solved provided that the requested change to Section 4.4 is implemented as for answer to Q13

Question 17

For the patient in Cohort C initially reported to meet the criteria for Hy's Law, the MAH should provide a narrative including laboratory test results and overall safety events reported during treatment.

Summary of MAH's response

The narrative for the subject, as well as additional laboratory results have been provided.

Subject [redacted] AST/ALT/ALK and Bilirubin Results

Study Day	ALT NR 30-65 IU/L	AST NR: 15-37 IU/L	ALK P NR: 50-135 IU/L	Tbili NR: 0-1 mg/dL	Dbili NR: 0-0.3 mg/dL
Screening/baseline	27	14	124	0.3	0.1
42	62	40	197	0.2	0.1
63	563	538	234	0.5	0.2
70	858	539	228	0.9	0.7
77	874	602	217	1.3	0.9
91	371	146	131	0.5	-
112	31	19	76	0.4	0.4
413	299	77	384	0.3	0.1
421	148	38	239	0.3	0.1
434	45	16	169	0.3	0.1

ALT = alanine aminotransferase; ALK = alkaline phosphatase; AST = aspartate aminotransferase; IU/L = international units/liter; NR = normal range; Tbili = total bilirubin; Dbili = direct bilirubin

The bilirubin level at the peak was 1.3 mg/dL on Day 77, not meeting Hy's Law criteria of 2x elevation above ULN. An erroneous manual CRF entry of the upper limit of normal for bilirubin on 2 occasions led to the classification despite normal bilirubin levels.

CHMP assessment

The MAH provided the requested information.

Issue solved

Question 18

The MAH is asked to discuss the higher rate of infections in the pembro-chemo combination group compared to in the chemotherapy alone group (62.7% vs. 37.1%, Grade 3-5 infection AEs 16.9% vs. 4.8%, SAEs 14.5% vs. 4.8%).

Summary of MAH's response

In response to this question the MAH has reviewed the rates of infections in the pembro combo arm in comparison with the chemo alone arm, specifically comparing all infection events in decreasing frequency, all Grade 3-5 infection events, as well as all infection SAEs.

The rates of individual infection events were generally greater in the pembro combo arm as compared to the chemo alone group:

Subjects With Adverse Events in the Body System Organ Class of Infections and Infestations
(Incidence >0% in One or More Treatment Groups)
Cohort C and G1 Subjects
(ASaT Population)

	Pembro Combo C+G1 Pooled		Control	
	n	(%)	n	(%)
Subjects in population	83		62	
with one or more adverse events	56	(67.5)	25	(40.3)
with no adverse events	27	(32.5)	37	(59.7)
Upper respiratory tract infection	20	(24.1)	4	(6.5)
Urinary tract infection	15	(18.1)	3	(4.8)
Cellulitis	8	(9.6)	1	(1.6)
Sinusitis	8	(9.6)	2	(3.2)
Conjunctivitis	7	(8.4)	2	(3.2)
Bronchitis	5	(6.0)	0	(0.0)
Pneumonia	5	(6.0)	0	(0.0)
Rhinitis	4	(4.8)	6	(9.7)
Skin infection	4	(4.8)	1	(1.6)
Otitis media	3	(3.6)	0	(0.0)
Candida infection	2	(2.4)	1	(1.6)
Herpes zoster	2	(2.4)	3	(4.8)
Lung infection	2	(2.4)	1	(1.6)
Mucosal infection	2	(2.4)	0	(0.0)
Sepsis	2	(2.4)	1	(1.6)
Viral upper respiratory tract infection	2	(2.4)	3	(4.8)
Clostridium difficile infection	1	(1.2)	0	(0.0)
Diverticulitis	1	(1.2)	1	(1.6)
Ear infection	1	(1.2)	0	(0.0)
Eye infection	1	(1.2)	0	(0.0)
Fungal infection	1	(1.2)	1	(1.6)
Gastroenteritis	1	(1.2)	2	(3.2)
Gastroenteritis viral	1	(1.2)	0	(0.0)
Gingival abscess	1	(1.2)	0	(0.0)
Hordeolum	1	(1.2)	0	(0.0)
Infection	1	(1.2)	0	(0.0)
Influenza	1	(1.2)	0	(0.0)
Onychomycosis	1	(1.2)	0	(0.0)
Oral candidiasis	1	(1.2)	2	(3.2)
Oral herpes	1	(1.2)	0	(0.0)
Pyelonephritis acute	1	(1.2)	0	(0.0)
Rash pustular	1	(1.2)	0	(0.0)
Tinea pedis	1	(1.2)	0	(0.0)
Tooth abscess	1	(1.2)	0	(0.0)
Tooth infection	1	(1.2)	0	(0.0)
Urosepsis	1	(1.2)	0	(0.0)
Vaginal infection	1	(1.2)	0	(0.0)
Vulvovaginal mycotic infection	1	(1.2)	0	(0.0)
Folliculitis	0	(0.0)	1	(1.6)
Herpes simplex	0	(0.0)	1	(1.6)
Herpes virus infection	0	(0.0)	1	(1.6)
Periorbital cellulitis	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
(Database Cutoff Date: 31MAY2017).

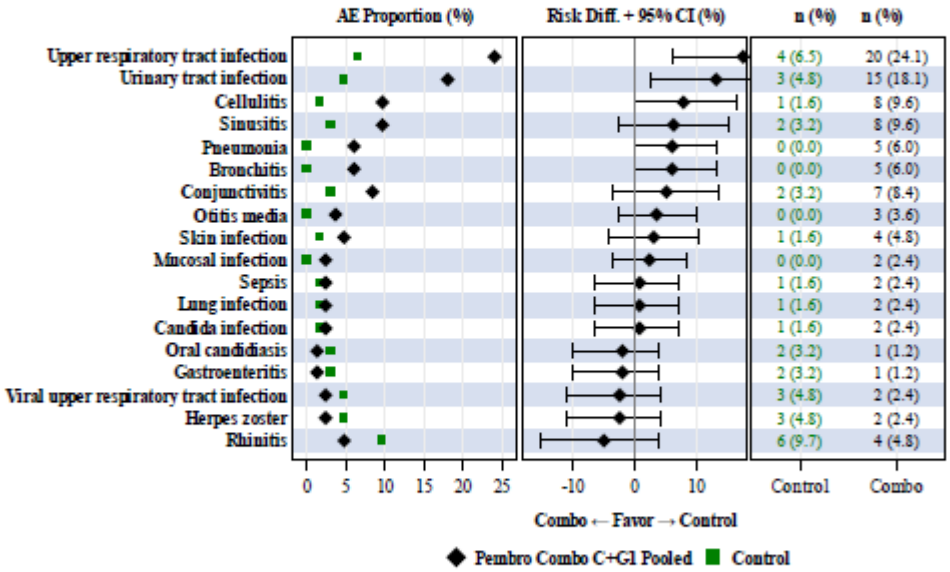
Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

The most frequent events in the pembro combo group were upper respiratory tract infection (URTI), urinary tract infection (UTI), cellulitis, sinusitis, and conjunctivitis, with URTI and UTI accounting for a third of all infection events. The URTI and UTI events were predominantly Grade 1 or 2.

As shown in the following Figure, with the exception of URTI and UTI, the confidence intervals of the risk difference between the pembro combo and the chemo alone groups for all infection events crossed zero.

Therefore a comment as to a risk difference for infection events between the 2 groups can only be made for URTI and UTI. The risk of URTI may be higher in the pembro combo group as compared to the chemo alone group. Results from other chemotherapy combination trials currently underway will be required to confirm or refute this observation.

Between-Treatment Comparisons in Adverse Events in the Body System Organ Class of Infections and Infestations
Selected Adverse Events (>=2% Incidence) and Sorted by Risk Difference
(ASaT Population)
Pembro Combo C+G1 Pooled (N = 83) vs. Control (N = 62)



Database Cutoff Date: 31MAY2017
Source: [P021V01MK3475: analysis-adsl; adae][P021V01MK3475: tabulation-aeplus]

The rates of individual Grade 3-5 infection events were generally higher in the pembro combo group compared with the chemo alone group.

Subjects With Grade 3-5 Adverse Events in the Body System Organ Class of Infections and Infestations
(Incidence >0% in One or More Treatment Groups)
Cohort C and G1 Subjects
(ASaT Population)

	Pembro Combo C+G1 Pooled		Control	
	n	(%)	n	(%)
Subjects in population	83		62	
with one or more adverse events	14	(16.9)	5	(8.1)
with no adverse events	69	(83.1)	57	(91.9)
Cellulitis	5	(6.0)	0	(0.0)
Pneumonia	4	(4.8)	0	(0.0)
Sepsis	2	(2.4)	1	(1.6)
Urinary tract infection	2	(2.4)	1	(1.6)
Pyelonephritis acute	1	(1.2)	0	(0.0)
Skin infection	1	(1.2)	0	(0.0)
Tooth abscess	1	(1.2)	0	(0.0)
Upper respiratory tract infection	1	(1.2)	0	(0.0)
Urosepsis	1	(1.2)	0	(0.0)
Diverticulitis	0	(0.0)	1	(1.6)
Gastroenteritis	0	(0.0)	1	(1.6)
Periorbital cellulitis	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 31MAY2017).

Source: [P021V01MK3475: analysis-adsl; adae] [P021V01MK3475: tabulations-aeplus]

The rates of individual infection SAEs were generally higher in the pembro combo group compared with the chemo alone group. The most frequent infection SAEs in the pembro combo group were cellulitis (5 subjects), pneumonia (4 subjects), and sepsis (2 subjects), with the others reported for 1 subject each. As shown above, the confidence intervals of the risk difference between the pembro combo and chemo alone groups for cellulitis, pneumonia, and sepsis crossed zero. Therefore any conclusion as to a risk difference between the 2 groups cannot be made for these events and the observed numerical difference in the rates of cellulitis, pneumonia, and sepsis is likely the result of small sample sizes.

Discussion

The overall rates of infections, Grade 3-5 infection AEs, as well as infection SAEs were higher in the pembro combo group compared with the chemo alone group. URTI and UTI, which together made up about a third of all the infection AEs reported in the pembro combo group, appear to be at least in part the drivers for this observed difference, also noting that more patients remained on treatment longer in the pembro combo arm compared to the chemo alone arm. It is notable that a vast majority of the URTI and UTI events were nonserious (Grade 1-2). With regard to the Grade 3-5 infection events and infection SAEs, including specifically cellulitis, pneumonia, and sepsis, the observed differences between the 2 groups are more likely a result of small sample size.

In conclusion, after a review of the data, the only differences between the pembro combo and the chemo alone arms with regard to infection AEs that may not be due to chance are the higher rates of predominantly nonserious URTIs and UTIs in the pembro combo arm. Given the intended indication of the pembrolizumab combination as treatment for a potentially fatal medical condition, this higher rate of nonserious infection AEs does not alter the positive benefit-risk assessment of the combination.

CHMP assessment

The overall rates of infections, Grade 3-5 infection AEs and infection SAEs were higher in the pembro combo group compared with the chemo alone group with upper respiratory tract infection (URTI) and urinary tract infection (UTI) being the most common and having the highest risk difference between both arms. However as already discussed in the response assessment to Q13 the overall small numbers preclude a definitive assessment whether these numerical differences are due to chance findings or based on an actual higher risk of infections for the combination therapy compared to chemotherapy alone or pembrolizumab monotherapy. As pointed out by the MAH results from other chemotherapy combination trials currently underway will be required to confirm or refute this observation. In the meanwhile the limitations of the currently available safety data for the combination therapy should be addressed in section 4.4 (see response assessment to Q13).

Issue solved.