21 May 2015
EMA/444458/2015 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/0000

Note

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

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List of abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
AEOSI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotrasferase
APaT	All Patients as Treated
APS	Allred Proportion Score
AST	Aspartate aminotrasferase
AUC	Area under the curve
CHMP	Committee for Medicinal Products for Human User
CHO	Chinese Hamster Ovary
CI	Confidence Interval(s)
CYP	Cytochrome P
CL	Clearance
Cmax	Maximum concentration
CNS	Central Nervous System
CR	Complete Response
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA4	Cytotoxic T-Lymphocite antigen-4
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DTIC	dacarbazine
EC50	Half-Maximal Effective Concentration
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-Linked Immunosorbent assay
EORTC- QLQ	European Organisation for Research and Treatment of Care core Quality of Life

questionnaire	
ERA	Environmental Risk Assessment
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FU	Fluorouracil
FcRn	Fc Receptor Neonatal
GCP	Good clinical practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
hr	Hour(s)
IA2	Interim Analysis 2
IC50	Half-maximal inhibitory concentration
ICH	International Conference of Harmonisation
IFN	Interferon
IgG	Immunoglobulin gamma
IHC	immunohistochemistry
IL	Interleukin
IL-2	Interleukin 2
IPI	ipilimumab
IRO	Integrated radiology and oncology assessment
irRC	immune-related Response Criteria
ITT	intention to treat
IV	intravenous
i.v.	intravenous
KD	Dissociation constant
KM	Kaplan-Meier
λz	Terminal rate constant
LDH	Lactate dehydrogenase
LLN	lower limit normal
mAb	monoclonal antibody
MA	Marketing Authorisation
MAA	Marketing Authorisation Application

mg	Milligram
mL	Milliliter
mk-3475	pembrolizumab, Keytruda
mM	Millimolar
MRI	magnetic resonance imaging
MSD	Meso Scale Discovery
N/A	Not Applicable
NAb	Neutralizing antibody(ies)
nM	Nanomolar
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PAES	Post-authorisation efficacy studies
PK	pharamcokinetics
PBMC	Peripheral blood (mononuclear) cell
PD	pharmacodynamic
PD	Progressive disease
PD-1	Programmed Cell Death Receptor-1
PD-L1	Programmed Cell Death Receptor- Ligand 1
PD-L2	Programmed Cell Death Receptor- Ligand 2
PK	Pharmacokinetic
PIP	Paediatric Investigation Plan
PFS	Progression Free Survival
pM	Picomolar
PS	Performance Status
PSUR	Periodic Safety Update Report
PR	Partial Response
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient reported outcome
Q	Distribution clearance
Q2W	every 2 weeks
Q3W	every 3 weeks

QTc	QT interval corrected
RECIST	Response Evaluation Criteria In Solid Tumors
RMP	Risk Management Plan
RR	Response Rate
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable disease
SEB	Staphylococcal Enterotoxin B
SmPC	Summary of Product Characteristics
t1/2	Elimination half-life
TK	Toxicokinetics
Tmax	Time to reach maximum concentration
TNF	Tumor Necrosis Factor
TT	Tetanus toxoid
ULN	upper limit normal
Vc	Volume of distribution central compartment
Vp	Peripheral volume of distribution
Vss	Distribution Volume at steady state
WBC	Whole blood cells
µg	Microgram

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MERCK SHARP & DOHME LIMITED submitted on 4 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Keytruda, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

"KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in adults."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that pembrolizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0059/2014 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

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

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance pembrolizumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Scientific Advice

The applicant received Scientific Advice from the CHMP on 13 December 2012, The Scientific Advice

pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Keytruda has been given a Marketing Authorisation in the USA on 4 September 2014.

1.2. Manufacturers

Manufacturer of the biological active substance

MedImmune, LLC Frederick Manufacturing Center (FMC)
633/636/660 Research Court Frederick
MD 21703-8619, USA

Manufacturer responsible for batch release

Schering-Plough Labo NV
Industriepark 30
Heist-op-den-Berg
B-2220, Belgium

1.3. Steps taken for the assessment of the product

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

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

CHMP Peer reviewer: Pieter de Graeff

- The application was received by the EMA on 4 June 2014.
- The procedure started on 25 June 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2014.
- The PRAC RMP Advice and assessment overview were adopted by PRAC on 9 October 2014.
- During the meeting on 20-23 October 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 October 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 April 2015.
- The PRAC RMP Advice and assessment overview were adopted by PRAC on 10 April 2015.
- During the CHMP meeting on 20-23 April 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 27 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the CHMP List of Outstanding Issues on 5 May 2015.
- PRAC RMP Advice and assessment overview was adopted on 4 May 2015.
- During the meeting on 21 May 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Keytruda.

2. Scientific discussion

2.1. Introduction

Melanoma is the most aggressive form of skin cancer. Melanoma is the sixth and seventh most common malignancy in men and women, respectively.[1] The median age at diagnosis is 59 years. The incidence of melanoma varies between different European countries but the estimated incidence was about 39.6 cases /100.000 men and 42.5 cases /100.000 women in 2012. In Europe in 2012, the mortality rate was approximately 8.8 cases/100.000 in males and 6.9 cases/100.000 in females.[1] The outcome of melanoma depends on the stage at presentation[2]. Approximately 85% of patients with melanoma present with localised disease, 10% with regional disease and 5% with distant metastatic disease. The 5-year survival rates in patients who present with localised disease and primary tumours 1.0mm or less in thickness are very good, with more than 90% of patients surviving. The 5-year survival rates decrease as the tumour spreads: for tumours of more than 1.0mm in thickness, survival rates range from 50% to 90%, with regional node involvement survival rates are around 50%, for within stage III (regional metastatic melanoma) 5-year survival rates range between 20-70%, depending on primary nodal involvement. The long term survival for distant metastatic melanoma, the 5-year survival is less than 10%.

Current treatments for metastatic melanoma include systemic therapy, surgery and radiotherapy. Spontaneous regression of melanoma has been reported with an incidence of less than 1%. Complete resection of isolated metastases to one anatomic site (lung, gastrointestinal tract, bone or brain) may occasionally achieve long term survival. Systemic treatment may consist of chemotherapy, and/or immunotherapy. Palliative radiotherapy is indicated for symptomatic relief of metastases to brain, bones and viscera.

Chemotherapy with dacarbazine (DTIC) may achieve objective response rates of about 20%, of which less than 5% is complete remission. Higher response rates have been seen using combination chemotherapy, however no increase in over-all survival has been demonstrated with combination regimens when compared to dacarbazine alone. Immunotherapeutic agents used for metastatic melanoma are interferon-alfa (IFNα) and interleukine-2 (IL-2). Recurrent melanoma is resistant to most standard systemic therapy and no standardized effective second line treatment is established.

[1] Ferlay J., Steliarova-Foucher E., Lortet-Tieulent J., et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer; 49, 1374– 1403, 2013
[2] Balch CM., Gershenwald JE., Soong SJ., et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol; 27(36):6199-206, 2009

In EU Countries, dacarbazine was used for many years as standard first line treatment of patients with metastatic melanoma[3]. Clinical trials with dacarbazine have shown low response rates ranging from 11% -25%, low rate of complete responses and of short duration (3 to 6 months). The median survival time ranged from 4.5 to 6 months[4,5,6]. Ipilimumab (Yervoy), a human monoclonal antibody against CTLA-4, was approved in the EU in 2011 for melanoma patients who have received prior therapy. The approval of ipilimumab was based on the results of a phase III study performed in previously treated melanoma patients was associated with a statistically significant improvement in overall survival (OS) compared with the gp100 vaccine (10.1 versus 6.4 months; HR: 0.66; p= 0.003). In recent times, the serine-threonine kinase BRAF was discovered mutated in many cancers[7]. BRAF mutations have been found in approximately 50% of melanoma, 30-70% of thyroid carcinomas, 30% of ovarian carcinoma and 10% of colorectal carcinoma. Oncogenic mutations in BRAF result in constitutive activation of the RAF-MEK-ERK pathway which in turn stimulates cell growth, proliferation and cell survival in the absence of typical growth factors[8]. For patients with tumours harbouring the BRAFV600 mutation, kinase inhibitors vemurafenib (Zelborarf) and dabrafenib (Tafinlar) were approved in the EU in 2012 and 2013, respectively, and target directly the mutated protein BRAFV600. Vemurafenib (Zelboraf), as first line treatment was approved based on the results of the pivotal phase III study (BRIM3) and was associated with a median progression-free survival (PFS) 6.9 vs 1.6 months, respectively (HR 0.38, 95%CI: 0.32-0.46, p<0.0001) and median OS 13.6 vs 9.7 months (HR: 0.70, 95%CI: 0.57-0.87, p<0.0001) compared with DTIC. Dabrafenib (Tafinlar), as first line therapy was approved based on the results of the pivotal trial BREAK-3 that showed a median PFS of 6.9 vs 2.7 months for the dabrafenib and DTIC group respectively, (HR: 0.37; 95% CI: 0.24, 0.58; p-value<0.0001) and OS (HR 0.76, 95%CI: 0.48, 1.21); a 12 month OS rate of 70 % and 63 % for dabrafenib and DTIC treatments, respectively). Trametinib (Mekinist) was approved in 2014 to target the mitogen-activated extracellular signal regulated kinase 1 (MEK 1 and MEK 2) proteins to dampen the signalling pathway that promotes proliferation and survival in BRAFV600 mutated melanoma. Mekinist as first line of treatment was approved based on the results of a phase III study that showed a median PFS 4.8 vs 1.5 months, respectively (HR 0.45; 95%CI:0.33, 0.63; p-value <0.0001) and median OS of 15.6 vs 11.3 months (HR 0.78; 95%CI 0.57, 1.06) for trametinib and dacarbazine respectively.

The co-inhibitory receptor programmed cell death – 1 (PD-1) is a key regulator of T cell activity that belongs to the same immunoglobulin superfamily which includes the co-stimulatory receptor CD28 and the co-inhibitory receptor CTLA-4.[9,] Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. It binds to the PD-1 receptor and blocks its interaction with PD-1 ligand (PD-L1) and PD-1 ligand 2 (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. Engagement of PD-1 with the ligands 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, results in inhibition of T cell proliferation and cytokine secretion. Pembrolizumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

[3] Serrone L, Zeuli M, Sega FM, et al. Dacarbazine- based chemotherapy for metastatic melanoma: Thirty year experience overview. J Exp Clin Cancer Res; 19: 21-34, 2000
[4] Luce JK, Thurman WG, Isaacs BL, et al. Clinical trials with the antitumor agent 5-(3,3–dimethy-1-triazeno)imidazole-4-carboxamide. Cancer Chemother Rep; 54:119-124, 1970
[5] Hill GJ, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma. Cancer; 47:2556-2562, 1981
[6] Falkson G, Van der Merwe AM, Falkson HC: Clinical experience with 5-(3,3–bis(2-chloroethyl)- 1-triazeno)-imidazole-4-carboxamide (NSC 82196) in the treatment of metastatic malignant melanoma. Cancer Chemother Rep; 56:671-677, 1972
[7] Davies H, et al. Mutations of the BARF gene in human cancer. Nature; 417:949-954, 2002
[8] Garnett MJ and Marais R. Guilty as charged: B-RAF is a human oncogene. Cancer Cell; 6:313-319, 2004
[9] Nurieva RI, Liu X., Dong C., Molecular mechanism of T-cell tolerance J Immunol; 241: 133–44, 2011

The applicant applied for the following indication:

“KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in adults.”

The final approved indication was:

“KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.”

The recommended dose of KEYTRUDA is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Guidelines for withholding or discontinuation of KEYTRUDA are described in Table 1 of the SmPC. KEYTRUDA should be permanently discontinued:

- For Grade 4 toxicity except for endocrinopathies that are controlled with replacement hormones
- If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- If any event occurs a second time at Grade ≥ 3 severity

2.2. Quality aspects

2.2.1. Introduction

The active substance of Keytruda (50 mg powder for concentrate for solution for IV infusion) is pembrolizumab (MK-3475), which is a humanised monoclonal antibody that binds to human PD-1 and blocks the interaction between PD-1 receptor and its ligands. MK-3475 is an IgG4 monoclonal antibody with Class-II mechanism of action (binding to cell-bound antigen not involving Fc effector function).

2.2.2. Active Substance

It is an IgG4/kappa isotype with a stabilizing SER228PRO sequence alteration in the Fc region; it could be demonstrated that the S228P mutation introduced into MK-3475 in the IgG4 hinge region prevents the formation of half molecules. Induction of half molecules, if not in that way engineered, is typical for IgG4 antibodies. The molecular characteristics were determined by a combination of techniques including mass spectrometry, peptide mapping, and N-glycan profiling.
The antibody is heterogeneously glycosylated at Asn297 within the Fc domain of each heavy chain, yielding a molecular weight of approximately 149 kDa for intact MK-3475. The dominant glycoform is the fucosylated agalacto diantennary glycan form (G0F).

The observed molecular weight of the most abundant form of the intact antibody is 148.9 kDa, while the most abundant forms of the heavy and light chains are 50.7 kDa and 23.7 kDa, respectively.

Manufacturing process
MK-3475 is a humanised monoclonal antibody that is expressed as a secreted product from a suspension Chinese Hamster Ovary (CHO) cell line. A fully characterised Master Cell Bank (MCB) as well as a Working Cell Bank (WCB) was established. Cells from the WCB are expanded in shake flasks, disposable rocker bags, and a seed bioreactor to generate the inoculum for a production bioreactor to produce the antibody product. The downstream processing includes three chromatography steps, two

orthogonal viral clearance steps, ultrafiltration/diafiltration, and a final 0.2 µm filtration step. All raw materials used in upstream/downstream manufacturing processes are animal component free. Upstream and downstream processing is considered as state of the art for production of monoclonal antibodies.

Definitions of key terms were provided by the Applicant as follows:

- Critical Quality Attribute (CQA): A critical quality attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8).
- Critical Process Parameter (CPP): A process parameter whose variability has an impact on critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8).
- Key Process Attribute (KPA): Process and/or product attributes that are primary measure(s) of the consistency of performance for each step.
- Key Operating Parameter (KOP): Parameter whose variability has an impact on a KPA and therefore should be monitored or controlled to ensure the desired consistency of performance.

Process development
There have been no major process changes other than scale and site changes between non-clinical and clinical manufacturing: non-clinical manufacturing was performed at the pilot plant facility using the MSB. Initial clinical manufacturing was performed at the clinical manufacturing facility. For initial clinical supplies, manufacture started from the MCB. Meanwhile, a working cell bank (WCB) has been qualified and introduced into the process. To enable facility fit at larger scale and also to increase productivity and robustness of downstream steps to ensure an adequate supply of MK-3475, the active substance manufacturing process has been transferred from the clinical site to a commercial manufacturing facility with greater capacity (MedImmune (FMC); Frederick Manufacturing Center, Frederick, MD). In addition to a change in scale of the active substance manufacture, other changes were made to further enhance the robustness of the commercial active substance manufacturing process.

Process validation, also referred to as Process Performance Qualification (PPQ), demonstrated that for all four PPQ batches, the predefined acceptance criteria for the upstream CQAs (of the unprocessed bulk) and for the downstream CQAs (active substance) were consistently met.

The active substance is already finally formulated. Active substance from FMC is stored at -40 ± 5°C and shipped at ≤ -35°C to the finished product manufacturing location.

Site changes were supported following ICH guideline Q5E by process and analytical comparability studies (comparative release testing and comparative extended site by site characterisation studies) including comparative long term stability assessments. Sufficient comparability for active substance from the clinical manufacturing site and active substance from FMC was demonstrated. Minor differences were sufficiently characterised (and understood). These root cause investigations (characterisations) were considered adequate and the outcome (i.e. no effect on safety and/or efficacy may be expected) seems plausible.

Characterisation
The primary, secondary, tertiary, and quaternary structures of MK-3475 were evaluated using a series of biochemical, biophysical and functional characterisation techniques. The single characterisation methods are considered scientifically justified, sufficient sensitive and state of the art and therefore suitable for characterisation of the active substance.

Product-related species of MK-3475 active substance were adequately separated by methods that exploit differences in molecular size, charge, and hydrophobicity.

Process-related impurities were adequately determined and include CHO host cell proteins (HCP), CHO host cell DNA and Protein A.

Control
The active substance Quality Control for batch release includes identity, potency (competitive binding ELISA), purity and impurities and several other general tests.

Reference Standard

As defined by ICH Q6B, an in-house reference material, manufactured at WAG facility, has been established for MK-3475.

Stability
Based on the presented 18 months real time real condition long-term stability data for the three primary batches the claimed shelf life of 18 months at -40ºC is considered justified.

2.2.3. Finished Medicinal Product

Description and composition
Finished product, powder for solution for infusion, single-use 50 mg/vial is reconstituted with sterile water for injection and further diluted with normal saline (0.9% sodium chloride injection) or 5% dextrose (5% dextrose injection; also referred to as 5% glucose) prior to IV administration.

Formulation development and optimisation studies have shown the pH of optimum product stability to be pH 5.2-5.8. Further low moisture content of the finished product lyophilisate ensures product stability. MK-3475 finished product does not contain any overages.

Process development
Initially, clinical materials have been manufactured at the clinical manufacturing facility. Increasing demand for finished product based on promising clinical data required an increase in capacity. Therefore, a second site, Schering-Plough (Brinny) in Innishannon, Ireland (further referred to as Brinny) was added as a finished product manufacturing site to supply the clinical trials.

Site changes were supported following ICH guideline Q5E by process and analytical comparability studies (comparative release testing and comparative site by site extended characterisation studies) including comparative long term stability assessments.

Manufacture
For the manufacture of MK-3475 finished product, FMC active substance is delivered as frozen final formulated bulk (FFB) solution containing the exact formulation of the final finished product. The finished product manufacturing process consists of thawing, pooling, bioburden reduction filtration, sterile filtration, filling, lyophilisation, capping, and visual inspection.

The manufacturing process for finished product and its controls (in-process control (IPC) and critical process parameters (CPP) ranges) are adequately presented. The defined critical process parameters are justified. The proven acceptable ranges and the defined normal operating ranges are considered acceptable for the critical process parameters.

The defined IPCs and their ranges are considered justified. Overall adequate IPCs are in place as part of the overall control system to ensure consistent manufacturing of the finished product.

All PPQ study objectives and CPP, IPC, PPQ samples and CQA acceptance criteria were met. Based on the study results, the process is considered principally sufficient validated for commercial manufacturing.

Control
The finished product Quality Control for batch release includes identity, potency (competitive binding ELISA), purity and impurities and several other general tests.

Reference standards are identical to the active substance material.

Container closure system
The container closure system is adequately described. It consists of Type-I glass vials, stoppered with bromobutyl stoppers and sealed with flip-off seals Stability leachable data as well as a careful characterisation and risk assessment of the observed leachables were provided to exclude any impact on patient's safety.

Stability

The primary stability batches are not produced at the proposed commercial full scale, and have been justified to be representative for the commercial process.

The updated 18 months real time real condition long-term stability data for the primary batches support the claimed shelf life of 18 months at 5ºC.

Adventitious agents safety
Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.
The active drug substance of MK-3475 is produced in a serum-free culture medium. No animal-derived material is added during fermentation of MK-3475.

Virus safety
The fermentation process of the monoclonal antibody MK-3475 is in a serum-free medium. No animal derived material is added during fermentation of MK-3475. This minimises a possible contamination for adventitious viruses. The cells used for production of MK-3475 have been sufficiently screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB of MK-3475 with the exception of intracellular A-type retroviral particles which are well known to be present in CHO cells. However, this is acceptable since there is sufficient capacity within the manufacturing procedure of MK-3475 for reduction of this type of viral particles. Therefore, there are no concerns for the use in the production process of MK-3475. The purification process of MK-3475 includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

In summary, the adventitious agents safety of MK-3475 is considered to be sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall the quality data presented by the Applicant are detailed. However, Major Objections were identified during the review as well as numerous Other Concerns. It was acknowledged that characterisation of the active substance (and its microheterogeneity / product-related impurities) as well as extended characterisation in comparability studies were carried out very carefully using a large set of suitable and sufficient sensitive (wherever possible orthogonal) state-of-the-art analytical methods.

A Major Objection was raised in relation to the use of two significantly different manufacturing routes. In their responses, the Applicant withdrew one site as commercial active substance manufacturing site.

The Applicant acknowledged the relatively broad comparability acceptance criteria included in the original submission, when results were compared with the specification in effect at time of study initiation; therefore, the Applicant performed a thorough comparative assessment of product quality attributes.

In the description of the manufacturing process, the Applicant was asked to clarify the intended use of so-called Proven Acceptable Ranges (PARs).

It was acknowledged that several orthogonal bioassay formats were used in the characterisation of Fab and Fc domains of MK-3475. However with regard to the Fab-related assays, the binding ELISA, which was initially proposed to be the sole potency test, did not fully reflect the mechanism of action of MK-3475. Although there may be some lack of correlation, the notion that neither the cell-based competitive binding assay nor the functional cell-based assay contribute to any additional information necessary for correct release and stability decisions is endorsed.

The final specifications proposed by the Applicant for active substance and finished product are considered acceptable.

An issue was raised in relation to the evidence that the container closure system proposed for the finished product may not be suitable although adequate certificates and Ph. Eur. compliance is presented. Evidence is based on two leachable stability studies. Additional data were provided by the Applicant in their responses indicating that patient exposure to these materials results in leachable levels which are below the doses known to cause adverse events and therefore can be considered toxicologically safe. The issue was considered resolved.

On the basis of additional stability data provided by the Applicant, the 18 month shelf life for the finished product was considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Keytruda is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall Quality of Keytruda is considered acceptable. Several recommendations for future quality development were agreed by the Applicant.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The binding of pembrolizumab (MK-3475, SCH 900475, ORG 307488-0) to human PD-1 was evaluated in different experimental test systems. In vitro studies were performed in cell lines expressing either PD-1 or PD-L1, in cynomolgus and human PBMCs and in vivo studies were performed mainly in mouse models. Given the lack of cross-reactivity of MK-3475 with murine PD-1, a commercially available hamster anti-murine PD-1 mAb, J43, was used as surrogate for in vivo pharmacology studies.

The parental antibody to pembrolizumab was produced by immunizing mice with hPD-1 cDNA and CHO-PD-1 cells. The pembrolizumab antibody was generated by humanization of the parental murine anti-human PD-1 antibody.The pharmacokinetics (PK) of pembrolizumab were evaluated in a non-GLP single dose pharmacokinetic study and two GLP repeat dose toxicokinetic (TK) studies (1-month and 6-month) in cynomolgus monkeys. A non-GLP study in SCID mice was also conducted to evaluate the Fab-arm exchange of pembrolizumab in vivo.

Toxicology was evaluated in the relevant non-primate model cynomolgus monkey the only relevant and pharmacologically responsive model.

2.3.2. Pharmacology

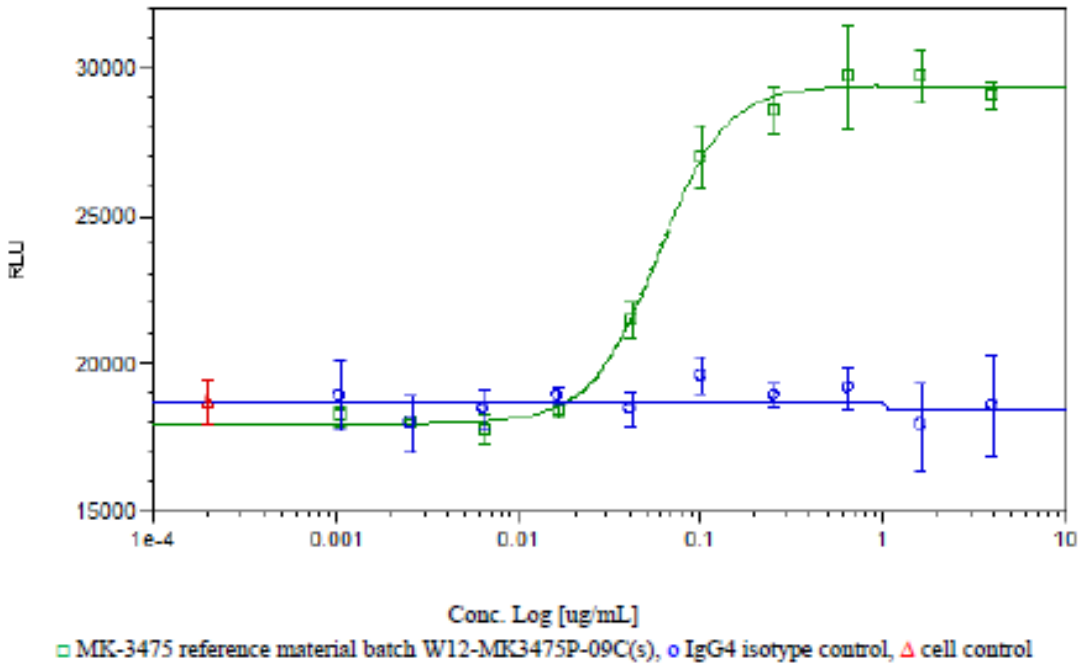
Primary pharmacodynamic studies

Functional Cell-Based Assay

A cell-based assay evaluating downstream biological responses of pembrolizumab uses co-culture of immortalized Jurkat T cells with monocytic cells mimicking the biological interplay of activated T-cells

expressing the PD-1 receptor and PD-L1 expressing cells (carcinoma cells, native dendritic cells, macrophages, B cells, etc.) presenting the inhibitory signal. The result of IL-2 production is presented in Figure 4.

Figure 4: Pembrolizumab functional cell based assay



Assessment of Functional Activity of pembrolizumab In Vitro

Binding of pembrolizumab to cynomolgus PD-1

The binding affinity of pembrolizumab for cynomolgus PD-1 was evaluated by ELISA, cellular ELISA and by bio-light interferometry (study PD001). In these studies, the binding affinity of pembrolizumab to cynomolgus and human PD-1 was found to be in the same range, albeit slightly lower for cynomolgus PD-1. By kinetic analysis, KD was 29 pM for human PD-1 and 118 pM for cynomolgus PD-1 (Table 4). Functionally, pembrolizumab blocked the binding of human PD-1 ligands to cells expressing human or cynomolgus PD-1 with a comparable potency (Table 5).

Table 4: Assessment of affinity of binding of pembrolizumab to PD-1

	k_{assoc} (1/s)	k_{dissoc} (1/Ms)	K_D (± SEM) (pM)
Human	1.04×10^6	3.05×10^{-5}	29 (6)
Cynomolgus monkey	2.05×10^6	2.42×10^{-5}	118

The results for binding of MK-3475 to human PD-1 are an average of 2 independent experiments; the results for binding to cynomolgus monkey PD-1 are from a single experiment.
k_{assoc} = association-rate constant; K_D = dissociation constant; k_{dissoc} = dissociation-rate constant; SEM = standard error of the mean.

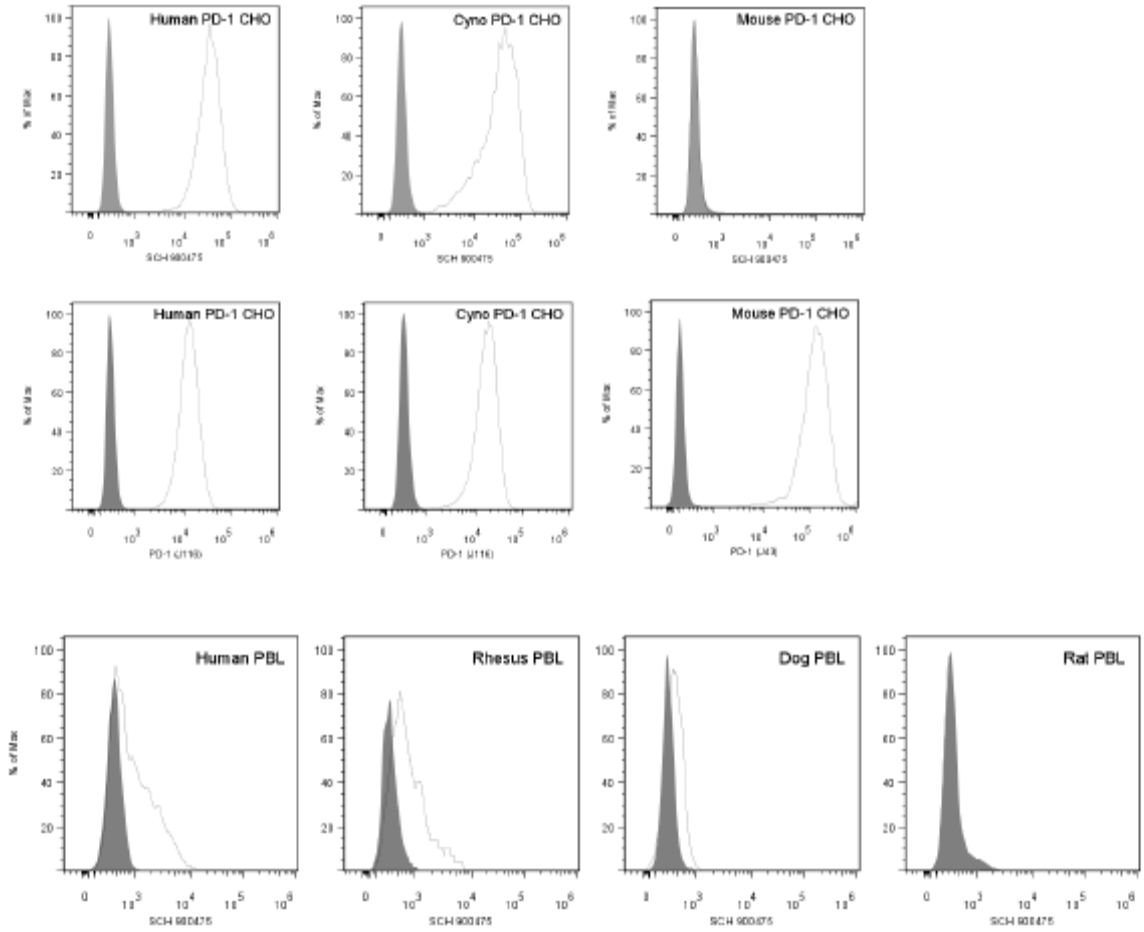
Table 5: Assessment of blocking the binding of PD-1 to PD-L1 and PD-L1 mediated by pembrolizumab

	PD-L1 IC_{50} (pM) (± SEM)	PD-L2 IC_{50} (pM) (± SEM)
Human	625 (130)	695 (360)
Cynomolgus monkey	721 (150)	762 (200)

The results presented are an average of 3 independent experiments.
IC_{50} = half-maximal inhibitory concentration; SEM = standard error of the mean.

For testing binding of pembrolizumab to PD-1 expressed in human, mouse and cynomolgus macaque, stable cell lines were used. The results are shown in Figure 5.

Figure 5: Binding of pembrolizumab to human and cynomolgus macaque PD-1 - Study PD003 (SN 09536)

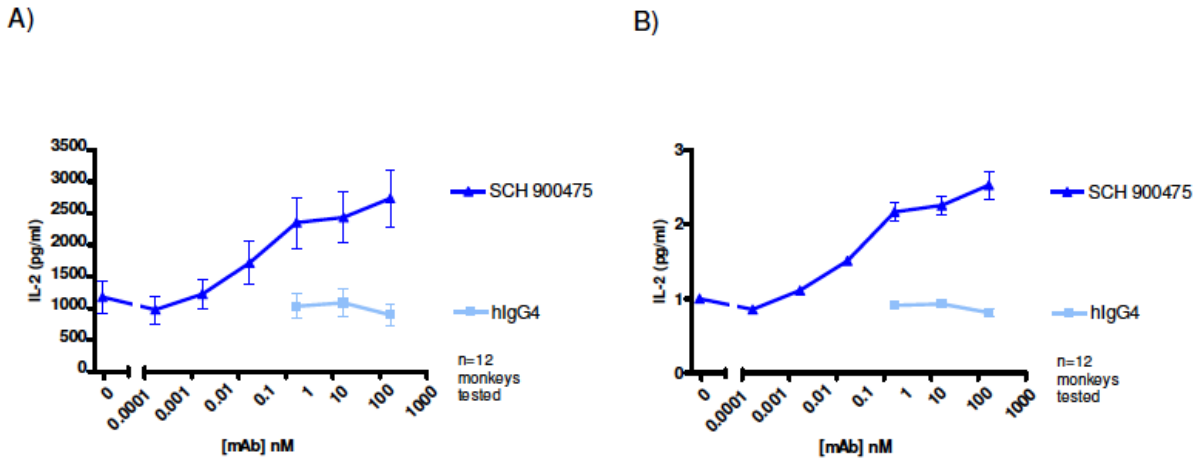


(Top) SCH 900475 binds to CHO cells expressing human and cynomolgus macaque PD-1, but not to CHO cells expressing mouse PD-1. (Middle) Human, cynomolgus and mouse PD-1 is expressed at similar levels on CHO cells and detected with commercially available antibodies (J116: human/cyno; J43 mouse). (Bottom) SCH 900475 binds in a similar fashion to PBL derived from human and rhesus, but not dog or rat whole blood by flow cytometry.

In vitro T cell modulation (study no. PD002 = SN 09545; PD004 = SN 10121)

The functional capacity of pembrolizumab to potentiate IL-2 production in an *in vitro* blocking assay in cynomolgus monkeys was demonstrated in Figure 6.

Figure 6: Potentiation of IL-2 production in blood cells by PD-1 blockade in PBLs from cynomolgus monkeys - Study PD002 (SN 09545)



SHC 900475=pembrolizumab; hIgG4=human immunoglogulin isotype 4 (control)

Efficacy of Anti-Mouse PD-1 Surrogate Antibody in Syngeneic Tumor Models In vivo studies

Study PD006 report SN 09546: anti-tumor activity of anti-mouse PD-1 antibody J43, in syngeneic mouse tumor models.

The following cell lines were used to set syngeneic mouse tumor models:

- MC38- Colon adenocarcinomas of C57BL/6 origin

- C1498- Acute myeloid leukemia of C57BL/6 origin

- PDV6- Squamous cell carcinoma of C57BL/6 origin

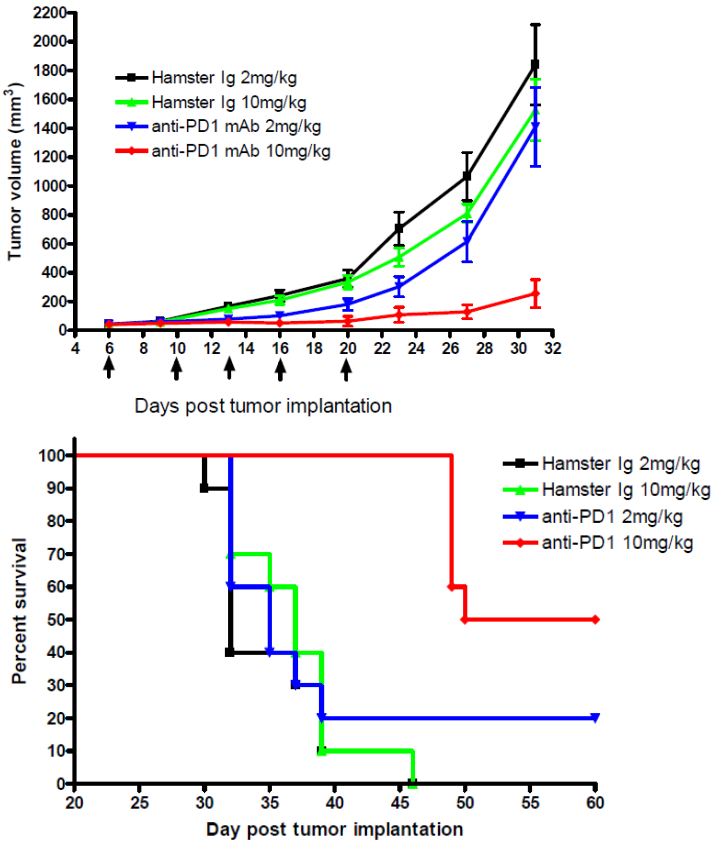
- A20- B cell lymphoma of Balb/c origin.

Tumor cells were subcutaneously injected into the ventral surface of the lower flank of syngeneic mice. Treatment with antibodies was initiated when tumors reached a volume of 50-70 mm^3.

The Figure 7 shows results obtained by administrating IP J43 antibody or isotype control into mice SC implanted with MC38. The efficacy of anti-PD-1 was assessed in the MC38 syngeneic model of colon adenocarcinoma in C57BL/6 mice as monotherapy or in combination with 5-fluorouracil (5-FU) or gemcitabine. Anti-mouse PD-1 mAb J43 or hamster IgG were administered IP at 2 or 10 mg/kg every 3-4 days for a total of 5 doses.

Figure 7: Antitumour response of monotherapy with mouse anti-PD-1 in MC38 colon adenocarcinoma model

A) Tumour volume (mm3) **B) Survival rate (%)**

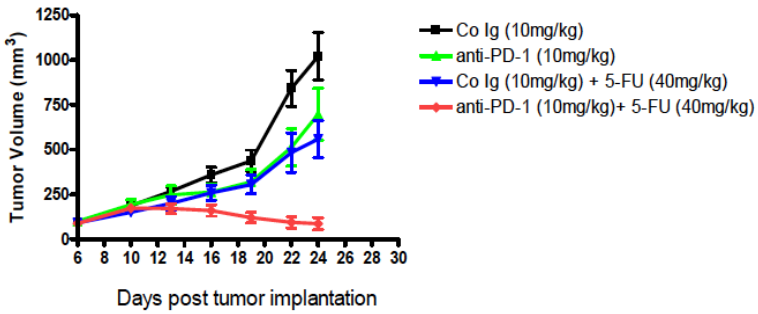


C57BL/6 female mice were implanted subcutaneously with 1 x 10^6 MC38 syngeneic colon adenocarcinomas cells. On day 6 when tumour volumes were approximately 50-80 mm^3 , mice were injected i.p. with either control hamster Ig or hamster anti-mouse PD-1 (J43) at 2mg/kg or 10mg/kg. Injections were repeated on day 10, 13, 16, and 20 (black arrows). Tumour volumes were measured every 3-4 days until day 30 and the results are presented as the means + standard errors. Survival was followed for 60 days.

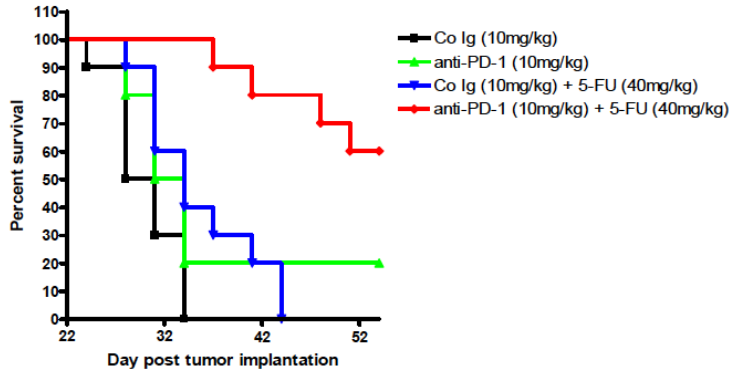
In addition to monotherapy, anti-PD1 immunotherapy was evaluated in combination with either 5 FU or gemcitabine. The results are shown in Figure 8.

Figure 8: Antitumour response of immunotherapy with mouse anti-PD-1 in combination with 5-FU or gemcitabine in MC38 colon adenocarcinoma model

A) Tumour volume (mm3)



B) Survival rate (%)



Together with 5-FU, mouse anti-PD-1 inhibited tumour growth and prolonged survival; i.e. 60% of mice receiving concurrent treatments of 5-FU and J43 survived beyond 50 days with no evidence of tumour relapse.

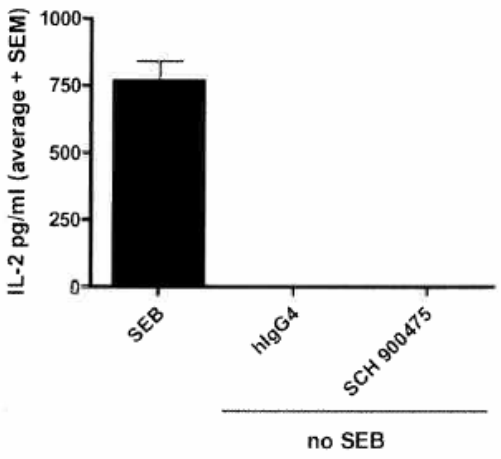
Secondary pharmacodynamic studies

No studies evaluating secondary pharmacodynamics of pembrolizumab have been submitted. However, the applicant submitted a study to evaluate the ability of anti-PD-1 antibody to spontaneously activate the immune system.

Assessment of the Ability of pembrolizumab to Spontaneously Activate the Immune System

The ability of pembrolizumab to activate the immune system (as measured by levels of IL-2) without concurrent T-cell receptor triggering was assessed in two in vitro assays (study PD004; SN 10121) . In the first assay, peripheral blood from healthy human donors was diluted, pre-incubated with pembrolizumab or human IgG4 isotype control antibody, and then stimulated with SEB or left unstimulated. In this assay, SEB represented a concurrent specific stimulus for the T-cell receptor. Pembrolizumab enhanced production of IL-2 only in the presence of SEB; in the absence of SEB, pembrolizumab had no effect on the level of IL-2.

Figure 9: Evaluation of the potential of SCH 900475 to stimulate cytokine release without concurrent direct antigen T cell stimulation in healthy blood donor



Safety pharmacology programme

Stand-alone studies evaluating safety pharmacology of pembrolizumab were not submitted (see non-clinical discussion).

Pharmacodynamic drug interactions

No non-clinical no clinical dedicated pharmacodynamic drug-drug interactions studies with pembrolizumab have been conducted (see non-clinical discussion).

2.3.3. Pharmacokinetics

No tissue distribution/mass balance or metabolism studies with pembrolizumab were submitted (see non-clinical discussion).

No excretion studies with pembrolizumab were submitted (see non-clinical discussion).

No non-clinical PK drug-drug interactions studies were submitted (see non-clinical discussion).

Non-GLP pharmacokinetics of pembrolizumab following a single IV dose administration in female cynomolgus monkeys (PK001 = SN 08S00372)

Female cynomolgus monkeys (3/group) were given a single IV dose of pembrolizumab at 0, 0.3, 3 or 30 mg/kg and followed for a period of 84 days. Concentration of serum pembrolizumab was determined by ELISA. An overview of the PK parameters obtained after non-compartmental analysis is provided in Table 6.

Table 6: PK parameters following single IV administration of pembrolizumab in cynomolgus monkeys (mean ± SEM)

Dose [a] (mg/kg)	Cmax (mg/L)	AUC_last [b] (day/mg/L)	AUC_inf [b] (day/mg/L)	t½, el (day)	Vss (ml/kg)	CL (ml/day/kg)
0.3	15.3 ± 4.3	41.0 ± 2.9	51.1 ± 1.5	3.9 ± 0.7	30.9 ± 6.0	5.7 ± 0.2
3	117.7 ± 5.2	700.0 ± 76.5	729.3 ± 79.5	5.9 ± 1.6	36.8 ± 4.6	4.2 ± 0.4
30	1265 ± 73	6374 ± 767	8124 ± 416	10.6 ± 0.4	54.8 ± 5.7	3.7 ± 0.1

[a] All three monkeys in each dose group were included in the analysis

[b] Because of ADA, sample concentrations that were less than 1 mg/L were excluded from the calculation. Therefore, $AUC_{0\text{-last}}$ was different for different animals: the last time point for three monkeys in the 0.3 mg/kg group were 14, 7 and 14 days; for 3 mg/kg last three time points were 42, 28 and 14 days and for 30 mg/kg last three time points were 28, 14 and 63 days.

There was a dose-dependent increase in exposure; the increase was more than dose-proportional between 0.3 and 3 mg/kg and dose-proportional between 3 and 30 mg/kg. Clearance varied from 2.5 – 11.3 ml/kg/day and was higher for the low dose. The elimination half-life was prolonged and the distribution volume increased in the high-dose group. From day 10 on, a drop in serum pembrolizumab levels (in 8 of 9 animals) correlated with detection of ADA.

Anti-pembrolizumab ADA (as measured by bridging ELISA) were detected in 8 out of 9 animals at variable time points starting as soon as day10 and most visible at day 21 after dosing. However, it should be noted that ADA could only be measured if the concentration of pembrolizumab was not interfering with the assay (< 5 µg/ml).

2.3.4. Toxicology

The pembrolizumab toxicological program has been performed according to ICH S6 guideline for biotechnology products and ICH S9 nonclinical evaluation for anticancer pharmaceuticals, and consisted of pivotal 1-month and 6-month repeat-dose chronic toxicity studies both with 4-month recovery periods in Cynomolgus monkey, supported by toxicokinetic analysis. In addition, two cross-reactivity studies in both normal human and Cynomolgus monkey tissues were submitted.

Table 7: List of non-clinical toxicology studies supporting pembrolizumab

Study Type and Duration	Route	Species	Dose Levels (mg/kg)	GLP	Study No.
Repeat dose toxicity					
1 month	IV	Cynomolgus monkey	6, 40, 200	Yes	SN 08396
6 months	IV	Cynomolgus monkey	6, 40, 200	Yes	TT #11-1084
Other toxicity studies					
Tissue Cross Reactivity	*In vitro*	Cynomolgus monkey tissues	N/A	Yes	SN 08395
Tissue Cross Reactivity	*In vitro*	Human tissues	N/A	Yes	SN 08394

Single dose toxicity

No dedicated single-dose toxicity studies were submitted (see non-clinical discussion).

Repeat dose toxicity

The 1-month and 6-month repeat-dose toxicity was conducted in the Cynomolgus monkey and results are presented in Table 8.

Table 8: Overview of the repeat-dose toxicity studies conducted with Keytruda

Study ID GLP status Duration	Species (N)	Route Dose/(mg/kg/day)	NOAEL (mg/kg/d)	Major findings
SN 08396 GLP One-month with a 4-month Recovery Period	Cynomolgus Monkeys 6/sex/dose ≈ 24 to 51 months (2-4.25 years) 4/sex/dose (euthanized wk 5), 2/sex/dose (euthanized wk	i.v. (bolus) once weekly for a total of 5 doses. 6, 40, or 200.	200 AUC_{0-7d} 170000 µg·day/mL	Increased incidence of inguinal swelling (left, right or bilateral) in males receiving 200 mg/kg. Inguinal swelling persisted in one of two males in the 200 mg/kg dose group and resolved in the other. Higher mean absolute and relative spleen weights in males (200 mg/kg) at the end of dosing period (Week 5). No changes in spleen weight at the Week 23 sacrifice,

Study ID GLP status Duration	Species (N)	Route Dose/(mg/kg/day)	NOAEL (mg/kg/d)	Major findings
	23)			indicating recovery.
TT #11-1084 GLP Six-month with a 4-month Recovery Period	Cynomolgus Monkeys 5 /sex/dose ≈ 1 to 3 years 3/sex/dose for interim necropsy (3 days after the last dose Wk 23) 2/sex/dose final necropsy following the 4-month treatment-free period	i.v. (bolus) once every other week for a total of 12 doses. 6, 40, or 200.	200 $AUC_{0\text{-}14d}$ 67500 µg·day/mL	End of dosing necropsy Focal mononuclear cellular infiltration of the parathyroid gland, thyroid gland, skeletal muscle, esophagus, and kidney, without parenchymal organ tissue disruption or degeneration, and inflammation in the vagina. End of treatment-free period 40 mg/kg monkey (#11-0136) Slight decreases in red blood cell counts, hemoglobin, hematocrit, platelet count, and fibrinogen; increases in reticulocytes and red cell distribution width in Study Week 40 only. Slight decreases in total protein, albumin, potassium, calcium, and phosphorus; very slight to moderate increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), cholesterol, and triglycerides in Study Week 40 only. Very slight to slight focal mononuclear cell infiltrates (primarily lymphocytes and histiocytes in multiple tissues greater than what is observed in historical control population. Increased amounts of lymphoid tissue (spleen and some lymph nodes) from this monkey consisting in very slight increase in numbers of lymphoid cells composing the periarteriolar lymphoid sheath (PALS) of the spleen that was associated with an increase in spleen weight. A very slight expansion of lymphoid tissue was observed in the cortex and paracortex of cervical and inguinal lymph nodes In the thymus, a marked decrease in the cortical lymphoid tissue correlated with a decrease in thymic weight,

Study ID GLP status Duration	Species (N)	Route Dose/(mg/kg/day)	NOAEL (mg/kg/d)	Major findings
				accompanied by a concurrent moderate increase in the amount of lymphoid cells in the medulla, and occasional foci of chronic inflammation centered on mineralized debris.

In order to evaluate whether there was an increase in lymphocytes accumulation in the spleen derived from the increased T cells activation from anti-PD-1 therapy, the weight of the spleens were measured in treated animals. A trend of higher mean absolute and relative spleen weights in comparison to control was observed in males starting from the low dose (6 mg/kg), reaching a significant 60% increase in males administered 200 mg/kg and euthanized during Week 5 (Table 9). However, no remarkable macroscopic observations were reported in spleens of high dosed animals.

Table 9: Principal organ weight changes at week 5 in 1-one month study (& difference from concurrent control mean)

Principal Organ Weight Changes at Week 5: Percent Difference from Concurrent Control Mean								
Dose Group (mg/kg):	0 (Control)		6 (SCH 900475)		40 (SCH 900475)		200 (SCH 900475)	
Sex:	M	F	M	F	M	F	M	F
Organ	Mean Weight		Percent Difference from Concurrent Control Mean (%)					
Spleen								
- absolute weight	6.06 g	4.80 g	+16	-3	+20	+21	+61*	+4
- relative weight[a]	0.17%	0.16%	+18	-3	+31	+26	+59*	+19
a: Relative to body weight * = Test article-related finding								

Genotoxicity

The applicant did not submit studies on genotoxicity with pembrolizumab (see non-clinical discussion).

Carcinogenicity

The applicant did not submit studies on carcinogenicity with pembrolizumab (see non-clinical discussion).

Reproduction Toxicity

No reproductive toxicity studies were conducted with pembrolizumab (see non-clinical discussion).

However, the applicant provided literature data on the role of PD-1 on the maintenance of immune tolerance during foetal development. During pregnancy, foetal antigens can be detected in the maternal spleen, where they cause proliferation of antigen-specific T lymphocytes in response[10]. The

[10] Erlebacher A, Vencato D, Price KA, Zhang D, Glimcher LH. 2007. Constraints in antigen presentation severely restrict T cell recognition of the allogeneic fetus. J. Clin. Invest. 117: 1399-1411.

PD-L1 molecule is expressed at the utero-placental interface, where it protects the concepti from maternal T-cell mediated immunity[11] . Its expression is detected at the utero-placental interface of the placentas of CBA x C57BL/6 mice concepti as early as 10 days post-conception while it is negligible, as expected for syngeneic concepti, at the utero-placental interface of the placentas of CBA x CBA mice.

In human and non-human primate foetuses, maternal antibodies can cross the placenta via active transport across the chorioallantoic placenta. This transfer is mediated principally via the neonatal Fc receptor (FcRn) and there is general agreement that immunoglobulins of the IgG1 subclass are transported most efficiently. Foetal IgG levels remain low during the first two trimesters of pregnancy and typically rise during the third trimester so that the levels of IgG4 in the foetus are similar to those in the maternal circulation[12] . Blockade of PD-L1 signaling has been shown in murine models of allogeneic pregnancy (developed by mating different strains of mice) to abrogate feto-maternal tolerance to the concepti and to result in an increase in fetal resorption[13]. The rate of spontaneous abortion in the allogeneic pregnancy in crossed CBA x C57BL/6 mice is 18%. Treatment with anti-PDL1 resulted in a significant increase in the rate of abortion of those allogeneic concepti to 86%.

The role of T cell-mediated immunity in foetal rejection was then confirmed in an experiment by the demonstration of infiltrations of T cells congregated at the site of foetal resorption in anti-PD-L1-treated animals from allogeneic pregnancy using immunohistochemistry of placental sections[13]. Confirmation that T cells are required for anti-PD-L1 rejection was obtained in the following set of experiments. RAG-1 -/- mice (on a C57BL/6 background), which lack T and B cells, were mated with CBA males and treated with anti-PD-L1 mAb. All RAG-1 -/-females had normal numbers of healthy embryos, whereas RAG sufficient C57BL/6 females mated with CBA males and treated with anti-PD-L1 mAb showed increased foetal resorption[13]. Further implication of T cells in PD-1/PD-L1-mediated fetal resorption was demonstrated by the allogeneic mating of B cell-deficient mice followed by anti-PD-L1 mAb treatment. Blocking the PD-1/PD-L1 pathway resulted in foetal rejection in 100% of these mice. Wafula et al.[14] identified PD-1 as an important player in the protection of the foetus that appears to be mediated by regulatory T cells (Tregs). Regulatory T cells from normal pregnant mice transferred into abortion-prone mice allowed abortion-prone mice to pursue a successful pregnancy by restoring normal physiological protection to the concepti. Subsequent treatment of these mice with anti-PD1 abrogated the protective effect of Tregs and resulted in the previous abortion rates. PD-L1 expressed on the surface of Tregs was shown to be essential to control the maternal immune response[15]. From the literature provided by the applicant, there was no evidence of malformations related to the blockade of PD-L1 signaling[13, 14, 15].

Fertility and early embryonic development

Reproductive and developmental toxicity studies with pembrolizumab were not submitted (see non-clinical discussion).

[11] Guleria I, Khosroshahi A, Ansari MJ, Habicht A, Azuma M, Yagita H, Noelle RJ, Coyle A, Mellor AL, Khoury SJ, Sayegh MH. 2005. A critical role for the programmed death ligand 1 in fetomaternal tolerance. J. Exp. Med. 202: 231-237.
[12] Pentsuk N, van der Laan, JW. 2009. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. Birth Defects Res.. 86:328 -344.
[13] Guleria I, Khosroshahi A, Ansari MJ, Habicht A, Azuma M, Yagita H, Noelle RJ, Coyle A, Mellor AL, Khoury SJ, Sayegh MH. 2005. A critical role for the programmed death ligand 1 in fetomaternal tolerance. J. Exp. Med. 202: 231-237.
[14] Walfula P.O., Teles A., Schumacher A., Pohl K., Yagita H., Volk H.D., Zenclussn A.C. 2009. PD-1 but not CTLA-4 blockage abrogates the protective effect of regulatory T cells in a pregnancy murine model. Am. J. Reprod. Immunol. 62: 283-292.
[15] Habicht A, Dada S, Jurewicz M, Fife BT, Yagita H, Azuma M, Sayegh MH, Guleria I. 2007. A link between PDL1 and T regulatory cells in fetomaternal tolerance. J. Immunol. 179: 5211-5219.

Toxicokinetic data

In both the ELISA and ECL assays, the concentrations of pembrolizumab in monkey serum were determined by ligand (hPD1-Fc) as capture followed by anti-human kappa chain antibody (Ab) as detection.

Toxicokinetics of pembrolizumab following repeated dosing for 1-month study (study SN 08396)

In this toxicity study, cynomolgus monkeys (6/sex/group) received IV doses of 0, 6, 40 or 200 mg/kg pembrolizumab, once weekly for a total of 5 doses. Toxicokinetics were evaluated after the first dose (day 1) and after the fifth dose (day 28). The results are shown in Table 10.

Table 10: Summary of TK parameters following weekly repeat IV dosing in cynomolgus monkeys

Dose [a] (mg/kg)	Study day	C0 [b] (µg/ml)	Cmax [b] (µg/ml)	Tmax [c] [h] (hr)	AUC(0-7days) [b] (µg*day/ml)	t1/2 [g] (day)	R [d] [i]
6	1	322 [e]	292	1 (1-24)	923		
	28	338	350	2 (1-24)	1790	15.7	1.78
40	1	2950	2510	1 (1-168)	7240		
	28	4390	4770	2 (1-168)	24100	22.3	3.12
200	1	14800	14800	1 (1-48)	49700		
	28	58900	86200	3 (1-24)	170000	19.8	5.58

a) N = 12/dose (6 M and 6 F) unless otherwise noted
b) Arithmetic means unless otherwise noted
c) Median (minimum – maximum)
d) AUC ratio: R=AUC(0-7 days) dosing interval 5 ÷ AUC(0-7 days) dosing interval 1; mean calculated from R values from individual animals
e) N=13
g) t½ values were determined for the animals assigned to the recovery period
h) Tmax = 168 hrs was observed for 1 animal after the 1st dose and for a different animal after the 5th dose
i) N = 4 (2/sex)

In the 6 mg/kg group, development of ADA during the dosing phase was observed. When taking into account only the ADA-negative samples for the 5th dosing interval, Cmax is 524 µg/ml and AUC(0-7day) is 2350 µg*day/ml. The terminal half-life was determined for the animals assigned to the recovery period. For the 6 mg/kg and 40 mg/kg group, these parameters were derived from ADA-negative animals only.

Toxicokinetics of pembrolizumab in the 6-month study (study TT #11-1084)

Cynomolgus monkeys (5/sex/group) received IV doses of 0, 6, 40 or 200 mg/kg pembrolizumab, once every 2 weeks for a total of 12 doses. Toxicokinetics were evaluated after the 1st dose (day 1), the sixth dose (day 71), and the eleventh dose (Day 141.) The T1/2 was evaluated after the last dose (dose 12 at day 155).

Anti-pembrolizumab antibodies were detected in 5 animals of the 6 mg/kg group (during the dosing period) and in 1 animal in the 200 mg/kg group (during the recovery period) and were associated with an increase in elimination of pembrolizumab. Due to drug interference, the presence of ADA in mid- and high-dose animals cannot be excluded.

Table 11: Summary of TK parameters following biweekly IV doses in cynomolgus monkeys

Dose [a] (mg/kg)	Study day	Cmax [b] (µg/ml)	Tmax [b] (hr)	AUC(0-14days) [b] (µg*hr/ml)	t1/2 [c] (day)	R [d]

6	1	174 ± 7.72	0.33 ± 0.083	21,400 ± 808		
	71	215 ± 43.8	1.3 ± 0.58	24,100 ± 8480		1.13 (2.2)
	141	224 ± 33.9	0.25 ± 0	28,800 ± 9630		1.34 (2.69)
	155				21.4	
40	1	1840 ± 216	1.6 ± 0.59	176,000 ± 11,000		
	71	1930 ± 93.8	2.0 ± 0.75	313,00 ± 16,500		1.78
	141	1890 ± 180	1.5 ± 180	322,000 ± 27,000		1.83
	155				21.1 ± 2.3	
200	1	7470 ± 529	4.8 ± 2.2	848,000 ± 60,400		
	71	10,500 ± 489	0.55 ± 0.12	1,540,000 ± 59,100		1.81
	141	10,400 ± 772	1.1 ± 0.55	1,620,000 ± 107,000		1.91
	155 [f]				22.0 ± 2.2	

a) N=5/sex/group

b) mean ± SEM

c) t1/2 was evaluated after the last dose from animals that had not ADA-positive samples

d) AUC ratio: Day 71 R= $AUC_{0\text{-}14days}$ of day 71 interval ÷$AUC_{0\text{-}14days}$ of day 1 interval; Day 141 R= $AUC_{0\text{-}14days}$ of day 141 interval ÷ $AUC_{0\text{-}14days}$ of day 1 interval; 6 mg/kg dose has two values, the one in the bracket being the R after exclusion of ADA positive samples.

The monkey AUC values at the end of period treatment are summarised in Table 12.

Table 12: Summary of the Cynomolgus monkey AUC

Study ID **Day of analysis**	**Daily Dose (mg/kg)**	**AUC $_{0\text{-}tau}$ (µg·day/ml) Dosing interval 5 or 11 [a]**	**Animal:Human Exposure Multiple (EM)**	
			2.0 mg/kg [b,d]	10 mg/kg [c,d]
		♂ and ♀		
SN 08396 Monkeys one month (study week 5)	6	1790	2.5	0.5
	40	24100	33	6.7
	200 (NOAEL)	170000	236	47
TT #11-1084 Monkeys 6 months (study week 21-22)	6	1200	1.7	0.3
	40	13417	19	3.7
	200 (NOAEL)	67500	94	19

a) tau = 7 days in 1 month study and data are from Dosing Interval 5 (Study Week 5); tau = 14 days in 6 month study and data are from Dosing Interval 11 (Study Weeks 21-22) .

b) EM @ predicted AUC(0-tau) of 721.5 µg·day/mL for the clinical dose of 2 mg/kg, Q3W.

c) EM @ predicted AUC(0-tau) of 3607.3 µg·day/mL for the clinical dose of 10 mg/kg, Q3W and Q2W. AUC(0-tau) is by definition independent of schedule and therefore the EMs for Q2W and Q3W are identical.

d) Clinical AUC at steady state calculated from clearance as dose divided by clearance and normalized to one week. Clearance was determined by popPK modeling at 0.219 L/day.

Local Tolerance

The applicant did not submit dedicated studies on local tolerance (see discussion on non-clinical aspects).

Other toxicity studies

Immunogenicity

Three normal female cynomolgus monkeys per group were administered a single intravenous (IV) dose (vehicle control, 0.3, 3.0 and 30 mg/kg) of pembrolizumab. Blood was collected at predose day -7, day 0 and after SCH 900475 or vehicle administration at day 1, day 7, day 28, day 56 and day 84 for ex-vivo PD analysis.

ADA were detected in most of the treated animals: in all animals in the 0.3 mg/kg (14-day samples after dosing) and 3 mg/kg (21-day samples after dosing) dose groups, and in 2 out of 3 animals in the 30 mg/kg dose group (21-day samples after dosing). No assay was performed to assess whether ADA were neutralizing.

Table 13 shows the PK parameters following administration of pembrolizumab in the presence or absence of detectable anti-drug-antibodies (ADA). PK results showed a dose dependent increase in exposure. The clearance varied from 3.7 – 5.7 mL/kg/day and was higher for the low dose; the elimination half-life was prolonged and the distribution volume in steady state increased in the high dose group regardless of the ADA status.

Table 13: PK parameters following single IV administration in female cynomolgus monkey in the presence or absence of anti-drug-antibodies (ADA)

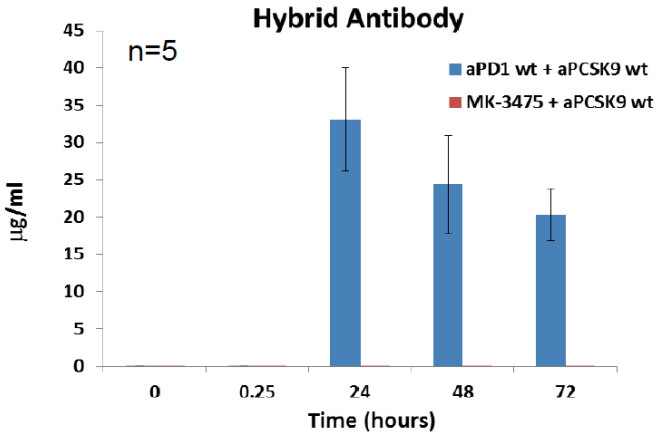
	0.3 mg/kg SCH 900475 Average ± sem *(monkey 11116, 12412,5294)* ***With ADA***	3 mg/kg SCH 900475 Average ± sem *(monkey 11250,11258,1382)* ***With ADA***	30 mg/kg SCH 900475 Average ± sem *(monkey 10304,11252,12082)* ***With/ without ADA***	30 mg/kg SCH 900475 *(monkey 12082)* ***Without ADA***
Corr	-0.968 ± 0.011	-0.933 ± 0.043	-0.0961 ± 0.008	-0.9711
Cmax (mg/L)	15.3 ± 4.3	117.7 ± 5.2	1265 ± 73	1188
AUC_extrap (%)	19.5 ± 6.7	4.0 ± 1.3	21.0 ± 11.2	1.2
AUC_last (day/mg/L)	41.0 ± 2.9	700.0 ± 76.5	6374 ± 767	7616
AUC_inf (day/mg/L	51.1 ± 1.5	729.3 ± 79.5	8124 ± 416	7725
T ½ _Terminal (day[s])	3.9 ± 0.7	5.9 ± 1.6	10.6 ± 0.4	10.4
$T_{1/2}$ –VSS / Cl (days)	3.7 ± 0.8	6.3 ± 1.4	10.2 ± 0.2	10.7
CL (mL/day/kg)	5.7 ± 0.2	4.2 ± 0.4	3.7 ± 0.1	3.9
Vss (mL/kg)	30.9 ± 6.0	36.8 ± 4.6	54.8 ± 5.7	60.0

Lack Fab arm exchange in vivo (study report TRPT-002743)

In vivo studies were conducted to confirm the lack of Fab-arm or half-molecule exchange for pembrolizumab. The potential of pembrolizumab to engage in Fab arm exchange in vivo was studied in

SCID mice by co-injecting either pembrolizumab or anti-PD-1 wt with anti-PCSK9 wt. The amount of hybrid antibodies formed in vivo was detected by a hybrid-specific ELISA. As shown in Figure 10, hybrid antibodies can be detected in sera of mice injected with the mixture of wildtype anti-PD-1 and anti-PCSK9 mAb. In contrast no hybrid antibodies were detected when pembrolizumab and anti-PCSK9 wt mAb were co-injected.

Figure 10: Formation of hybrid antibodies in vivo



2.3.5. Ecotoxicity / environmental risk assessment

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

2.3.6. Discussion on non-clinical aspects

Keytruda (pembrolizumab, SCH 900475, MK-3475) is a humanized antibody where only the complementarity determining regions (CDRs) of the variable regions are of mouse-sequence origin.

The pharmacology of pembrolizumab was evaluated in Cynomolgus monkey as the similarities in binding affinities with human PD-1 were observed in in vitro experiments compared to mouse, rat and dog, where no binding was observed. The antitumor activity induced by blocking PD-1 was shown in vivo in mice in a syngeneic tumour model where MC38 colon adenocarcinoma was injected subcutaneously and mice were treated using a commercially available homologous anti-mouse PD-1 monoclonal antibody J43 at 2 mg/kg and 10 mg/kg doses every 3-4 weeks. J43 10 mg/kg administered IP, alone or in combination with 5-fluorouracil or gemcitabine, significantly inhibited the growth of the tumours. The proposed clinical dose for pembrolizumab is 2 mg/kg every 3 weeks. Given the availability of clinical data from humans, the lack of a non-clinical proof-of-concept at the 2 mg/kg every 3 weeks dose is acceptable.

The applicant did not submit studies on distribution, metabolism and excretion. No radiolabeled tissue distribution/mass balance or metabolism studies with pembrolizumab were submitted and no serum protein binding assay was submitted. This is acceptable as in accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6), no tissues distribution studies, metabolism studies,

mass balance are considered necessary. Following a single 0.3, 3.0, 30-mg/kg IV dose of pembrolizumab to female cynomolgus monkeys, the Vss mean value (30.9, 36.8, 54.8 ml/kg) was similar to the plasma volume of monkeys suggesting that pembrolizumab has a limited distribution out of the plasma compartment. The elimination half-life was prolonged and the distribution volume increased in the high-dose group. Systemic exposure to pembrolizumab was independent of sex and increased with increasing dose. Exposure (AUC(0-7d)) was greater after 5 administrations than after the 1st administration of pembrolizumab. This indicates accumulation. pembrolizumab was eliminated following multiphasic kinetics. Terminal half-life (t1/2) ranged from 11.8 to 23.7 days across doses. From day 10 on, a drop in serum pembrolizumab levels (in 8 of 9 animals) correlated with detection of ADA. ADA were detected in all of the treated animals except in 1 animal dosed 30 mg/kg. At lower dose ADA were detected earlier in time (after 14-day) vs 21-day for higher doses. In the 6-month study, the systemic exposure to pembrolizumab was independent of sex and increased with increasing dose. The AUC(0-14d) and Cmax values were slightly greater than dose proportional from 6 to 40 mg/kg and approximately dose-proportional from 40 – 200 mg/kg. With repeated administration, the systemic exposure to pembrolizumab increased. However, the systemic exposure was similar on study day 71 and 141 across doses, indicating that steady state had been reached. The terminal elimination half-life ranged from 21 to 22 days across doses. Both the ADA assay and the neutralizing antibody assay are currently under revalidation and the validation report is expected to be finalized in December, 2015. The CHMP recommends the post-approval submission of stability data of the labelled reagents.

No excretion studies with pembrolizumab were submitted. This is acceptable according to the current ICH S6 (R1) guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals.

Stand-alone studies evaluating safety pharmacology of pembrolizumab were not submitted. This is acceptable given that safety pharmacology was evaluated as part of the 1-month and 6-months repeat-dose toxicity study in cynomolgus monkeys. The following parameters were evaluated: electrocardiograms, general veterinary and physical examinations with body temperature and blood pressure, clinical observations (within 1 to 3 hours post-dose), and histopathology of tissues from the cardiovascular, respiratory, renal, and nervous systems. No pembrolizumab-related effects were observed in any parameter evaluated. This limited safety pharmacology evaluation of pembrolizumab is supported by ICH guidelines S6(R1), S7A, and S9, which do not require specific safety pharmacology studies for biotechnology-derived products, such as monoclonal antibodies, or for anticancer pharmaceuticals.

No non-clinical dedicated pharmacodynamic drug-drug interactions studies with pembrolizumab were submitted. Since pembrolizumab is designed to modulate the functional activity of T lymphocytes, there is potential for pharmacodynamic drug-drug interactions of pembrolizumab in relation to cytotoxic, immunosuppressive or immunomodulatory therapies. In the SmPC section 4.5 it is reported to avoid the use of systemic corticosteroids or other immunosuppressants before start of pembrolizumab treatment but systemic corticosteroids or other immunosuppressants can be used during pembrolizumab treatment to treat immune-related adverse reactions."Potential PD interaction with systemic immunosuppressants" is listed among the missing information in the RMP.

The toxicity of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose study in cynomolgus monkeys. Overall, pembrolizumab was well tolerated and the NOAEL in both studies was the highest dose tested.

The applicant did not submit studies for genotoxicity, carcinogenicity as well as fertility and early embryonic development. This is acceptable as according to ICH guideline S6(R1) “Preclinical safety evaluation of biotechnology-derived pharmaceuticals” (EMA/CHMP/ICH/731268/1998), these studies

are not required and are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH guideline S9 “Nonclinical evaluation for anticancer pharmaceuticals” EMEA/CHMP/ICH/646107/2008), the lack of studies is acceptable.

No reproductive toxicity studies were submitted with pembrolizumab. According to the literature submitted, there appears to be sufficient weight of evidence suggests that pembrolizumab has an adverse effect on pregnancy outcome. Therefore, the lack of studies in animal models is acceptable and information on the potential for an adverse effect on pregnancy was included in section 5.3 of the SmPC. Pembrolizumab is not expected to cause adverse effects in the male and female reproductive system, however as the number of sexually mature male treated with pembrolizumab for a sufficiently long duration (≥ 3 months according to ICH S6(R1) was too low to draw any conclusions about the effect of pembrolizumab on male fertility, a statement has been included in the SmPC section 5.3.

It is not known whether pembrolizumab is secreted in human milk. Since it is known that in general IgG antibodies are secreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the treatment to the mother. Pembrolizumab adverse effect on pregnancy outcome and potential secretion in human milk are adequately reflected in sections 4.6 and 5.3 of the SmPC. "Reproductive and lactation data" and are listed as missing information in the RMP.

The applicant did not submit separate local tolerance studies with pembrolizumab. This is acceptable as no clinical signs, macroscopic findings and histopathologic examination of the injection site (IV administration) were observed in the repeat dose toxicological studies.

The applicant did not submit an ERA. According to the guideline (EMEA/CHMP/SWP/4447/00), in the case of products containing proteins as active pharmaceutical ingredient(s), an ERA justifying the lack of ERA studies is acceptable.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for pembrolizumab, were considered adequate and acceptable for the assessment of non-clinical aspects. The lack of carcinogenicity, mutagenicity, fertility and early embryonic development was well justified. Based on the literature data, there is a potential risk for foetal loss in the third semester in humans. In addition, the Cynomolgus monkey model showed the development of ADAs after repeat administration. These risks are adequately addressed in the SmPC and RMP.

The CHMP recommends the following measures necessary to address the non-clinical issues:

- The Applicant is requested to submit the addendum to the validation report AR3607 (regarding the stability of labelled reagents used in PK studies in cynomolgus).

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

P001

Study ID	No. of study centres enrolling patients / locations	Cohort	Design	Study Posology	N. pts	Gender M/F Median Age	PD-L1 Status	Primary efficacy endpoint
P001	17 sites US (13), France (1), Australia (2), Canada (1)	**Part A: Dose escalation in solid tumours**						
		A	Non-randomized	1,3 and 10 mg/kg Q2W	10		NA	NA
		A1	Non-randomized	10 mg/kg Q2W	7		NA	NA
		A2	Randomized	2 or 10 mg/kg Q3W	13		NA	NA
		Part B: Expansion for advanced melanoma patients						
		B1 IPI naive or treated	Non-randomized	2 mg/kg Q3W or 10 mg/kg Q2W or Q3W	87◇	53/34 64 years	All comers	ORR
					48●	26/22 59 years		ORR
		B2 IPI refractory	Randomized	2 or 10 mg/kg Q3W	173	104/69 61 years	All comers	ORR
		B3 IPI naive or treated or refractory	Randomized	10 mg/kg Q2W or Q3W	244	159/85 61 years	All comers	ORR
		Part C:Expansion for NSCLC patients						
		C	Non-randomized	10 mg/kg Q3W	38		All comers	ORR
		Part D: Expansion for advanced melanoma patients						
		D IPI naive	Randomized	2 or 10 mg/kg Q3W	103	63/40 60 years	All comers	ORR
		Part F:Expansion for NSCLC PD-L1 positive patients						
		F1	Randomized	10 mg/kg Q2W or Q3W	43		Positive	ORR
		F2 PD-L1 + or negative	Randomized	10 mg/kg Q2W or Q3W	200		Positive or Negative	ORR

Data cutoff: 18 April 2014. The enrollment in the Part F of the study was still ongoing.

◇IPI-naïve patients

●IPI-treated patients

° in combination with chemotherapy

ORR: Objective Response Rate

The initial application included data from Protocol 001, an open label Phase I study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumour activity of pembrolizumab in patients with melanoma (IPI-naïve or previously treated with IPI) and non-small cell lung cancer (NSCLC).

Part A (including A1 and A2) of the study involved dose escalation that used a traditional 3+3 design and was an exploratory dose escalation in patients with solid tumours. Cohorts of 3- 6 patients were enrolled sequentially at escalating doses of 1, 3 or 10 mg/kg administered every 2 weeks (Q2W). Once the dose escalation was completed, additional patients were enrolled into Parts A1 and A2. Part B (B1, B2, and B3) and Part D investigate the efficacy and safety of pembrolizumab in patients with advanced melanoma at dose regimens of 2 mg/kg Q3W, 10 mg/kg Q3W or 10 mg/kg Q2W.

P002

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-002 [Ref. 5.3.5.1: P002V01]	II	Worldwide: Argentina, Australia, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, USA	Randomized, Phase II Study of Pembrolizumab (MK-3475) versus Chemotherapy in Subjects with Advanced Melanoma who were Refractory to Ipilimumab (IPI) Primary objectives: 1) Evaluate progression-free-survival 2) Evaluate overall survival	Randomized, double-blind, active-controlled trial. Subjects were randomized in a 1:1:1 fashion to pembrolizumab or standard of care (SOC) chemotherapy. Pembrolizumab dosing (2 mg/kg vs. 10 mg/kg) was blinded to Investigator, subject, and Sponsor.	Pembrolizumab: 2 mg/kg every three weeks 10 mg/kg every three weeks Pembrolizumab: IV infusion administered over 30 minutes with +10/-5 minutes. Chemotherapy: Investigator-choice of treatment administered according to SOC with IV or oral options	Males and females Age: ≥ 18 years of age[1] Advanced melanoma subjects refractory to IPI	Pembrolizumab 2 mg/kg: 178 subjects Pembrolizumab 10 mg/kg: 179 subjects Chemotherapy: Carboplatin plus Paclitaxel: 42 subjects Paclitaxel: 28 subjects Carboplatin: 13 subjects Dacarbazine: 45 subjects Temozolomide (oral): 43 subjects

P006

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-006	*III*	*Worldwide* *Australia, Austria, Belgium, Canada, Chile, Colombia France, Germany Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, USA*	A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma	Randomized, controlled, three-arm pivotal study of two dosing regimens of MK-3475 versus ipilimumab in patients with unresectable or metastatic melanoma who have not received ipilimumab treatment. Patients randomized	All MK-3475 dosing is iv infusion given over 30 minutes +10/-5 minutes: MK-3475 10 mg/kg Q2W or MK-3475 10 mg/kg Q3W or ipilimumab administered to standard of care	Male and female patients >=18 years of age on the day of consent with unresectable or metastatic melanoma who have not received ipilimumab treatment	*Cut off date: 03-Sep-2014* *MK-3475 10 mg/kg/Q2W 279 pts* *MK-3475 10 mg/kg/Q3W 277 pts* *Ipilimumab 278 pts*

				1:1:1 - MK-3475 10 mg/kg Q2W, MK-3475 10 mg/kg Q3W, and ipilimumab respectively			

2.4.2. Pharmacokinetics

The PK of pembrolizumab was investigated in patients with solid malignancies enrolled in the Phase I study, Protocol 001 titled 'Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma' (P001). PK data were obtained through a combination of intensive (parts A, A1, A2) and sparse sampling (parts B1, B2, C and D) using a clinical data cut-off date of 26-Jul-2013. Additionally, serum samples for the assessment of ADA were obtained at regular intervals during the study (analysis dataset cut-off date 26-Jul-2013, subsequent analysis update with cut-off date 31-Dec-2013). During the procedure, the Applicant presented an enlarged data set based on a pooled dataset across studies P001 and P002 (Total N=1139) with data cut-off date of 18-April-2014 for P001 and 12-May-2014 for P002.

In study 001, the PK of pembrolizumab was investigated following i.v. administration of:

- **Part A** (including A1 and A2): 1, 3 or 10 mg/kg administered every 2 weeks (Q2W)
- **Part B** (B1, B2, and B3) and **Part D**: 2 mg/kg Q3W, 10 mg/kg Q3W or 10 mg/kg Q2W
- **Part C**: 10 mg/kg Q3W.

Absorption

The applicant did not submit studies on absorption (see clinical pharmacology discussion).

Distribution

The volume of distribution of pembrolizumab at steady state is 8.1 L, in between the volumes of serum and extracellular water. Pembrolizumab has a clearance of 0.23 L/day and an elimination half-life (t½) of 26 days as determined by population PK modelling (Table 14).

Steady-state is achieved by 18 weeks of repeated dosing, with ~2.1-fold accumulation in exposure during administration every 3 weeks relative to exposure observed following single dose administration.

Table 14: Population pharmacokinetic parameters of pembrolizumab are estimated with high precision and associated with relatively low variability

Parameter	Value	%SE	95% CI	%CV	5th percentile	95th percentile
CL (L/day)	0.22	2.5	[0.21, 0.23]	28	0.14	0.35
Vc (L)	3.7	1.8	[3.6, 3.8]	14	3.0	4.6
Q (L/day)	0.90	14	[0.66, 1.2]	28	0.57	1.4
Vp (L)	3.9	5.9	[3.4, 4.4]	14	3.2	4.9
Residual error (%)	30	3.3	[28, 32]	45[a]	15	61
Derived parameters						
Vd,ss (L)	7.7	NA	[7.1, 8.1]	14	6.1	9.5
t½ (day)	26	NA	[24, 28]	24	18	38
Time to steady state (week)	18	NA	[17, 20]	NA	NA	NA

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

	Initial Model N=479 [Ref. 5.3.5.3: 03TLC8]				Update Model N=1139 [Ref. 5.3.5.3: 042W89]			
Parts and Studies included in the analysis	A, A1, A2, B1, B2, C and D from PN001				A, A1, A2, B1, B2, B3, C and D from PN001 and PN002			
Data cut-off date	PN001; 26-Jul-2013				PN001; 18-April-2014 PN002; 12-May-2014			
Parameter	**Value**	**%RSE**	**95% CI**	**%CV[a]**	**Value**	**%RSE**	**95% CI**	**%CV[a]**
CL (L/day)	0.22	2.5	[0.21, 0.23]	28	0.23	2.0	[0.22, 0.24]	41
Vc (L)	3.7	1.8	[3.6, 3.8]	13	3.8	1.4	[3.7, 3.9]	22
Q (L/day)	0.90	14	[0.66, 1.2]	28	1.2	9.8	[0.98, 1.4]	41
Vp (L)	3.9	5.9	[3.4, 4.4]	13	4.4	5.9	[3.8, 4.9]	22
Residual error	0.302	3.3	[0.282, 0.318]	42	0.325	2.5	[0.309, 0.339]	NA
Derived parameters								
Vd,ss (L)	7.7	NA	[7.1, 8.1]	14	8.1	NA	[7.6 - 8.6]	22
t½ (day)	26	NA	[24, 28]	24	26	NA	[24, 28]	43
Time to steady state (weeks)	18	NA	[17, 20]	NA	18	NA	[17, 20]	NA

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

Presented population parameter estimates exclude effects of covariates; therefore apply to a hypothetical typical patient with average characteristics. CL: clearance; Vc: central volume of distribution; Q: intercompartmental clearance; Vp: peripheral volume of distribution; Vd,ss: volume of distribution at steady state; t1/2: terminal half-life; %RSE: relative standard error (%); 95% CI: 95% confidence interval of parameter estimate based on bootstrap results; %CV: coefficient of variation of between-subject distributions of parameters; NA: not applicable.

Elimination

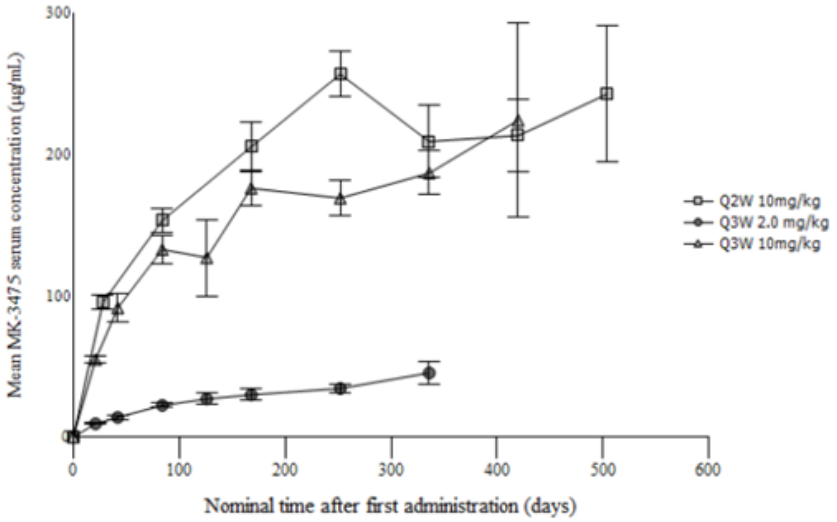
The applicant did not submit studies on elimination or metabolism of pembrolizumab (see pharmacology discussion).

Dose proportionality

The PK of pembrolizumab following multiple-dose administration is consistent with that observed after single-dose administration, indicating time-independent disposition. This is supported by the population PK model, that describes the observed concentrations following first-dose and multiple-dose

administration across a range of doses (1 to 10 mg/kg) and regimens (Q2W and Q3W) in a single integrated model with a linear clearance term.

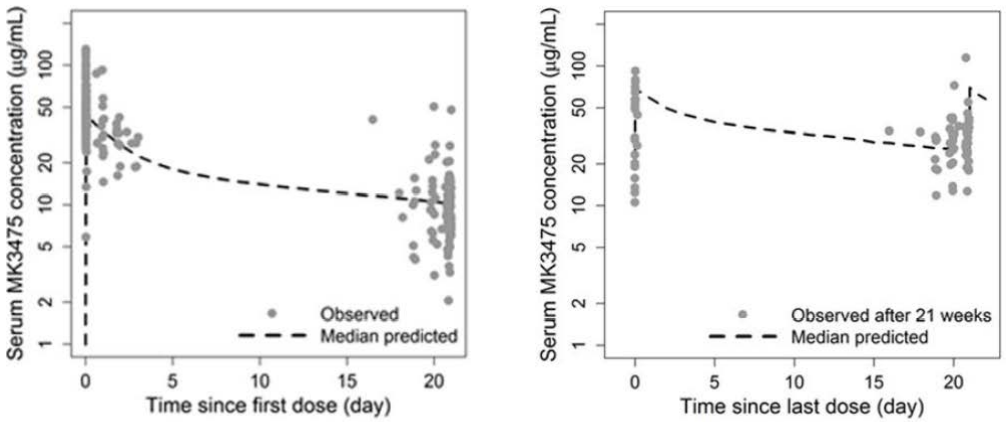
Figure 11: Arithmetic Mean (SE) Predose concentration-Time profiles of pembrolizumab following multiple IV administrations of 2 or 10 mg/kg every 2 or 3 weeks to Patients in Part B (linear scale)



Time dependencies

Steady state of pembrolizumab was achieved in 18 weeks (Figure 11). The accumulation ratio based on AUC at a Q3W dosing interval is 2.1. The majority (~82%) of this accumulation has occurred after the third dose. Pembrolizumab concentrations both after single dose and at steady state can be described with the same population PK model, indicating the absence of any time dependency in pembrolizumab pharmacokinetics (Figure below).

Figure 12: Pembrolizumab concentration –time profiles during the first dose (left panel) and at steady state (right panel) of repeated dosing at 2 mg/kg Q3W



Solid markers represent observed MK-3475 serum concentrations. Dashed line represents median predicted concentration time profile, based on population PK model.

Special populations

An initial pooled population PK analysis was performed to generate individual pembrolizumab exposure estimates to support exposure-response analysis for clinical efficacy and to support dose recommendations. The analysis included data from 476 patients from parts A, B1, B2, C, and D of protocol PN001. In total, 7034 PK observations were included in the analysis. Covariates included in the analysis were age, gender, creatine clearance, anti-drug antibody, race, tumour burden, ALP, AST,ALT, albumin and bilirubin, baseline ECOG performance status and geographical location.

An updated pooled population PK analysis was also was performed to investigate the effects of selected covariates on pembrolizumab exposure in patients with melanoma and NSCLC, as included in study P001 and P002. The population PK analysis was performed using a non-linear mixed effects modelling approach. Model selection was based on the Log-Likelihood, goodness of fit plots and scientific plausibility. Identification of covariates was based on step-wise forward addition (at alpha level of 0.01) and backward elimination (at alpha level of 0.001). The covariates tested included demographic factors (age, sex, diagnosis), a measure of renal function [baseline estimated glomerular filtration rate (eGFR) assessed by MDRD (Modification of Diet in Renal Disease formula)], measures of hepatic function (baseline total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP), with degree of hepatic impairment classified according to NCI guidelines), laboratory parameters related to FcRn capacity (baseline albumin, IgG) and measures of disease severity [baseline ECOG (Eastern Cooperative Oncology Group) performance status and tumour size (SLD)].

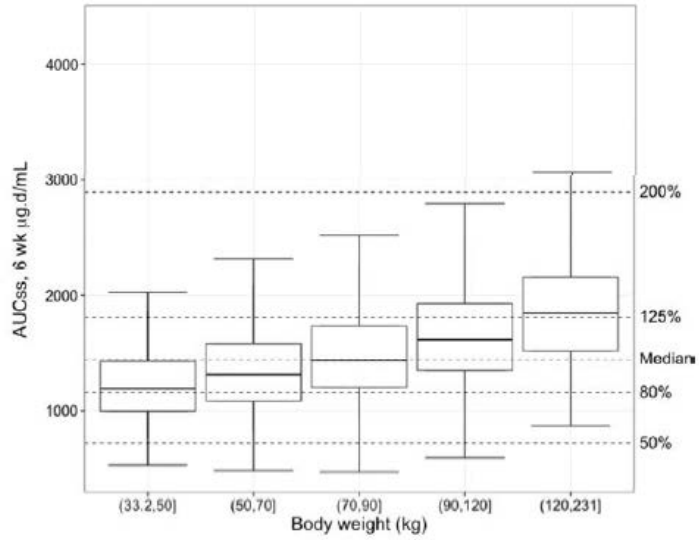
The results showed that age, gender, albumin, impaired renal and hepatic impairment had no impact on pembrolizumab PK parameters. Results from PopPK analysis showed that after incorporation of the effect of body weight, most of the investigated covariates had no effect on the PK of pembrolizumab.

Weight

Within the population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight when dose is accounted for in the model on an absolute (mg) level (Figure 13). Body weight was not included in the list of covariates that were investigated, as it was included as a covariate on clearance and volume terms as part of the structural model.

The population PK model results have been applied to investigate the dependency of pembrolizumab exposure on body weight in the general population under body weight normalized dosing. Under this dosing paradigm, body weight has a limited impact on exposure, with the lowest exposure in the lowest weight class and the highest in the highest weight class.

Figure 13: Exposure as a function of body weight is controlled by body-weight normalised dosing

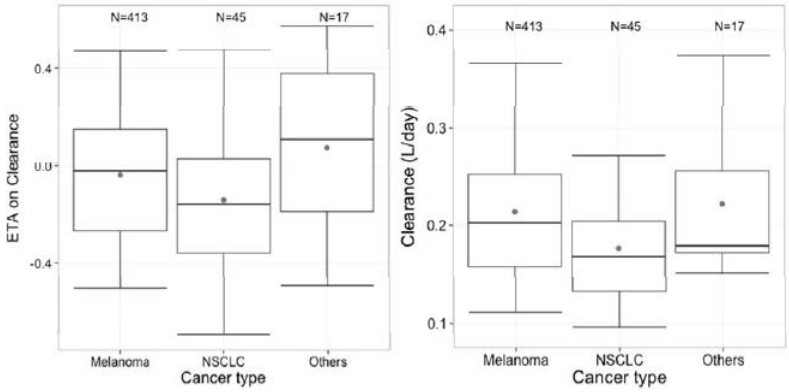


Exposure distribution of AUC at steady state, over 6 weeks are depicted for 5 categories of body weight for a dose of 2 mg/kg every 3 weeks. Dotted lines depict the following percentiles compared to median AUC ; 50, 80,100, 125 and 200%. Straight lines; median box 25th and 75th percentile, whiskers: 5th and 95th percentile.

Types of cancers

The clearance of pembrolizumab was evaluated in different types of cancer. Results of the population PK parameters are shown in Figure 14.

Figure 14: Distribution of cancer type versus PK-parameters



Pharmacokinetic interaction studies

The applicant did not submit pharmacokinetic interaction studies (see pharmacology discussion).

Pharmacokinetics using human biomaterials

The applicant did not submit pharmacokinetic using biomaterials (see pharmacology discussion).

2.4.3. Pharmacodynamics

Mechanism of action

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumour cells to inhibit active T-cell immune surveillance. Pembrolizumab is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

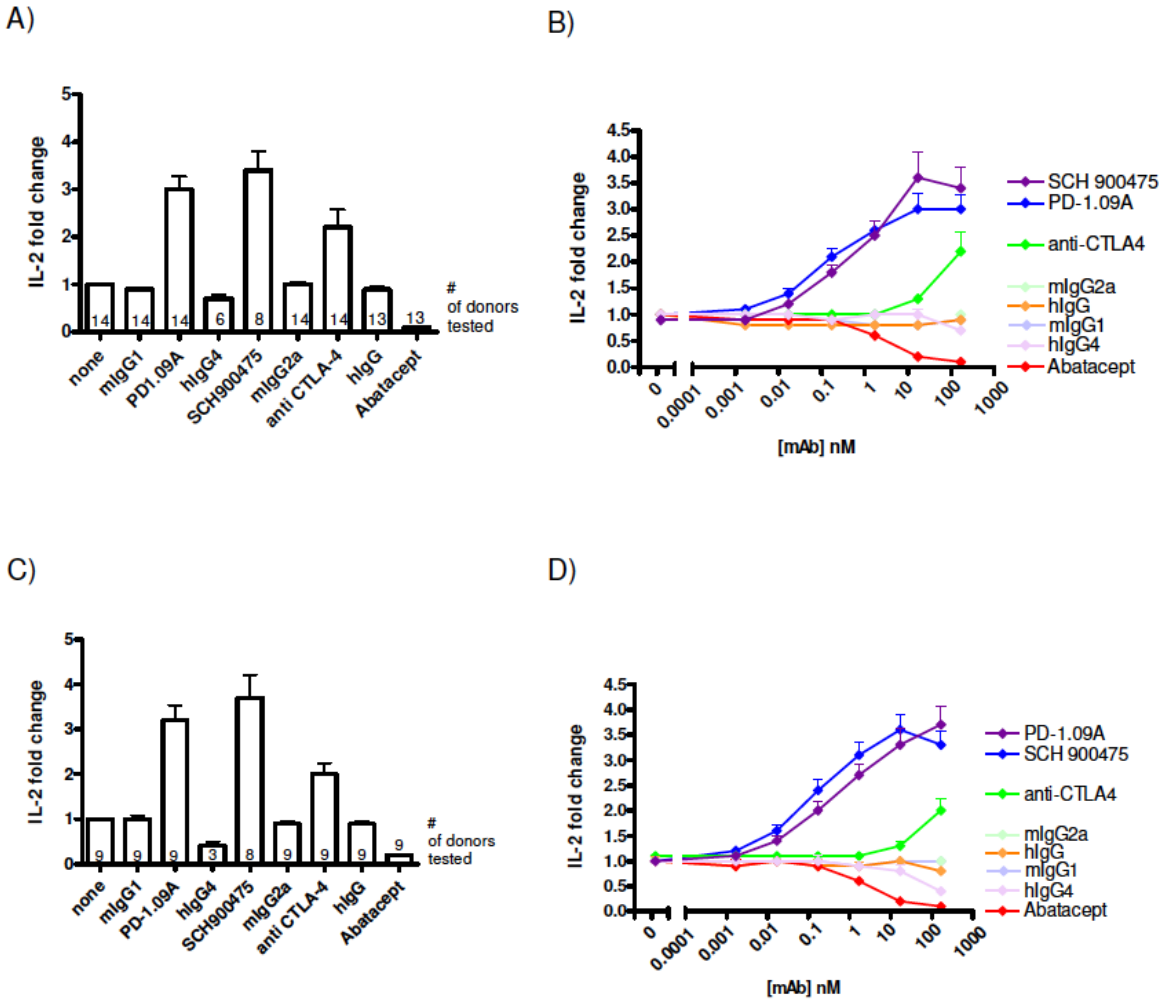
Primary and Secondary pharmacology

Functional activity of pembrolizumab to PD-1 from healthy subjects and cancer patients

The ability of pembrolizumab to modulate the activity of T-cells was assessed *in vitro* using peripheral blood from healthy human donors or patients with cancer. Staphylococcus enterotoxin B (SEB) was used to activate T-cells for the production of cytokines including interleukin (IL)-2 (Study PD002 report SN 09545).

WBC isolated form healthy volunteers, prostate and melanoma cancer patients and were cultured in the presence or absence of pembrolizumab, its murine precursor PD-1.09A, abatacept and a neutralizing anti-CTLA4 antibody (ipilimumab (Yervoy) (all used 25ug/ml). Cells were then stimulated with SEB. The results for cancer patients are presented in Figure 15. The results in healthy donors were comparable with those observed in cancer patients.

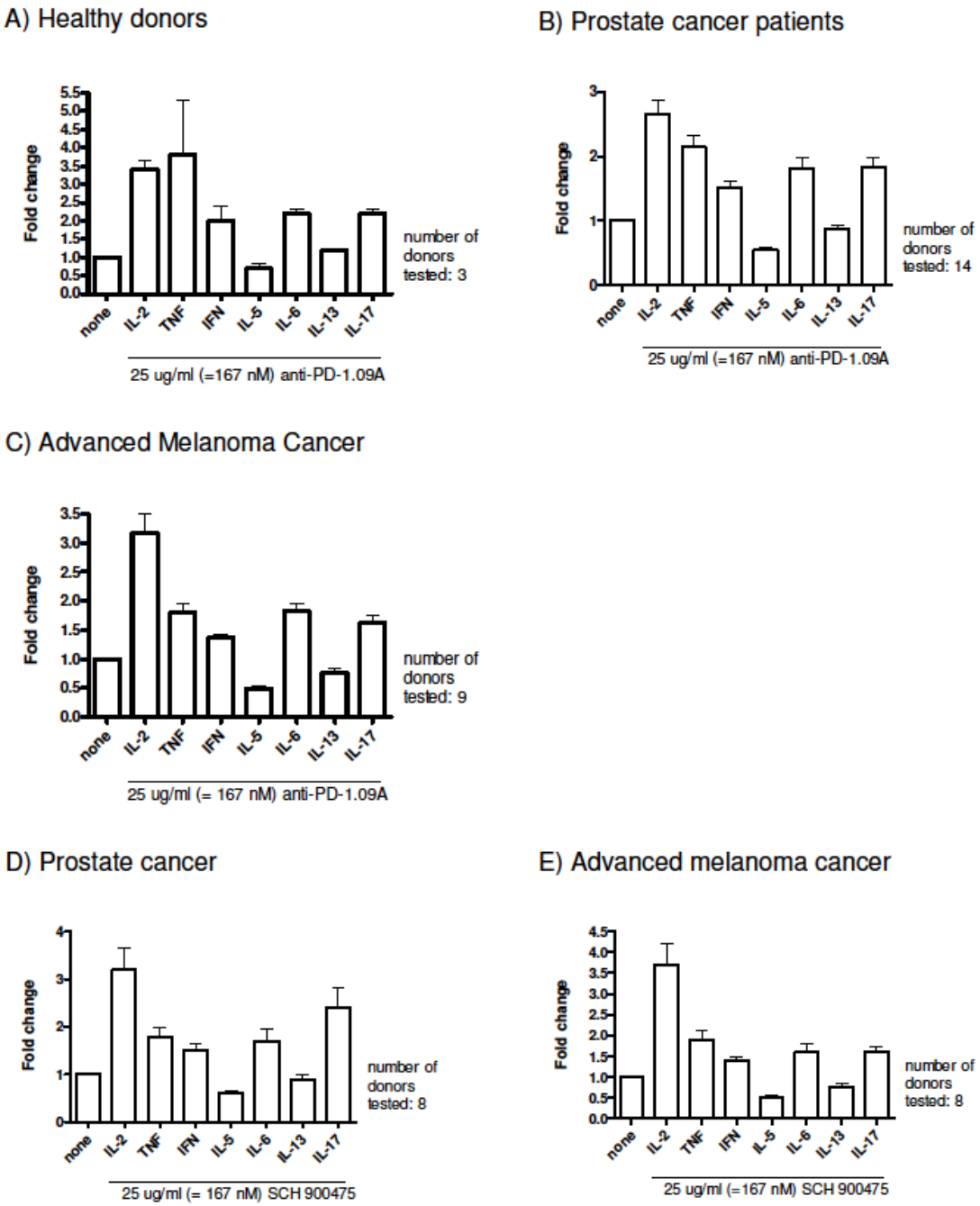
Figure 15: PD-1 blockade enhances IL-2 production in blood cells from prostate and advanced melanoma patients



To demonstrate that antigen-specific T cell receptor triggering was modulated by anti-PD-1, a human T-cell recall assay for tetanus toxoid (TT) was used. Pre-existing memory T-cells in PBMC from healthy human donors were stimulated with TT (7 days) and the production of interferon (IFN)-gamma in the culture supernatants was determined after incubation with mouse anti-PD-1.09A, anti-CTLA4 or with a dose range of SCH 900475 by ELISA. Results were in agreement with the IL-2 assay.

In addition to IL-2, TNF-α, IFN-γ, IL-6 and IL-17 were found to be enhanced by PD-1 blockade (either PD-1.09A or MK-3475) in SEB-stimulated blood from healthy donors, prostate cancer patients and advanced melanoma cancer patients (Figure 16). IL-5 was decreased, while no modulation was observed for IL-13, FGF, IL-1β, IL-1Ra, IL-4, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-15, G-CSF, GM-CSF, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, RANTES, and VEGF (data not shown).

Figure 16: PD-1 blockade enhances IL-2 , IFN-gamma, IL-6, TNF-alpha, IL-17 and decreases IL-5 cytokine production



Early population PK/PD modelling based on ex-vivo IL-2 release measured in solid tumor patients.

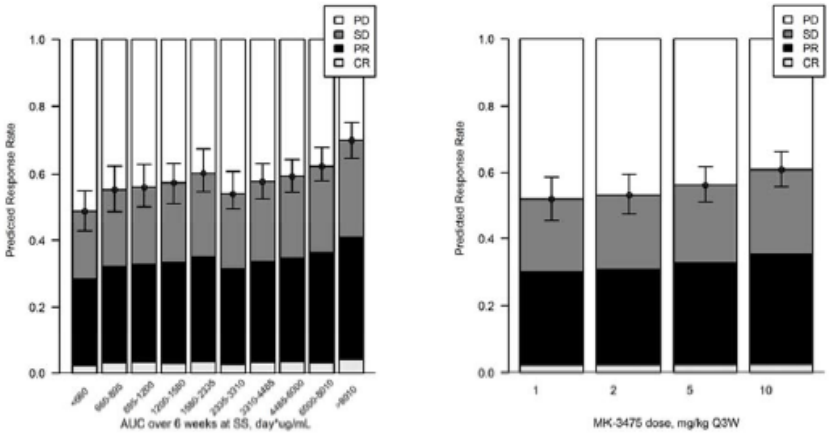
Target engagement was analysed in an ex-vivo IL-2 stimulation assay. Results obtained from blood samples in patients with solid tumour were included in the early PK/PD model. The assay measured post-dose reduction in the ex-vivo stimulation ratio (SEB w/o addition of 25µg/mL pembrolizumab) as an indirect measure of PD-1 receptor occupancy on T-cells. A reduction of IL-2 stimulation ratio indicated high pre-existing receptor occupancy. The maximum response was a 2.7-fold increase of the IL-2 stimulation ratio. Furthermore, in the lower dose range, a plateau was only hypothesized and the differences in the IL-2 stimulation ratio obtained with different doses was found to be very little. In light of this, the assay's reliability is questionable. The early PK/PD model is based on poor data

source, coming from assumptions (which may not be true at the tumour site) and therefore the PK/PD relationship results inconclusive. Furthermore, plasma concentration values were not simultaneously measured. Overall, the model is not considered robust enough for the simulation.

A nonlinear mixed effects model of tumour size as quantified by SLD has been developed to describe tumour size as a function of underlying tumour growth rate and tumour kill rate due to PD-1 inhibition.

The model-estimated relative tumour size response at Week 28, presented as categories similar to those used in RECIST, versus exposure or dose. Results indicated the absence of a clear association between exposure (or dose) and efficacy.

Estimated Tumor Size Effects of MK-3475 at 28 Weeks after Start of Treatment as Response Categories Versus Exposure (Panel A) and Dose (Panel B) Indicating a Plateau in Efficacy

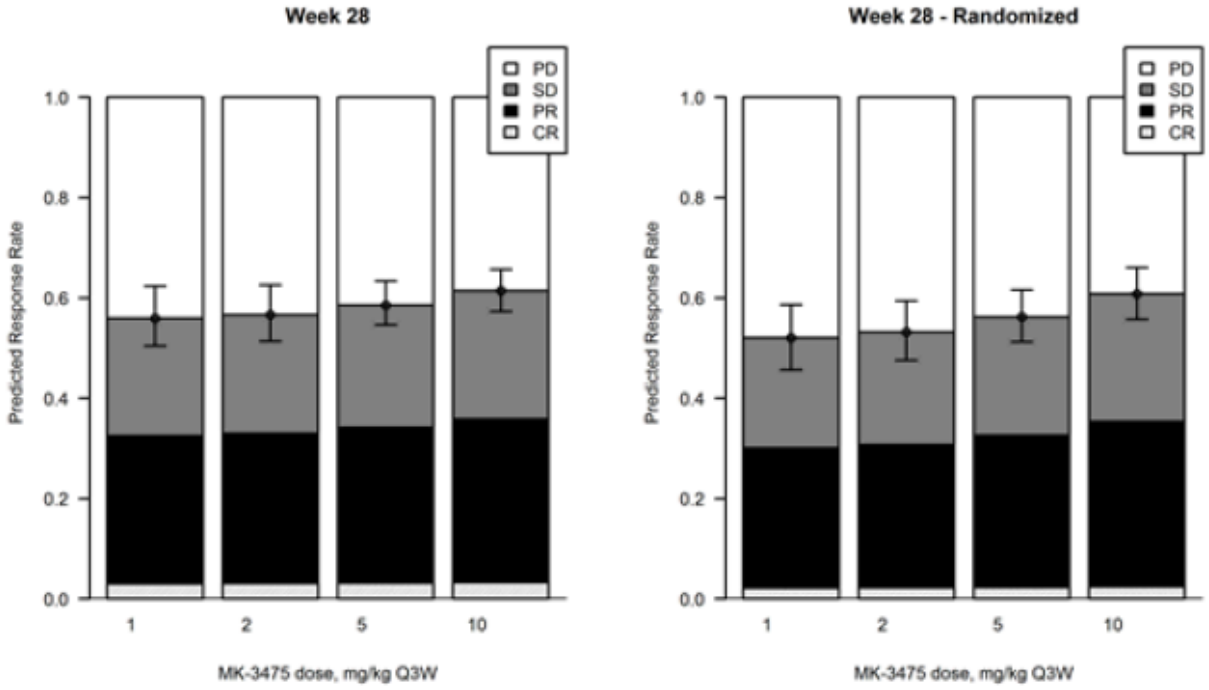


Panel A: Median response categories for tumor size effects of 1000 simulated trials, each with 10,000 patients receiving 1, 2, 5, or 10 mg/kg Q3W. Correlations between patient body weight, number of target lesions and nodal lesions were preserved by case sampling and were allowed to influence exposure through body weight. The results are summarized in AUC groups of approximately equal numbers of patients. Panel B shows the same results categorized by dose. PD=progressive disease (change from baseline (CFB)>20%), SD=stable disease (CFB -30% to 20%), PR=partial response (CFB <-30% and SLD>5mm), CR=complete response (SLD <=5mm). The error bars represent the 90% confidence intervals for the probability of PD. Data Source: [Ref. 5.3.5.3: 03TLCV]

Exposure-response simulation

The relationship of plasma concentration and effect was analysed in a tumour size reduction model based on a total of 365 melanoma patients with a median number of tumour size measurements of 3 (1-14) per patient and median time to last scan of 16 weeks (maximum 93 weeks). No clinically relevant exposure-response relationship was observed. In addition, no differences were seen across the wide range of exposures (<660 µg/ml to >8010 µg/ml) and doses (1 to 10 mg/kg). Altogether these evidences indicated that efficacy is near to plateau. Moreover, results suggest that 1 mg/kg Q3W may be sufficient to achieve clinical efficacy.

Figure 17: Median response rates of 1000 simulated trials, each with 10000 patients receiving 1, 2, 5, or 10 mg/kg Q3W



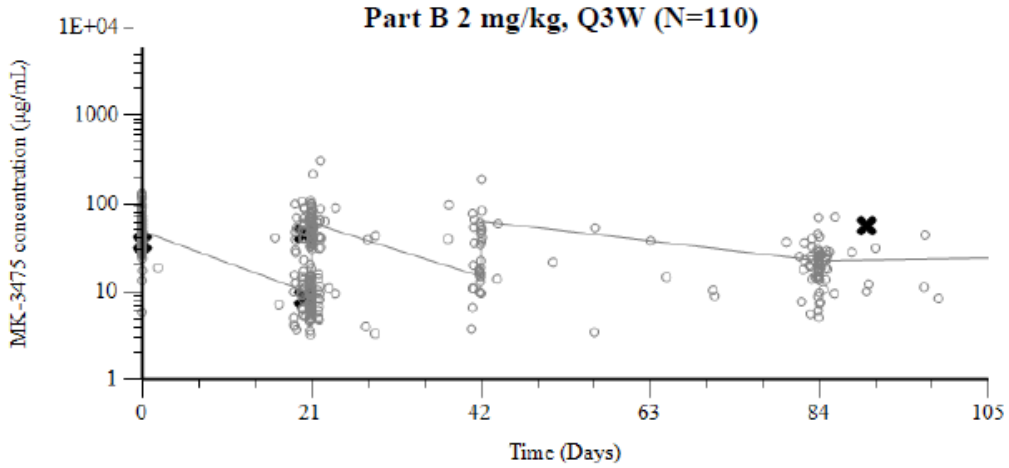
PD=progressive disease (CFB≥ 20%), SD=stable disease (CFB -30% to 20%), PR=partial response (CFB -<30% and SLD≥ 5mm), CR=complete response (SLD <5mm). Simulations were also performed with parameters of the underlying multinomial logistic regression model derived from a bootstrap of randomized patients only (right); Error bar: 90%CI around median rate of progression

Impact of ADA on pembrolizumab exposure

The effect of ADA on pembrolizumab levels, for the patients with ADA positive samples, is shown by dose group in the following figures.

The following Figure 18 shows the exposure of patient AN 0263 to pembrolizumab was similar to pembrolizumab exposure for other patients who were treated with pembrolizumab in a 2 mg/kg Q3W regimen (Part B, n=110).

Figure 18: Effect of ADA on pembrolizumab levels: pembrolizumab exposure for patients with ADA positive samples and other patients treated with the same regimen (Part B 2 mg/kg, Q3W)



FOOTNOTE: Individual MK-3475 concentrations for AN 0263 (black symbol ✖) and other patients (grey symbol ○). The arithmetic mean (grey line –) is also provided. Exposure to MK-3475 was not compromised for AN 0263 (non-treatment emergent positive).

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology profile of pembrolizumab has been characterised based on data from study P001, a phase I study expanded cohorts of patients, investigating pembrolizumab doses of 1, 2, 3 and 10 mg/kg at various dosing schedules (see section 2.4.1) and study P002, a phase II study investigating 2mg/kg and 10 mg/kg every 3 weeks. The studies were conducted in melanoma patients as well as in patients with other solid tumours (eg. NSCLC).

The dose proposed for pembrolizumab monotherapy is 2 mg/kg administered over 30 min every 3 weeks.

The applicant did not submit studies on absorption, bioavailability or food effect as pembrolizumab is administered via the i.v. route and is therefore completely (100%) bioavailable (SmPC section 5.2). Since the expected consequence of metabolism of pembrolizumab is degradation to small peptides and single amino acid, as per ICH S6(R1) guideline, the lack of studies submitted for elimination, excretion and metabolism [e.g., cytochrome P450 enzymes (CYPs), glucuronosyltransferases] is acceptable.

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (approximately 8.1L, CV:22%) and between the volumes of serum and extracellular water. Pembrolizumab does not bind to plasma proteins binds to receptors for the IgG4 Fc region. The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 41%) and the terminal half life (t½) is ~26 days (CV: 43%).

Dose proportionality studies showed that exposure increased with dose from 1 to 10 mg/kg. Cmax and AUC0-28 increased in a supra-proportional manner. However, no clear conclusion can be drawn because of the low number of patients at the two lower doses (N = 4 for 1 mg/kg and N = 3 for 3 mg/kg, compared to N = 10 at 10 mg/kg). Mean estimated t½ values range from 14.1 to 21.6 days.

Exposure to pembrolizumab as expressed by peak concentration (Cmax) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.1 fold when administered every 3 weeks. Near steady state concentrations of pembrolizumab were achieved by 18 weeks; the mean Cmin at 18 weeks was approximately 22 mcg/mL at a dose of 2 mg/kg every 3 weeks. The majority (~82%) of this

accumulation occurred after the third dose. In the dose range studied for efficacy (2 – 10 mg/kg) pembrolizumab exposure increases in a dose-proportional manner, with clearance being independent of time or pembrolizumab concentration. Pembrolizumab has relatively low to moderate PK variability [inter subject coefficient of variation (CV) of 22-41%]. As also observed with other therapeutic antibodies (trastuzumab, pertuzumab), there is a deviation from linearity in the low dose range (≤ 1 mg/kg), which is linked to a decrease of CL with increasing doses. With doses higher than 2 mg/kg, however, exposure increases in a dose-proportional way.

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The clearance of pembrolizumab increased with increasing body weight; resulting exposure differences are adequately addressed by administration on a mg/kg basis. The choice to apply a body weight-based dosing regimen for pembrolizumab seemed appropriate to control the resulting variability in exposure across a broad range of body weights. The observed increasing trend in AUCss with body weight appears to be related to the effect of body weight on clearance, and is unrelated to the observed effect on volume of distribution. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15 to 94 years), gender, mild or moderate renal impairment, mild hepatic impairment, and tumour burden. The effect of race could not be assessed due to limited data available in non Caucasian ethnic groups. No overall differences in clearance were reported between elderly patients (65 years and over) and younger patients (less than 65 years), and for this reason no dose adjustment was recommended in this population (see section 4.2 of the SmPC).

The impact of renal or hepatic impairment on pembrolizumab PK has not been studied. Renal function has no impact on pembrolizumab clearance when evaluated as continuous covariate or as categorical classification of impairment severity. At the same time, bilirubin, AST, ALT and ALP had no impact on clearance in patients with mild hepatic impairment and no dose adjustment was needed in these patients (see section 4.2 and 5.2 of the SmPC) and has been included as missing information in the RMP.

Interaction with systemic corticosteroids (glucocorticoids) administration was assessed as potential covariate in the population PK analysis. The population PK analysis showed that concomitant treatment of pembrolizumab with corticosteroids had no significant impact on pembrolizumab exposure (P = 0.77). Information about the lack of drug interaction studies and about concomitant administration of corticosteroid are included in section 4.5 of the SmPC and as missing information in the RMP.

The ex-vivo biomarker (IL-2 release from PBMC) study supports the lowest dose studied in the clinical program. The PK/PD evaluations and the IL-2 PK/PD model provided an hypothesis for the clinical response based on human PK data and preclinical efficacy of an anti-PD-1 antibody.

The ability of pembrolizumab to modulate the activity of T-cells was assessed *in vitro* using peripheral blood from healthy human donors or patients with cancer. This evaluation was based on the assumption that the target engagement processes (including potential receptor up-regulation) in the peripheral blood cells were similar to tumour cells. Peripheral whole blood samples from healthy donors and melanoma cancer patients were assayed to determine the release of IL-2. Following activation with Staphylococcus enterotoxin B (SEB), pembrolizumab was equally able to enhance the IL-2 release from both in healthy subjects and melanoma cancer patients. Pembrolizumab enhanced the T-cell production of IL-2 induced by SEB up to ~3 to 4-fold in a dose-dependent fashion. Pembrolizumab also demonstrated enhanced tetanus toxoid (TT)-mediated production of IFN-gamma.

Thus, T-cell activation in peripheral blood of melanoma patients as well as the predicted tumor size reduction in response to pembrolizumab both appear to be moderate, and both analyses suggest dose-

independence in the clinical dose range (2 mg/kg q3w and 10 mg/kg q3w). However, the assumption of exposure independence on the basis of the tumor-size-reduction model is not considered reliable as the exposure value used for modelling of its relationship to tumor-growth is derived from the population PK model. The high variability in the melanoma source data of the tumor-size reduction model suggest that the response to pembrolizumab is not uniform and varies for individual patients, which is conceivable for a drug with an immune-mediated mechanism of action. However, this aspect also complicates the evaluation of an exposure response relationship. In consequence, despite the acknowledged modelling effort no quantitative assumptions should be drawn on the pharmacodynamics effect of pembrolizumab from the submitted data.

The presence of anti-drug antibodies (ADA) and their neutralizing ability was assessed in 4042 samples taken from 1094 subjects. ADA concentration results obtained in 729, out of the 997 assessable patients were considered inconclusive, due to the circulating pembrolizumab above the test tolerance level. Only in 268 patients ADA results were conclusively assessed; four patients were declared ADA positive at screening and in the confirmatory assay; in one patient ADAs were seen as treatment emergent. This single patient with a treatment-emergent immunogenicity response and no impact on the exposure to pembrolizumab was found.

2.4.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of pembrolizumab has been mainly characterised by means of a population PK model which is considered acceptable. The body weight-based dosing regimen is considered justified as body weight may have a relative impact on exposure for patients in the lowest and highest weight classes,

The CHMP recommends the following measures to address the issues related to pharmacology:

- The Applicant is requested to provide the validation report for neutralizing antibodies assay. In addition, the matrix interferences for NSCLC samples and the matrix effects in unfortified lipemic human serum samples in the ADA assay should be addressed and results should be reported.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

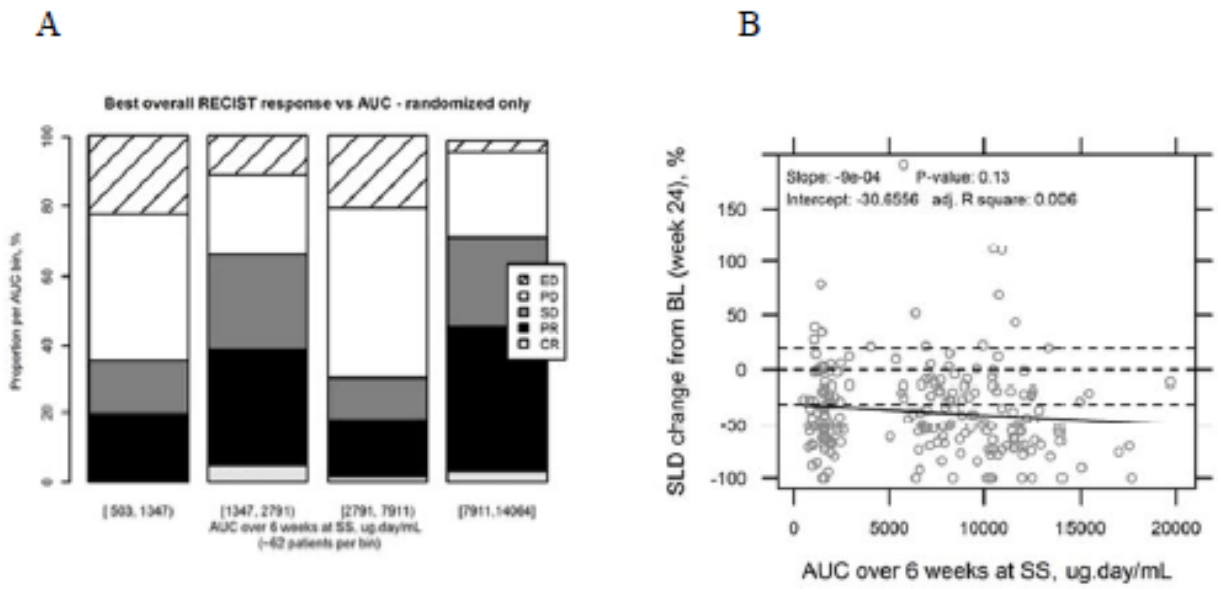
The development program for pembrolizumab in advanced melanoma has focused on doses that have a high likelihood of providing a meaningful efficacy response. PD-1 receptor occupancy on circulating T-cells was measured as an indication of target engagement. In addition, an ex-vivo assay measuring induction of IL-2 (a measure of T-cell activity) was used to assess functional modulation of target activity on circulating T-cells by pembrolizumab.

These two types of PK-PD evaluations (a clinical biomarker approach and a translational projection of clinical response based on pre-clinical efficacy) converge on supporting the use of 2 mg/kg Q3W as lower end of the dose range in the program. As no DLT has been observed in Part A of study P001, higher doses (10 mg/kg Q3W or Q2W) have been also explored.

Exposure response analysis of tumour size data was used to characterize the relationship between exposure to pembrolizumab and tumour size reduction in the clinical dose range of 1 mg/kg to 10 mg/kg.

Graphical exploration was conducted on tumour size observations, i.e., observed tumour size per RECIST sum of longest dimensions (SLD) relative to baseline at specified time intervals (landmark analysis).

Figure 19: Graphical exploration of MK-3475 anti-tumour efficacy indicated lack of clinically relevant exposure-response relationship (randomised patients – Parts B2 and D)



(A) response rate (Best Overall Response) versus binned quartiles of steady-state AUCss, 6-wk; and (B) SLD (sum of longest dimensions) change from baseline at 24 weeks versus AUC. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ED: 'early drop-out', (patients who dropped out before the first scheduled post-baseline scan). Solid line represents log-linear regression line. Data Source: [Ref. 5.3.5.3: 03TLCV]

In addition to the scatter plots with regression line, box plots across were also provided. Each box represents the (25th – 75th) percentile spread. For each category, the number of subjects is split roughly into 6 equal buckets. As a point of reference, the median exposure for the 2 mg/kg Q3W dose group is 1617 mg.day/L, the median exposure for the 10 mg/kg Q3W dose group is 9425 mg.day/L and that for the 10 mg/kg Q2W is 13757 mg.day/L, yielding an exposure range of 8.63.

Figure 20: Box Plots of Observed Pembrolizumab Exposure-Response Data in IPI-naïve (P001, P006)

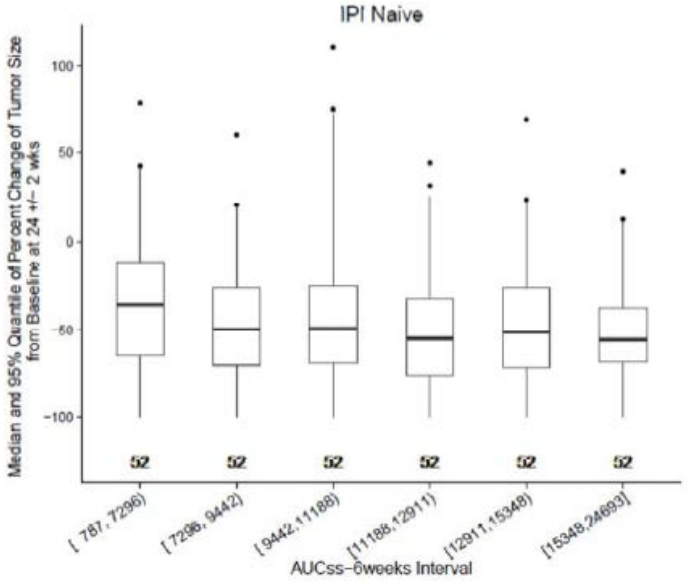
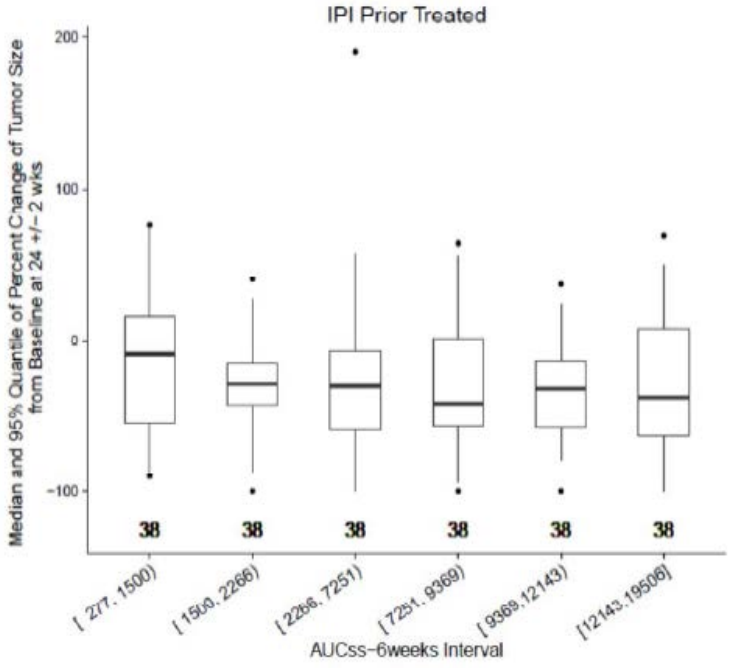


Figure 21: Box Plots of Observed Pembrolizumab Exposure-Response Data in IPI-treated (P001, P002)



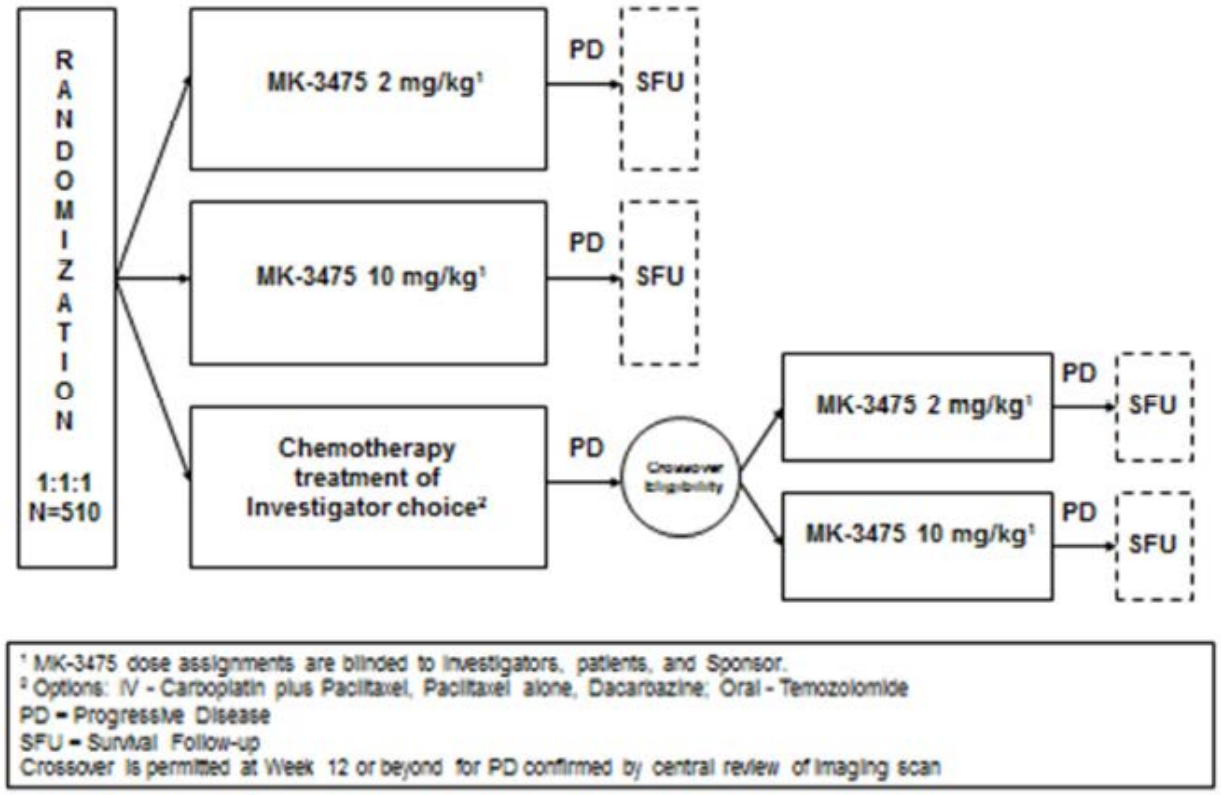
2.5.2. Main study(ies)

Study P002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma – Interim analysis 2 (database lock: 29 August 2014)

Methods

A schematic of the study design is presented in Figure 22:

Figure 22: Study design for P002



Study Participants

Main inclusion criteria

A subject must meet all of the following criteria to be eligible to participate in this study:

1) Subject must have a histologically or cytologically confirmed diagnosis of unresectable stage III or metastatic melanoma not amenable to local therapy.

- Subject may not have a diagnosis of uveal melanoma

2) Subjects must be refractory to ipilimumab, defined as (subjects must meet all of the following criteria):

- Received at least two doses of ipilimumab (minimum dose of 3 mg/kg given Q3W)
- Progressive disease after ipilimumab will be defined according to immunerelated response criteria (irRC). The initial evidence of PD is to be confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression. (This determination is made by investigator; SPONSOR will collect imaging scans for retrospective analysis. Details for submitting scans to central imaging vendor are in the Investigator Imaging Operations Manual (IIOM). Once PD is confirmed, initial date of PD documentation will be considered the date of disease progression.

- Documented disease progression within 24 weeks of the last dose of ipilimumab. Subjects who were re-treated with ipilimumab and subjects who were on maintenance ipilimumab will be allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with ipilimumab).
- Ipilimumab does not need to be the last treatment prior to entering current trial as long as the subject meets the above described criteria
- 3) Resolution/improvement of ipilimumab-related adverse events (including irAEs) back to Grade 0-1 and ≤ 10 mg/day prednisone (or equivalent dose) for irAEs for at least two weeks prior to first dose of study drug.
- No history of Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 irAEs from ipilimumab
- No history of CTCAE Grade 3 requiring steroid treatment (>10 mg/day prednisone or equivalent dose) >12 weeks
    - Minimum of four weeks (wash out period) from the last dose of ipilimumab

4) Subjects must consent to provide a newly obtained tumor tissue/biopsy (or specimen obtained within 60 days prior to consenting) for biomarker analysis from a core or excisional biopsy of a tumor lesion not previously irradiated.

- The subject must be able to undergo tumor biopsy
- If a newly obtained biopsy is not feasible, the subject requires sponsor approval to be eligible

5) BRAF V600E or V600K mutation status must be known at Screening. Subject with BRAF mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF and/or MEK inhibitor.

6) Subject must have at least one radiologically measurable lesion as per RECIST 1.1 (Appendix 6.1 of the protocol) defined as a lesion that is 10mm in longest diameter or lymph node that is 15mm in short axis imaged by computed tomography (CT) scan or magnetic resonance imaging (MRI).

7) Subject is ≥ 18 years of age on day of signing informed consent.

8) Subject must have a performance status of 0 or 1 on the ECOG Performance Scale (Appendix 6.4 of the protocol).

9) Subject must have adequate organ function as indicated by the following laboratory values.

- Renal: Serum creatinine ≤ 1.5 X upper limit of normal (ULN)
- Hepatic: Serum total bilirubin ≤ 1.5 X ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN; AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases

<u>Main exclusion criteria</u>

1) Subject who has had chemotherapy, radioactive, or biological cancer therapy within four weeks prior to the first dose of study drug, or who has not recovered to CTCAE Grade 1 or better from the AEs due to cancer therapeutics administered more than four weeks earlier.

2) Subject who received ipilimumab only as an adjuvant therapy.

3) Subject is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of study drug.

4) Subject expected to require any other form of systemic or localized antineoplastic therapy while on study.

5) Subject on chronic systemic steroid therapy (>10 mg/day prednisone or equivalent) within two weeks before the planned date for first dose randomized treatment or on any other form of immunosuppressive medication. (Subjects that are expected to require premedication with corticosteroid for pembrolizumab will not be eligible for this study.)

6) Subjects who received treatment with live vaccines within 30 days prior to the first dose of study medication. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, bacille Calmette-Guérin (BCG), and typhoid vaccine.

7) Subject has a known history of a hematologic malignancy, primary central nervous system (CNS) malignancy or sarcoma, or of another primary solid tumor, unless the subject has undergone potentially curative therapy with no evidence of that disease for five years.

8) Subject has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they meet the following criteria:

9) Subject previously had a severe hypersensitivity reaction to treatment with another mAb.

10) Subject has an active autoimmune disease or a history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule.

11) Subject had prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent.

12) Subject has an active infection requiring systemic therapy.

13) Subject has known history of Human Immunodeficiency Virus (HIV) (HIV ½ antibodies).

14) Subject is positive for active Hepatitis B surface antigen (HBsAg reactive) or Hepatitis C virus ribonucleic acid (HCV RNA [qualitative] is detected). Subjects with negative Hepatitis C antibody testing may not require RNA testing if deemed appropriate by treating physician.

Treatments

Patients were randomised to one of the following 3 treatment arms:

a) Pembrolizumab (MK-3475) 2 mg/kg every three weeks (Q3W)

b) Pembrolizumab (MK-3475) 10 mg/kg every three weeks (Q3W)

c) Investigator-choice standard of care (SOC) chemotherapy (supplied locally)

- P002-00: Options: 1) Carboplatin plus paclitaxel, 2) Carboplatin, 3) Paclitaxel, 4) Dacarbazine, or 5) Temozolomide (oral or IV)
- P002-01: Options: 1) Carboplatin plus paclitaxel, 2) Paclitaxel, 3) Dacarbazine, or 4) Temozolomide (oral)

Objectives

Primary

1) To evaluate the progression-free-survival (PFS) in subjects with ipilimumab refractory advanced melanoma receiving either pembrolizumab or chemotherapy.

2) To evaluate the overall survival (OS) in subjects with ipilimumab refractory advanced melanoma receiving either pembrolizumab or chemotherapy.

Secondary

1) To evaluate the overall response rate (ORR) in subjects with ipilimumab refractory advanced melanoma receiving either pembrolizumab or chemotherapy.

2) To evaluate the response duration in subjects with ipilimumab refractory advanced melanoma receiving either pembrolizumab or chemotherapy.

3) To evaluate OS, PFS, and ORR in the biomarker positive subgroup defined by programmed cell death 1 ligand (PDL1) expression level (cutoff point to be estimated from external data) receiving either pembrolizumab or chemotherapy.

4) To further characterize the pharmacokinetic (PK) profile of single agent pembrolizumab at 2 mg/kg and 10 mg/kg.

5) To evaluate safety, tolerability and adverse experience profile of single agent pembrolizumab 2 mg/kg and 10 mg/kg.

Key exploratory

1) To evaluate health-related quality of life changes from baseline in patients with ipilimumab refractory melanoma treated with pembrolizumab compared to patients treated with chemotherapy using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).

Outcomes / endpoints

Co-Primary endpoints

1) Progression-Free-Survival (PFS) was based on assessment from a central imaging vendor using the RECIST 1.1 criteria, or death due to any cause, whichever occurred first.

Progression-free survival is defined as the time from randomization to the first documented disease progression (based on assessment from a central imaging vendor using the RECIST 1.1 criteria) or death due to any cause, whichever occurs first. See protocol ([16.1.1], Section 3.5.5.1) for definition of censoring. For patients whose subsequent assessments right after RECIST-defined PD show a stable disease or better and who remains on study treatment, a sensitivity analysis will be conducted that does not count the initial RECIST defined PD assessment as an event. Analysis of PFS based on investigator assessment using RECIST 1.1 will be performed as a supportive analysis.

2) Overall Survival (OS) was defined as the time from randomization to documented death due to any cause.

Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary endpoints

1) Overall Response Rate (ORR) was defined as the proportion of the subjects in the analysis population who had a complete response (CR) or partial response (PR). Responses were based on confirmed assessments from a central imaging vendor using the RECIST 1.1 criteria.

2) Confirmed CR or PR at the time from first documented evidence of CR or PR until disease progression or death.

3) ORR, PFS and OS in the biomarker positive subgroup:

- ORR: Based on proportion of subjects with complete response (CR) or partial response (PR) based on confirmed central review assessment (IRO) using RECIST 1.1 criteria by PD-L1 expression level.
- PFS: Based on assessment of independent central review (IRO) using RECIST 1.1 by PD-L1 expression level from randomization until progression or death due to any cause, whichever occurred first.
- OS: Based on time from randomization to death due to any cause by PD-L1 expression level.

The PD-L1 cutoff point was defined and validated using data from the melanoma subjects in P001 prior to any biomarker analysis in P002. PD-L1 positive is defined as Allred proportion score (APS) of 2 or higher and PD-L1 negative is defined as APS of 0 or 1.

Key Exploratory endpoints

1) The key PRO endpoint was the score changes from baseline and the proportions of improvement/deterioration at week 12, as measured by the EORTC QLQ-C30 global health status/quality of life score.

2) The supportive PRO Endpoints were the score changes from baseline and the proportions of improvement/deterioration at week 12, as measured by each of the EORTC QLQ-C30 functional subscales and each of the

Sample size

The study is OS event-driven and planned to randomize 510 patients with a 1:1:1 ratio into two pembrolizumab arms (2 mg/kg and 10 mg/kg) and one control arm. If one of the pembrolizumab arms discontinued at the interim analysis, the study would complete after 245 deaths have occurred in the remaining pembrolizumab arm and the control arm.

The sample size calculation was based on the following assumptions: 1) overall survival follows an exponential distribution with a median of six months in the control arm; 2) the hazard ratio between pembrolizumab and control is 0.65; 3) an enrollment period of 15 months and a minimum of 9 months follow-up after enrollment completion; and 4) a drop-out rate of 2% in 12 months. If both pembrolizumab arms continued to the end, barring early stopping at interim analyses, the study would complete after 370 deaths had occurred (i.e., a 50% increase from 245).

The overall type I error rate for this study was strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS at the second interim analysis and 2% allocated to OS. PFS was only be tested at the second interim analysis. The Bonferroni method was used for testing the two null hypotheses on PFS at the second interim analysis with each tested at 0.25%. If any of the two null hypotheses was rejected, the corresponding alpha level was rolled into the overall OS hypothesis (i.e., the OS hypothesis tested

at 2%, 2.25% and 2.5% respectively if none, exactly one and both hypotheses were rejected at the second interim analysis).

The PFS hypotheses will be tested at the second interim analysis when all patients were enrolled and at least 270 PFS events among three arms (at least 180 PFS events if one MK- 3475 arm is discontinued at IA 1) have occurred. By the time of the second interim analysis, approximately 180 to 200 PFS events should have occurred between one pembrolizumab arm and the control arm. With 180-200 PFS events, the study had 88% to 92% power to detect a hazard ratio of 0.55 in PFS between a pembrolizumab arm and control at alpha=0.25% (one-sided). The sample size and power calculation for PFS were based on the following assumptions: 1) PFS follows an exponential distribution with a median of 2 months in the control arm, 2) the hazard ratio between pembrolizumab and control is 0.55, 3) an enrollment period of 15 months.

With 2% to 2.5% type I error allocated to OS (depending on the number of PFS hypotheses being positive at the second interim analysis), the reference type I error rate is 1% to 1.25% between one pembrolizumab arm and control. With 245 deaths between a pembrolizumab arm and control, the study had 85% power to detect a 0.65 hazard ratio and 95% power to detect a 0.6 hazard ratio on OS at alpha=1%.

Randomisation

An interactive voice response system (IVRS)/IXRS was used to centrally randomize subjects. Prior to entering information into IVRS, the Investigator defined the chemotherapy treatment of Investigator choice (TIC) for each subject in the event the subject was randomized to the chemotherapy arm.

Patients were randomised to one of the following treatments:

a) 180 subjects randomized to receive pembrolizumab (MK-3475) 2 mg/kg every three weeks (Q3W)

b) 181 subjects randomized to receive pembrolizumab (MK-3475) 10 mg/kg every three weeks (Q3W)

c) 179 subjects randomized to receive chemotherapy administered according to SOC

The randomization of enrolled subjects was stratified based on ECOG performance (0 vs. 1), lactate dehydrogenase (LDH) levels (normal versus elevated LDH levels) and BRAF mutational status.

Blinding (masking)

The pembrolizumab (MK-3475) dosing assignment was blinded to site and the applicant's personnel directly associated with the conduct of the trial. The study site assigned a designated unblinded pharmacist who was responsible for preparing the pembrolizumab study medication that was administered to the subject in a blinded fashion.

The applicant had access to individual study medication data (except for the dose information of pembrolizumab) for medical monitoring purpose, while the treatment assignment (pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg) was blinded according to in-house blinding procedures. Pembrolizumab doses remained blinded for medical monitoring.

Statistical methods

An outline of the efficacy analysis strategy is presented in Table 15.

Table 15: Primary analysis strategy for efficacy endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Progression-free survival	Stratified Log-rank test Stratified Cox model with Efron's tie handling method for estimation	ITT	Model based
Overall survival	Stratified Log-rank test Stratified Cox model with Efron's tie handling method for estimation	ITT	Model based
Secondary:			
Overall response rate	Stratified Miettinen and Nurminen method	FAS and ITT	Patients with missing data are considered non-responders
Response duration	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis

There were two planned interim analyses for this study. Table 16 summarizes the strategy and timing of each interim analysis.

Table 16: Summary of interim analysis strategy

Interim Analysis Number	Key Endpoints for Interim Analysis	Anticipated Approximate Timing of Interim Analysis (from study start)	Sample size included for analysis (Three arms)	Number of events included for analysis (Three arms)	Purpose of Analysis
Interim Analysis 1	ORR	10 months	120	NA	Discontinue one inferior MK-3475 arm
Interim Analysis 2	PFS/OS	15 months	510	270 PFS events	• Demonstrate superiority of MK-3475 in PFS • Stop for futility based on OS
Final analysis	OS	24 months	510	370 OS events	Demonstrate superiority of MK-3475 in OS

The first IA occurred after the first 120 randomized patients have a minimum of 3 months follow-up (approximately 10 months into the study). The primary objective of this analysis was to discontinue 2 mg/kg or 10 mg/kg from the study if one arm is clearly not as effective as the other arm. Only responses from two pembrolizumab arms (2 mg/kg and 10 mg/kg) were compared in this analysis. The overall response rate based on assessments from a central imaging vendor between the 10 mg/kg and the 2 mg/kg arms was evaluated. If the p-value of the difference of response rate is less than 10% (two-sided), the MK arm with lower observed response rate will be discontinued. A 15% difference (i.e., 25% in one arm and 10% in the other) will approximately meet the criterion for discontinuing the less effective arm. There was no intention to stop the trial for efficacy or futility at

this analysis. To prevent the study from premature stopping, a nominal alpha of 0.001% is spent on the OS hypothesis with negligible impact on the overall type I error rate.

The IA2 was planned to occur when all study subjects had been enrolled and at least 270 PFS events had been observed among three arms. It was expected that at least 240 subjects would have a minimum of 4 months follow-up and approximately 210 deaths at the time of IA2, assuming no pembrolizumab arms would be dropped earlier. Between-treatment comparison of OS was tested using stratified log-rank test, the hazard ratio and its 95% confidence interval was estimated using the stratified Cox model with efron's tie handling. OS curve is estimated using Kaplan-Meier (KM) method in each treatment group.

Results

Participant flow

Table 17: Disposition of subjects (ITT population)

	Control		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	179		180		181		540	
Study Medication Disposition								
Did Not Take Study Medication	8	(4.5)	2	(1.1)	2	(1.1)	12	(2.2)
Crossed Over to MK-3475[‡]	86	(48.0)	0	(0.0)	0	(0.0)	86	(15.9)
Discontinued	71	(39.7)	126	(70.0)	118	(65.2)	315	(58.3)
Progressive Disease	42	(23.5)	89	(49.4)	76	(42.0)	207	(38.3)
Adverse Event	18	(10.1)	21	(11.7)	24	(13.3)	63	(11.7)
Death	1	(0.6)	0	(0.0)	1	(0.6)	2	(0.4)
Non-Compliance With Study Drug	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)
Physician Decision	3	(1.7)	6	(3.3)	7	(3.9)	16	(3.0)
Withdrawal By Subject	7	(3.9)	9	(5.0)	9	(5.0)	25	(4.6)
Other	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)
Ongoing	14	(7.8)	52	(28.9)	61	(33.7)	127	(23.5)

Each subject is counted once for Study Medication Disposition.
[‡] In the control group, progressive disease is required prior to crossing over to MK-3475. Therefore, the total number of patients with disposition as "Progressive Disease" is 86+42=128.
(Database Cutoff Date: 12MAY2014).

At the time of this interim analysis, 86 SOC chemotherapy subjects had crossed over to the pembrolizumab treatment arm (2 or 10 mg/kg Q3W). Of these 86 subjects, 33 (38.4%) remained in the study on pembrolizumab, 1 (1.2%) subject discontinued treatment due to AE, and 48 (55.8%) discontinued treatment due to progressive disease.

Table 18: Disposition of subjects (crossover population)

	Crossover MK-3475 2 mg/kg Q3W		Crossover MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	46		40		86	
Study Medication Disposition						
Discontinued	27	(58.7)	26	(65.0)	53	(61.6)
Progressive Disease	24	(52.2)	24	(60.0)	48	(55.8)
Adverse Event	1	(2.2)	0	(0.0)	1	(1.2)
Physician Decision	1	(2.2)	0	(0.0)	1	(1.2)
Withdrawal By Subject	1	(2.2)	2	(5.0)	3	(3.5)
Ongoing	19	(41.3)	14	(35.0)	33	(38.4)

Each subject is counted once for Study Medication Disposition.
(Database Cutoff Date: 12MAY2014).

Recruitment

As of data cut-off date (12-May-2014), the trial was conducted in 73 trial centers worldwide: 34 trial centers in the United States; 11 in Germany; 5 in France; 4 trial centers each for Netherlands, Spain,

and Switzerland; 3 trial centers each for Israel and Italy; 2 in Argentina; 1 trial center each for Australia, Norway, and Sweden.

Conduct of the study

There were 333 subjects randomized under the original protocol (P002-00), 205 subjects randomized under amendment 01 (P002-01), and two subjects randomized under amendment 02 (P002-02).

Amendment 01

Key changes included modification to indication statement for clarity, modifications to the primary and secondary objectives (moved ORR from primary to secondary, removed evaluations for ORR, OS, and disease control rate [DCR] at Week 12). Additional key changes included modification to the IPI-refractory definition in the Inclusion Criteria (provided minimum IPI dose; added text to indicate that PD is based on irRC; clarified requirements in the absence of rapid clinical progression, added sponsor collection of imaging scans, and clarification in documenting date of progression); revised Inclusion Criterion to specify that lesions must be measured radiologically. There were modifications to the timing for the second (move to 15 months; occur after study enrollment was completed) and final analyses as well as clarifications to the efficacy measurements (defined minimal criteria that must be met in subject with radiological PD at Week 12 assessment which enabled the subject to continue receiving pembrolizumab).

Additional changes were in response to Investigator feedback and additional information gained in the progression of P001 trial. Amendment 01 also reflected changes in Inclusion Criteria regarding baseline samples collected for biomarker analysis (only newly obtained tumor tissue was acceptable) and updated the eligibility age (deleted ≥ 16 years of age and replaced with ≥ 18 years of age). Exclusion Criteria was revised to exclude subjects who received ipilimumab only as an adjuvant therapy. Chemotherapy treatment arm options were reduced in response to regulatory agency feedback: carboplatin monotherapy and temozolomide IV were removed; specified dosing regimens for the chemotherapy option.

Progression of the cancer under study is not considered an SAE unless it results in hospitalization. Death unrelated to the study medication and due to progressive melanoma is not considered an SAE. Death unrelated to the study medication and due to clinical signs or symptoms of progressive melanoma (without meeting RECIST 1.1 requirement for PD) is reported as an SAE.

Amendment 02

Key changes included modification to the efficacy analysis sections (revised test regarding Full Analysis Set [FAS], added ITT to ORR analysis), updated dose modification guidelines to indicate that pembrolizumab will be withheld in the event of a Grade 4 drug-related hematologic toxicity, modified the supportive care guidelines for Grade 2 and Grade 3 reactions, added a section providing guidance for recommended treatment in subjects who experienced pneumonitis during the trial.

Cross-over to pembrolizumab treatment arm

Subjects in the control arm were allowed to cross over to pembrolizumab arm (dose level pre-decided at original randomization) after Week 12 and once the progressive disease was confirmed by the IRO. By the time of the data cutoff for IA2 (i.e., 12 May 2014), a total of 86 of 179 subjects (48%) who were randomized to the control arm had crossed over and were treated with pembrolizumab.

Baseline data

The following tables represent the baseline characteristics, demographic data and prior medications.

Table 19: Subject characteristics (ITT population)

	Control		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	179		180		181		540	
Gender								
Male	114	(63.7)	104	(57.8)	109	(60.2)	327	(60.6)
Female	65	(36.3)	76	(42.2)	72	(39.8)	213	(39.4)
Age (Years)								
<65	98	(54.7)	102	(56.7)	106	(58.6)	306	(56.7)
>=65	81	(45.3)	78	(43.3)	75	(41.4)	234	(43.3)
Mean	60.5		59.5		60.1		60.1	
SD	12.7		14.9		13.3		13.6	
Median	63.0		62.0		60.0		61.5	
Range	27 to 87		15 to 87		27 to 89		15 to 89	
Race								
American Indian Or Alaska Native	3	(1.7)	0	(0.0)	0	(0.0)	3	(0.6)
Asian	1	(0.6)	2	(1.1)	2	(1.1)	5	(0.9)
Black Or African American	1	(0.6)	2	(1.1)	0	(0.0)	3	(0.6)
Missing	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)
Native Hawaiian Or Other Pacific Islander	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)
White	172	(96.1)	176	(97.8)	179	(98.9)	527	(97.6)
Ethnicity								
Hispanic Or Latino	7	(3.9)	7	(3.9)	4	(2.2)	18	(3.3)
Not Hispanic Or Latino	169	(94.4)	165	(91.7)	174	(96.1)	508	(94.1)
Not Reported	2	(1.1)	5	(2.8)	3	(1.7)	10	(1.9)
Unknown	1	(0.6)	3	(1.7)	0	(0.0)	4	(0.7)
ECOG								
0	99	(55.3)	98	(54.4)	98	(54.1)	295	(54.6)
1	80	(44.7)	80	(44.4)	83	(45.9)	243	(45.0)
Missing	0	(0.0)	2	(1.1)	0	(0.0)	2	(0.4)
Metastatic Staging								
M0	2	(1.1)	1	(0.6)	1	(0.6)	4	(0.7)
M1A	15	(8.4)	9	(5.0)	13	(7.2)	37	(6.9)
M1B	15	(8.4)	22	(12.2)	17	(9.4)	54	(10.0)
M1C	147	(82.1)	148	(82.2)	150	(82.9)	445	(82.4)
BRAF Mutation								
Mutant	41	(22.9)	44	(24.4)	40	(22.1)	125	(23.1)

	Control		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
BRAF Mutation								
Wild Type	138	(77.1)	136	(75.6)	141	(77.9)	415	(76.9)
Baseline Tumor Size (mm)								
Subjects with data	165		165		163		493	
Mean	126.1		121.9		122.6		123.5	
SD	96.6		89.2		99.6		95.1	
Median	102.0		95.0		101.0		99.0	
Range	11 to 568		10 to 428		12 to 560		10 to 568	
Baseline Lactate Dehydrogenase								
Normal	107	(59.8)	99	(55.0)	105	(58.0)	311	(57.6)
Elevated	68	(38.0)	77	(42.8)	73	(40.3)	218	(40.4)
Unknown	3	(1.7)	2	(1.1)	0	(0.0)	5	(0.9)
Missing	1	(0.6)	2	(1.1)	3	(1.7)	6	(1.1)
Number of Prior Lines of Therapies‡								
0	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)
1	47	(26.3)	40	(22.2)	56	(30.9)	143	(26.5)
2	78	(43.6)	79	(43.9)	66	(36.5)	223	(41.3)
3	32	(17.9)	32	(17.8)	34	(18.8)	98	(18.1)
4	12	(6.7)	12	(6.7)	18	(9.9)	42	(7.8)
5 or more	10	(5.6)	16	(8.9)	7	(3.9)	33	(6.1)
Prior Systemic Therapies - Chemotherapy								
Y	86	(48.0)	90	(50.0)	84	(46.4)	260	(48.1)
N	93	(52.0)	90	(50.0)	97	(53.6)	280	(51.9)
Prior Systemic Therapies - IL-2								
Y	12	(6.7)	21	(11.7)	16	(8.8)	49	(9.1)
N	167	(93.3)	159	(88.3)	165	(91.2)	491	(90.9)
Prior Systemic Therapies - Immunotherapy (Excluding Ipilimumab and IL-2)								
Y	23	(12.8)	25	(13.9)	18	(9.9)	66	(12.2)
N	156	(87.2)	155	(86.1)	163	(90.1)	474	(87.8)
Prior Systemic Therapies - BRAF inhibitor								
Y	43	(24.0)	46	(25.6)	45	(24.9)	134	(24.8)
N	136	(76.0)	134	(74.4)	136	(75.1)	406	(75.2)
Prior Systemic Therapies - Other								
Y	17	(9.5)	16	(8.9)	17	(9.4)	50	(9.3)
N	162	(90.5)	164	(91.1)	164	(90.6)	490	(90.7)
PDL1 Status								

	Control		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
PDL1 Status								
PD-L1 Positive	98	(54.7)	98	(54.4)	95	(52.5)	291	(53.9)
PD-L1 Negative	37	(20.7)	47	(26.1)	46	(25.4)	130	(24.1)
Unknown	44	(24.6)	35	(19.4)	40	(22.1)	119	(22.0)

‡Number of prior lines of therapies equal to 0 indicates patients only received adjuvant/ neoadjuvant therapies.
(Database Cutoff Date: 12MAY2014).

Table 20: Summary of prior ipilimumab (ITT population)

	MK 3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Control		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients In Population	180		181		179		540	
Line Of Therapy								
Patients With Data	180	(100.0)	181	(100.0)	179	(100.0)	540	(100.0)
First Line	55	(30.6)	78	(43.1)	64	(35.8)	197	(36.5)
Second Line	83	(46.1)	69	(38.1)	78	(43.6)	230	(42.6)
Third Line	24	(13.3)	25	(13.8)	30	(16.8)	79	(14.6)
Fourth Line	7	(3.9)	7	(3.9)	4	(2.2)	18	(3.3)
Fifth Line Or Greater	9	(5.0)	2	(1.1)	3	(1.7)	14	(2.6)
Adjuvant	2	(1.1)	0	(0.0)	0	(0.0)	2	(0.4)
Dose								
Patients With Data	166	(92.2)	170	(93.9)	168	(93.9)	504	(93.3)
3 Mg/Kg	161	(89.4)	165	(91.2)	163	(91.1)	489	(90.6)
4 Mg/Kg	2	(1.1)	1	(0.6)	0	(0.0)	3	(0.6)
10 Mg/Kg	3	(1.7)	4	(2.2)	5	(2.8)	12	(2.2)
Total Number Of Cycles								
Patients With Data	180	(100.0)	180	(99.4)	179	(100.0)	539	(99.8)
Mean (Std)	3.8 (0.8)		3.8 (1.3)		3.7 (0.9)		3.8(1.0)	
Median (Range)	4.0(2.0 to 8.0)		4.0(1.0 to 19.0)		4.0(1.0 to 12.0)		4.0(1.0 to 19.0)	
Best Therapeutic Response								
Patients With Data	180	(100.0)	181	(100.0)	179	(100.0)	540	(100.0)
Complete Response	4	(2.2)	0	(0.0)	1	(0.6)	5	(0.9)
Partial Response	8	(4.4)	9	(5.0)	6	(3.4)	23	(4.3)
Progressive Disease By Clinical Evaluation Only	8	(4.4)	7	(3.9)	6	(3.4)	21	(3.9)
Progressive Disease By Imaging	120	(66.7)	126	(69.6)	122	(68.2)	368	(68.1)
Stable Disease	22	(12.2)	24	(13.3)	31	(17.3)	77	(14.3)
Relapse	0	(0.0)	1	(0.6)	2	(1.1)	3	(0.6)
Unable To Assess	2	(1.1)	2	(1.1)	1	(0.6)	5	(0.9)
Not Applicable	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.4)
Unknown	16	(8.9)	12	(6.6)	8	(4.5)	36	(6.7)
Interval From Last Dose Ipilimumab† To First Dose Of Study Treatment† (Weeks)								
Patients With Data	178	(98.9)	179	(98.9)	171	(95.5)	528	(97.8)
Mean (Std)	26.2 (22.0)		27.2 (23.2)		29.7 (25.3)		27.7 (23.5)	
Range	4.1 to 155.7		4.3 to 131.1		3.7 to 133.6		3.7 to 155.7	
Interval Between Last Dose Ipilimumab† And Ipilimumab Progression Within 24 Week								
Y	177	(98.3)	178	(98.3)	177	(98.9)	532	(98.5)
N‡	3	(1.7)	3	(1.7)	2	(1.1)	8	(1.5)

†Only patients who received at least one dose of study medication and had at least partial date of last ipilimumab dose are included in this section.

If the last dose date of ipilimumb is a partial date, imputed date would be used for summary.

Only the last Ipilimumab treatment prior to study drug is counted if a patient has multiple courses of Ipilimumab treatment.

†Date of Ipilimumab progression is imputed with Day='15' if day is missing.

‡ Only six subjects truly did not meet the 24 weeks interval criteria. The following subjects had transcriptional error in data for interim analysis and are now within 24 week window after data after interim analysis. 000700015-101826 and 003300006 – 100012.

(Database Cutoff Date: 12MAY2014).

Data Source: [16.4]

Table 21: Summary of prior BRAF / MEK inhibitors among BRAF mutant patients (ITT population)

	Control n (%)	MK 3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	Total n (%)
BRAF Mutant Patients In Population	41	44	40	125
Number of BRAF Mutant Patients Receiving Prior BRAF/MEK Inhibitor	40	42	40	122
Type of BRAF/MEK Inhibitors				
Dabrafenib	2 (4.9)	3 (6.8)	2 (5.0)	7 (5.6)
Dabrafenib (+) Trametinib	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Dabrafenib Mesylate	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.8)
Mitogen-Activated Protein Kinase Kinase Inhibitor (Unspecified)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.8)
Mitogen-Activated Protein Kinase Kinase Inhibitor (Unspecified) (+) Raf Kinase	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Raf Kinase Inhibitor (Unspecified)	0 (0.0)	1 (2.3)	2 (5.0)	3 (2.4)
Trametinib	2 (4.9)	1 (2.3)	1 (2.5)	4 (3.2)
Vemurafenib	36 (87.8)	35 (79.5)	33 (82.5)	104 (83.2)
Line of Therapy				
Patients With Data	40 (97.6)	42 (95.5)	40 (100.0)	122 (97.6)
First Line	16 (39.0)	18 (40.9)	14 (35.0)	48 (38.4)
Second Line	12 (29.3)	7 (15.9)	15 (37.5)	34 (27.2)
Third Line	7 (17.1)	10 (22.7)	7 (17.5)	24 (19.2)
Fourth Line	3 (7.3)	2 (4.5)	3 (7.5)	8 (6.4)
Fifth Line Or Greater	2 (4.9)	5 (11.4)	1 (2.5)	8 (6.4)
Total Number of Cycles				
Patients With Data	21 (51.2)	22 (50.0)	25 (62.5)	68 (54.4)

	Control n (%)	MK 3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	Total n (%)
Mean (Std)	6.7 (6.5)	8.4 (5.9)	7.0 (4.8)	7.4 (5.7)
Median (Range)	4.0 (1.0 to 26.0)	7.5 (1.0 to 20.0)	5.0 (1.0 to 18.0)	5.5 (1.0 to 26.0)
Best Therapeutic Response				
Patients With Data	40 (97.6)	42 (95.5)	39 (97.5)	121 (96.8)
Complete Response	0 (0.0)	1 (2.3)	1 (2.5)	2 (1.6)
Partial Response	10 (24.4)	14 (31.8)	3 (7.5)	27 (21.6)
Progressive Disease	21 (51.2)	15 (34.1)	14 (35.0)	50 (40.0)
Stable Disease	4 (9.8)	5 (11.4)	15 (37.5)	24 (19.2)
Unable To Assess	1 (2.4)	2 (4.5)	0 (0.0)	3 (2.4)
Not Applicable	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Unknown	4 (9.8)	5 (11.4)	5 (12.5)	14 (11.2)
Interval From Last Dose of BRAF/MEK† To First Dose of Study Treatment (Weeks)				
Patients With Data	37 (90.2)	42 (95.5)	40 (100.0)	119 (95.2)
Mean (Std)	21.6 (16.5)	25.4 (18.8)	24.0 (24.1)	23.7 (20.0)
Range	4.9 to 76.3	3.3 to 96.3	3.1 to 118.4	3.1 to 118.4

† Only patients who received at least one dose of study medication and had at least partial date of last BRAF/MEK inhibitor dose are included in this section.
If the last dose date of BRAF/MEK inhibitor is a partial date, imputed date would be used for summary.
Only the last BRAF/MEK inhibitor treatment prior to study drug is counted if a patient has multiple courses of I BRAF/MEK inhibitor treatment.
(Database Cutoff Date: 12MAY2014).

Data Source: [16.4]

Numbers analysed

The intention-to-treat (ITT) population served as the primary population for the analyses of PFS and OS in this study. Both ITT population and Full Analysis Set (FAS) population were used for analysis of overall ORR. The FAS included all randomized patients with measurable disease at baseline, which was defined separately under investigator evaluation and independent radiologic review. Subjects were included in the treatment group to which they were randomized for the analysis of efficacy data using both the ITT and FAS populations. The primary efficacy endpoints were PFS (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first)

based on blinded central reviews from an external imaging vendor per RECIST 1.1 and OS (i.e., the time from randomization to death due to any cause). The secondary endpoints for this study were ORR based on confirmed responses from blinded central reviews and response duration. Progression-free survival and ORR based on investigator's assessment was analyzed as supportive analyses.

The All-Patients-as-Treated (APaT) population was employed for safety analyses.

Table 22: Study population

	Control Group n	MK-3475 2 mg/kg Q3W n	MK-3475 10 mg/kg Q3W n	Total n
Number of Patients Screened				672
Number of Patients Randomized (ITT Population)	179	180	181	540
Number of Patients Received Treatment (APaT Population)	171	178	179	528
Crossed Over to MK-3475	86			
Number of Patients with Measurable Disease at Baseline per IRC (FAS Population per IRC)	165	165	163	493
Number of Patients with Measurable Disease at Baseline per Investigator (FAS Population per Investigator)	179	180	181	540
(Database Cutoff Date: 12MAY2014).				

Outcomes and estimation – Interim Analysis 2

Co-primary endpoint: PFS analyses based on IRO evaluation

Study P002 compared the activity of pembrolizumab in IPI-refractory melanoma versus investigator's choice of chemotherapy. Both pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W treatment arms met the pre-specified criteria for a positive PFS outcome at the second interim analysis, with a HR of 0.57 and 0.50 for the 2 mg/kg and 10 mg/kg treatment arms compared to chemotherapy. The median PFS was similar in the three treatment arms, at 2.7 months for the chemotherapy control arm and 2.9 months for both pembrolizumab arms by independent central review (IRO), and coincides approximately with the first scheduled disease assessment at Week 12. Although the number of subjects at risk at longer time points is small at the time of the interim analysis, curves for pembrolizumab appear to flatten out, with around 22% (at 2 mg/kg Q3W) and 24% (at 10 mg/kg Q3W) of subjects in the pembrolizumab arms appearing to derive PFS benefit from treatment at one year and beyond, in comparison to 4% of patients in the chemotherapy arm.

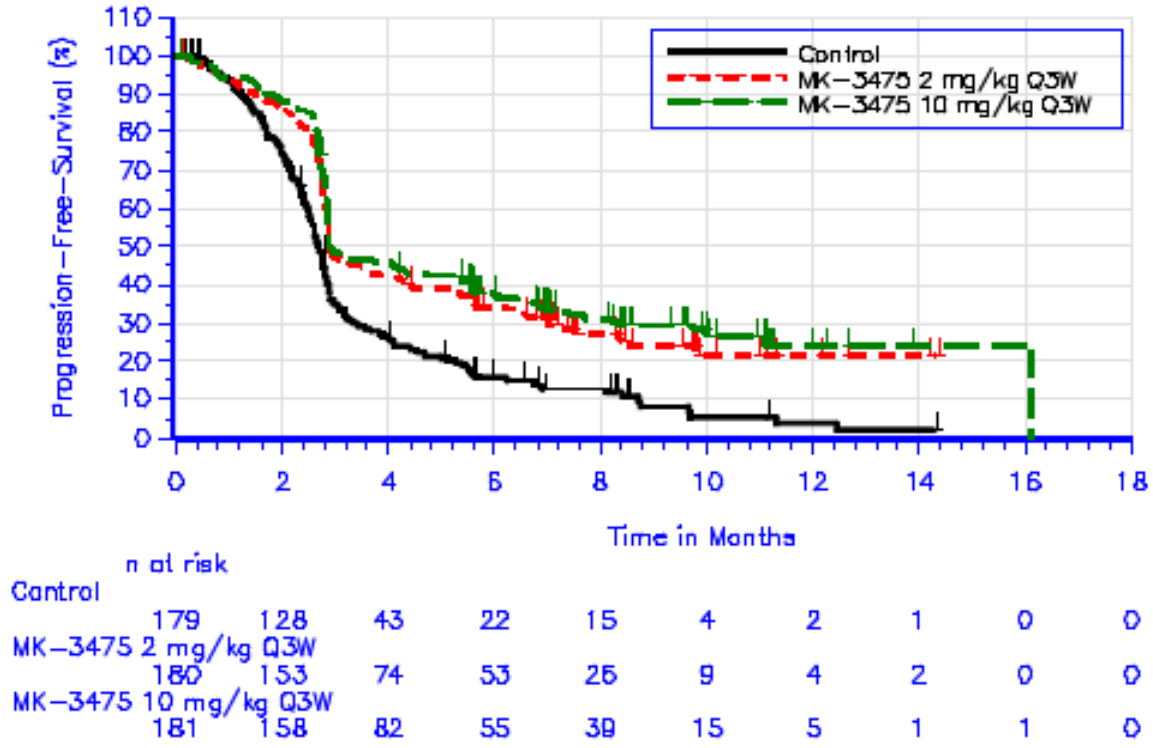
Table 23 summarise the primary analysis of PFS based on IRO assessment and Figure 23 shows the KM estimate of PFS for the three treatment arms.

Table 23: Analysis of progression-free survival based on IRO assessment (primary censoring rule) (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)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Control	179	155 (86.6)	584.3	26.5	2.7 (2.5, 2.8)	15.6 (10.5, 21.5)	---	---
MK-3475 2 mg/kg Q3W	180	129 (71.7)	804.6	16.0	2.9 (2.8, 3.8)	34.3 (27.4, 41.3)	0.57 (0.45, 0.73)	<0.0001
MK-3475 10 mg/kg Q3W	181	126 (69.6)	881.1	14.3	2.9 (2.8, 4.7)	37.7 (30.6, 44.8)	0.50 (0.39, 0.64)	<0.0001
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W							0.91 (0.71, 1.16)	0.4390

IRO: Integrated Radiology and Oncology Assessment.
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ One-sided p-value based on stratified log-rank test.
‖ Two-sided p-value based on stratified log-rank test.
(Database Cutoff Date: 12MAY2014).

Figure 23: Kaplan-Meier of progression-free survival based on IRO assessment (primary censoring rule) (ITT population)(cutoff:12May2014)



Co-primary endpoint: OS analyses

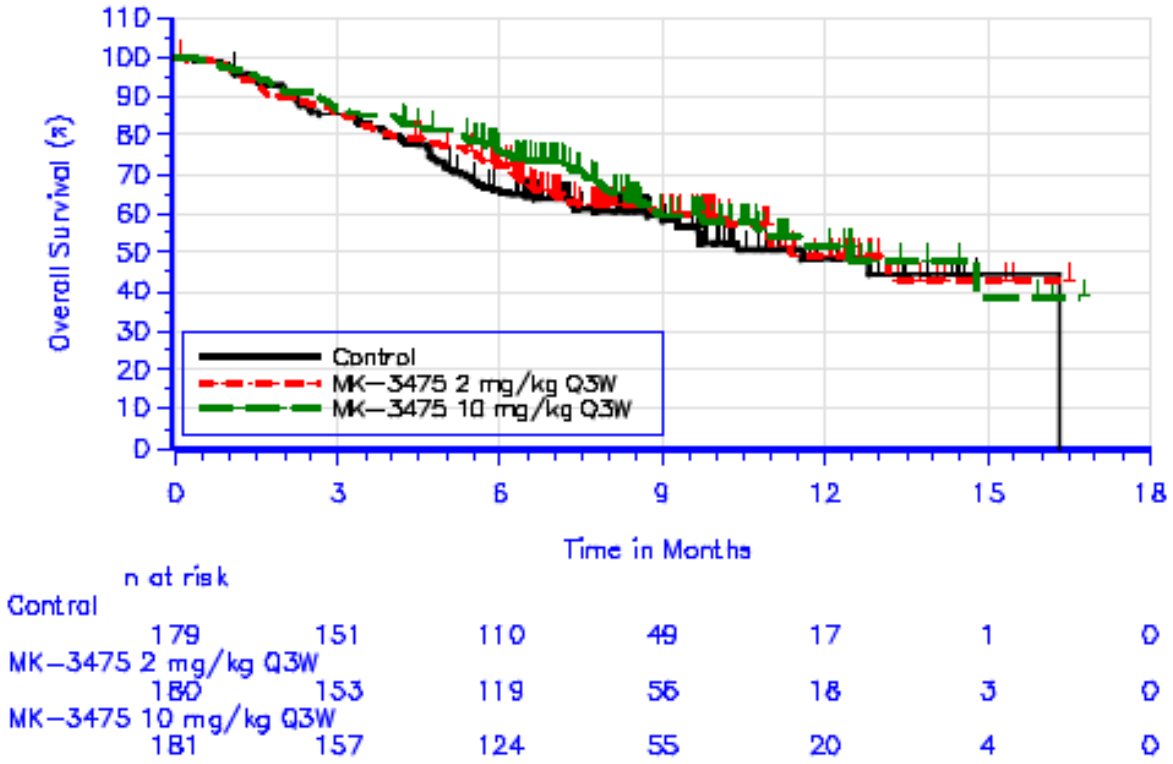
The data on OS is summarised in Table 24 and Figure 24. The median OS was 11.4 months in the pembrolizumab 2 mg/kg Q3W arm, 12.5 months in the pembrolizumab 10 mg/kg Q3W arm, and 11.6 months in the control arm. The results were not statistically significant at the time of the IA2.

Table 24: Analysis of overall survival (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 3 in %[†] (95% CI)	Treatment vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Control	179	78 (43.6)	1247.2	6.3	11.6 (9.0, 16.3)	85.3 (79.2, 89.8)	---	---
MK-3475 2 mg/kg Q3W	180	73 (40.6)	1289.6	5.7	11.4 (10.2, .)	85.5 (79.4, 89.9)	0.88 (0.64, 1.22)	0.2294
MK-3475 10 mg/kg Q3W	181	69 (38.1)	1348.3	5.1	12.5 (9.7, .)	86.7 (80.9, 90.9)	0.78 (0.56, 1.08)	0.0664
Pairwise Comparison							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W							0.88 (0.63, 1.22)	0.4395

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
[§] One-sided p-value based on stratified log-rank test.
[‖] Two-sided p-value based on stratified log-rank test.
(Database Cutoff Date: 12MAY2014).

Figure 24: Kaplan-Meier of overall survival (ITT population)



A sensitivity analysis of OS was conducted where subjects were censored at the time of crossover. The hazard ratio was 0.85 for pembrolizumab 2 mg/kg Q3W over the control group and 0.75 for pembrolizumab 10 mg/kg Q3W over the control group.

Secondary endpoint: ORR based on IRO per RECIST 1.1

The ORR for pembrolizumab was 21.1% and 25.4% in the 2 mg/kg Q3W arm and 10 mg/kg Q3W arm, respectively, compared to 4.5% in the control arm (see Table 25).

Table 25: Analysis of overall response based on IRO assessment (ITT population)

Treatment	N	Number of Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Control	179	8	4.5 (1.9,8.6)		
MK-3475 2 mg/kg Q3W	180	38	21.1 (15.4,27.8)	12.8 (7.0,20.6)	<0.0001
MK-3475 10 mg/kg Q3W	181	46	25.4 (19.2,32.4)	18.4 (11.4,26.7)	<0.0001
Pairwise Comparison				Estimate (95% CI)†	p-Valu
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W				5.5 (-3.2,14.4)	0.2094

IRO: Integrated Radiology and Oncology Assessment.
Responses are based on IRC global radiological assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1) and LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0.
(Database Cutoff Date: 12MAY2014).

Data Source: [16.4]

Ancillary analyses

Subgroup analyses of PFS

A number of sensitivity analyses, pre-specified and post-hoc, using different censoring rules, or based on scheduled tumour assessment, were performed. The results confirm the primary PFS analyses. Results from PFS analysis based on investigator evaluation are reported below:

Table 26: Analysis of PFS based on investigator assessment (Primary Censoring Rule) (ITT Population)

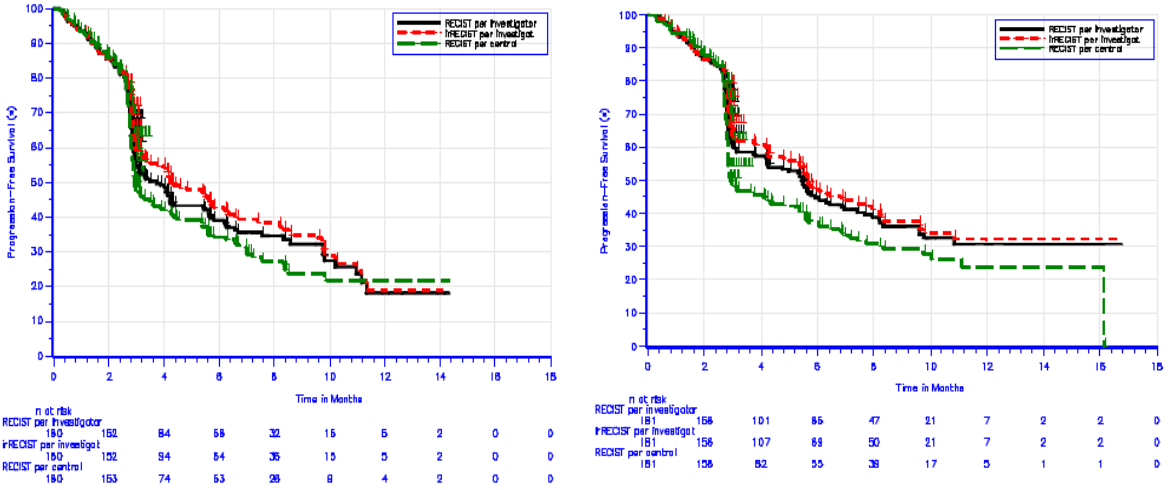
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Control	179	157 (87.7)	594.1	26.4	2.6 (2.4, 2.8)	15.2 (10.2, 21.0)	---	---
MK-3475 2 mg/kg Q3W	180	122 (67.8)	864.7	14.1	3.7 (2.9, 5.4)	38.9 (31.6, 46.1)	0.49 (0.38, 0.62)	<0.0001
MK-3475 10 mg/kg Q3W	181	112 (61.9)	979.2	11.4	5.4 (3.8, 6.8)	44.9 (37.3, 52.1)	0.41 (0.32, 0.52)	<0.0001
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W							0.81 (0.63, 1.05)	0.1178

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ One-sided p-value based on stratified log-rank test.
‖ Two-sided p-value based on stratified log-rank test.
(Database Cutoff Date: 12MAY2014).

Data Source: [16.4]

Table 27: Kaplan-Meier of PFS for 2 and 10 mg/kg Q3W under Three Assessments

2mg/kg **10 mg/kg**



Subgroup analyses of PFS were performed to further evaluate the treatment effect of pembrolizumab in various subgroups based on clinically relevant baseline subject or tumor characteristics.

Table 28: Forest plot of PFS hazard ratio by subgroup factors IRO assessment (primary censoring rule) pembrolizumab 2 mg/kg Q3W versus control

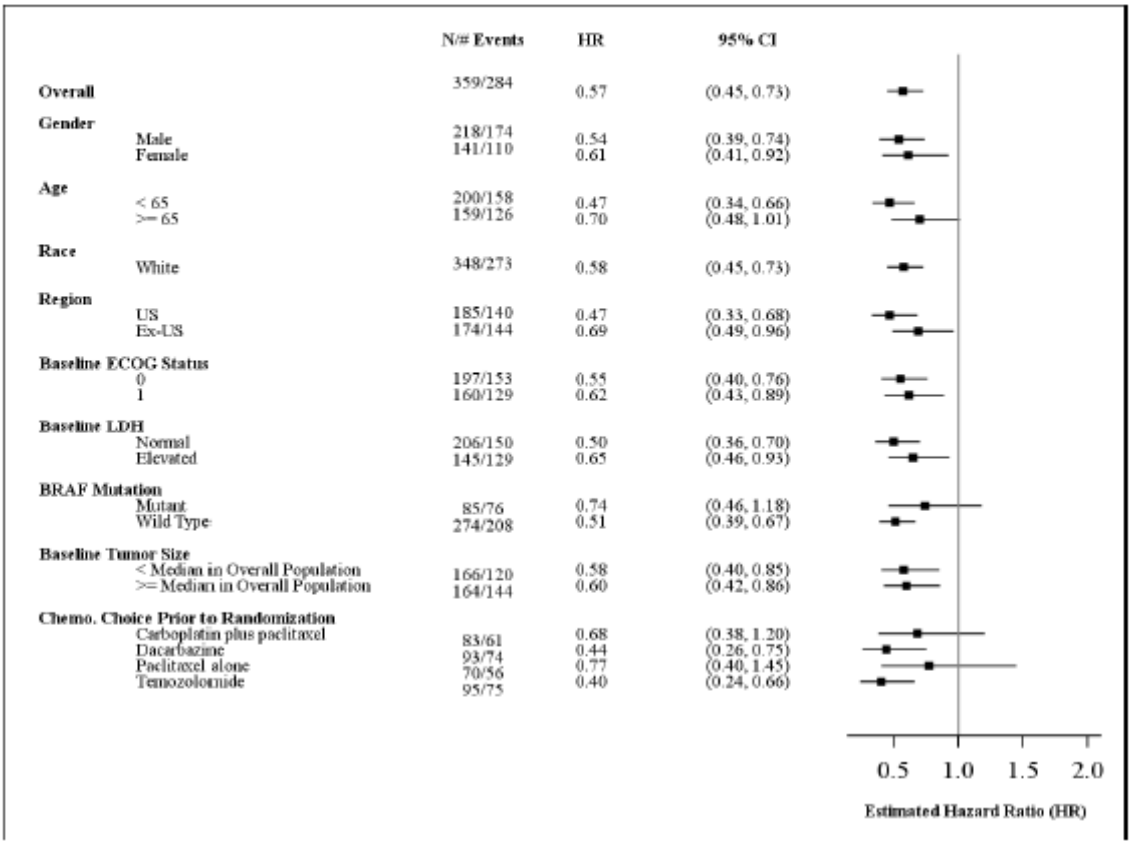
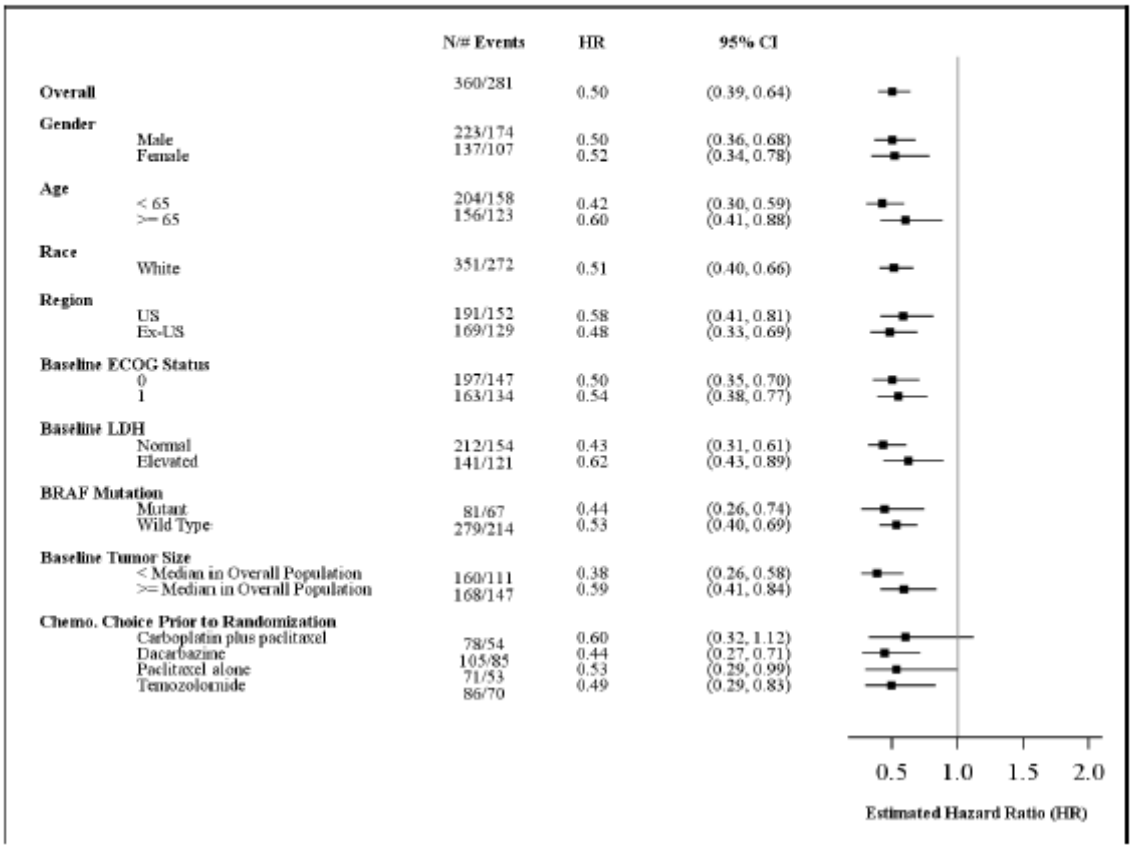


Table 29: Forest plot of PFS hazard ratio by subgroup factors IRO assessment (primary censoring rule) pembrolizumab 10 mg/kg Q3W versus control



Efficacy analyses based on PD-L1 positivity

The benefit of pembrolizumab in IPI-naive subjects in Study P002, based on PD-L1 expression has been analyzed. The results are shown in the tables below.

Table 30: Comparison of PFS by IRO assessment by PD-L1 status and treatment

	Control		2 mg/kg Q3W		10 mg/kg Q3W	
IRO	PD-L1 Positive (n=98)	PD-L1 Negative (n=37)	PD-L1 Positive (n=98)	PD-L1 Negative (n=47)	PD-L1 Positive (n=95)	PD-L1 Negative (n=46)
Hazard Ratio (95% CI) Treatment vs Control	–	–	0.54 (0.39, 0.75)	0.89 (0.53, 1.50)	0.49 (0.35, 0.69)	0.41 (0.23, 0.72)
PFS Rate at Month 6 in % (95% CI)	12.8 (7.0, 20.5)	21.6 (10.2, 35.8)	38.1 (28.5, 47.6)	19.3 (9.4, 31.9)	41.5 (31.3, 51.3)	32.6 (19.7, 46.1)
Median PFS (Months) (95% CI)	2.8 (2.6, 2.9)	2.7 (2.0, 3.0)	3.5 (2.9, 5.6)	2.8 (2.7, 2.8)	4.0 (2.8, 6.0)	2.8 (2.8, 5.6)
Data Cutoff Date: 12MAY2014.						

Table 31: Summary of overall survival (ITT population PD-L1 positive)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 3 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Control	98	38 (38.8)	663.8	5.7	16.3 (8.7, 16.3)	87.5 (79.1, 92.7)	---	---
MK-3475 2 mg/kg Q3W	98	37 (37.8)	714.6	5.2	Not Reached (10.2, .)	86.7 (78.3, 92.1)	0.93 (0.58, 1.49)	0.3834
MK-3475 10 mg/kg Q3W	95	32 (33.7)	728.2	4.4	14.8 (8.9, .)	91.6 (83.9, 95.7)	0.73 (0.45, 1.19)	0.1025
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W							0.78 (0.48, 1.27)	0.3170

†From product-limit (Kaplan-Meier) method for censored data.
‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§One-sided p-value based on log-rank test.
‖Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 32: Summary of overall survival (ITT population PD-L1 negative)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 3 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Control	37	19 (51.4)	268.1	7.1	10.4 (5.4, .)	78.4 (61.4, 88.5)	---	---
MK-3475 2 mg/kg Q3W	47	25 (53.2)	326.9	7.6	8.9 (6.2, 13.2)	83.0 (68.8, 91.1)	1.19 (0.58, 2.46)	0.6768
MK-3475 10 mg/kg Q3W	46	21 (45.7)	345.3	6.1	10.8 (4.6, .)	78.3 (63.4, 87.7)	0.60 (0.30, 1.18)	0.0677
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 10 mg/kg Q3W vs. MK-3475 2 mg/kg Q3W							0.81 (0.43, 1.53)	0.5296

†From product-limit (Kaplan-Meier) method for censored data.
‡Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§One-sided p-value based on log-rank test.
‖Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 33: Summary of response in PD-L1 subgroup versus overall study population

ORR by IRO per RECIST (%) in PD-L1 Subgroups					
	PD-L1 Positive	PD-L1 Negative	PD-L1 Evaluable	PD-L1 Unknown	Overall Study Population
Control (%)	4	8	5	2	4
MK-3475 2 mg/kg Q3W (%)	23	11	19	29	21
MK-3475 10 mg/kg Q3W (%)	29	20	26	23	25

Table 34: Summary of key efficacy endpoints comparing BRAF mutant vs BRAF wild type (P002 subjects treated with pembrolizumab)

	Pembrolizumab (both doses combined)		Chemotherapy Arm	
	BRAF Mutant	BRAF Wild-Type	BRAF Mutant	BRAF Wild-Type
Number of Subjects	84	277	41	138
Progression-Free Survival (IRO per RECIST 1.1)				
Median in months (95% CI)	2.8 (2.7, 2.9)	3.8 (2.9, 5.5)	2.4 (2.1, 2.8)	2.8 (2.6, 2.9)
6-month PFS rate	19.5%	40.9%	2.7%	19.3%
Comparison of pembrolizumab to chemotherapy, HR (95% CI)	0.56 (0.37, 0.85)	0.51 (0.41, 0.65)	---	---
Overall Survival				
Median in months (95% CI)	10.7 (6.2, -)	13.2 (10.8, -)	7.7 (4.7, -)	11.6 (9.3, 16.3)
6-month OS rate	63.8%	77.3%	56.0%	68.0%
Comparison of pembrolizumab to chemotherapy, HR (95% CI)	0.82 (0.47, 1.43)	0.83 (0.60, 1.15)	---	---
BOR Analysis (IRO per RECIST 1.1)				
Overall Response – CR + PR (95% CI)	11.9% (5.9, 20.8)	26.7% (21.6, 32.3)	0 (0.0, 8.6)	5.8% (2.5, 11.1)
Disease Control – CR + PR + SD + NN (95% CI)	22.6% (14.2, 33.0)	46.2% (40.2, 52.3)	9.8% (2.7, 23.1)	26.8% (19.6, 35.0)
Response Duration-Confirmed Response (IRO per RECIST 1.1)				
Median in weeks (range)[1]	36 (6+ - 36+)	Not Reached (5+ - 50+)	N/A	37 (7+-41)
% of non-progressing subjects (among responders)	60%	93%	N/A	63%
Median Time to Response in Weeks (range)	12 (12-18)	16 (12-30)	N/A	13 (12-18)

MK-3475, P002 Database Cutoff Date: 12-May-2014
1 "+" indicates non-PD at the last assessment (censored)
NN = NonCR/NonPD
N/A = Not Available

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 35: Summary of efficacy for trial P002

	Title: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma		
Study identifier	**P002**		
Design	Multicenter, partially blinded, randomized (1:1:1), Phase II study of pembrolizumab versus investigator-choice (standard of care) chemotherapy in IPI-treated advanced melanoma patients.		
	Duration of main phase: not applicable Duration of Run-in phase: not applicable Duration of Extension phase: not applicable		
Hypothesis		Superiority	
Treatments groups	Pembrolizumab		2 mg/kg Q3W patients enrolled/treated: 180/178
	Pembrolizumab		10 mg/kg Q3W patients enrolled/treated: 181/179

	Investigator choice chemotherapy (Standard of care)		patients enrolled/treated:179/171 -carboplatin/paclitaxel IV: 42 patients -paclitaxel IV: 28 patients -carboplatinIV: 13 patients -dacarbazine IV: 45 patients -temozolomide (oral): 43 patients
Endpoints and definitions	Co-primary endpoint	PFS	time from randomization to the first documented disease progression (based on assessment from a central imaging vendor using the RECIST 1.1 criteria) or death due to any cause, whichever occurs first.
	Co-primary endpoint	OS	time from randomization to death due to any cause.
	Secondary endpoints	ORR	proportion of patients who had a complete response (CR) or partial response (PR)based on confirmed assessments from a central imaging vendor using the RECIST 1.1 criteria.
		Response duration	time from first documented evidence of CR or PR until disease progression or death
		ORR, PFS and OS in the biomarker positive subgroup:	ORR, PFS and OS by PD-L1 expression level
Data cut-off date Database lock	12 May 2014 29 August 2014		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population			
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab 2 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	Control SoC
	Number of subject	180	181	179
	Co-Primary endpoints			
	PFS (IRO RECIST 1.1) N. with events (%)	129 (71.7)	126 (69.6)	155 (86.6)
	Median PFS months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
	Hazard Ratio treatment vs control (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	--
	p-value (stratified Log-Rank Test)	<0.0001	<0.0001	
	OS N. with events n(%)	73 (40.6)	69 (38.1)	78 (43.6)
	Median OS months (95% CI)	11.4 (10.2, NR)	12.5 (9.7, NR)	11.6 (9.0, 16.3)
	Hazard Ratio treatment vs control (95% CI)	0.88 (0.64, 1.22)	0.78 (0.56, 1.08)	--
	p-value (stratified Log-Rank Test)	P=0.229	P=0.066	

	Secondary endpoints			
	ORR (IRO RECIST1.1) ITT n(%) (95% CI)	38 (21.1) (15.4, 27.8)	46 (25.4) (19.2, 32.4)	8(4.5) (1.9, 8.6)
	Difference % vs control (95% CI)	12.8 (7.0, 20.6)	18.4 (11.4, 26.7)	--
	p-value (stratified on Miettinen & Nurminen method)	<0.0001	<0.0001	
	Response Duration (IRO RECIST1.1) Subjects with responses (n)	38	46	8
	Median in weeks (range)	Not reached (6+-50+)	Not reached (5+-48+)	37 (7+-41)
	Non-PD subjects n (%)	35 (92)	40 (87)	5 (63)
	Median time to response in weeks (range)	13 (12-30)	15 (12-30)	13 (12-18)

Study P006: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma – Interim Analysis 1 (IA1) and 2 (IA2)

Methods

This is a randomized, controlled, open-label, three-arm pivotal study of two dosing regimens of intravenous (IV) pembrolizumab versus IPI in patients with unresectable or metastatic MEL who have not received IPI treatment.

Study Participants

Main inclusion criteria:

1. Histologically confirmed diagnosis of unresectable stage III or metastatic melanoma not amenable to local therapy.
    - Patient may not have a diagnosis of uveal or ocular melanoma.
    - Patients who have not received prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (first line) or who have received one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (second line) are both eligible.
    - Patients must have testing for a BRAF mutation prior to study entry. Patients with BRAF V600E mutant melanoma may have received prior BRAF inhibitor therapy as first-line systemic therapy and be eligible for this study as second line treatment. At the discretion of the investigator, patients with BRAF V600E mutant melanoma who have NOT received a BRAF inhibitor are also eligible for this study as first line treatment if they meet the following additional criteria:
        - LDH < local ULN

- No clinically significant tumor related symptoms in the judgment of the investigator
- Absence of rapidly progressing metastatic melanoma in the judgment of the investigator

2. ECOG 0 or 1 and adequate organ function
3. Patient has a tumor sample (archival or newly obtained biopsy) that is adequate for PD-L1 assessment prior to randomization. Patients will be eligible to participate regardless of the level of PD-L1 expression, but will be stratified by PD-L1 expression level (high or low PD-L1 expression level) at the time of randomization
4. Measurable disease

Main exclusion criteria:

1. Patient had prior treatment with IPI or other anti-CTLA-4 agent, any anti-PD-1, anti-PD-L1, or anti- PD-L2 agent.
2. Patient who has had chemotherapy, radioactive, or biological cancer therapy within four weeks prior to the first dose of study drug, or who has not recovered to CTCAE Grade 1 or better from the AEs due to cancer therapeutics administered more than four weeks earlier.
3. Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of study drug.
4. Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.
5. Patient is on any systemic corticosteroid therapy within one week before the planned date for first dose of randomized treatment or on any other form of immunosuppressive medication.
6. Patient has a history of a malignancy (other than the disease under treatment in the study) within 5 years prior to first study drug administration. This should exclude adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other in situ cancers.
7. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by MRI for at least four weeks prior to the first dose of study drug), have no evidence of new or enlarging brain metastases and are off systemic steroids for at least two weeks.
8. Patient previously had a severe hypersensitivity reaction to treatment with another mAb.
9. Patient has an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement will not be excluded from the study.
10. Patient has an active infection requiring systemic therapy.
11. Patient has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

12. Patient has a known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected).
13. Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
14. Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
16. Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.
17. Patient has received a live vaccine within 30 days prior to first dose.

Treatments

Patients randomized to one of the pembrolizumab arms received pembrolizumab as IV infusion at a dose of 10 mg/kg given once every 2 weeks or once every 3 weeks, for up to 2 years until disease progression, intolerable toxicity, confirmed complete response, withdrawal of consent, or they require another form of antineoplastic therapy as determined by the Investigator. Patients randomized to the IPI arm will receive IPI at 3 mg/kg as IV infusion once every 3 weeks for a total of 4 doses.

Patients on the IPI arm will receive IPI treatment for a total of 4 doses according to the label. Patients will remain on study and will continue to be monitored with scheduled disease assessments up to 24 months as described in the protocol for safety and efficacy evaluations until disease progression, unacceptable toxicity, the withdrawal of consent, or they require another form of antineoplastic therapy as determined by the Investigator. Patients receiving IPI are not eligible for re-treatment with IPI as part of study treatment.

Objectives

The primary objective of the study is to evaluate for superiority of pembrolizumab to IPI in PFS or OS. The overall type I error rate for this study is strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS and 2.0% allocated to the overall OS hypothesis.

Outcomes/endpoints

The primary endpoint of the study will be progression free survival (PFS) and overall survival (OS). Other endpoints include response rate, response duration, Health Related Quality of Life (HRQoL), and safety.

After the baseline tumor evaluation, tumor assessment during the study will be performed by radiological scans every 6 weeks starting from Week 12 until Week 48. At the discretion of investigators, patients who remain on study after 48 weeks and are clinically stable may decrease imaging frequency to every 12 weeks. Patients will be evaluated for tumor response and patient management by sites based on the Immune Related Response Criteria [irRC] (Appendix 6.6 with

further details outlined in IIOM) by the investigator with site radiology reading. Copies of tumor images will be collected and provided to a central imaging vendor, and subjected to independent central review. Independent central review will utilize RECIST 1.1 criteria for response assessment. During the course of the study, the Data Monitoring committee (DMC) will monitor all safety information to ensure patient safety in accordance with a separate charter. The DMC will also evaluate the data at the planned interim analyses and make recommendations of stopping or continuing the study according to a separate charter. There are two planned interim efficacy analyses. The primary objective of the first interim analysis is to demonstrate clinical benefit in PFS. The study may stop early for futility based on PFS and OS at the first interim analysis. The primary objective of the second interim analysis is to evaluate treatment effect based on OS. In addition to the IAs, the study will also take into account data external to the study from PN001, which also has an ongoing cohort of advanced melanoma patients who are being randomized to 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks. As data from PN001 may become available prior to the first IA for PN006, if there is sufficient evidence of superiority or futility for one of the two dosing regimens of pembrolizumab from data external to the study, the SPONSOR may elect to discontinue one of the two pembrolizumab arms in PN006 prior to the first interim analysis via a protocol amendment.

Sample size

The study will enrol approximately 645 patients randomized to one of two pembrolizumab arms or IPI in a 1:1:1 ratio, stratified by line of therapy, PD-L1 expression and ECOG performance status. The sample size was based on a target of 435 OS events among the two pembrolizumab arms and IPI arm at the final analysis of OS.

Randomisation

Patients were randomized 1:1:1 to IPI (3 mg/kg every 3 weeks for 4 doses), pembrolizumab 10 mg/kg every 3 weeks for up to 2 years, or pembrolizumab 10 mg/kg every 2 weeks for up to 2 years. The study was stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).

Blinding (masking)

This study was designed as an open label study.

Statistical methods

The study is considered to be positive if at least one pembrolizumab arm is superior to IPI in PFS at an interim analysis OR at least one pembrolizumab arm is superior to IPI in OS at either an interim analysis or the final analysis of OS.

The data cutoff date for IA1 was 03SEP2014, driven by the fact that all patients have had at least 6 months of follow-up, which was deemed important for unbiased estimation of PFS effect based on data from PN001. The over enrollment and the requirement of a minimum of 6 months follow-up for all patients led to the actual number of PFS events of 489 based on IRO assessments at IA1.

The overall type I error rate for this study was controlled at 2.5% (one-sided) with 0.5% allocated to PFS and 2.0% allocated to the overall OS hypothesis. The study is consider to be positive if at least one pembrolizumab arm is superior to IPI in PFS at an interim analysis OR at least one pembrolizumab arm is superior to IPI in OS at either an interim analysis or the final analysis of OS.

IA2 was planned to take place when minimum follow-up is at least 9 months and approximately 290 deaths have been observed, unless it takes longer than 12 months of follow-up to observe 290 deaths, in which case the analysis would be performed when the minimum follow-up is 12 months. The data cutoff date for IA2 was 03-Mar-2015, driven by the minimum follow-up of 12 months. The total number of deaths is 289. The median OS follow-up is 13.8 months. OS was tested at the alpha level of 0.005 using the Hochberg step-up procedure at IA2 . Using the Hochberg procedure, if the p-value for both pembrolizumab arms is <0.005, both pembrolizumab arms are superior to IPI arm in OS; if the least significant (larger) p-value is >0.005 then the most significant (smaller) p-value needs to be compared with 0.0025 (0.005/2).

Results

Recruitment

Enrollment of PN006 was completed in 6 months on 03MAR2014 with a total of 834 patients randomized, which is 29% over the target enrollment of 645 patients.

Conduct of the study

In order to best evaluate the overall survival objective of this study, patients who progress during the study will not be allowed to cross-over from one arm to the other as part of study therapy, and patients who progress on the IPI arm will be excluded from participation in other pembrolizumab trials unless the DMC or the SPONSOR determine that the study has achieved its efficacy objective(s). Following the results from the IA1, the DMC recommended unblinding the study internally to facilitate regulatory filing while continuing study follow-up.

Baseline data

The baseline characteristics in the ITT population are presented in Table 36.

Table 36: Baseline characteristics in the ITT population – Study P006

	Control		MK-3475 10 mg/kg Q2W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	278		279		277		834	
Gender								
Male	162	(58.3)	161	(57.7)	174	(62.8)	497	(59.6)
Female	116	(41.7)	118	(42.3)	103	(37.2)	337	(40.4)
Age (Years)								
< 65	166	(59.7)	153	(54.8)	152	(54.9)	471	(56.5)
>=65	112	(40.3)	126	(45.2)	125	(45.1)	363	(43.5)
Mean	59.9		59.9		61.2		60.3	
SD	14.2		14.6		13.6		14.1	
Median	62.0		61.0		63.0		62.0	
Range	18 to 88		18 to 89		22 to 89		18 to 89	
Race								
Asian	5	(1.8)	2	(0.7)	3	(1.1)	10	(1.2)
Multiple	1	(0.4)	2	(0.7)	2	(0.7)	5	(0.6)
White	272	(97.8)	273	(97.8)	271	(97.8)	816	(97.8)
Missing	0	(0.0)	2	(0.7)	1	(0.4)	3	(0.4)
Ethnicity								
Hispanic Or Latino	13	(4.7)	13	(4.7)	10	(3.6)	36	(4.3)
Not Hispanic Or Latino	260	(93.5)	257	(92.1)	255	(92.1)	772	(92.6)
Not Reported	2	(0.7)	5	(1.8)	2	(0.7)	9	(1.1)
Unknown	3	(1.1)	4	(1.4)	10	(3.6)	17	(2.0)
Race								
White	272	(97.8)	273	(97.8)	271	(97.8)	816	(97.8)
Non-White	6	(2.2)	4	(1.4)	5	(1.8)	15	(1.8)
Missing	0	(0.0)	2	(0.7)	1	(0.4)	3	(0.4)
Region								
US	64	(23.0)	50	(17.9)	47	(17.0)	161	(19.3)
Ex-US	214	(77.0)	229	(82.1)	230	(83.0)	673	(80.7)
PD-L1 Status								

	Control		MK-3475 10 mg/kg Q2W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
PD-L1 Status								
PD-L1 Negative	47	(16.9)	49	(17.6)	54	(19.5)	150	(18.0)
PD-L1 Positive	225	(80.9)	225	(80.6)	221	(79.8)	671	(80.5)
Missing	6	(2.2)	5	(1.8)	2	(0.7)	13	(1.6)
Line of Systemic Therapy								
FIRST LINE	181	(65.1)	183	(65.6)	185	(66.8)	549	(65.8)
SECOND LINE	97	(34.9)	96	(34.4)	91	(32.9)	284	(34.1)
THIRD LINE	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
ECOG								
0	188	(67.6)	196	(70.3)	189	(68.2)	573	(68.7)
1	90	(32.4)	83	(29.7)	88	(31.8)	261	(31.3)
Cancer Stage								
III	2	(0.7)	1	(0.4)	1	(0.4)	4	(0.5)
IIIA	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.1)
IIIB	1	(0.4)	3	(1.1)	2	(0.7)	6	(0.7)
IIIC	9	(3.2)	6	(2.2)	6	(2.2)	21	(2.5)
IV	265	(95.3)	269	(96.4)	268	(96.8)	802	(96.2)
Metastatic Staging								
M0	14	(5.0)	9	(3.2)	9	(3.2)	32	(3.8)
M1	5	(1.8)	6	(2.2)	4	(1.4)	15	(1.8)
M1A	30	(10.8)	21	(7.5)	34	(12.3)	85	(10.2)
M1B	52	(18.7)	64	(22.9)	41	(14.8)	157	(18.8)
M1C	177	(63.7)	179	(64.2)	189	(68.2)	545	(65.3)
Baseline Lactate Dehydrogenase								
NORMAL	178	(64.0)	193	(69.2)	175	(63.2)	546	(65.5)
ELEVATED	91	(32.7)	81	(29.0)	98	(35.4)	270	(32.4)
MISSING	9	(3.2)	5	(1.8)	4	(1.4)	18	(2.2)
Brain Metastasis								
Yes	28	(10.1)	23	(8.2)	27	(9.7)	78	(9.4)
No	249	(89.6)	253	(90.7)	247	(89.2)	749	(89.8)

	Control		MK-3475 10 mg/kg Q2W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Brain Metastasis								
Missing	1	(0.4)	3	(1.1)	3	(1.1)	7	(0.8)
Baseline Tumor Size (mm)								
Subjects with data	244		236		240		720	
Mean	80.4		81.4		81.0		80.9	
SD	78.0		70.7		70.3		73.0	
Median	55.2		57.5		61.7		58.0	
Range	10 to 465		11 to 390		11 to 554		10 to 554	
BRAF Mutation								
MUTANT	107	(38.5)	98	(35.1)	97	(35.0)	302	(36.2)
WILD TYPE	170	(61.2)	177	(63.4)	178	(64.3)	525	(62.9)
UNDETERMINED	1	(0.4)	4	(1.4)	2	(0.7)	7	(0.8)
Prior Lines of Systemic Therapy								
None	158	(56.8)	161	(57.7)	165	(59.6)	484	(58.0)
ADJUVANT	23	(8.3)	22	(7.9)	20	(7.2)	65	(7.8)
FIRST LINE	97	(34.9)	96	(34.4)	91	(32.9)	284	(34.1)
SECOND LINE	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Prior Adjuvant/Neo-adjuvant Therapy								
Yes	37	(13.3)	42	(15.1)	30	(10.8)	109	(13.1)
No	241	(86.7)	237	(84.9)	247	(89.2)	725	(86.9)
Prior Chemotherapy Therapy†								
Yes	29	(10.4)	36	(12.9)	41	(14.8)	106	(12.7)
No	249	(89.6)	243	(87.1)	236	(85.2)	728	(87.3)
Prior Immunotherapy Therapy†								
Yes	12	(4.3)	8	(2.9)	7	(2.5)	27	(3.2)
No	266	(95.7)	271	(97.1)	270	(97.5)	807	(96.8)
Prior BRAF/MEK inhibitor†								
Yes	56	(20.1)	50	(17.9)	45	(16.2)	151	(18.1)
No	222	(79.9)	229	(82.1)	232	(83.8)	683	(81.9)

	Control		MK-3475 10 mg/kg Q2W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Type of Prior Immunotherapy - Interferon								
Yes	6	(2.2)	3	(1.1)	2	(0.7)	11	(1.3)
No	272	(97.8)	276	(98.9)	275	(99.3)	823	(98.7)
Type of Prior Immunotherapy - Peg Interferon								
Yes	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.1)
No	278	(100.0)	278	(99.6)	277	(100.0)	833	(99.9)
Type of Prior Immunotherapy - IL-2								
Yes	2	(0.7)	1	(0.4)	3	(1.1)	6	(0.7)
No	276	(99.3)	278	(99.6)	274	(98.9)	828	(99.3)

† Prior systemic therapy for advanced/metastatic disease
(Database Cutoff Date: 03MAR2015).

Numbers analysed

Table 37 summarizes the disposition of the patient populations analysed.

Table 37: Analysis populations

	Control n	MK-3475 10 mg/kg Q2W n	MK-3475 10 mg/kg Q3W n	Total n
Randomized patients (ITT population)	278	279	277	834
All Patients as Treated (APaT)	256	278	277	811
Patients with measurable disease at baseline by IRC (FAS Population by IRC)	244	236	240	720
Patients with measurable disease at baseline by investigator (FAS Population by Investigator)	277	279	277	833
(Database Cutoff Date: 03MAR2015)				

Outcomes and estimation

Primary endpoint for IA1: PFS based on IRO review per RECIST 1.1

Both pembrolizumab arms met the pre-specified criteria for a positive PFS outcome at the first interim analysis, with a HR of 0.58 for both treatment arms (individually) compared to IPI (one-sided p-value <0.00001 in both comparisons, favoring pembrolizumab) (Table 38 and Figure 25).

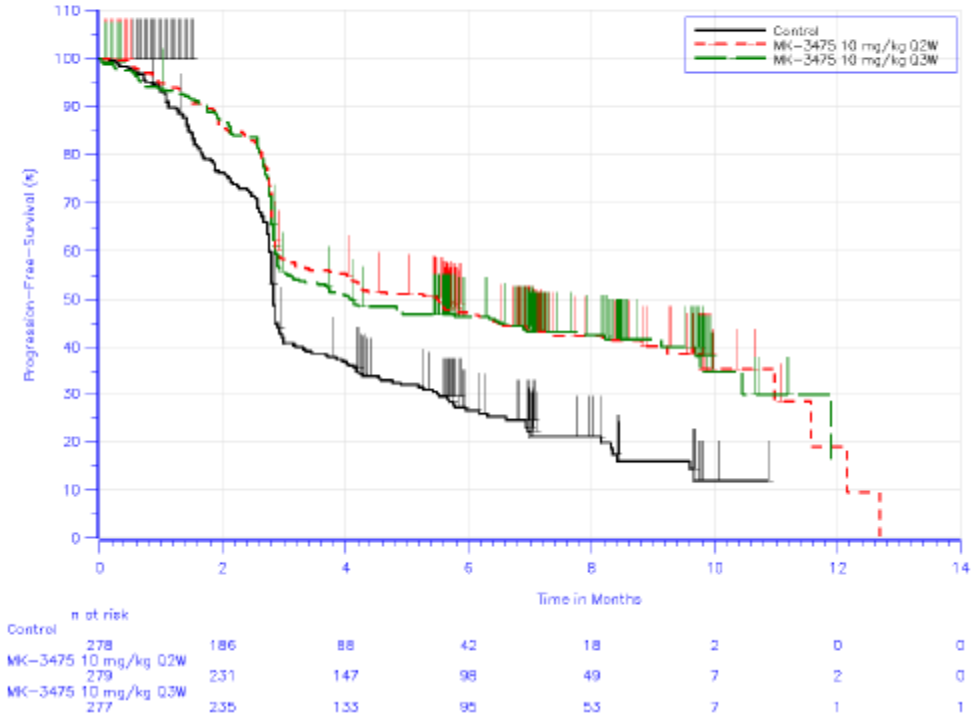
Table 38: Analysis of PFS Based on IRO Assessment (Primary Censoring Rule) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Months 6 in %[†] (95% CI)	Treatment vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Control	278	188 (67.6)	910.9	20.6	2.8 (2.8, 2.9)	26.5 (20.9, 32.4)	---	---
MK-3475 10 mg/kg Q2W	279	157 (56.3)	1334.4	11.8	5.5 (3.4, 6.9)	47.3 (41.2, 53.2)	0.58 (0.46, 0.72)	0.00000
MK-3475 10 mg/kg Q3W	277	157 (56.7)	1303.1	12.0	4.1 (2.9, 6.9)	46.4 (40.3, 52.3)	0.58 (0.47, 0.72)	0.00000
Pairwise Comparison							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶]
MK-3475 10 mg/kg Q2W vs. MK-3475 10 mg/kg Q3W							0.97 (0.77, 1.21)	0.75869

IRO: Independent Radiology plus Oncologist Review.
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).
[§] One-sided p-value based on log-rank test.
[¶] Two-sided p-value based on log-rank test.
(Database Cutoff Date: 03SEP2014)

Data Source: [16.4]

Figure 25: K-M of progression free survival based on IRO assessment (primary censoring rule) (ITT ppulation)



The primary PFS analysis was based on independent central review, applying RECIST 1.1. A supportive analysis based on investigator disease assessments, applying irRC criteria showed very similar results (HR 0.56 in both individual pembrolizumab arms over the control, one-sided p-value <0.00001).The median PFS is 7.0 months in pembrolizumab 10 mg/kg Q2W arm, 7.2 months in the pembrolizumab 10 mg/kg Q3W arm, and 3.3 months in the control arm. Six-month PFS rates are 55% for both of the pembrolizumab arms compared to 34% for the IPI arm.

Primary endpoint for IA2: OS

The primary objective of the planned second interim analysis (IA2) was to evaluate treatment effect based on OS. The total number of deaths is 289. The median OS follow-up is 13.8 months.

Table 39 and Figure 26 show the results of OS analysis for the second interim analysis.

Table 39: Analysis of OS (ITT population) – Study P006

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)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Control	278	112 (40.3)	2572.3	4.4	Not Reached (12.7, .)	74.5 (68.7, 79.4)	---	---
MK-3475 10 mg/kg Q2W	279	85 (30.5)	3152.8	2.7	Not Reached (., .)	84.8 (80.0, 88.5)	0.63 (0.47, 0.83)	0.00052
MK-3475 10 mg/kg Q3W	277	92 (33.2)	3105.7	3.0	Not Reached (., .)	87.3 (82.7, 90.7)	0.69 (0.52, 0.90)	0.00358
Pairwise Comparison							Hazard Ratio‡ (95% CI)‡	p-Value‖
MK-3475 10 mg/kg Q2W vs. MK-3475 10 mg/kg Q3W							0.91 (0.67, 1.22)	0.51319

Subjects who had survival follow-up after data cutoff date have been censored at date of data cutoff (03MAR2015)
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs. 2nd), PD-L1 status (positive vs. negative) and ECOG (0 vs. 1); if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
§ One-sided p-value based on log-rank test.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 03MAR2015)

Data Source: [16.4]

Figure 26: K-M of OS (ITT population) – Study P006

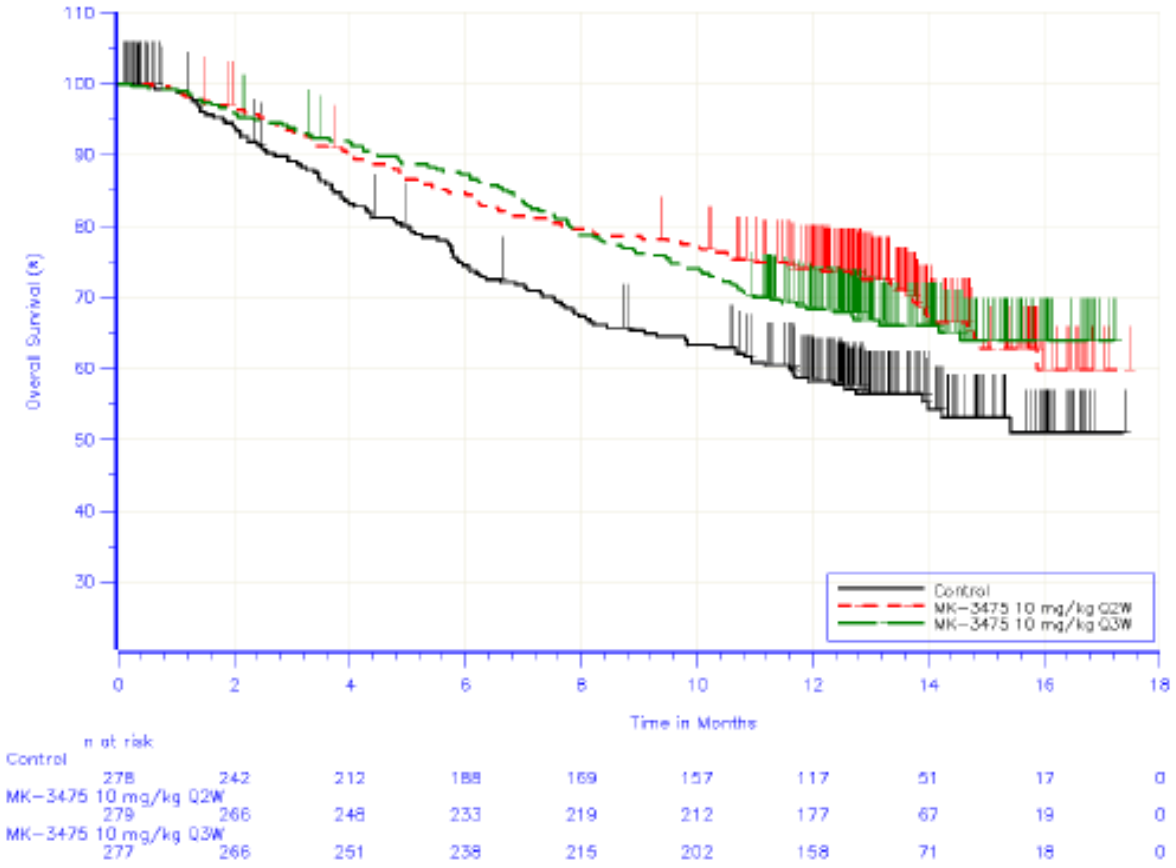


Table 40: OS rate at 4, 6, 12 and 15 months (ITT population)

Table 3 OS Rate at 4, 6, 12 and 15 Months
(ITT Population)

	Control (N=278)	MK-3475 10 mg/kg Q2W (N=279)	MK-3475 10 mg/kg Q3W (N=277)	MK-3475 combined (N=556)
OS Rate at 4 Months in % (95% CI)†	83.2 (78.0, 87.3)	90.2 (86.1, 93.2)	92.0 (88.1, 94.7)	91.1 (88.4, 93.2)
OS Rate at 6 Months in % (95% CI)†	74.5 (68.7, 79.4)	84.8 (80.0, 88.5)	87.3 (82.7, 90.7)	86.0 (82.8, 88.7)
OS Rate at 12 Months in % (95% CI)†	58.2 (51.8, 64.0)	74.1 (68.5, 78.9)	68.4 (62.5, 73.6)	71.3 (67.3, 74.9)
OS Rate at 15 Months in % (95% CI)†	53.1 (45.9, 59.7)	62.8 (54.8, 69.7)	64.0 (57.3, 69.9)	63.4 (58.2, 68.0)
Subjects who had survival follow-up after data cutoff date have been censored at date of data cutoff (03MAR2015) (Database Cutoff Date: 03MAR2015)				

Secondary endpoint: Overall response

The ORR is 33.7% in the pembrolizumab 10 mg/kg Q2W arm, 32.9% in the pembrolizumab 10 mg/kg Q3W arm, and 11.9% in the control arm based on independent radiologist plus oncologist review. Since most of the responses are ongoing in each arm the median DoR has not been reached.

Table 41: Summary of Time to Response and Response Duration (ITT Population)

	Control (N=278)	MK-3475 10 mg/kg Q2W (N=279)	MK-3475 10 mg/kg Q3W (N=277)	MK-3475 combined (N=556)
IRO Assessment per RECIST 1.1				
Number of Patients with Response[†]	33	94	91	185
Time to Response [†] (days)				
Mean (SD)	106 (36)	95 (26)	99 (35)	97 (31)
Median (Range)	87 (80-250)	86 (32-212)	85 (36-251)	85 (32-251)
Response Duration[‡] (days)				
Median (Range)[§]	Not reached (33+ - 239+)	251 (42+ - 251)	Not reached (42+ - 246+)	251 (42+ - 251)
Number of Response Ongoing (%)	29 (88)	84 (89)	88 (97)	172 (93)
IRC Assessment per RECIST 1.1				
Number of Patients with Response[†]	35	95	93	188
Time to Response [†] (days)				
Mean (SD)	105 (36)	96 (27)	98 (35)	97 (31)
Median (Range)	87 (77-250)	86 (32-212)	85 (36-251)	86 (32-251)
Response Duration[‡] (days)				
Median (Range)[§]	Not reached (33+ - 239+)	251 (42+ - 251)	Not reached (42+ - 246+)	251 (42+ - 251)
Number of Response Ongoing (%)	31 (89)	88 (93)	91 (98)	179 (95)
Investigator Assessment per irRC				
Number of Patients with Response[†]	45	104	104	208
Time to Response [†] (days)				
Mean (SD)	108 (36)	98 (30)	95 (25)	97 (28)
Median (Range)	87 (43-202)	86 (58-216)	85 (58-212)	85 (58-216)

	Control (N=278)	MK-3475 10 mg/kg Q2W (N=279)	MK-3475 10 mg/kg Q3W (N=277)	MK-3475 combined (N=556)
Response Duration[‡] (days)				
Median (Range)[§]	Not reached (33+ - 254+)	Not reached (29+ - 254+)	Not reached (42+ - 253+)	Not reached (29+ - 254+)
Number of Response Ongoing (%)	41 (91)	97 (93)	96 (92)	193 (93)

IRO: Independent Radiologist plus Oncologist Review.

IRC: Independent Review Committee.

[†] Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.

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

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

(Database Cutoff Date: 03SEP2014)

Ancillary analyses

The subgroup analyses for PFS and OS are shown in the table below.

Figure 27: Forest plot of PFS Hazard ratio by subgroup factors IRO assessment (primary censoring rule) pembrolizumab 10 mg/kg Q2W vs Control (IA1) – Study P006

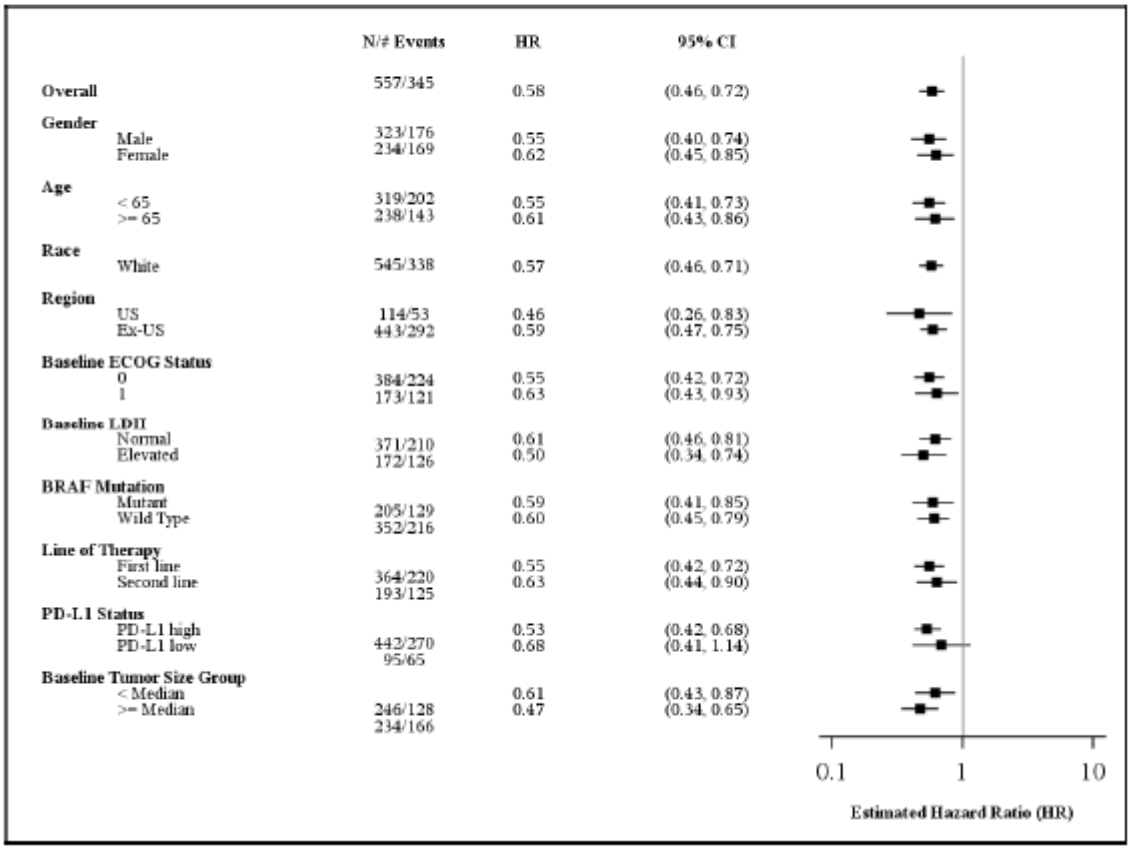


Figure 28: Forest plot of PFS Hazard ratio by subgroup factors IRO assessment (primary censoring rule) pembrolizumab 10 mg/kg Q3W vs Control (IA1) – Study P006

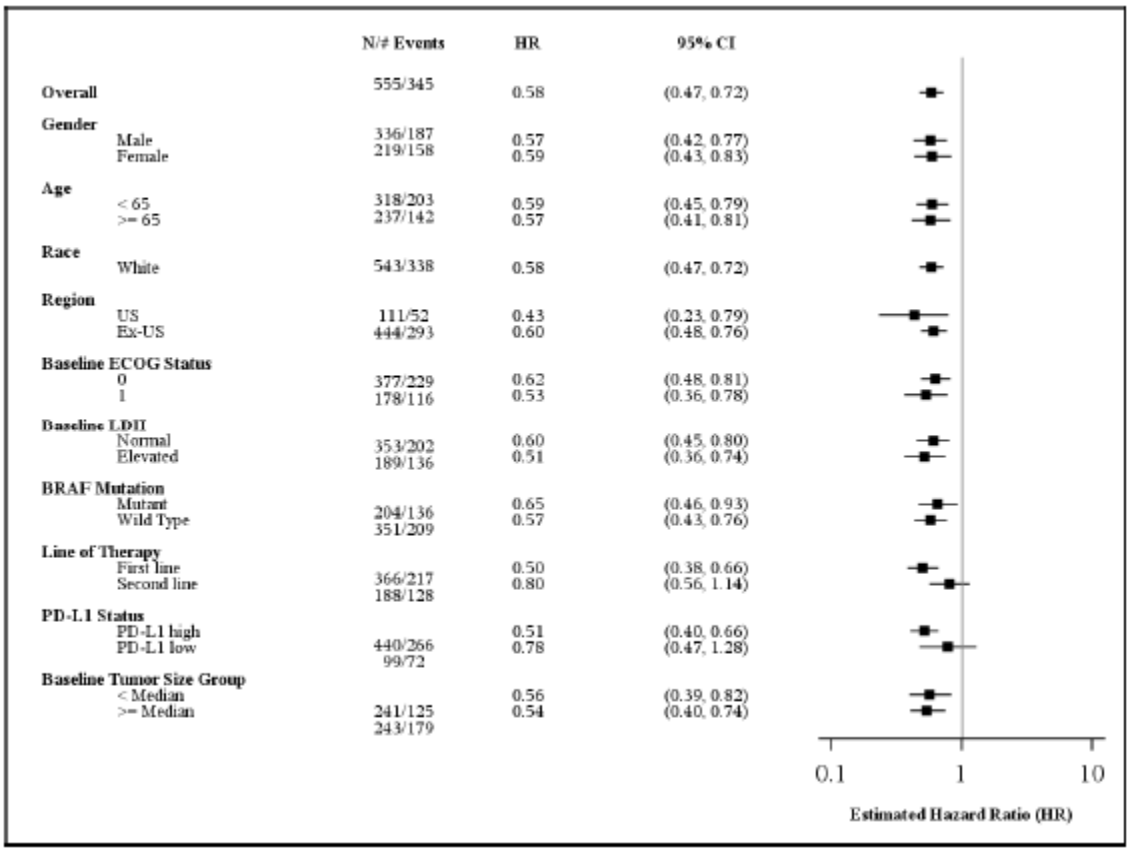


Figure 29: Forest plot of OS Hazard ratio by subgroup factors pembrolizumab 10 mg/kg Q2W vs Control (IA2) – Study P006

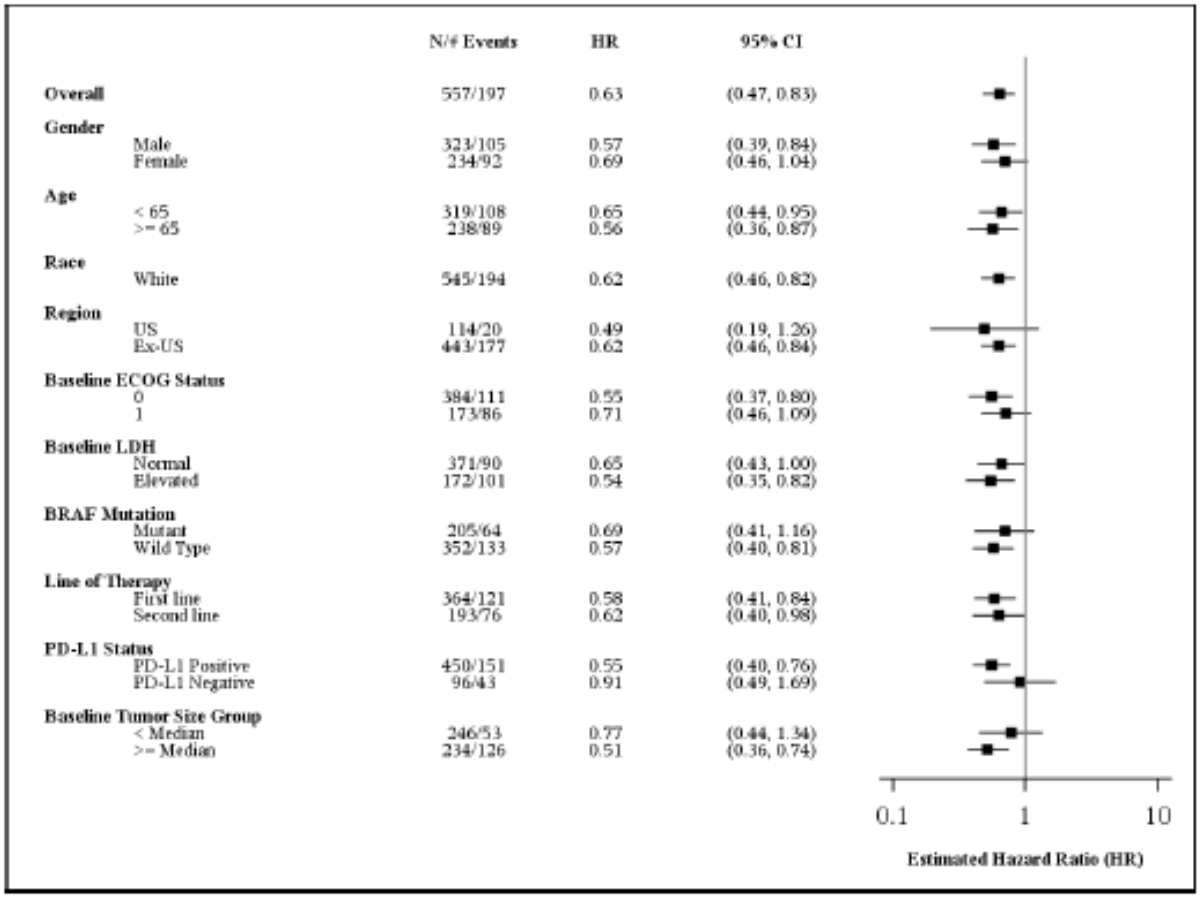
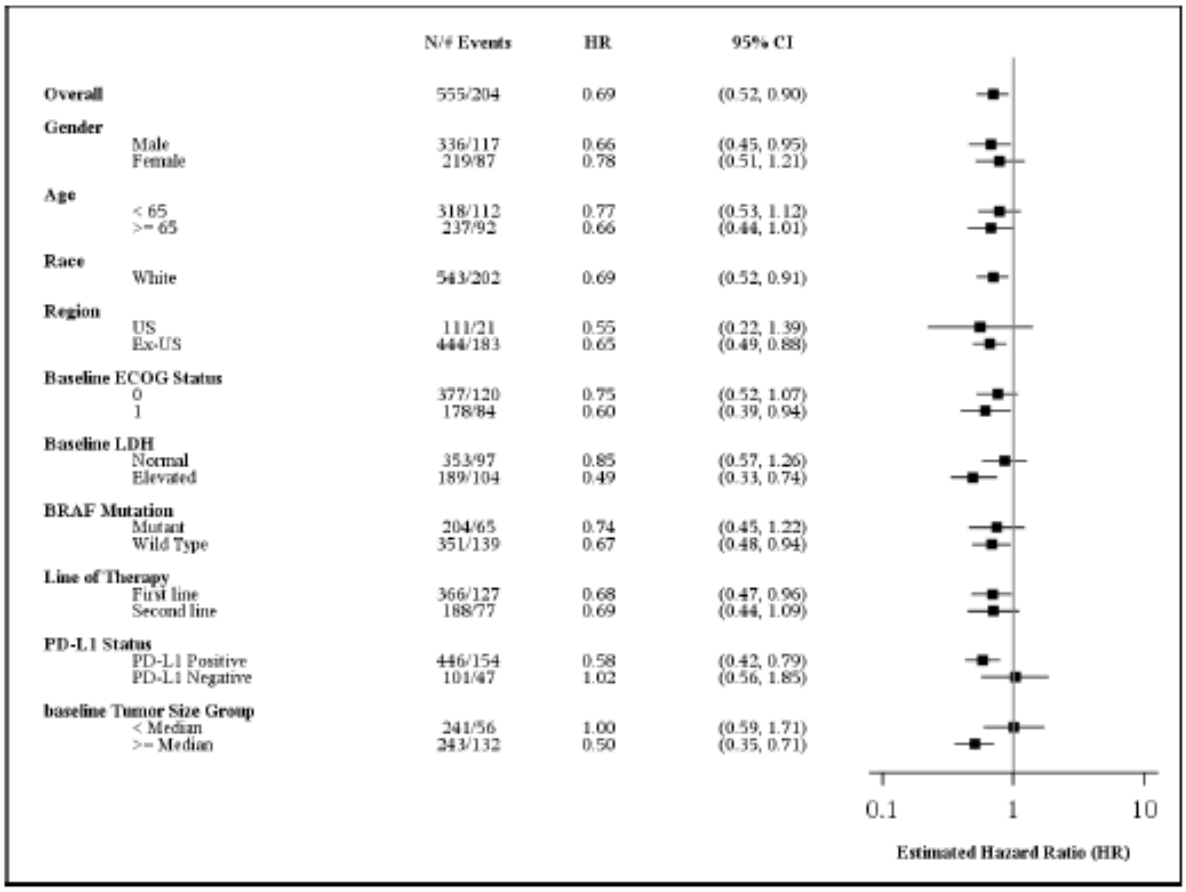


Figure 30: Forest plot of OS Hazard ratio by subgroup factors pembrolizumab 10 mg/kg Q3W vs Control (IA2) – Study P006



A supplemental subgroup analysis based on BRAF mutation status from Study P006 was submitted. Since in this study patients with BRAF V600E mutant melanoma may or may not have received a prior BRAF inhibitor, depending on the baseline presence/absence of elevated LDH, clinically significant tumour related symptoms or rapidly progressing disease in the judgment of the investigator, patients who had BRAF mutant tumours and were BRAF inhibitor naive had more favourable disease characteristics than the other subgroups. In contrast, patients with BRAF mutant tumours who had received prior BRAF inhibitor had the worst baseline characteristics.

Table 42: Analyses of patients based on BRAF mutation status and BRAF inhibitor treatment stratified by baseline characteristics

	BRAF wild-type	BRAF mutant	BRAF mutant without prior BRAF inhibitor	BRAF mutant with prior BRAF inhibitor
Received 1 line of prior therapy	24%	52%	11%	100%
ECOG 1	34%	27%	21%	34%
M1c stage	66%	65%	58%	73%
Elevated LDH	36%	26%	17%	37%
Brain metastases	8%	11%	8%	15%
Baseline tumor size, mean (mm) and median (mm)	86 61	72 54	57 51	89 62
PD-L1 negative	17%	20%	12%	28%

The subgroup analysis based on BRAF status shows a substantial benefit in terms of PFS, OS and ORR in all subgroups, with an effect slightly less evident in patients with BRAF mutant tumours who had received prior BRAF inhibitor.

Table 43: Summary of PFS in BRAF-defined subgroups

	Number of events/Number of patients		PFS HR (95% CI) pembro (both arms combined) vs. IPI	6 month PFS rate (%)	
	Pembro	IPI		Pembro	IPI
BRAF wild-type	199/355	111/170	0.57 (0.45, 0.73)	48.1	28.6
BRAF mutant	111/195	77/107	0.63 (0.47, 0.85)	44.5	22.4
BRAF mutant without prior BRAFi	51/108	39/55	0.50 (0.32, 0.77)	53.5	31.9
BRAF mutant with prior BRAFi	60/87	38/52	0.73 (0.48, 1.11)	34.2	11.6

Table 44: Summary of OS in BRAF-defined subgroups

	Number of Events/Number of Patients		OS HR (95% CI) pembro (both arms combined) vs. IPI	6 month OS rate (%)	
	Pembro	IPI		Pembro	IPI
BRAF wild-type	83/355	58/170	0.55 (0.39, 0.78)	86.0	73.3
BRAF mutant	33/195	27/107	0.63 (0.37, 1.05)	86.6	76.3
BRAF mutant without prior BRAFi	51/108	39/55	0.56 (0.22, 1.46)	93.5	84.6
BRAF mutant with prior BRAFi	24/87	18/52	0.67 (0.36, 1.24)	78.1	66.7

Table 45: Summary of ORR in BRAF-defined subgroups

	IPI			Pembrolizumab (both arms combined)			p-value*
	Number of objective responses/ number of patients	ORR (%)	95% CI	Number of objective responses/ number of patients	ORR (%)	95% CI	
BRAF wild-type	22/170	12.9	(8.3, 18.9)	121/355	34.1	(29.2, 39.3)	0.01268
BRAF mutant	10/107	9.3	(4.6, 16.5)	62/195	31.8	(25.3, 38.8)	0.00096
BRAF mutant without prior BRAFi	7/55	12.7	(5.3, 24.5)	44/108	40.7	(31.4, 50.6)	0.00527
BRAF mutant – with prior BRAFi	3/52	5.8	(1.2, 15.9)	18/87	20.7	(12.7, 30.7)	0.01935

*p-value for comparison of pembrolizumab arms combined vs. IPI arm based on Miettinen and Nurminen method

Table 46: Summary of efficacy for trial P006

Title: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma.			
Study identifier	P006		
Design	Randomized (1:1:1), controlled, phase III, open-label, three-arm pivotal study of two dosing regimens of intravenous (IV) MK-3475 versus IPI in patients with unresectable or metastatic MEL who have not received IPI treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable not applicable
Hypothesis	Superiority to Ipilimumab		
Treatments groups	Pembrolizumab		IV infusion at a dose of 10 mg/kg given once every 2 weeks Patients enrolled/treated:279/278
	Pembrolizumab		IV infusion at a dose of 10 mg/kg given once every 3 weeks Patients enrolled/treated:277/277
	Ipilimumab		3 mg/kg as IV infusion once every 3 weeks for a total of 4 doses Patients enrolled/treated:278/256
Endpoints and definitions	Co-Primary endpoint	PFS	time from randomization to the first documented disease progression (based on assessment from a central imaging vendor using the RECIST 1.1 criteria) or death due to any cause, whichever occurs first.
	Co-Primary endpoint	OS	time from randomization to death due to any cause.
	Secondary endpoint	ORR	proportion of patients who had a complete response (CR) or partial response (PR)based on confirmed assessments using the RECIST 1.1 criteria.
Database lock	03 September 2014		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab 10 mg/kg Q2W	Pembrolizumab 10 mg/kg Q3W	Ipilimumab (control)
	Number of subject	279	277	278
	Co-Primary endpoints			
	PFS (IRO RECIST 1.1) N. with events (%)	157 (56.3)	157 (56.7)	188 (67.6)
	Median PFS (months) (95% CI)	5.5 (3.4,6.9)	4.1 (2.9, 6.9)	2.8 (2.8, 2.9)
	HR (Hazard Ratio treatment vs control) (95% CI)	0.58 (0.46,0.72)	0.58 (0.47, 072)	--
	p-value (stratified Log-Rank Test)	<0.00001	<0.00001	--
	OS (IRO RECIST 1.1) N. with events (%)	<point estimate>	<point estimate>	<point estimate>
	Median OS (months) (95% CI)	Not reached	Not reached	Not reached
	HR (Hazard Ratio treatment vs control) (95% CI)	0.63 (0.47, 0.83)	0.69 (0.52, 0.90)	--
	p-value (stratified Log-Rank Test)	0.00132	0.00031	--
	Secondary endpoints			
	Number of Responder Overall Response Rate (%) (95% CI)	94 33.7 (28.2, 39.6)	91 32.9 (27.4, 38.7)	33 11.9 (8.3, 16.3)
	Difference % vs control (95% CI)	16.1 (7.8, 24.5)	17.2 (9.5, 25.6)	--

	p-value (stratified on Miettinen & Nurminen method)	0.00013	0.00002	--
Notes	Based on the results of the second interim analysis, the independent Data Monitoring Committee recommended the study results be unblinded and pembrolizumab made available to patients on the control arm based.			

Clinical studies in special populations

No dedicated studies in special population have been conducted.
Overall, 492 ≥65 years patients (41%) have been included in the studies P001 and P002. More than 10% of patients enrolled were ≥75 years old.

Analysis performed across trials (pooled analyses and meta-analysis)
Various pooled analyses across cohorts with all patients combined or segregated by prior ipilimumab exposure were performed.

An integrated efficacy analysis of study P001 Part B2 and study P002 have been conducted, considering the similar patients population (IPI-refractory melanoma patients) and the same pembrolizumab regimens compared. In both studies, patients were required to have confirmed PD in the absence of rapid clinical progression, with progression first documented within 6 months (24 weeks) of the last dose of IPI (minimum of 2 doses). In addition, subjects with BRAF V600 mutant melanoma must have had a prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors. Both Part B2 of P001 and P002 compared 2 mg/kg Q3W and 10 mg/kg Q3W in a randomized fashion.

The overall efficacy profile is consistent between the two trials:

Table 47: Summary of Key Efficacy Endpoints Comparing P001 Part B2 and P002 Subjects Treated with Pembrolizumab

	P001 Part B2[3] (2 mg/kg Q3W + 10 mg/kg Q3W Combined)		P002[3] Subjects Treated with Pembrolizumab (2 mg/kg Q3W + 10 mg/kg Q3W Combined)	P001 Part B2 + P002 Combined Subjects Treated with Pembrolizumab[3]
Number of Patients	173		361	534
BOR Analysis (IRO per RECIST 1.1)				
ORR (95% CI)	24.9% (18.6, 32.0)		23.3% (19.0, 28.0)	23.8% (20.2, 27.6)
Response Duration[1] (IRO per RECIST 1.1)				
Median in weeks	Not Reached		Not Reached	Not Reached
% of non-progressing subjects (among responders)	91		89	90
Median Time to Response in Weeks (range)	12 (7-48)		13 (12-30)	13 (7-48)
PFS (IRO per RECIST 1.1)				
	2 mg/kg Q3W (N=89)	10 mg/kg Q3W (N=84)		
Median in months (95% CI)	4.9 (2.8, 8.3)	3.2 (2.8, 5.5)	2.9 (2.8, 3.6)	3.0 (2.9, 4.0)
PFS rate at 6 months (%)	43.1	34.9	36.0	37.0
PFS rate at 12 months (%)	34.0	29.9	--	26.4%
OS				
	2 mg/kg Q3W (N=89)	10 mg/kg Q3W (N=84)		
Median in Months (95% CI)	Not Reached (10.9, -)	18.3 (11.4, -)	12.5 (10.8, -)	18.3 (11.5, -)
OS Rate at 6 months (%)	--	--	74.2	75.5
OS Rate at 12 months (%)	59.6	61.5	--	54.8
OS Rate at 18 months (%)	56.8	61.5	--	--

[1] Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
[2] APaT Population for P001, ITT Population for P002
[3] Efficacy Analysis Population
n/a= not available
Data Cutoff Date P001: 18-Apr-2014
Data Cutoff Date P002: 12-May-2014

Confirmed responses (CR + PR) were reported in 22% (95% CI: 18-28%) of patients who were treated at 2 mg/kg Q3W compared to 25% (95% CI: 20-31%) of subjects who were treated at 10 mg/kg Q3W, including complete responses in 3% (95% CI: 1-5%) and 4% (95% CI: 2-7%) at 2 mg/kg Q3W and 10 mg/kg Q3W, respectively. In both treatment arms, approximately 43% of patients achieved disease control.

The median response duration has not been reached at the time of the analysis and ranged from 5+ to 62+ weeks.

At the time of this analysis, 70% of the subjects in the 2 mg/kg Q3W cohort and 69% of the subjects in the 10 mg/kg Q3W cohort had a PFS event (progression by independent central review or death). The median PFS was 3 months for both the 2 mg/kg Q3W and 10 mg/kg Q3W treatment groups. The 6-month progression-free rate was 37% for both the 2 mg/kg Q3W group and the 10 mg/kg Q3W group.

The median OS was not reached for the 2 mg/kg Q3W group and was 18.3 months for the 10 mg/kg Q3W group and the lower bound of the 95% CI was 10.9 and 11.5 for the 2 mg/kg Q3W group and the 10 mg/kg Q3W group, respectively, and the upper bound of the CI was not estimable for either group. The OS rate at 6 months was comparable in both treatment groups with 75% for subjects treated 2 mg/kg Q2W and 76% for subjects treated 10 mg/kg Q3W. The 12-month OS rate was comparable for the 2 dose groups, with 53% alive in the 2 mg/kg Q2W group vs. 56% alive in for the 10 mg/kg Q3W group.

Analysis of PD-L1 Immunohistochemistry in melanoma patients from P001 (Parts B1+B2+D)

The relationship between tumour PD-L1 expression via immunohistochemistry (IHC) and the anti-tumour activity of pembrolizumab was evaluated to examine the potential usefulness of this assay to identify patients responsive to pembrolizumab treatment.

PD-L1 expression was scored by board-certified pathologists. The Allred Proportion Score (APS) was chosen because it is basic (a six-point scale), it is familiar to pathologists, and has been shown to be a highly reproducible method of scoring hormone receptors in breast cancer. The scoring method for PD-L1 omits an intensity score for simplicity. The cut-off of APS=2 was selected. The proposed cut-off of APS=2 was associated with a positive predictive value (PPV) of 49.4% and a negative predictive value (NPV) of 86.7%.

The following table displays the breakdown of confirmed responses by APS score:

	APS Score						
	0	1	2	3	4	5	All
Responder	2	2	7	14	11	9	45
Non-responder	16	10	11	18	5	8	68
% Responders and 95% CI	11.1 (1.4,34.7)	16.7 (2.1,48.4)	38.9 (17.3,64.3)	43.8 (26.4,62.3)	68.8 (41.3,89.0)	52.9 (27.8,77.0)	39.8 (30.7,49.5)

APS Cutoff	Prevalence ≥ Cutoff	PPV	NPV
1	95/113 = 84.1%	43/95 = 45.3%	16/18 = 88.9%
2	83/113 = 73.5%	41/83 = 49.4%	26/30 = 86.7%
3	65/113 = 57.5%	34/65 = 52.3%	37/48 = 77.1%
4	33/113 = 29.2%	20/33 = 60.6%	55/80 = 68.8%

PD-L1 Subgroup Analysis (Positive vs. Negative)

Across the 534 IPI-refractory subjects in P001 and P002 combined who were treated with pembrolizumab, 410 (77%) subjects were evaluable for PD-L1 expression, including 295 (72%) subjects PD-L1 positive and 115 (28%) subjects are PD-L1 negative as defined by the assay and scoring methods used for these studies.

The ORR was 24% (95% CI: 20-28%) in the 410 PD-L1 evaluable subjects, slightly higher in PD-L1 positive subjects (28%, 95% CI: 23-33%), whereas was lower in PD-L1 negative patients (13%, 95% CI 8-21%). In responding subjects, the median duration of response was not reached, regardless of PD-L1 status, and 91% (PD-L1 positive) to 80% (PD-L1 negative) were non-progressing at the time of the analysis. The median PFS was 4.2 months in PD-L1 positive and 2.8 months in PD-L1 negative patients. In PD-L1 negative patients, the 6-month and 12 month PFS rate was 25% and 14%, respectively. Median OS is currently 18.5 months for PD-L1 positive and approximately 11 months for PD-L1 negative patients.

Table 48: Summary of Key Efficacy Endpoints Comparing PD-L1 Status (Positive vs. Negative)(P001 Part B2 and P002 Subjects Treated with pembrolizumab)

	PD-L1 Positive	PD-L1 Negative	Total (PD-L1 Evaluable)
Number of Subjects (% out of PD-L1 evaluable)	295 (72.0)	115 (28.0)	410 (100)
BOR Analysis (IRO per RECIST 1.1)			
Overall Response – CR + PR (95% CI)	27.8% (22.8, 33.3)	13.0% (7.5, 20.6)	23.7 (19.6, 28.1)
Disease Control – CR + PR + SD + NN (95% CI)	47.5% (41.6, 53.3)	27.8% (19.9, 37.0)	42.0 (37.1, 46.9)
Progression-Free Survival (IRO per RECIST 1.1)			
Median in months (95% CI)	4.2 (2.9, 5.5)	2.8 (2.8, 2.8)	2.9 (2.8, 3.9)
6-month PFS rate	40.6%	24.5%	36.0%
12-month PFS rate	29.4%	13.6%	24.8%
Overall Survival			
Median in months (95% CI)	18.5 (11.5, -)	10.8 (6.9, -)	18.5 (11.0, -)
6-month OS rate	79.8%	64.2%	75.4%
12-month OS rate	56.3%	45.4%	53.3%
Response Duration-Confirmed Response (IRO per RECIST 1.1)			
Median in weeks (range)[1]	Not Reached (5+ - 62+)	Not Reached (6+ - 48+)	Not Reached (5+ - 62+)
% of non-progressing subjects (among responders)	91%	80%	90%
Median Time to Response in Weeks (range)	13 (11-48)	13 (12-36)	13 (11-48)

MK-3475, P001 Database Cutoff Date: 18-Apr-2014
MK-3475, P002 Database Cutoff Date: 12-May-2014
1 "+" indicates non-PD at the last assessment (censored)
NN = NonCR/NonPD

BRAF Mutant vs. Wild-Type in IPI-Refractory Subjects in P001 Part B2 and P002

Key efficacy endpoints for pembrolizumab treated subjects (both dose levels combined) in BRAF mutant and BRAF wild-type subjects are shown below:

Table 49: Summary of Key Efficacy Endpoints Comparing BRAF Mutant vs. BRAF Wild-Type(P001 Part B2 and P002 Subjects Treated with pembrolizumab)

	BRAF Mutant	BRAF Wild-Type	Total
Number of Subjects	114	420	534
BOR Analysis (IRO per RECIST 1.1)			
Overall Response – CR + PR (95% CI)	12.3% (6.9, 19.7)	26.9% (22.7, 31.4)	23.8 (20.2, 27.6)
Disease Control – CR + PR + SD + NN (95% CI)	25.4% (17.7, 34.4)	47.6% (42.8, 52.5)	42.9 (38.6, 47.2)
Progression-Free Survival (IRO per RECIST 1.1)			
Median in months (95% CI)	2.8 (2.8, 2.9)	4.1 (2.9, 5.5)	3.0 (2.9, 4.0)
6-month PFS rate	21.8%	41.0%	37.0%
12-month PFS rate	9.4%	31.2%	26.4%
Overall Survival			
Median in months (95% CI)	11.0 (7.2, -)	18.3 (12.7, -)	18.3 (11.5, -)
6-month OS rate	63.7%	78.7%	75.5%
12-month OS rate	46.5%	57.0%	54.8%
Response Duration-Confirmed Response (IRO per RECIST 1.1)			
Median in weeks (range)[1]	36 (6+ - 60+)	Not Reached (5+ - 62+)	Not Reached (5+ - 62+)
% of non-progressing subjects (among responders)	64%	93%	90%
Median Time to Response in Weeks (range)	12 (12-36)	13 (7-48)	13 (7-48)

MK-3475, P001 Database Cutoff Date: 18-Apr-2014
MK-3475, P002 Database Cutoff Date: 12-May-2014
1 "+" indicates non-PD at the last assessment (censored)
NN = NonCR/NonPD

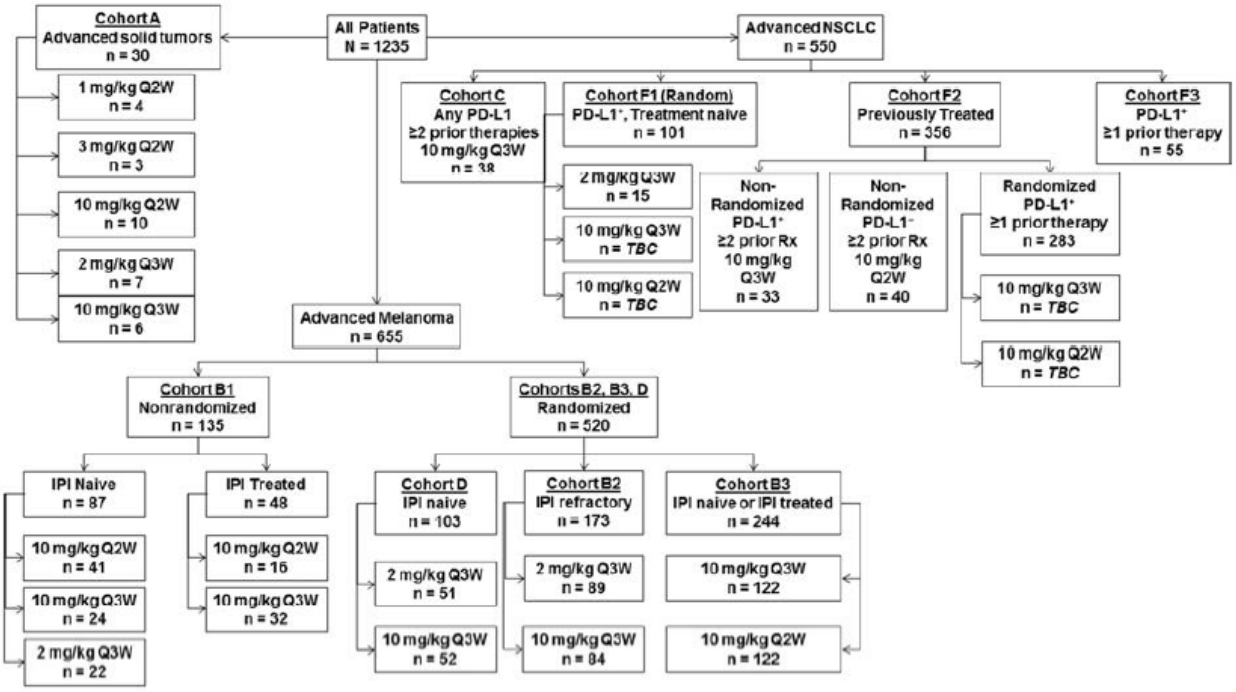
Supportive study(ies)

Study P001: "Phase I study of single agent MK-3475 in patients with progressive locally advanced or metastatic carcinoma, melanoma, and Non-Small Cell Lung Carcinoma"

Study P001 was a multi-center, open-label, first in human Phase 1 trial in subjects with locally advanced or metastatic melanoma, NSCLC, or advanced solid tumor. The trial was initially designed as a standard dose escalation study, now called Part A, in which several melanoma patients were enrolled and had objective responses. Therefore, the study was expanded to evaluate efficacy in melanoma in Part B (now Part B1). Through a series of amendments, P001 evolved into 4 Phase 2-like melanoma sub-studies, known as Parts B1, B2, B3, and D. In addition, study P001 was further expanded in Parts C and F to evaluate the activity of pembrolizumab in NSCLC.

All cohorts of study P001 are depicted in the following Figure:

Figure 31: Trial Design P001



Part B1 was the initial evaluation of the efficacy of pembrolizumab in subjects with advanced melanoma, including subjects who were naïve to IPI or who had been previously treated with IPI. In Cohort B2, eligibility criteria required the enrolment of patient that were refractory ipilimumab (progression documented in two separate assessment and following at least 2 doses of IPI at a minimum dose of 3 mg/kg and within 6 months of the last dose of IPI) and excluded patients that were potentially delayed IPI responders. Furthermore, patients with known BRAF V600E mutations were required to have received a prior BRAF and/or MEK inhibitor, and could have received an unlimited number of prior therapies. Part B3 enrolled both IPI-naïve and IPI-exposed (treated or refractory) patients. Eligibility criteria in part D allowed the enrolment of IPI-naïve patients that may have received up to 2 prior lines of treatment. Of note, patients with known BRAF V600E mutation may or may have not received prior treatment with BRAF/MEK inhibitors.

Across the cohorts, pembrolizumab has been administered at 3 different dosing regimens: 2 mg/kg Q3W or 10 mg/kg Q2W or Q3W in Part B1; 2 mg/kg or 10 mg/kg every 3 weeks in both Cohorts B2 and D; 10 mg/kg Q2W or 10 mg/kg Q3W in Part B3.

The correlation of the extent of tumour response with the degree of biomarker positivity in IPI-naïve patients treated with pembrolizumab, and the anti-tumour activity per RECIST 1.1 of pembrolizumab in IPI-refractory melanoma patients both unselected and with PD-L1 expressing tumours were also considered for evaluation.

Baseline characteristics

Part B1 (IPI-naïve and IPI-treated)

Hundred-thirty five patients (IPI-naïve and IPI-treated) were enrolled in Part B1 (22 patients at 2 mg/kg Q3W, 56 patients at 10 mg/kg Q3W, and 57 patients at 10 mg/kg Q2W). In the total B1

population, 59% of patients were male and 46% were ≥65 years old. All but 2 patients were white and 73% of patients were ECOG PS 0. A majority of the patients had had no history of brain metastasis (92%) and 22% harbored BRAF V600 mutations. 69% of patients had elevated baseline lactate dehydrogenase (LDH) and in 72% the stage of disease was M1c. In addition, 50 patients had at least 2 prior systemic therapies. In the total population, 27% had been previously treated with an immunotherapy (excluding IPI), 34% had previously received chemotherapy, and only 10% had been previously treated with a BRAF/MEK inhibitor (vemurafenib, dabrafenib, or trametinib). There was no notable difference in prior therapy between arms.

Part B2 (IPI-Refractory)

Hundred-seventy three IPI-refractory patients were randomized in this Cohort (89 subjects at 2 mg/kg Q3W and 84 subjects at 10 mg/kg Q3W). In this Part, 60% of subjects were male and 36% were 65 years old or older. All but 5 subjects were white, and 67% of patients were ECOG PS 0. Most of patients had no history of brain metastasis (91%) and 17% harbored BRAF V600 mutations. Subjects in Part B2 had significant tumor burden at baseline evidenced by 42% with elevated baseline LDH and 82% with stage M1c melanoma. Approximately 73% (126/173) of subjects had at least 2 prior systemic therapies; 32% had been previously treated with an immunotherapy (excluding IPI), 47% had previously received chemotherapy, and the remainder (21%) had other (unclassified) therapy. A previous treatment with a BRAF/MEK inhibitor is registered in around 20%.

Part B3 (IPI-naïve and IPI-exposed)

Two-hundred forty four patients (IPI-naïve and IPI-exposed) enrolled (121 patients at 10 mg/kg Q3W and 123 patients at 10 mg/kg Q2W).In this Cohort, 65% of subjects were male, and 40% were ≥65 years old. All but 8 subjects were white and 59% of subjects were ECOG PS 0. In this Part, nearly a quarter of the subjects (24%) harbored BRAF V600 mutations, 41 % had elevated baseline LDH and 80% stage M1c melanoma. In addition, 91% of subjects had no history of brain metastasis and 93 of the 244 subjects (38%) had at least 2 prior systemic therapies.

There were 123 subjects naïve to IPI, while 121 subjects received prior IPI (IPI-treated or IPI-refractory). In the total population, 25% had been previously treated with an immunotherapy and 28% had previously received chemotherapy, including 18% previously treated with a BRAF/MEK inhibitor. The treatment arms were generally comparable although a higher percentage of subjects in the 10 mg/kg Q3W arm previously treated with a BRAF/MEK inhibitor (22% vs 14%). Overall, 59 (24%) subjects had BRAF mutant melanoma, and 44 (18%) were previously treated with an approved BRAF/MEK inhibitor (vemurafenib, dabrafenib, or trametinib) prior to study entry.

Part D (IPI-Naïve)

Hundred-three IPI-naïve patients were enrolled (51 patients at 2 mg/kg Q3W and 52 patients at 10 mg/kg Q3W). In this Part D, 61% of subjects were male and 36% were ≥65 years old. All but 4 subjects were white and 85% of subjects were ECOG PS 0. A majority of the patients had no history of brain metastasis (93%) and 35% harbored BRAF V600 mutations. Baseline LDH was elevated in 35% of patients and stage M1c melanoma was registered in 72%. In the total population, previous treatment was immunotherapy in 20%, chemotherapy in 20%, and BRAF/MEK inhibitor (vemurafenib, dabrafenib, or trametinib) in 18%. The treatment arms were generally comparable with regard to prior therapy, with the exception of a higher percentage of previously treated subjects in the 2 mg/kg Q3W arm (65%) compared to the 10 mg/kg Q3W arm (52%).

Results

The primary efficacy endpoint of this study is ORR by independent central review (IRO) using RECIST 1.1. The primary method of analysis includes review of images by independent radiologists and review of objective clinical data (e.g. qualitative skin photographs, biopsy reports from suspicious lesions if performed) by independent oncologists when such data were available, referred to as the IRO assessment. In P001, subjects were managed by irRC based on Investigator assessment, and independent central review was also performed based on irRC.

The primary analyses are based on the FAS population including all patients who received at least one dose of study treatment and with measurable disease as defined by independent central review. Therefore, due to discrepancies between investigator and central reviewers the FAS population did not include all treated patients. The response rate has also been analysed in the APaT population (All Patients as Treated, consisting in all patients who received at least 1 dose of study treatment).

A summary of ORR based on different methods of analysis across all doses is shown below:

Table 50: Comparison of Overall Response Rate RECIST 1.1 by IRO vs. irRC by IRO vs. INV by irRC (FAS and APaT Population) – All Dose Levels

	IRO Assessment per RECIST 1.1 FAS Population n (total) % (95% CI)			IRO Assessment per irRC FAS Population n (total) % (95% CI)			INV Assessment per irRC APaT Population n (total) % (95% CI)		
Part B1 (IPI-naïve+IPI-treated)	2 mg/kg Q3W 8 (19) 42.1 (20.3, 66.5)	10 mg/kg Q3W 15 (43) 34.9 (21.0, 50.9)	10 mg/kg Q2W 23 (51) 45.1 (31.1, 59.7)	2 mg/kg Q3W 7 (19) 36.8 (16.3, 61.6)	10 mg/kg Q3W 16 (43) 37.2 (23.0, 53.3)	10 mg/kg Q2W 24 (51) 47.1 (32.9, 61.5)	2 mg/kg Q3W 8 (22) 36.4 (17.2, 59.3)	10 mg/kg Q3W 20 (56) 35.7 (23.4, 49.6)	10 mg/kg Q2W 34 (57) 59.6 (45.8, 72.4)
Part B2 (IPI – refractory)	2 mg/kg Q3W 22 (79) 27.8 (18.3, 39.1)		10 mg/kg Q3W 21 (76) 27.6 (18.0, 39.1)	2 mg/kg Q3W 24 (79) 30.4 (20.5, 41.8)		10 mg/kg Q3W 24 (76) 31.6 (21.4, 43.3)	2 mg/kg Q3W 26 (89) 29.2 (20.1, 39.8)		10 mg/kg Q3W 30 (84) 35.7 (25.6, 46.9)
Part D (IPI-naïve)	2 mg/kg Q3W 15 (45) 33.3 (20.0, 49.0)		10 mg/kg Q3W 18 (47) 38.3 (24.5, 53.6)	2 mg/kg Q3W 15 (45) 33.3 (20.0, 49.0)		10 mg/kg Q3W 18 (47) 38.3 (24.5, 53.6)	2 mg/kg Q3W 21 (51) 41.2 (27.6, 55.8)		10 mg/kg Q3W 22 (52) 42.3 (28.7, 56.8)
Part B3 (IPI Naïve+ IPI exposed)	10 mg/kg Q3W 33 (107) 30.8 (22.3, 40.5)		10 mg/kg Q2W 41 (117) 35.0 (26.5, 44.4)	10 mg/kg Q3W 35 (107) 32.7 (24.0, 42.5)		10 mg/kg Q2W 42 (117) 35.9 (27.2 45.3)	10 mg/kg Q3W 44 (121) 36.4 (27.8, 45.6)		10 mg/kg Q2W 44 (123) 35.8 (27.3, 44.9)
Part B3 (IPI-naïve)	10 mg/kg Q3W 20 (57) 35.1 (22.9, 48.9)		10 mg/kg Q2W 21(56) 37.5 (24.9, 51.5)	10 mg/kg Q3W 20 (57) 35.1 (22.9, 48.9)		10 mg/kg Q2W 22 (56) 39.3 (26.5, 53.2)	10 mg/kg Q3W 28 (65) 43.1 (30.8,56.0)		10 mg/kg Q2W 24 (58) 41.4 (28.6, 55.1)
Part B3 (IPI-exposed)	10 mg/kg Q3W 13 (50) 26.0 (14.6, 40.3)		10 mg/kg Q2W 20 (61) 32.8 (21.3, 46.0)	10 mg/kg Q3W 15 (50) 30.0 (17.9, 44.6)		10 mg/kg Q2W 20 (61) 32.8 (21.3, 46.0)	10 mg/kg Q3W 16 (56) 28.6 (17.3, 42.2)		10 mg/kg Q2W 20 (65) 30.8 (19.9, 43.4)
Part B1+B2+D Pooled (IPI-naïve+IPI-treated)	2 mg/kg Q3W 45 (143) 31.5 (24.0, 39.8)	10 mg/kg Q3W 54 (166) 32.5 (25.5, 40.2)	10 mg/kg Q2W 23 (51) 45.1 (31.1, 59.7)	2 mg/kg Q3W 46 (143) 32.2 (24.6, 40.5)	10 mg/kg Q3W 58 (166) 34.9 (27.7, 42.7)	10 mg/kg Q2W 24 (51) 47.1 (32.9, 61.5)	2 mg/kg Q3W 55 (162) 34.0 (26.7, 41.8)	10 mg/kg Q3W 72 (192) 37.5 (30.6, 44.8)	10 mg/kg Q2W 34 (57) 59.6 (45.8, 72.4)

* FAS population by investigator assessment is the same as the APaT population, indicating that all patients treated fulfilled the eligibility criterion of having at least one measurable lesion according to investigator assessment.

Data Cutoff Date 18-Apr-2014

Data Source: [Table 11-1, Table 11-3, Table 11-5, Table 11-7, Table 11-9, Table 11-11, Table 11-13, Table 14-14, Table 14-16, Table 14-18, Table 14-20, Table 14-22, Table 14-24, Table 14-26, Table 14-28, Table 14-30, Table 14-32, Table 14-34, Table 14-36, Table 14-38]

Duration of Objective responses

The 135 patients in Part B1 were followed for the longest duration of time, having been enrolled between 1-Dec-2012 and 6-Sep-2012, and thus had at least 18 months of follow-up data at the time of the data cutoff for this analysis (18-Apr-2014). There were 51 patients with a confirmed objective response across all dose levels tested, and the median time to response was 13 weeks (range 10-84), which coincides primarily with the protocol-determined time of disease response assessment. The

median response duration has not been reached for the 2 mg/kg Q3W or 10 mg/kg Q2W cohorts, while was 93 weeks for the 10 mg/kg Q3W arm. Response durations ranged from 11+ to 98+ weeks. Among the 51 responses, 37 (73%) patients have non-PD by IRO.

In Part B2, patients were enrolled between 24-Aug-2012 and 5-Apr-2013, and thus had at least 12 months of follow-up at the time of the analysis. There were a total of 43 confirmed objective responses, with duration ranging from 12+ to 62+ weeks at the time of the analysis. The median time to response was 12 weeks (range 7-48), which coincides primarily with the protocol-determined time of disease response assessment. The median response duration was not reached. Similar duration of response was reported with pembrolizumab 2 mg/kg Q3W and pembrolizumab 10 mg/kg Q3W. Over 90% of patients (91% for 2 mg/kg Q3W and 90% for 10 mg/kg Q3W) had no disease progression.

In Part B3 patients were enrolled between 18-Apr-2013 and 13-Sep-2013, and thus had approximately 6 months of follow-up. The median time to response was 12 weeks (range 11-42). There were 74 patients with a confirmed objective response across all dose levels tested. The median response duration has not been reached for the cohort as a whole (range: 6+ to 36+ weeks), nor for any individual pembrolizumab dose. 91% of patients had non-PD by independent central review.

Patients in Part D were enrolled between 7-Sep-2012 and 11-Jan-2013, and thus had at least 15 months of follow-up. The median time to response was 12 weeks (range 11-39) and response duration ranged from 6+ to 61+ weeks across both arms. 83% of patients had non-PD at the time of the analysis.

Progression Free Survival

PFS was estimated by Kaplan-Meier methodology, and the primary method of analysis was based on RECIST 1.1 measurements by IRO assessments in the APaT population.

In Part B1, the median PFS was 13.6 months for the 2 mg/kg Q3W treatment arm, 5.5 months for the 10 mg/kg Q3W treatment arm, 8.8 months for 10 mg/kg Q2W treatment arm, and 7.2 months for all patients regardless of dose schedule. These results compare with those previously reported in which the median PFS was 72 weeks (16.6 months) for the 2 mg/kg Q3W treatment arm, 24 weeks (5.5 months) for the 10 mg/kg Q3W treatment arm, 50 weeks (11.5 months) for 10 mg/kg Q2W treatment arm, and 31 weeks (7.1 months) for all patients in the B1 cohort.

In Cohort B2, the median PFS was 4.9 months for the 2 mg/kg Q3W treatment arm and 3.2 months for the 10 mg/kg Q3W treatment arm (HR 0.90, p=0.6).

In Part B3, the median PFS was 3.0 months for the 10 mg/kg Q3W and 5.2 months for the 10 mg/kg Q2W treatment arm (HR = 1.19, p=0.3).

In Cohort D, the median PFS was 5.5 months for the 2 mg/kg Q3W and 4.2 months for the 10 mg/kg Q3W treatment arm (HR = 0.87, p=0.5).

A comparison of PFS as determined by IRO per RECIST 1.1 and IRO per irRC is displayed in the following Table 51.

Table 51: Comparison of PFS RECIST 1.1 by IRO vs. irRC by IRO vs. INV by irRC (APaT) – All Dose Levels

	IRO Assessment per RECIST 1.1 Number of Events, n (N) Median PFS, months (95% CI)			IRO Assessment per irRC Number of Events, n (N) Median PFS, months (95% CI)			INV Assessment per irRC Number of Events, n (N) Median PFS, months (95% CI)		
Part B2 (IPI – refractory)	2 mg/kg Q3W 58 (89) 4.9 (2.8, 8.3)	10 mg/kg Q3W 58 (84) 3.2 (2.8, 5.5)		2 mg/kg Q3W 59 (89) 8.2 (5.1, 11.0)	10 mg/kg Q3W 53 (84) 5.6 (3.9, 13.6)		2 mg/kg Q3W 53 (89) 8.2 (5.4, 12.8)	10 mg/kg Q3W 49 (84) 8.1 (5.2, 14.2)	
Part B3 (IPI-exposed)	10 mg/kg Q3W 37 (56) 2.8 (2.6, 5.5)	10 mg/kg Q2W 38 (65) 5.6 (2.8, 8.3)		10 mg/kg Q3W 31 (56) 5.5 (2.8, .)	10 mg/kg Q2W 39 (65) 5.6 (3.8, 8.6)		10 mg/kg Q3W 33 (56) 4.2 (2.8, .)	10 mg/kg Q2W 39 (65) 5.7 (4.4, 9.6)	
Part D (IPI-naïve)	2 mg/kg Q3W 33 (51) 5.5 (2.8, 14.0)	10 mg/kg Q3W 37 (52) 4.2 (2.8, 9.9)		2 mg/kg Q3W 35 (51) 8.3 (3.4, 13.8)	10 mg/kg Q3W 35 (52) 6.3 (3.7, 11.3)		2 mg/kg Q3W 30 (51) 11.1 (3.4, 16.6)	10 mg/kg Q3W 34 (52) 5.4 (2.8, 14.9)	
Part B3 (IPI-naïve)	10 mg/kg Q3W 39 (65) 4.1 (2.8, 8.3)	10 mg/kg Q2W 34 (58) 3.1 (2.8, .)		10 mg/kg Q3W 32 (65) 5.8 (3.4, .)	10 mg/kg Q2W 30 (58) 6.5 (5.2, .)		10 mg/kg Q3W 32 (65) 8.6 (4.5, .)	10 mg/kg Q2W 32 (58) 6.3 (2.8, 11.0)	
Part B1 (IPI-naïve+IPI treated)	2 mg/kg Q3W 15 (22) 13.6 (2.7,21.2)	10 mg/kg Q3W 44 (56) 5.5 (2.8,8.3)	10 mg/kg Q2W 36 (57) 8.8 (5.4,22.1)	2 mg/kg Q3W 12 (22) 16.5 (4.0,.)	10 mg/kg Q3W 38 (56) 10.5 (5.5,16.9)	10 mg/kg Q2W 30 (57) 22.1 (8.3,27.4)	2 mg/kg Q3W 14 (22) 11.4 (2.7,.)	10 mg/kg Q3W 37 (56) 6.8 (4.1,19.8)	10 mg/kg Q2W 32 (57) 22.1 (5.6,.)
Part B1+B2+D Pooled (IPI-naïve+IPI-treated)	2 mg/kg Q3W 106 (162) 5.1 (2.8,8.3)	10 mg/kg Q3W 139 (192) 4.2 (2.9,5.5)	10 mg/kg Q2W 36 (57) 8.8 (5.4,22.1)	2 mg/kg Q3W 106 (162) 8.3 (6.2,11.0)	10 mg/kg Q3W 126 (192) 7.0 (5.5,10.3)	10 mg/kg Q2W 30 (57) 22.1 (8.3,27.4)	2 mg/kg Q3W 97 (162) 10.3 (5.6,13.6)	10 mg/kg Q3W 120 (192) 8.0 (5.3,13.8)	10 mg/kg Q2W 32 (57) 22.1 (5.6,.)
Part B3 (IPI Naïve+ IPI exposed)	10 mg/kg Q3W 76 (121) 3.0 (2.8, 5.7)	10 mg/kg Q2W 72 (123) 5.2 (2.8, 8.1)		10 mg/kg Q3W 63 (121) 5.6 (3.7, .)	10 mg/kg Q2W 69 (123) 6.4 (5.5, 9.9)		10 mg/kg Q3W 65 (121) 5.7 (3.9, .)	10 mg/kg Q2W 71 (123) 5.7 (4.9, 9.6)	

* FAS population by investigator assessment is the same as the APaT population, indicating that all patients treated fulfilled the eligibility criterion of having at least one measurable lesion according to investigator assessment.

Data Cutoff Date 18-Apr-2014

Data Source: [Ref. 5.3.5.2: P001V02]

Overall Survival

Of the 135 patients in the APaT population in Part B1, 47 (35%) were reported to have died at the time of the analysis. The median OS was not reached for the entire study population or for any of the individual dose levels (95% CI 24.4 to not estimable). The 12-month and 18-month OS rates were respectively 81% and 62%.

In Part B2, there were a total of 70 deaths among 173 patients across both treatment arms. The median OS was not reached for the 2 mg/kg Q3W cohort (95% CI was 10.9 to not estimable) and was 18.3 months for the 10 mg/kg Q3W cohort (95% CI 11.4 to not estimable). There was no significant difference in OS between treatment arms (p=0.920). The 12-month OS rate was comparable for the 2 dose cohorts, with 60% in the 2 mg/kg Q3W arm vs. 62% in the 10 mg/kg Q3W arm. The 18-month OS rate was very similar to the 12-month OS rate, with 57% in the 2 mg/kg Q3W vs. 62% in the 10 mg/kg Q3W arm.

Of the 244 patients in the APaT population in Part B3, 36 (30%) were reported to have died in the 10 mg/kg Q3W cohort compared with 42 (34%) in the 10 mg/kg Q2W cohort at the time of the analysis. There was no significant difference in OS between treatment arms. The OS rate at 6 months was 75%

for the 10 mg/kg Q3W arm and 77% for the 10 mg/kg Q2W arm. The median OS and the OS rate at 12 months for both cohorts had not been reached at the time of data cut off.

In Part D, the median OS was not reached, with no significant difference in OS between treatment arms. The 12-month OS rate using the Kaplan-Meier estimate for the 2 dose cohorts was 72% in the 2 mg/kg Q3W arm and 64% in the 10 mg/kg Q3W arm. The 18-month OS rate was 61% in the 2 mg/kg Q3W arm and 55% in the 10 mg/kg Q3W arm.

The OS analyses are summarized in the table below:

Table 52: Summary of Overall Survival (APaT Population)

	Median Survival (Months)			OS rate at 12 Months in %		
	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2W	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2W
B1 IPI-treated + naïve	NR	NR	NR	85.7	79.3	81.8
B2 IPI-refractory	NR	18.3	-	59.6	61.5	-
D IPI-naïve	NR	NR	-	72.0	63.5	-
B1+B2+D	21.1	23.1	NR	67.1	67.2	81.8
B3 IPI-exposed + naïve	-	NR	NR	-	NR	NR
B3 IPI-naïve	-	NR	NR	-	NR	NR
B3 IPI-exposed	-	NR	NR	-	NR	NR

Data Cutoff Date: 18APR2014

Subgroup analysis in the pooled melanoma population (B1+B2+B3+D)

Subgroup analyses were performed based on major demographic factors and potentially important prognostic factors for patients with advanced melanoma. Analyses of patient cohorts based on dose and prior IPI treatment were pre-specified, while other subgroups were not pre-specified, but analyzed as post-hoc.

In the pooled melanoma population, including 655 subjects in the APaT population from Parts B1, B2, D, and B3, the ORR is 31% (95% CI 28-35%). No important differences were observed in ORR based on the age or gender of patients treated with pembrolizumab. Subjects with ECOG PS 0 versus 1, and baseline LDH normal versus elevated had generally similar ORR compared to the overall study population. With respect to M-stage, subjects with M1b tumor stage (lung metastases without other visceral metastases and with a normal LDH) had a higher ORR than the overall study population (52% vs. 31% in the B1/B2/B3/D pooled cohort). Subjects with M1c stage (non-pulmonary visceral metastases or elevated LDH) had a similar ORR to the overall population (27% vs 31%)

The 54 subjects with a history of brain metastases had a similar ORR (33%) compared to subjects without brain metastases (31%).

There were 155 subjects with BRAF mutations in the APaT population, and the ORR was 23% compared to 33% in subjects with a wild-type BRAF gene. Among the 110 subjects with reported prior treatment with a BRAF/MEK inhibitor, the ORR was 21% (95% CI: 14- 30%) in this subgroup.

Uveal melanoma

P001 enrolled a total of 20 subjects with uveal melanoma (3 subjects at 2 mg/kg Q3W; 14 subjects at 10 mg/kg Q3W; and 3 subjects at 10 mg/kg Q2W) across all parts of the study (B1, B2, B3, and D). As of the 18-Apr-2014 cutoff date, there were no objective responses based on IRO assessment per RECIST 1.1 in these 20 subjects, while there were 6 subjects (2 subjects for each dose cohort) with stable disease as the best response.

Best overall response based on IRO assessment per RECIST 1.1 for subjects with uveal melanoma in P001 is described in the table below.

Table 53: Summary of Best Overall Response Based on IRO Assessment per RECIST 1.1 Uveal Patients in PN001 (Part B1+B2+B3+D) (APaT Population)

Response Evaluation	MK-3475 2 mg/kg Q3W (N=3)			MK-3475 10 mg/kg Q3W (N=14)			MK-3475 10 mg/kg Q2W (N=3)			Total (N=20)		
	n	%	95% CI[a]	n	%	95% CI[a]	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)	0	0.0	(0.0, 70.8)	0	0.0	(0.0, 23.2)	0	0.0	(0.0, 70.8)	0	0.0	(0.0, 16.8)
Partial Response (PR)	0	0.0	(0.0, 70.8)	0	0.0	(0.0, 23.2)	0	0.0	(0.0, 70.8)	0	0.0	(0.0, 16.8)
Overall Response (CR+PR)	**0**	**0.0**	**(0.0, 70.8)**	**0**	**0.0**	**(0.0, 23.2)**	**0**	**0.0**	**(0.0, 70.8)**	**0**	**0.0**	**(0.0, 16.8)**
Stable Disease (SD)	2	66.7	(9.4, 99.2)	2	14.3	(1.8, 42.8)	2	66.7	(9.4, 99.2)	6	30.0	(11.9, 54.3)
Disease Control (CR+PR+SD)	**2**	**66.7**	**(9.4, 99.2)**	**2**	**14.3**	**(1.8, 42.8)**	**2**	**66.7**	**(9.4, 99.2)**	**6**	**30.0**	**(11.9, 54.3)**
Progressive Disease (PD)	1	33.3	(0.8, 90.6)	7	50.0	(23.0, 77.0)	1	33.3	(0.8, 90.6)	9	45.0	(23.1, 68.5)
Non-evaluable (NE)	0	0.0	(0.0, 70.8)	5	35.7	(12.8, 64.9)	0	0.0	(0.0, 70.8)	5	25.0	(8.7, 49.1)

Only confirmed responses are included in this table.
[a] Based on binomial exact confidence interval method.
(Database Cutoff Date: 18APR2014)

The duration of SD for the 6 subjects ranges from 86+ to 336+ days.

Table 54: Summary of efficacy for Study P001

Title: Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma				
Study identifier	001			
Design	Multi-center, open label, phase I study including:			
	Part	**Cohort**	**Treatment**	**N patients**
	Part A *Solid tumours*	A: dose escalation	1,3, 10 mg/kg Q2W	10
		A1: PK and PD	10 mg/kg Q2W	7
		A2: PK and PD	2 or 10 mg/kg Q3W	13
	Part B *Melanoma*	B1: non-randomized *(IPI-naïve or treated)*	2 or 10 mg/kg Q2W or Q3W	**135**
		B2: randomized *(IPI-refractory)*	2 or 10 mg/kg Q3W	**173**
		B3: randomized (*IPI-naïve, treated or refractory*	10 mg/kg Q2W or Q3W	248
	Part C *NSCLC*	non-randomized	10 mg/kg Q3W	38
	Part D *Melanoma IPI-naïve*	randomized	2 or 10 mg/kg Q3W	**103**
	Part F *NSCLC*	F1: randomized*(PD-L1 +)*	10 mg/kg Q2W or Q3W	43
		F2: Randomized*(PD-L1 +or -)*	10 mg/kg Q2W or Q3W	200

Endpoints and definitions	Co-Primary endpoint	BOR	The rate of patients who achieved a best overall response of confirmed complete or partial responses based on RECIST 1.1.
	Secondary endpoint	DCR	The sum of rates of complete response, partial response or stable disease as best overall response
	Secondary endpoint	Duration of response	Time from first documentation of response to first documentation of disease progression
	Secondary endpoint	PFS	Time from start of treatment to documentation of definitive disease progression or death due to any cause, whichever occurs first
	Secondary endpoint	OS	Time from treatment initiation to death due to any cause
Database lock	18 Oct 2013		
Note			

Results and Analysis

Analysis description	**Primary Analysis**	
	FAS: patients with measurable baseline disease who received at least one dose of pembrolizumab	
IPI-refractory (**Part B2**)	pembrolizumab 2 mg/kg Q3W (N=81)	pembrolizumab 10 mg/kg Q3W (N=76)
Results	**ORR** (n/%) 95% CI	21 (**25.9**) 16.8, 36.9	20 (**26.3**) 16.9, 37.7
	CR (n/%) 95% CI	1 (1.2) (0.0, 6.7)	1 (1.3) (0.0, 7.1)
	PR (n/%) 95% CI	20 (24.7) (15.8, 35.5)	19 (25.0) (15.8, 36.3)
	Duration of response (weeks) Median (range) Non-PD (%)	Not reached (6+,37+) 19 (90)	Not reached (8+,37+) 18(90)
	DCR (n/%) 95% CI	41 (**50.6**) 39.3, 61.9	38 (**50.0**) 38.3, 61.7
	APaT population	N=89	N=84
	PFS N (%) events Median (weeks) 95% CI	54 (60.7) 22 (12, 36)	54 (64.3) 14 (12, 24)

	Hazard Ratio 95% CI p-value	0.84 (0.57, 1.23) 0.355	
	OS N (%) events Median (weeks) 95% CI	32 (36.0) 13 (10.1,..)	22 (26.2) Not reached (..,..)
	Hazard Ratio 95% CI p-value	1.06 (0.61, 1.84) 0.827	
IPI-naïve (**Part D**)		pembrolizumab 2 mg/kg Q3W (N=45)	pembrolizumab 10 mg/kg Q3W (N=47)
Results	**ORR** (n/%) 95% CI	15 (33.3) (20.0, 49.0)	19 (40.4) (26.4, 55.7)
	CR (n/%) 95% CI	2 (4.4) (0.5, 15.1)	2 (4.3) (0.5, 14.5)
	PR (n/%) 95% CI	13 (28.9) (16.4, 44.3)	17 (36.2) (22.7, 51.5)
	Duration of response (weeks) Median (range) Non-PD (%)	 Not reached (7+, 36+) 16 (94)	 Not reached (6+, 39+) 18 (95)
	DCR(n/%) 95% CI	22 (48.9) (33.7, 64.2)	26 (55.3) (40.1, 69.8)
	APaT population	N=51	N=52
	PFS N (%) events Median (weeks) 95% CI	 28 (54.9) 27 (12.4,..)	 32 (61.5) 23 (12.1, 48.0)
	Hazard Ratio 95% CI p-value	0.85 (0.51, 1.42) 0.530	
	OS N (%) events Median (weeks) 95% CI	12 (23.5) Not reached (..,..)	17 (32.7) Not reached (..,..)
	Hazard Ratio 95% CI p-value	0.70 (0.34, 1.47) 0.350	

Notes	Responses are based on IRO assessment per RECIST 1.1 Duration of response and analyses of PFS and OS are based on the APaT population

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In order to support the indication for pembrolizumab for the treatment of adult patients with unresectable and metastatic melanoma at a dose of 2mg/kg Q3W, the applicant submitted the data from an ongoing phase I study P001 cohorts B1, B2, B3 and D, data from a randomised, controlled trial of pembrolizumab versus chemotherapy in IPI refractory advance melanoma patients study P002 and the early results of a randomised, controlled study P006 of pembrolizumab versus ipilimumab in IPI naïve patients. To support the first line indication in melanoma patients untreated with ipilumumab, data from patients randomised to cohort B1 and B3 which were naïve to ipilumumab as well as patients in cohort D and study P006, which recruited patients naïve to ipilimumab were submitted. For the support of the last line indication, patients that were previously treated with ipilimumab were recruited in cohort B1 (treated with ipilimumab), B2 (refractory to ipilimumab), B3 (treated and/or refractory to ipilimumab) as well as patients recruited for study P002 (refractory).. All trials are currently still ongoing.

During the assessment, the CHMP had requested a triggered GCP inspection for study P001, which had been subject to eight amendments. This study was initially submitted as the single pivotal trial to support the application in the broad indication and there were concerns identified during the assessment in relation to the Clinical Study report (CSR), with apparent inconsistency in the data presented in the submission and with that presented in the publication of the results of the trial[16] . The results of the inspection showed no critical findings and the overall conduct of the trial was found acceptable, providing reassurance on the integrity and reliability of the data.

Efficacy data and additional analyses

Dose rationale

Alternative schedules (10 mg/kg Q3w and 10 mg/kg Q2W) were evaluated in Study P001, and also in the on-going comparative studies P002 (IPI-refractory patients: 2 mg/kg Q3W or 10 mg/kg Q3W) and P006 (IPI-naive patients: 10 mg/kg Q3W or 10 mg/kg Q2W). The CHMP was initially concerned that the 10 mg/kg dose in study P002 had shown a better efficacy compared with the proposed dose 2 mg/kg for the indication. A higher ORR at 10 mg/kg Q2W dose was shown in comparison to other doses tested (2 mg/kg Q3W, 10 mg/kg Q3W) in cohort B1 as well. Subsequent investigations and analyses across studies presented by the applicant demonstrated that this high response in a single group appeared to be a chance event as the totality of the currently available data, including randomized cohort comparisons, was consistent with a lack of statistically significant and clinically meaningful differences in response across these doses and regimens. Exposure-response analyses at the individual trial level revealed that no clinically relevant exposure-response relationship was observed. Further analyses with an integrated exposure-response analysis for clinical efficacy, including all melanoma studies (P001, P002 and P006) showed a non- significant relationship between

[16] Robert C, Ribas A, Wolchok JD, et al. 2014 Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014 Sep 20;384(9948):1109-17.

pembrolizumab exposure and change in tumour size, which was slightly more evident in IPI-naïve patients. Box plots representing the 25^{th}-75^{th} percentile spread of change in tumour showed an overlap between the boxes at the different exposure level, with no apparent exposure-response relationship. No differences were seen across the wide range of exposures (<660 µg/ml to >8010 µg/ml) and doses (1 to 10 mg/kg). Based on these analyses, the CHMP is reassured that the extrapolation of the data shown in the trial P006 with the dose 10 mg/kg can be considered applicable for the 2mg/kg and that no differences in the efficacy are to be expected between the two doses.

Efficacy

Treatment of ipilimumab naïve patients

The use of pembrolizumab in IPI-naive patients was supported by Study P001, part D and preliminary data from Study P006.

Study P001, Part D, enrolled a patient population with similar characteristics of Study P006.

In study P001, around 35% of confirmed responses were reported in IPI-naive patients (37% and 35% in FAS and APaT population, respectively); an ORR of 33.3 has been reported at the proposed recommended dose of 2 mg/kg Q3W (see section 5.1 of the SmPC); overall, approximately half of the IPI-naïve patients achieved disease control as the best response (52.2% and 53.4% in FAS and APaT population, respectively). As for IPI-refractory patients, data on the duration of stable disease were reported showing an overall median duration of stable disease of 36 weeks (48.1 and 25.9 weeks for 2 mg/kg and 10 mg/kg arm, respectively), and the median duration of response was not reached

Study P006 enrolled patients with or without BRAF V600E mutant melanoma. Patients may have received a prior BRAF inhibitor, but it was not required if patients had normal LDH, no clinically significant tumour related symptoms and absence of rapidly progressing disease. All patients were required to submit a tumour tissue sample for PD-L1 expression evaluation. Patients were randomized 1:1:1 to one of the two pembrolizumab arms or IPI, and were stratified according to PD-L1 expression and ECOG PS. Cross-over was not allowed in order to avoid confoundment of OS results.

Overall baseline characteristics were well balanced in the three arms. Almost all patients (97.8%) were of white race. Around 60% of patients were male, and there was a slight prevalence of patients < 65 years old (56.5%). Over 65.3% of patients had stage M1c, and about 68% of patients had received no prior systemic therapies lines of treatment for advanced disease. The prevalence of BRAF mutation was higher than in study P002 and P001, with 36.2% of subjects with BRAF mutant tumours, and 18.1% of subjects had received prior BRAF inhibitor; PD-L1 status was missing in a slight minority of patients (1.6%), while 80.5 of patients had PD-L1 positive staining tumours.

The IA1 part of Study P006 was performed at the pre-specified 0.002 alpha level for each pembrolizumab arm compared to the ipilimumab arm. Based on a total of 502 events, with a minimum of 6-month follow-up, the HR is 0.58 for both pembrolizumab arms over IPI. The median PFS is 5.5 months in the pembrolizumab 10 mg/kg Q2W arm, 4.1 months in the 10 mg/kg Q3W arm, and 2.8 months in the control arm. The 6 month PFS rate is 47.3% (95% CI; 41.2%, 53.2%) in the pembrolizumab 10 mg/kg Q2W arm and 46.4% (95% CI; 40.3%, 52.3%) in the pembrolizumab 10 mg/kg Q3W arm, compared to 26.5% (95% CI; 20.9%, 32.4%) in the control arm.

The subgroup analyses for PFS show a consistent effect in all subgroups, at each pembrolizumab dose level.

The data cut-off date for IA2 was 03-mar-2015, and is based on a total of 289 OS events (66% of the 435 target events at the final analysis) with a minimum follow-up of 12 months and a median follow-

up of 13.8 months. OS was tested at the alpha level of 0.005. The hazard ratio for OS is 0.63 (p=0.00052) for pembrolizumab 10 mg/kg Q2W over the control arm and 0.69 (p=0.00358) for pembrolizumab 10 mg/kg Q3W over the control arm, respectively, with no difference between the two pembrolizumab arms compared to each other (HR 0.91, p=0.51319) (see section 5.1 of the SmPC). The median OS has not yet been reached in all three arms, and the 12-month OS rates are 74.1% (95% CI: 68.5%, 78.9%) and 68.4% (95% CI: 62.5%, 73.6%) for pembrolizumab at Q2W and Q3W, respectively, compared to 58.2% (95% CI: 51.8%, 64.0%) in the control arm.

Overall, the provided results of Study P006 confirm preliminary observations from Study P001, Part D, and show a clinically meaningful advantage of pembrolizumab over ipilimumab in IPI-naive patients with unresectable advanced melanoma and support the proposed indication which includes patients that have not been treated with ipilimumab.

Treatment of ipilimumab refractory patients

Data on the use of pembrolizumab in IPI-refractory patients were based on the results of Study P002 and supported by Study P001, part B2.

Overall baseline characteristics were well balanced in the three arms. The prevalence of BRAF mutation was less than expected in unselected population, with 23.1% of subjects with BRAF mutant tumours. PD-L1 status was undetermined in 22% of patients, and 53.9% of patients had PD-L1 positive tumours.

Study P001, Part B2, enrolled a patient population with similar characteristics.
Results from IA2 of Study P002 showed a substantial benefit from the treatment with pembrolizumab compared to chemotherapy, with a PFS HR of 0.57 (95% CI: 0.45, 0.73) and 0.50 (95% CI: 0.39, 0.64) in the 2 mg/kg Q3W arm and the 10 mg/kg Q3W arm, respectively, versus the chemotherapy arm (see section 5.1 of the SmPC).

Overall, no clinically or statistically significant difference was observed between the 2 pembrolizumab doses, even though a trend towards better efficacy was reported with pembrolizumab 10 mg/kg. Subgroups analyses showed a consistent effect in all subgroups. At the time of this interim analysis, 86 (48%) chemotherapy subjects had crossed over to the pembrolizumab treatment arm (2 or 10 mg/kg Q3W) confounding the OS results. Therefore, no conclusion can be drawn on the OS at this stage.

The ORR observed in study P002 is comparable to that observed in Study P001, including a similar patient population. The median time to response was similar for pembrolizumab and chemotherapy and was consistent with the first scheduled tumour assessment. Interestingly, responses occurred up to 30 weeks in both the 2 mg/kg Q3W arm and 10 mg/kg Q3W pembrolizumab arm, and only up to 18 weeks in the control arm. Median response duration was not reached in either of pembrolizumab arms, while been 37 weeks in the control arm.

P001 enrolled a total of 20 subjects with uveal melanoma. The sample size was too small to draw any conclusions. The information on limited available data in patients with ocular melanoma is reported in the SmPC section 5.1.

Overall, results from the randomized phase 2 Study P002, IA2, confirmed the benefit observed in Study P001 Part B2 in the IPI-refractory population, and demonstrated a substantial advantage of pembrolizumab over chemotherapy, supporting the proposed indication which includes patients that have been previously treated with ipilimumab (see section 5.1 of the SmPC).

Patients with tumours designated as PD-L1 positive and BRAF V600 mutation positive

The benefits observed in the overall patient population in studies P001, P002 and P006 appear to be consistent across all subgroups analysed, although in some cases it appears more limited in the PD-L1 negative subset. For study P006, it is acknowledged that the study was not sufficiently powered for subgroup analyses, and that confidence intervals are quite large and overlapping, due to the relatively small sample size. The CHMP was concerned over the substantial higher rate of events observed in the PD-L1 negative subset relative to the PD-L1 positive subgroup for both PFS (70.6 vs 60.7% patients with a PFS event in the PD-L1 negative and PD-L1 positive subgroups, respectively) and OS (45.6% vs 34% of patients with an OS event in the PD-L1 negative and PD-L1 positive subgroups, respectively). However, the integrated exposure-response analysis provided by the applicant showed a similar lack of exposure-efficacy correlation with PD-L1 expression status as well as for patients with BRAF V600 mutated tumours. These results provided reassurance to the CHMP that no differences in efficacy are to be expected for patients that have tumours designated as PD-L1 negative and for patients that harbour the BRAF V600 mutation. In order to further support the analysis of the data provided in the application and strengthen interpretation of data which is hampered by the scarse number of patients in these subgroups, the CHMP has imposed a post-authorisation efficacy study (PAES) to have the updated efficacy data from the P002 final analysis and from Parts B2 and D of P001 (data cut-off date:18-Oct-2014) by dose level based on BRAF mutation and PD-L1 expression status as these uncertainties with respect to the efficacy of a medicinal product in the sub-populations could not be resolved prior to marketing authorisation and require further clinical evidence.

BRAF mutation status

A subgroup analysis of KEYNOTE-002 in patients who were BRAF wild type (n=415; 77%) or BRAF mutant with prior BRAF treatment (n=125; 23%) was performed. The PFS HRs (pooled pembrolizumab [2 mg/kg or 10 mg/kg every 3 weeks] vs. chemotherapy) were 0.51 (95% CI: 0.41, 0.65) for BRAF wild type and 0.56 (95% CI: 0.37, 0.85) for BRAF mutant with prior BRAF treatment. The PFS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.51 (95% CI: 0.39, 0.67) for BRAF wild type and 0.74 (95% CI: 0.46, 1.18) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled pembrolizumab vs. chemotherapy were 0.83 (95% CI: 0.60, 1.15) for BRAF wild type and 0.82 (95% CI: 0.47, 1.43) for BRAF mutant with prior BRAF treatment. The OS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.80 (95% CI: 0.55, 1.18) for BRAF wild type and 1.03 (95% CI: 0.55, 1.91) for BRAF mutant with prior BRAF treatment. ORR for pooled pembrolizumab and pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy was 27% and 25% vs. 6% for BRAF wild type and 12% and 9% vs. 0% for BRAF mutant with prior BRAF treatment.

A subgroup analysis of KEYNOTE-006 in patients who were BRAF wild type (n=525; 63%), BRAF mutant without prior BRAF treatment (n=163; 20%) and BRAF mutant with prior BRAF treatment (n=139; 17%) was performed. The PFS hazard ratios (HRs) (pooled pembrolizumab [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.57 (95% CI: 0.45, 0.73) for BRAF wild type, 0.50 (95% CI: 0.32, 0.77) for BRAF mutant without prior BRAF treatment, and 0.73 (95% CI: 0.48, 1.11) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled pembrolizumab vs. ipilimumab were 0.61 (95% CI: 0.46, 0.82) for BRAF wild type, 0.69 (95% CI: 0.33, 1.45) for BRAF mutant without prior BRAF treatment, and 0.75 (95% CI: 0.45, 1.26) for BRAF mutant with prior BRAF treatment. ORR for pooled pembrolizumab vs. ipilimumab was 34% vs. 13% for BRAF wild type, 41% vs. 13% for BRAF mutant without prior BRAF treatment, and 21% vs. 6% for BRAF mutant with prior BRAF treatment.

PD-L1 status

A subgroup analysis of KEYNOTE-002 in patients who were PD-L1 positive (Allred proportion score of ≥2 representing PD-L1 membrane expression in ≥1% of tumour cells) vs. PD-L1 negative (Allred proportion score of 0 or 1) was performed. PD-L1 expression was tested retrospectively by immunohistochemistry research assay with the 22C3 anti-PD-L1 antibody. Among patients who were evaluable for PD-L1 expression (78%), 69% (n=291) were PD-L1 positive and 31% (n=130) were PD-L1 negative. The PFS HRs (pooled pembrolizumab [2 mg/kg or 10 mg/kg every 3 weeks] vs. chemotherapy) were 0.52 (95% CI: 0.39, 0.68) for PD-L1 positive patients and 0.60 (95% CI: 0.38, 0.94) for PD-L1 negative patients. The PFS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.54 (95% CI: 0.39, 0.75) for PD-L1 positive patients and 0.89 (95% CI: 0.53, 1.50) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. chemotherapy were 0.82 (95% CI: 0.55, 1.23) for PD-L1 positive patients and 0.77 (95% CI: 0.43, 1.37) for PD-L1 negative patients. The OS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.93 (95% CI: 0.58, 1.49) for PD-L1 positive patients and 1.19 (95% CI: 0.58, 2.46) for PD-L1 negative patients. ORR for pooled pembrolizumab and pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy was 26% and 23% vs. 4% for PD-L1 positive patients and 15% and 11% vs. 8% for PD-L1 negative patients.

A subgroup analysis of KEYNOTE-006 in patients who were PD-L1 positive (n=671; 80%) vs. PD-L1 negative (n=150; 18%) was performed. Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. The PFS HRs (pooled pembrolizumab [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.43, 0.65) for PD-L1 positive patients and 0.73 (95% CI: 0.47, 1.11) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. ipilimumab were 0.56 (95% CI: 0.43, 0.73) for PD-L1 positive patients and 0.95 (95% CI: 0.56, 1.62) for PD-L1 negative patients. The ORRs for the pooled pembrolizumab vs. ipilimumab group were 37% vs. 12% for PD-L1 positive patients and 18% vs. 11% for PD-L1 negative patients.

The European Medicines Agency has deferred the obligation to submit the results of studies with pembrolizumab in one or more subsets of the paediatric population in treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (see section 4.2 for information on paediatric use).

2.5.4. Conclusions on the clinical efficacy

In conclusion, the overall data support the efficacy of pembrolizumab as monotherapy in both patients that are naïve to ipilimumab treatment and patients that have been previously treated with ipilimumab in melanoma patients with advanced disease. The comparative studies P002 and P006 are still ongoing and only interim results have been submitted. Therefore, the CHMP has imposed two PAES to have the final study reports for studies P002 and P006.

The proposed dose of 2 mg/kg Q3W is considered sufficiently justified for the overall population and it is agreed that there is no significant differences between the 2 mg/kg Q3W and 10 mg/kg Q3W dose levels in the overall population. A similar conclusion can also be drawn for subgroups of patients that have tumours which harbour the BRAF V600 mutation and for the subset of patients that have tumours which have been designated as PD-L1 negative. However, the evidence is based on data that is considered limited. The CHMP is of the opinion that the relevance of PD-L1 and PD-L2 expression as biomarkers, in the tumour microenvironment as well as in the peripheral compartment, should be further explored. Therefore, the CHMP has imposed a PAES to have updated efficacy data from the

P002 final analysis and from P001 for Parts B2 and D of P001 by dose level in subgroups based on BRAF mutation status and PD-L1 expression status as an Annex II condition.

The CHMP considers the following measures necessary to be addressed as related to some aspects of efficacy of the medicinal product were identified and can be resolved only after the medicinal product has been marketed:

- Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma – Final Study Report
- Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P006: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma – Final Study Report
- Post-authorisation efficacy study (PAES): In order to confirm the benefit in BRAFV600 mutant and in PD-L1 negative patient subgroups at the recommended dose, the MAH should provide updated analyses from Study P001 and P002:
    - Updated efficacy data in subgroups comparing 2 vs 10 mg/kg Q3W from the P002 final analysis.
    - Efficacy data in subgroups comparing the 2 vs 10 mg/kg Q3W from P001, using the data cut-off date of 18-Oct-2014 from Parts B2 and D of P001 by dose level.
- The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically:
  Although PD-L1 status is predictive of response in advanced melanoma patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by IHC (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing melanoma studies (P001, P002 and P006):
    - PD-L1 IHC comparison of archival tissue vs newly obtained
    - PD-L1 IHC comparison between pre and post treatment tumour tissues
    - Nanostring RNA gene signature
    - PD-L2 IHC
    - RNA and proteomic serum profiling
    - Immune cell profiling (peripheral blood)

2.6. Clinical safety

The pembrolizumab safety database submitted for this MAA includes complete safety data from 1012 melanoma patients enrolled in Parts B1, B2, B3 and D of study P001 (cut-off date 18 April 2014) and in study P002 (cut-off date 12 May 2014). Data from 38 NSCLC patients included in Part C and 30 patients with solid tumours enrolled in Part A, A1 and A2 have been also provided at the start of the procedure.

In addition, SAEs have been submitted from Part F of the Study P001, and from the following ongoing studies:

- Study P006 (*A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma*): 87 patients with 44 exposed to pembrolizumab;
- Study P010 (*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*): 12 patients with 8 exposed to pembrolizumab;
- Study P012 (*A Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors*):109 patients, all exposed to pembrolizumab.

Patient exposure

Details of patients exposed to pembrolizumab are reported in the Table below:

Table 55: Patient exposed to pembrolizumab by dose (cut-off date P001:18 April 2014; P002: 12 May 2014)

Population	pembrolizumab 2 mg/kg Q3W	pembrolizumab 10 mg/kg Q3W	pembrolizumab 10 mg/kg Q2W	Patients with long term safety data	
				≥6 months	≥12 months
IPI-naive and IPI-treated (Parts B1)	22	56	57		
IPI-refractory (Part B2)	89	84	/	89	63
IPI- naïve/treated/ refractory (Part B3)	/	121	123	109	-
IPI-naive (Part D)	51	52	/	57	43
IPI-refractory (P002)	178	179	/	137	16

Drug exposure of IPI-naïve melanoma patients of study P006, at the first interim analysis, is reported in the following table:

Table 56: Summary of Drug Exposure P006 (APaT Population)

	Control	MK-3475 10 mg/kg Q2W	MK-3475 10 mg/kg Q3W
	N=256	N=278	N=277
Study Days On-Therapy (days)			
Mean	49.89	163.93	151.45
Median	63.00	183.00	168.00
SD	21.35	90.73	90.95
Range	1.00 to 92.00	1.00 to 336.00	1.00 to 332.00
Number of Administrations			
Mean	3.29	12.00	8.00
Median	4.00	13.00	9.00
SD	0.99	5.89	4.26
Range	1.00 to 4.00	1.00 to 20.00	1.00 to 16.00
(Database Cutoff Date: 03SEP2014).			

Adverse events

Overall, the safety profile for pembrolizumab is similar between all three dose groups, with only a few AEs (fatigue, headache, diarrhoea, and nausea) with incidence greater (>10% difference) in the 10 mg/kg Q2W group versus the 2 mg/kg Q3W group. Among all subjects, the SOCs in which ≥ 50% of events were reported included: Gastrointestinal disorders (66.3%), General disorders (72.4%),

Musculoskeletal and connective tissue disorders (55.2%), and Skin and subcutaneous tissue disorders (57.6%) (Table 57).

Table 57: Subjects with adverse events (incidence ≥ 10% in one or more treatment groups) –Pooled Studies P001 and P002 (APaT population)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	340		492		180		1,012	
with one or more adverse events	333	(97.9)	483	(98.2)	178	(98.9)	994	(98.2)
with no adverse events	7	(2.1)	9	(1.8)	2	(1.1)	18	(1.8)
Blood and lymphatic system disorders	**68**	**(20.0)**	**90**	**(18.3)**	**45**	**(25.0)**	**203**	**(20.1)**
Anaemia	58	(17.1)	63	(12.8)	28	(15.6)	149	(14.7)
Cardiac disorders	**27**	**(7.9)**	**40**	**(8.1)**	**21**	**(11.7)**	**88**	**(8.7)**
Endocrine disorders	**39**	**(11.5)**	**48**	**(9.8)**	**22**	**(12.2)**	**109**	**(10.8)**
Hypothyroidism	25	(7.4)	32	(6.5)	18	(10.0)	75	(7.4)
Eye disorders	**52**	**(15.3)**	**70**	**(14.2)**	**35**	**(19.4)**	**157**	**(15.5)**
Gastrointestinal disorders	**218**	**(64.1)**	**324**	**(65.9)**	**129**	**(71.7)**	**671**	**(66.3)**
Abdominal pain	44	(12.9)	59	(12.0)	27	(15.0)	130	(12.8)
Constipation	73	(21.5)	102	(20.7)	32	(17.8)	207	(20.5)
Diarrhoea	83	(24.4)	120	(24.4)	64	(35.6)	267	(26.4)
Nausea	86	(25.3)	135	(27.4)	64	(35.6)	285	(28.2)
Vomiting	43	(12.6)	77	(15.7)	35	(19.4)	155	(15.3)
General disorders and administration site conditions	**226**	**(66.5)**	**356**	**(72.4)**	**151**	**(83.9)**	**733**	**(72.4)**
Asthenia	33	(9.7)	64	(13.0)	26	(14.4)	123	(12.2)
Chills	24	(7.1)	44	(8.9)	22	(12.2)	90	(8.9)
Fatigue	139	(40.9)	228	(46.3)	103	(57.2)	470	(46.4)
Oedema peripheral	39	(11.5)	55	(11.2)	26	(14.4)	120	(11.9)
Pyrexia	39	(11.5)	72	(14.6)	35	(19.4)	146	(14.4)
Infections and infestations	**145**	**(42.6)**	**183**	**(37.2)**	**83**	**(46.1)**	**411**	**(40.6)**
Nasopharyngitis	26	(7.6)	36	(7.3)	22	(12.2)	84	(8.3)
Upper respiratory tract infection	24	(7.1)	27	(5.5)	18	(10.0)	69	(6.8)
Urinary tract infection	24	(7.1)	31	(6.3)	18	(10.0)	73	(7.2)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**57**	**(16.8)**	**64**	**(13.0)**	**24**	**(13.3)**	**145**	**(14.3)**
Investigations	**111**	**(32.6)**	**153**	**(31.1)**	**58**	**(32.2)**	**322**	**(31.8)**
Metabolism and nutrition disorders	**123**	**(36.2)**	**188**	**(38.2)**	**84**	**(46.7)**	**395**	**(39.0)**
Decreased appetite	63	(18.5)	103	(20.9)	44	(24.4)	210	(20.8)
Musculoskeletal and connective tissue disorders	**181**	**(53.2)**	**266**	**(54.1)**	**112**	**(62.2)**	**559**	**(55.2)**
Arthralgia	67	(19.7)	100	(20.3)	48	(26.7)	215	(21.2)
Back pain	44	(12.9)	53	(10.8)	24	(13.3)	121	(12.0)
Myalgia	35	(10.3)	49	(10.0)	33	(18.3)	117	(11.6)
Pain in extremity	39	(11.5)	46	(9.3)	26	(14.4)	111	(11.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**28**	**(8.2)**	**53**	**(10.8)**	**21**	**(11.7)**	**102**	**(10.1)**
Nervous system disorders	**136**	**(40.0)**	**196**	**(39.8)**	**83**	**(46.1)**	**415**	**(41.0)**
Dizziness	31	(9.1)	41	(8.3)	21	(11.7)	93	(9.2)
Headache	42	(12.4)	91	(18.5)	45	(25.0)	178	(17.6)
Psychiatric disorders	**63**	**(18.5)**	**86**	**(17.5)**	**43**	**(23.9)**	**192**	**(19.0)**
Renal and urinary disorders	**31**	**(9.1)**	**52**	**(10.6)**	**31**	**(17.2)**	**114**	**(11.3)**
Respiratory, thoracic and mediastinal disorders	**146**	**(42.9)**	**224**	**(45.5)**	**106**	**(58.9)**	**476**	**(47.0)**
Cough	79	(23.2)	114	(23.2)	49	(27.2)	242	(23.9)
Dyspnoea	48	(14.1)	89	(18.1)	39	(21.7)	176	(17.4)
Skin and subcutaneous tissue disorders	**184**	**(54.1)**	**293**	**(59.6)**	**106**	**(58.9)**	**583**	**(57.6)**
Pruritus	87	(25.6)	142	(28.9)	56	(31.1)	285	(28.2)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**184**	**(54.1)**	**293**	**(59.6)**	**106**	**(58.9)**	**583**	**(57.6)**
Rash	66	(19.4)	103	(20.9)	39	(21.7)	208	(20.6)
Vitiligo	29	(8.5)	41	(8.3)	24	(13.3)	94	(9.3)
Vascular disorders	**37**	**(10.9)**	**80**	**(16.3)**	**31**	**(17.2)**	**148**	**(14.6)**

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

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

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

Include all treated subjects in PN001 Part B1, B2, B3, D and all subjects in PN002 treated with Pembrolizumab in the original phase.

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

(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

The overall incidences of Grade 3-5 AEs across the 3 groups was 43.5%, 41.9%, and 45.0%, in the 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W groups respectively. The incidence of Grade 3-5 AEs was occurring in more than 7.1% (anaemia in 2 mg/kg Q3W) of subjects in any treatment group. The most commonly reported Grade 3-5 AEs, occurring in at least 2% of subjects in this pooled melanoma population were: anaemia (4.6%), hyponatraemia (3.0%), fatigue (2.6%), and dyspnoea (2.4%). In the pooled analysis, Grade 3-5 AEs did not appear to cluster in any particular SOC (incidence in any SOC was not >10%), with the biggest difference seen in the Metabolism SOC (9.4% in 2 mg/kg Q3W, 6.3% in 10 mg/kg Q3W, and 11.7% in 10 mg/kg Q2W).

Table 58 displays the number and percentage of subjects with ADRs (incidence >0% in one or more treatment groups) in the pooled melanoma population of P001 + P002. Drug-related AEs were reported for 798 of 1012 (78.9%) subjects in this pooled melanoma population. The most frequently reported drug-related AEs, reported for at least 10% of subjects in the pooled melanoma population, were: fatigue (33.3%), pruritus (23.8%), rash (16.9%), diarrhoea (14.7%), arthralgia (13.0%), and nausea (12.0%).

Table 58: Number and percentage of subjects with ADRs in the pooled melanoma population of P001 + P002.

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	340		492		180		1,012	
with one or more adverse events	255	(75.0)	393	(79.9)	150	(83.3)	798	(78.9)
with no adverse events	85	(25.0)	99	(20.1)	30	(16.7)	214	(21.1)
Blood and lymphatic system disorders	**22**	**(6.5)**	**26**	**(5.3)**	**18**	**(10.0)**	**66**	**(6.5)**
Anaemia	14	(4.1)	13	(2.6)	9	(5.0)	36	(3.6)
Eosinophilia	2	(0.6)	3	(0.6)	2	(1.1)	7	(0.7)
Haemolytic anaemia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Immune thrombocytopenic purpura	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Iron deficiency anaemia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Leukocytosis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Leukopenia	1	(0.3)	3	(0.6)	3	(1.7)	7	(0.7)
Lymph node pain	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Lymphadenitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Lymphopenia	1	(0.3)	2	(0.4)	2	(1.1)	5	(0.5)
Neutropenia	2	(0.6)	2	(0.4)	0	(0.0)	4	(0.4)
Pancytopenia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Thrombocytopenia	4	(1.2)	5	(1.0)	3	(1.7)	12	(1.2)
Cardiac disorders	**3**	**(0.9)**	**1**	**(0.2)**	**2**	**(1.1)**	**6**	**(0.6)**
Atrial fibrillation	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Palpitations	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Pericardial effusion	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Pericarditis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Tachycardia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Ear and labyrinth disorders	**3**	**(0.9)**	**8**	**(1.6)**	**0**	**(0.0)**	**11**	**(1.1)**
External ear pain	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Vertigo	2	(0.6)	8	(1.6)	0	(0.0)	10	(1.0)
Vertigo positional	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Endocrine disorders	**34**	**(10.0)**	**40**	**(8.1)**	**20**	**(11.1)**	**94**	**(9.3)**
Adrenal insufficiency	0	(0.0)	3	(0.6)	1	(0.6)	4	(0.4)
Autoimmune thyroiditis	0	(0.0)	4	(0.8)	0	(0.0)	4	(0.4)
Endocrine disorder	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Hyperparathyroidism	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Hyperthyroidism	9	(2.6)	8	(1.6)	4	(2.2)	21	(2.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Endocrine disorders	**34**	**(10.0)**	**40**	**(8.1)**	**20**	**(11.1)**	**94**	**(9.3)**
Hypophysitis	3	(0.9)	1	(0.2)	0	(0.0)	4	(0.4)
Hypopituitarism	1	(0.3)	2	(0.4)	1	(0.6)	4	(0.4)
Hypothyroidism	23	(6.8)	28	(5.7)	17	(9.4)	68	(6.7)
Thyroiditis	3	(0.9)	3	(0.6)	1	(0.6)	7	(0.7)
Eye disorders	**20**	**(5.9)**	**23**	**(4.7)**	**14**	**(7.8)**	**57**	**(5.6)**
Abnormal sensation in eye	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Diplopia	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Dry eye	4	(1.2)	4	(0.8)	6	(3.3)	14	(1.4)
Eczema eyelids	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Eye disorder	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Eye irritation	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Eye pain	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Eye pruritus	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Eyelash discolouration	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Eyelid disorder	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Eyelid exfoliation	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Growth of eyelashes	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Iridocyclitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Iritis	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Lacrimation increased	3	(0.9)	1	(0.2)	0	(0.0)	4	(0.4)
Macular degeneration	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Ocular hyperaemia	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Periorbital oedema	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Photophobia	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.2)
Photopsia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Uveitis	1	(0.3)	4	(0.8)	0	(0.0)	5	(0.5)
Vision blurred	3	(0.9)	3	(0.6)	1	(0.6)	7	(0.7)
Visual impairment	5	(1.5)	2	(0.4)	2	(1.1)	9	(0.9)
Vitreous floaters	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.2)
Gastrointestinal disorders	**88**	**(25.9)**	**154**	**(31.3)**	**74**	**(41.1)**	**316**	**(31.2)**
Abdominal discomfort	2	(0.6)	6	(1.2)	2	(1.1)	10	(1.0)
Abdominal distension	2	(0.6)	4	(0.8)	4	(2.2)	10	(1.0)
Abdominal pain	12	(3.5)	11	(2.2)	11	(6.1)	34	(3.4)
Abdominal pain lower	2	(0.6)	1	(0.2)	0	(0.0)	3	(0.3)
Abdominal pain upper	2	(0.6)	10	(2.0)	3	(1.7)	15	(1.5)
Aphthous stomatitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Ascites	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**88**	**(25.9)**	**154**	**(31.3)**	**74**	**(41.1)**	**316**	**(31.2)**
Chapped lips	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Cheilitis	1	(0.3)	0	(0.0)	1	(0.6)	2	(0.2)
Colitis	3	(0.9)	6	(1.2)	2	(1.1)	11	(1.1)
Colitis microscopic	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Constipation	13	(3.8)	18	(3.7)	9	(5.0)	40	(4.0)
Diarrhoea	40	(11.8)	67	(13.6)	42	(23.3)	149	(14.7)
Dry mouth	5	(1.5)	8	(1.6)	9	(5.0)	22	(2.2)
Duodenitis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Dyspepsia	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Dysphagia	3	(0.9)	2	(0.4)	0	(0.0)	5	(0.5)
Enterocolitis	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Epigastric discomfort	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Faeces hard	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Faeces soft	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Flatulence	0	(0.0)	4	(0.8)	0	(0.0)	4	(0.4)
Food poisoning	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Frequent bowel movements	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Gastritis	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Gastrointestinal disorder	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Gastrointestinal sounds abnormal	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Gastrooesophageal reflux disease	3	(0.9)	2	(0.4)	2	(1.1)	7	(0.7)
Gingival pain	2	(0.6)	1	(0.2)	0	(0.0)	3	(0.3)
Glossitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Haemorrhoids	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Intestinal obstruction	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Intussusception	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Mucous stools	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Nausea	26	(7.6)	63	(12.8)	32	(17.8)	121	(12.0)
Odynophagia	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Oral pain	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Pancreatitis	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Periodontal disease	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Retching	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Small intestinal perforation	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Stomatitis	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**88**	**(25.9)**	**154**	**(31.3)**	**74**	**(41.1)**	**316**	**(31.2)**
Tooth demineralisation	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Tooth disorder	2	(0.6)	0	(0.0)	1	(0.6)	3	(0.3)
Upper gastrointestinal haemorrhage	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Vomiting	11	(3.2)	24	(4.9)	10	(5.6)	45	(4.4)
General disorders and administration site conditions	**135**	**(39.7)**	**231**	**(47.0)**	**117**	**(65.0)**	**483**	**(47.7)**
Asthenia	17	(5.0)	38	(7.7)	22	(12.2)	77	(7.6)
Chest discomfort	1	(0.3)	0	(0.0)	1	(0.6)	2	(0.2)
Chest pain	2	(0.6)	3	(0.6)	2	(1.1)	7	(0.7)
Chills	16	(4.7)	24	(4.9)	12	(6.7)	52	(5.1)
Death	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Face oedema	3	(0.9)	1	(0.2)	0	(0.0)	4	(0.4)
Facial pain	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Fatigue	90	(26.5)	162	(32.9)	85	(47.2)	337	(33.3)
Feeling cold	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Feeling hot	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Gait disturbance	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
General physical health deterioration	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Generalised oedema	2	(0.6)	2	(0.4)	0	(0.0)	4	(0.4)
Hyperthermia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Hypothermia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Inflammation	2	(0.6)	1	(0.2)	1	(0.6)	4	(0.4)
Inflammatory pain	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Influenza like illness	4	(1.2)	13	(2.6)	5	(2.8)	22	(2.2)
Injection site extravasation	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Injection site reaction	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Local swelling	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Localised oedema	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Malaise	4	(1.2)	2	(0.4)	0	(0.0)	6	(0.6)
Mucosal discolouration	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Mucosal inflammation	4	(1.2)	4	(0.8)	2	(1.1)	10	(1.0)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Oedema	2	(0.6)	3	(0.6)	0	(0.0)	5	(0.5)
Oedema peripheral	10	(2.9)	10	(2.0)	9	(5.0)	29	(2.9)
Pain	4	(1.2)	3	(0.6)	1	(0.6)	8	(0.8)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**135**	**(39.7)**	**231**	**(47.0)**	**117**	**(65.0)**	**483**	**(47.7)**
Performance status decreased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Pyrexia	10	(2.9)	33	(6.7)	16	(8.9)	59	(5.8)
Swelling	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Temperature intolerance	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Thirst	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Xerosis	2	(0.6)	2	(0.4)	0	(0.0)	4	(0.4)
Hepatobiliary disorders	**6**	**(1.8)**	**5**	**(1.0)**	**1**	**(0.6)**	**12**	**(1.2)**
Autoimmune hepatitis	4	(1.2)	2	(0.4)	0	(0.0)	6	(0.6)
Cholestasis	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Hepatitis	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Hyperbilirubinaemia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Immune system disorders	**3**	**(0.9)**	**5**	**(1.0)**	**0**	**(0.0)**	**8**	**(0.8)**
Anaphylactic reaction	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Atopy	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Autoimmune disorder	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Cytokine release syndrome	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Drug hypersensitivity	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Hypersensitivity	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Infections and infestations	**10**	**(2.9)**	**22**	**(4.5)**	**12**	**(6.7)**	**44**	**(4.3)**
Candida infection	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Clostridium difficile infection	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Conjunctivitis	0	(0.0)	5	(1.0)	1	(0.6)	6	(0.6)
Diverticulitis	0	(0.0)	2	(0.4)	1	(0.6)	3	(0.3)
Erysipelas	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Folliculitis	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Fungal skin infection	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Gastroenteritis viral	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Herpes zoster	1	(0.3)	0	(0.0)	2	(1.1)	3	(0.3)
Hordeolum	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Influenza	2	(0.6)	1	(0.2)	0	(0.0)	3	(0.3)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**10**	**(2.9)**	**22**	**(4.5)**	**12**	**(6.7)**	**44**	**(4.3)**
Lung infection	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Nasopharyngitis	2	(0.6)	1	(0.2)	0	(0.0)	3	(0.3)
Oral candidiasis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Oral herpes	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Pharyngitis	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Pneumonia	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Rhinitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Skin infection	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Staphylococcal infection	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Tuberculosis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Upper respiratory tract infection	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Urinary tract infection	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.2)
Injury, poisoning and procedural complications	**1**	**(0.3)**	**9**	**(1.8)**	**1**	**(0.6)**	**11**	**(1.1)**
Contusion	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Excoriation	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Incision site complication	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Infusion related reaction	0	(0.0)	5	(1.0)	1	(0.6)	6	(0.6)
Radiation skin injury	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Sunburn	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Investigations	**43**	**(12.6)**	**65**	**(13.2)**	**28**	**(15.6)**	**136**	**(13.4)**
Activated partial thromboplastin time prolonged	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Alanine aminotransferase	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Alanine aminotransferase increased	11	(3.2)	17	(3.5)	8	(4.4)	36	(3.6)
Amylase increased	3	(0.9)	0	(0.0)	0	(0.0)	3	(0.3)
Aspartate aminotransferase increased	11	(3.2)	13	(2.6)	8	(4.4)	32	(3.2)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**43**	**(12.6)**	**65**	**(13.2)**	**28**	**(15.6)**	**136**	**(13.4)**
Autoantibody positive	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Blood alkaline phosphatase decreased	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Blood alkaline phosphatase increased	2	(0.6)	4	(0.8)	4	(2.2)	10	(1.0)
Blood bicarbonate decreased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Blood bilirubin increased	3	(0.9)	2	(0.4)	4	(2.2)	9	(0.9)
Blood calcium increased	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Blood cholesterol increased	2	(0.6)	1	(0.2)	2	(1.1)	5	(0.5)
Blood cortisol decreased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Blood creatine phosphokinase increased	2	(0.6)	1	(0.2)	1	(0.6)	4	(0.4)
Blood creatinine increased	1	(0.3)	4	(0.8)	4	(2.2)	9	(0.9)
Blood glucose abnormal	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Blood glucose increased	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Blood parathyroid hormone increased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Blood phosphorus decreased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Blood testosterone decreased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Blood thyroid stimulating hormone decreased	2	(0.6)	5	(1.0)	0	(0.0)	7	(0.7)
Blood thyroid stimulating hormone increased	2	(0.6)	4	(0.8)	0	(0.0)	6	(0.6)
Blood triglycerides increased	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**43**	**(12.6)**	**65**	**(13.2)**	**28**	**(15.6)**	**136**	**(13.4)**
Blood uric acid increased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Body temperature increased	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
C-reactive protein increased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Electrocardiogram QT prolonged	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Electrocardiogram repolarisation abnormality	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Eosinophil count increased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Gamma-glutamyltransferase increased	3	(0.9)	1	(0.2)	1	(0.6)	5	(0.5)
Haemoglobin decreased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Hepatic enzyme increased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Lipase	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Lymphocyte count decreased	3	(0.9)	4	(0.8)	1	(0.6)	8	(0.8)
Neutrophil count decreased	2	(0.6)	3	(0.6)	0	(0.0)	5	(0.5)
Neutrophil count increased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Platelet count decreased	0	(0.0)	4	(0.8)	2	(1.1)	6	(0.6)
Thyroglobulin increased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Thyroxine decreased	1	(0.3)	5	(1.0)	0	(0.0)	6	(0.6)
Thyroxine free increased	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Thyroxine increased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Transaminases increased	0	(0.0)	1	(0.2)	2	(1.1)	3	(0.3)
Tri-iodothyronine decreased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Tri-iodothyronine increased	2	(0.6)	0	(0.0)	1	(0.6)	3	(0.3)
Weight decreased	4	(1.2)	12	(2.4)	4	(2.2)	20	(2.0)
Weight increased	2	(0.6)	1	(0.2)	0	(0.0)	3	(0.3)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**43**	**(12.6)**	**65**	**(13.2)**	**28**	**(15.6)**	**136**	**(13.4)**
White blood cell count decreased	2	(0.6)	3	(0.6)	0	(0.0)	5	(0.5)
White blood cell count increased	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Metabolism and nutrition disorders	**37**	**(10.9)**	**54**	**(11.0)**	**32**	**(17.8)**	**123**	**(12.2)**
Cell death	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Decreased appetite	23	(6.8)	36	(7.3)	22	(12.2)	81	(8.0)
Dehydration	3	(0.9)	3	(0.6)	4	(2.2)	10	(1.0)
Diabetes mellitus	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Failure to thrive	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Fluid overload	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Fluid retention	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Gout	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Hypercalcaemia	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Hypercholesterolaemia	2	(0.6)	0	(0.0)	1	(0.6)	3	(0.3)
Hyperglycaemia	2	(0.6)	2	(0.4)	2	(1.1)	6	(0.6)
Hyperkalaemia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Hyperlipidaemia	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Hypertriglyceridaemia	1	(0.3)	2	(0.4)	1	(0.6)	4	(0.4)
Hyperuricaemia	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Hypoalbuminaemia	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Hypocalcaemia	1	(0.3)	5	(1.0)	0	(0.0)	6	(0.6)
Hypokalaemia	0	(0.0)	6	(1.2)	2	(1.1)	8	(0.8)
Hypomagnesaemia	0	(0.0)	2	(0.4)	2	(1.1)	4	(0.4)
Hyponatraemia	2	(0.6)	3	(0.6)	1	(0.6)	6	(0.6)
Hypophosphataemia	3	(0.9)	4	(0.8)	2	(1.1)	9	(0.9)
Increased appetite	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Insulin resistant diabetes	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Iron deficiency	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Type 1 diabetes mellitus	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Vitamin B12 deficiency	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Musculoskeletal and connective tissue disorders	**71**	**(20.9)**	**112**	**(22.8)**	**56**	**(31.1)**	**239**	**(23.6)**
Arthralgia	41	(12.1)	61	(12.4)	30	(16.7)	132	(13.0)
Arthritis	2	(0.6)	3	(0.6)	5	(2.8)	10	(1.0)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**71**	**(20.9)**	**112**	**(22.8)**	**56**	**(31.1)**	**239**	**(23.6)**
Arthropathy	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Back pain	7	(2.1)	7	(1.4)	4	(2.2)	18	(1.8)
Bone pain	1	(0.3)	2	(0.4)	1	(0.6)	4	(0.4)
Flank pain	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Groin pain	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Joint range of motion decreased	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Joint stiffness	3	(0.9)	3	(0.6)	1	(0.6)	7	(0.7)
Joint swelling	2	(0.6)	4	(0.8)	0	(0.0)	6	(0.6)
Muscle atrophy	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Muscle spasms	6	(1.8)	6	(1.2)	3	(1.7)	15	(1.5)
Muscle twitching	1	(0.3)	0	(0.0)	1	(0.6)	2	(0.2)
Muscular weakness	7	(2.1)	8	(1.6)	3	(1.7)	18	(1.8)
Musculoskeletal chest pain	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Musculoskeletal discomfort	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Musculoskeletal pain	2	(0.6)	6	(1.2)	2	(1.1)	10	(1.0)
Musculoskeletal stiffness	3	(0.9)	8	(1.6)	3	(1.7)	14	(1.4)
Myalgia	19	(5.6)	33	(6.7)	24	(13.3)	76	(7.5)
Myopathy	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Myositis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Neck pain	1	(0.3)	4	(0.8)	1	(0.6)	6	(0.6)
Pain in extremity	4	(1.2)	10	(2.0)	9	(5.0)	23	(2.3)
Pain in jaw	1	(0.3)	4	(0.8)	0	(0.0)	5	(0.5)
Plantar fasciitis	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Polyarthritis	1	(0.3)	0	(0.0)	1	(0.6)	2	(0.2)
Polymyalgia rheumatica	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Rhabdomyolysis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Sensation of heaviness	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Synovitis	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Tendon pain	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Tendonitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Tenosynovitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Torticollis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(0.9)**	**5**	**(1.0)**	**1**	**(0.6)**	**9**	**(0.9)**
Acrochordon	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Malignant melanoma	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Melanocytic naevus	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Metastatic pain	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Neoplasm swelling	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Skin papilloma	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Tumour pain	1	(0.3)	3	(0.6)	0	(0.0)	4	(0.4)
Nervous system disorders	**48**	**(14.1)**	**60**	**(12.2)**	**36**	**(20.0)**	**144**	**(14.2)**
Amnesia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Amnestic disorder	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Balance disorder	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.2)
Brain oedema	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Carpal tunnel syndrome	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Cognitive disorder	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Convulsion	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Depressed level of consciousness	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Disturbance in attention	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.2)
Dizziness	4	(1.2)	4	(0.8)	8	(4.4)	16	(1.6)
Dysaesthesia	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Dysarthria	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Dysgeusia	6	(1.8)	9	(1.8)	1	(0.6)	16	(1.6)
Encephalopathy	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Epilepsy	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Headache	16	(4.7)	29	(5.9)	18	(10.0)	63	(6.2)
Hyperaesthesia	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Hypersomnia	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Hypoaesthesia	4	(1.2)	2	(0.4)	2	(1.1)	8	(0.8)
Hypogeusia	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Hypotonia	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Judgement impaired	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Lethargy	5	(1.5)	2	(0.4)	0	(0.0)	7	(0.7)
Memory impairment	3	(0.9)	2	(0.4)	1	(0.6)	6	(0.6)
Meningitis noninfective	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Myasthenic syndrome	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Neuralgia	1	(0.3)	2	(0.4)	1	(0.6)	4	(0.4)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**48**	**(14.1)**	**60**	**(12.2)**	**36**	**(20.0)**	**144**	**(14.2)**
Neuropathy peripheral	3	(0.9)	5	(1.0)	6	(3.3)	14	(1.4)
Paraesthesia	2	(0.6)	7	(1.4)	3	(1.7)	12	(1.2)
Partial seizures	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Peripheral motor neuropathy	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Peripheral sensory neuropathy	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Polyneuropathy	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Restless legs syndrome	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Sciatica	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Sensory disturbance	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Syncope	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Tremor	4	(1.2)	0	(0.0)	0	(0.0)	4	(0.4)
Psychiatric disorders	**6**	**(1.8)**	**13**	**(2.6)**	**9**	**(5.0)**	**28**	**(2.8)**
Affective disorder	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Agitation	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Anxiety	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Confusional state	1	(0.3)	1	(0.2)	3	(1.7)	5	(0.5)
Depression	0	(0.0)	1	(0.2)	2	(1.1)	3	(0.3)
Disorientation	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Hallucination	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Insomnia	2	(0.6)	5	(1.0)	2	(1.1)	9	(0.9)
Libido decreased	1	(0.3)	3	(0.6)	0	(0.0)	4	(0.4)
Sleep disorder	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Trance	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Renal and urinary disorders	**3**	**(0.9)**	**7**	**(1.4)**	**6**	**(3.3)**	**16**	**(1.6)**
Chromaturia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Dysuria	0	(0.0)	1	(0.2)	1	(0.6)	2	(0.2)
Pollakiuria	0	(0.0)	2	(0.4)	1	(0.6)	3	(0.3)
Proteinuria	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Renal failure	0	(0.0)	2	(0.4)	2	(1.1)	4	(0.4)
Renal failure acute	0	(0.0)	2	(0.4)	1	(0.6)	3	(0.3)
Renal failure chronic	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Renal impairment	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Urinary incontinence	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**3**	**(0.9)**	**7**	**(1.4)**	**6**	**(3.3)**	**16**	**(1.6)**
Urine odour abnormal	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Reproductive system and breast disorders	**5**	**(1.5)**	**8**	**(1.6)**	**3**	**(1.7)**	**16**	**(1.6)**
Breast pain	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Dysmenorrhoea	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Erectile dysfunction	0	(0.0)	3	(0.6)	0	(0.0)	3	(0.3)
Genital rash	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Haematospermia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Menorrhagia	1	(0.3)	0	(0.0)	1	(0.6)	2	(0.2)
Nipple pain	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Nipple swelling	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Pelvic pain	2	(0.6)	2	(0.4)	0	(0.0)	4	(0.4)
Pruritus genital	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Scrotal erythema	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**49**	**(14.4)**	**67**	**(13.6)**	**30**	**(16.7)**	**146**	**(14.4)**
Cough	22	(6.5)	27	(5.5)	11	(6.1)	60	(5.9)
Dysphonia	2	(0.6)	0	(0.0)	1	(0.6)	3	(0.3)
Dyspnoea	17	(5.0)	24	(4.9)	12	(6.7)	53	(5.2)
Dyspnoea exertional	4	(1.2)	3	(0.6)	3	(1.7)	10	(1.0)
Epistaxis	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Haemoptysis	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Hiccups	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Hypoxia	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Interstitial lung disease	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Laryngeal inflammation	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Nasal congestion	1	(0.3)	4	(0.8)	0	(0.0)	5	(0.5)
Nasal dryness	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Oropharyngeal pain	0	(0.0)	4	(0.8)	0	(0.0)	4	(0.4)
Painful respiration	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Pleural effusion	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Pleuritic pain	0	(0.0)	1	(0.2)	2	(1.1)	3	(0.3)
Pneumonitis	3	(0.9)	11	(2.2)	7	(3.9)	21	(2.1)
Productive cough	2	(0.6)	1	(0.2)	3	(1.7)	6	(0.6)
Respiratory failure	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Respiratory tract congestion	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**49**	**(14.4)**	**67**	**(13.6)**	**30**	**(16.7)**	**146**	**(14.4)**
Rhinorrhoea	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Sinus congestion	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Sneezing	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Throat irritation	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Wheezing	2	(0.6)	3	(0.6)	0	(0.0)	5	(0.5)
Skin and subcutaneous tissue disorders	**147**	**(43.2)**	**236**	**(48.0)**	**86**	**(47.8)**	**469**	**(46.3)**
Acne	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Actinic keratosis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Alopecia	6	(1.8)	5	(1.0)	0	(0.0)	11	(1.1)
Blister	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Dermatitis	0	(0.0)	3	(0.6)	0	(0.0)	3	(0.3)
Dermatitis acneiform	4	(1.2)	5	(1.0)	0	(0.0)	9	(0.9)
Dermatitis contact	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Dermatitis psoriasiform	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Dry skin	12	(3.5)	17	(3.5)	4	(2.2)	33	(3.3)
Eczema	3	(0.9)	9	(1.8)	3	(1.7)	15	(1.5)
Erythema	11	(3.2)	11	(2.2)	4	(2.2)	26	(2.6)
Erythema multiforme	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Erythema nodosum	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Exfoliative rash	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Granuloma skin	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Hair colour changes	4	(1.2)	1	(0.2)	4	(2.2)	9	(0.9)
Hair growth abnormal	0	(0.0)	3	(0.6)	0	(0.0)	3	(0.3)
Hair texture abnormal	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Hyperhidrosis	3	(0.9)	3	(0.6)	4	(2.2)	10	(1.0)
Hypertrichosis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Keratosis pilaris	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Lichenoid keratosis	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Macule	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Madarosis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Nail discolouration	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Nail growth abnormal	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Neutrophilic dermatosis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Night sweats	7	(2.1)	9	(1.8)	8	(4.4)	24	(2.4)
Onychoclasis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Pain of skin	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**147**	**(43.2)**	**236**	**(48.0)**	**86**	**(47.8)**	**469**	**(46.3)**
Palmar-plantar erythrodysaesthesia syndrome	2	(0.6)	0	(0.0)	1	(0.6)	3	(0.3)
Papule	2	(0.6)	1	(0.2)	1	(0.6)	4	(0.4)
Parapsoriasis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Photosensitivity reaction	1	(0.3)	3	(0.6)	0	(0.0)	4	(0.4)
Pigmentation disorder	2	(0.6)	0	(0.0)	0	(0.0)	2	(0.2)
Prurigo	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Pruritus	76	(22.4)	121	(24.6)	44	(24.4)	241	(23.8)
Pruritus generalised	2	(0.6)	7	(1.4)	4	(2.2)	13	(1.3)
Psoriasis	0	(0.0)	2	(0.4)	1	(0.6)	3	(0.3)
Purpura	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Pustular psoriasis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Rash	58	(17.1)	80	(16.3)	33	(18.3)	171	(16.9)
Rash erythematous	0	(0.0)	3	(0.6)	3	(1.7)	6	(0.6)
Rash follicular	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Rash generalised	3	(0.9)	6	(1.2)	4	(2.2)	13	(1.3)
Rash macular	1	(0.3)	3	(0.6)	2	(1.1)	6	(0.6)
Rash maculo-papular	9	(2.6)	22	(4.5)	4	(2.2)	35	(3.5)
Rash papular	2	(0.6)	3	(0.6)	0	(0.0)	5	(0.5)
Rash pruritic	2	(0.6)	4	(0.8)	4	(2.2)	10	(1.0)
Rash vesicular	1	(0.3)	0	(0.0)	1	(0.6)	2	(0.2)
Rosacea	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Scab	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Seborrhoeic dermatitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Skin depigmentation	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.2)
Skin discolouration	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Skin disorder	0	(0.0)	4	(0.8)	0	(0.0)	4	(0.4)
Skin exfoliation	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Skin haemorrhage	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Skin hyperpigmentation	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Skin hypopigmentation	3	(0.9)	11	(2.2)	2	(1.1)	16	(1.6)
Skin irritation	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Skin lesion	1	(0.3)	2	(0.4)	1	(0.6)	4	(0.4)
Skin mass	1	(0.3)	2	(0.4)	1	(0.6)	4	(0.4)
Skin ulcer	1	(0.3)	1	(0.2)	0	(0.0)	2	(0.2)
Solar dermatitis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Stevens-Johnson syndrome	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**147**	**(43.2)**	**236**	**(48.0)**	**86**	**(47.8)**	**469**	**(46.3)**
Transient acantholytic dermatosis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Urticaria	1	(0.3)	2	(0.4)	0	(0.0)	3	(0.3)
Vitiligo	25	(7.4)	39	(7.9)	24	(13.3)	88	(8.7)
Vascular disorders	**6**	**(1.8)**	**12**	**(2.4)**	**7**	**(3.9)**	**25**	**(2.5)**
Flushing	0	(0.0)	3	(0.6)	1	(0.6)	4	(0.4)
Hot flush	3	(0.9)	4	(0.8)	3	(1.7)	10	(1.0)
Hypertension	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Hypotension	0	(0.0)	2	(0.4)	1	(0.6)	3	(0.3)
Jugular vein thrombosis	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Lymphoedema	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Pallor	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Peripheral ischaemia	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Raynaud's phenomenon	1	(0.3)	1	(0.2)	1	(0.6)	3	(0.3)
Vasculitis	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Include all treated subjects in PN001 Part B1, B2, B3, D and all subjects in PN002 treated with Pembrolizumab in the original phase.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Overall, drug-related Grade 3-5 AEs were reported for 137 of 1012 subjects (13.5%). The most frequently reported drug-related Grade 3-5 AE was fatigue, reported for 15 subjects (1.5%). Aside from fatigue, the only drug-related Grade 3-5 AEs, reported in more than 5 subjects (0.5%), were: diarrhoea (0.8%), colitis (0.7%), asthenia (0.6%), anaemia (0.5%), dyspnoea (0.5%), and vomiting (0.5%).

Early safety results from study P006 for those AEs which were prespecified in the protocol to be compared between treatment arms with p-values are summarized in the following Table 59. The comparison was performed using a stratified Miettinen & Nurminen method.

Table 59: P006-Analysis of Adverse Event Summary- Tier 1 (APaT Population)

Treatment	n	(%)	Difference in % vs Control: Estimate (95% CI)†	Difference in % vs Control: p-value†	Difference in % vs MK-3475 10 mg/kg Q2W: Estimate (95% CI)†	Difference in % vs MK-3475 10 mg/kg Q2W: p-value†
Subjects in population						
Control	256					
MK-3475 10 mg/kg Q2W	278					
MK-3475 10 mg/kg Q3W	277					
Sponsor Defined Events of Clinical Interest						
Control	127	(49.6)				
MK-3475 10 mg/kg Q2W	126	(45.3)	-9.9 (-21.7, 2.3)	0.111		
MK-3475 10 mg/kg Q3W	122	(44.0)	-14.1 (-25.4, -2.4)	0.018	-4.2 (-15.0, 6.7)	0.449
Grade ≥ 3 Hyperthyroidism, hypophysitis, and hypothyroidism or any grade resulting in dose modification						
Control	4	(1.6)				
MK-3475 10 mg/kg Q2W	3	(1.1)	-0.4 (-2.9, 1.4)	0.332		
MK-3475 10 mg/kg Q3W	5	(1.8)	0.4 (-2.6, 2.9)	0.723	0.8 (-1.8, 3.3)	0.406
Grade ≥ 2 Pneumonitis						
Control	1	(0.4)				
MK-3475 10 mg/kg Q2W	1	(0.4)	-0.2 (-3.3, 2.6)	0.586		
MK-3475 10 mg/kg Q3W	4	(1.4)	1.5 (-1.3, 5.1)	0.139	1.6 (-0.6, 5.3)	0.083
Grade ≥ 3 Rash or any grade resulting in dose modification						
Control	6	(2.3)				
MK-3475 10 mg/kg Q2W	2	(0.7)	-2.2 (-6.6, 0.7)	0.089		
MK-3475 10 mg/kg Q3W	3	(1.1)	-2.0 (-6.3, 1.3)	0.159	0.3 (-2.4, 3.1)	0.449
Grade ≥ 2 Renal (Nephritis, nephritis autoimmune, renal failure, renal failure acute) or any grade resulting in dose modification						
Control	4	(1.6)				
MK-3475 10 mg/kg Q2W	2	(0.7)	-0.4 (-2.7, 1.2)	0.376		
MK-3475 10 mg/kg Q3W	4	(1.4)	0.5 (-2.2, 2.9)	0.645	0.9 (-1.5, 3.3)	0.350
Grade ≥ 2 Eye (Uveitis or iritis) or any grade resulting in dose modification						
Control	0	(0.0)				
MK-3475 10 mg/kg Q2W	1	(0.4)	0.7 (-2.3, 4.0)	0.361		
MK-3475 10 mg/kg Q3W	2	(0.7)	0.4 (-2.3, 3.3)	0.199	-0.3 (-3.4, 2.7)	0.704
Grade ≥ 2 Hepatitis (Hepatitis or autoimmune hepatitis) or any grade resulting in dose modification						
Control	1	(0.4)				
MK-3475 10 mg/kg Q2W	3	(1.1)	0.2 (-2.3, 2.9)	0.566		
MK-3475 10 mg/kg Q3W	4	(1.4)	0.4 (-2.0, 3.0)	0.410	0.2 (-2.3, 2.6)	0.753
Investigator Assessed Immune-related Adverse Event						
Control	110	(43.0)				
MK-3475 10 mg/kg Q2W	114	(41.0)	-3.4 (-14.1, 6.7)	0.525		
MK-3475 10 mg/kg Q3W	109	(39.4)	-4.4 (-15.4, 6.0)	0.418	-1.1 (-11.8, 9.5)	0.846

† Based on Miettinen & Nurminen method stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive), and ECOG (0 vs. 1).
Every subject is counted a single time for each applicable specific adverse event category.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
MedDRA preferred terms /Malignant neoplasm progression< and 'Neoplasm progression' not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
(Database Cutoff Date: 03SEP2014).

Serious adverse event / deaths / other significant events

SAEs were reported for 377 of 1012 subjects (37.3%). Overall, the incidences were 40.6%, 35.4%, and 36.1% in the 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W arms, respectively. The most commonly reported SAE overall was pneumonia, which was reported for 23 subjects (2.3%). The only other SAE reported in more than 2% of subjects was: dyspnoea, which was reported in 21 subjects (2.1%). The SAE profile of pembrolizumab was similar in the 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W groups, and the incidences of SAEs across SOCs were comparable across the three groups.

Overall, ADR related SAEs were reported for 93 of 1012 subjects (9.2%). By treatment arm, ADR-related SAEs were reported for 29 of 340 subjects (8.5%) in the 2 mg/kg Q3W group, 42 of 492 subjects (8.5%) in the 10 mg/kg Q3W group, and 22 of 180 subjects (12.2%) in the 10 mg/kg Q2W

group. ADR-related SAEs did not predominantly occur in any one SOC. With the exception of colitis (n=8, 0.8%), pneumonitis (n=8, 0.8%), pyrexia (n=7, 0.7%), and diarrhoea (n=6, 0.6%), no single AE was reported as both serious and drug related for more than 5 subjects. The percentage of drug-related SAEs was numerically higher in the 10 mg/kg Q2W group (12.2%), compared to the 2 mg/kg Q3W and 10 mg/kg Q3W groups (8.5% in each group) with the difference spread over small increases in individual AEs.

SAEs occurred in 37.9%, 33.5%, and 35.0% of subjects, and drug-related SAEs occurred in 8.5%, 7.7%, and 12.2% of subjects in the 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W groups, respectively.

At the proposed regimen of 2 mg/kg Q3W, the estimated mean change in QTc interval at peak concentrations is 0.83 msec (upper 90% CI of 0.93 msec), well below 20 msec, the level of concern in the setting of advanced cancer. These findings were confirmed based on an analysis of triplicate ECG data from Part F of P001, which indicated an estimated mean change in QTc interval at peak concentrations of the 2 mg/kg Q3W regimen of 0.91 msec (upper 90% CI of 1.4 msec).

There were no drug-related deaths in any of the melanoma cohorts in P001.

In study P002, there were 26 (2.6%) deaths due to AEs, of which all but one was considered by the Investigator to be not related to study drug. Deaths were generally similar across treatment arms, occurring in 6.2% and in 4.5% of subjects in the 2 mg/kg Q3W and the 10 mg/kg Q3W pembrolizumab arms, respectively, versus 4.7% of subjects in the chemotherapy control arm. The one drug-related death that occurred in the 2 mg/kg Q3W arm was originally reported by the investigator as drug-related. However, after the database was locked, the investigator changed the attribution of the death to unrelated. Although the cause of death was not clear, the investigator indicated that probable causes were disease progression and bleeding from intestinal metastasis.

In study P006, a total of 44 cases with a fatal outcome were identified, including 40 cases considered not related and 4 related to study therapy (IPI or pembrolizumab) by the investigator. There were only 2 pembrolizumab cases entered as related to pembrolizumab, 1 case reported as related by the investigator and 1 reported as unknown. One case was reported as renal failure as related to pembrolizumab by the investigator. The other case was likely related to malignant disease progression.

In study P010, A total of 67 cases with a fatal outcome were identified, including 62 events considered by the investigator not related and 5 events related to study therapy (docetaxel or pembrolizumab). There were two cases that were related to febrile neutropenia and cardiac failure acute, respectively, that occurred while on treatment with docetaxel. The remaining 3 cases that were considered related to pembrolizumab by the investigator showed that in one case insufficient information was provided for a complete medical assessment,another case had an alternative explanation confounding causality assessment, such as, underlying malignant disease progression and the third case related to pneumonitis in a patient with NSCLC in which a causal association between the fatal event and pembrolizumab could not be excluded.

In study P012, a total of 21 fatal cases were identified, including 19 cases considered not related and 2 cases related to pembrolizumab. In one case, there was insufficient information provided for a complete medicalassessment. The other case was related to a rapid onset of tracheobronchomalacia without etiology for which the investigator assessed as related to pembrolizumab.

Immunogenicity

A 10 mL sample of blood for anti-pembrolizumab antibodies was collected at specified time points. The samples were assayed for anti-pembrolizumab antibodies presence using a validated electrochemiluminescence (ECL) assay on the Sector Imager 2400 analyser from MesoScale Discovery (MSD). Samples were analysed for the presence of anti pembrolizumab antibodies with further characterization of anti-pembrolizumab antibodies and assessment of their neutralizing capacity.

A validated bridging electrochemiluminescence (ECL) immunoassay was used for the detection of anti-pembrolizumab antibodies in human serum (see above under section “Analytical methods”).

Overall, 2063 samples from 480 subjects from study parts A, B, C and D were available. A subset of 31 patients was not evaluable for drug-induced immunogenicity, because only a pre-treatment ADA sample was available. The remaining 449 patients were evaluable for immunogenicity (all 2063 samples were tested in the ADA screening assay).

Overview of Clinical Sample Results in Screening and Confirmatory Assay for Anti-MK-3475 Antibodies

	All samples	MK-3475 conc. < DTL	MK-3475 conc. > DTL	MK-3475 conc. unknown
Total number of samples	**2063**	864	1118	81
N.R.	2			2
QNS	1		1	
Reportable result from screening assay	**2060**	864	1117	79
Negative result in screening assay	2005	831	1097	77
Positive result in screening assay	55	33	20	2
Suspected positive samples tested in confirmatory assay				
Negative result in confirmatory assay	53	32	19	2
Positive result in confirmatory assay	2	1	1	0
Composite result from screening and confirmatory assay				
Negative	2058	863	1116	79
Positive	2	1	1	0
False positive rate screening assay	**53 out of 2058 2.6%**	32 out of 863 3.7%	19 out of 1116 1.7%	2 out of 79 2.5%
Results CSR for reference: False positive rate screening assay	CSR P001V01: 47 out of 1750 2.7%	CSR P001V01: 32 out of 793 4.0%	CSR P001V01: 14 out of 884 1.6%	CSR P001V01: 1 out of 73 1.4%

DTL: Drug Tolerance Level (25 µg/mL MK-3475)
N.R.: Non Reportable
QNS: Quantity Not Sufficient

(Source: Appendix II)

Interference by pembrolizumab in the ADA assays may occur, especially at concentrations above the drug tolerance level of 25 µg/mL. Therefore, samples with a negative test result in the screening or confirmatory anti-MK3475 assay could only be confirmed to be negative in the case of an pembrolizumab concentration below25 µg/mL. The immunogenicity status of a patient could only be confirmed to be negative if all pre-treatment and post-dose samples were negative in the confirmatory assay for antibodies against pembrolizumab and if the concentration of pembrolizumab in the last post-dose sample was below the drug tolerance level.

The following table presents the immunogenicity status of all 449 evaluable patients (with at least one post-dose ADA sample):

Table 60: Summary of immunogenicity results

Part	dose (mg/kg)	Number of patients[a] (% of total number of patients)		Immunogenicity status			
		Total	With last sample below drug tolerance level[b]	Negative	Inconclusive	Treatment emergent positive	Non-treatment emergent positive
A	1	3	3 (100%)	3 (100%)	0	0	0
	3	3	0	0	3 (100%)	0	0
	10	8	1 (13%)	1 (13%)	7 (88%)	0	0
A2	Cohort 1 0.005-0.3-2.0	4	1 (25%)	1 (25%)	3 (75%)[e]	0	0
	Cohort 2 0.02-0.3-2.0	3	2 (67%)	2 (67%)	1 (33%)[f]	0	0
	Cohort 3 0.06-1.0-10	5	1 (20%)	1 (20%)	4 (80%)[g]	0	0
B	2	108	72 (67%)	72 (67%)	35 (32%)[c]	0	1 (0.9%)[c]
	10 (Q2W + Q3W)	187	20 (11%)	20 (11%)	166 (89%)[d]	1 (0.5%)[d]	0
C	10	33	3 (9%)	3 (9%)	30 (91%)	0	0
D	2	47	25 (53%)	25 (53%)	22 (47%)[c]	0	0
	10	48	1 (2%)	1 (2%)	47 (98%)	0	0
Overall		**449**	**129 (29%)**	**129 (29%)**	**318 (71%)**	**1 (0.2%)**	**1 (0.2%)**
For reference: CSR P001V01		CSR P001V01: 449	CSR P001V01: 123 (27%)	CSR P001V01: 123 (27%)	CSR P001V01: 324 (72%)	CSR P001V01: 1 (0.2%)	CSR P001V01: 1 (0.2%)

a: Included are patients with at least one ADA sample after treatment with MK-3475.
b: Drug tolerance level of the ADA assay is 25 µg/mL.
For ADA samples with missing PK results, the PK concentration is considered as above drug tolerance level.
c: AN 0263 has a confirmed positive pre-treatment sample.
d: AN 0383 has one confirmed positive post-treatment sample (Cycle 5).
e: Three patients have a last ADA sample with missing PK result.
f: One patient has a last ADA sample with missing PK result.
g: Seven patients have a last ADA sample with missing PK result.

(Source: Appendix II)

Two patients had one sample each that tested positive in the tier 2 confirmatory assay for antibodies against pembrolizumab:

For patient AN 0263, the pre-treatment sample was found to be positive. This sample was negative in the confirmatory NAb assay. Post-dose samples were negative in the screening assay at Day 21 (Cycle 2) and inconclusive at Day 91 (Safety Follow Up). The immunogenicity status of this patient was classified as non-treatment emergent positive.

For patient AN 0383, the Day 84 post-dose sample (Cycle 5) tested positive in the screening and confirmatory assays, and was also confirmed positive in the NAb assay. Two additional immunogenicity samples were collected on day 169 (Cycle 9) and Day 253 (Cycle 13). Both samples tested positive in the screening assay but were inconclusive in the confirmatory assay

(i) all dose regimens

Study / cut off date	Patients tested	Patients with Keytruda < 25 yg/mL >>> samples assessable	In % of patients tested	Drug-dependent ADA (+)	In % of pts with assessable samples
PN001 / Dec 13	449	131	29%	1	0.8%
PN001+ PN002 / April 14	997	268	27%	1	0.4%

(ii) 2mg/kg q3w only

Study / cut off date	Patients tested	Patients with Keytruda < 25 yg/mL >>> samples assessable	In % of patients tested	Drug-dependent ADA (+)	In % of pts with assessable samples
PN001 / Dec 13	155	97	63%	0	0
PN001+ PN002 / April 14	345	220	64%	0	0

Immune-related AEs

Based on updated pooled data from studies P001 and P002, the following cumulative incidences for immune-related AEs were calculated: 7.4% for hypothyroidism, 2.6% for pneumonitis, 2.4% for hyperthyroidism, 2.0% for infusion-related reaction, 1.6% for colitis, 1.5% for severe skin-reactions, 1.1% for thyroiditis, 1.0% for hypophysitis, 0.8% for hepatitis, 0.8% for uveitis, 0.4% for nephritis, 0.4% for myositis, 0.2% for adrenal insufficiency, 0.2% for pancreatitis, 0.1% for type 1 diabetes mellitus, 0.1% for myasthenic syndrome, 0.1% for pericarditis, 0.1% for vasculitis.

Following this safety review, Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis), Pneumonitis, Colitis and Hepatitis were confirmed as immune-related events causally associated with pembrolizumab, and further adverse reactions (Hypophysitis, including Hypopituitarism and Secondary Adrenal Insufficiency; Uveitis; Type 1 Diabetes Mellitus, Nephritis, Pancreatitis, Myositis, Severe Skin Reaction and Infusion-Related Reaction) were newly added to the list of Important Identified Risk. Gastrointestinal perforation secondary to colitis was considered as Potential Risk.

Table 61: Summary of AEOSI – Pneumonitis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Pneumonitis	6 (1.8)	13 (2.6)	7 (3.9)	26 (2.6)
Time to Onset of First Pneumonitis (days)†				
Mean (Std)	127.8 (39.1)	191.0 (151.5)	125.4 (104.9)	158.8 (122.7)
Median	130.5	169.0	85.0	130.5
Range	82 to 170	6 to 588	2 to 291	2 to 588
Total episodes of Pneumonitis	6	14	10	30
Average Episodes per subject	1.00	1.08	1.43	1.15
Episode duration (days)‡				
Median	105.0	59.0	79.0	86.0
Range	25 to 459	2 to 210	7 to 359	2 to 459

(%) = Number of subjects with Pneumonitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Pneumonitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Except for 9 patients in whom pneumonitis apparently persisted at the time of the analysis, all other cases (17) of pneumonitis were reported to have resolved. In the 2 mg/kg Q3W and 10 mg/kg Q3W dose groups, no subjects reported more than 1 event of pneumonitis. In the 10 mg/kg Q2W dose group, there were 9 events of pneumonitis in 7 subjects. Corticosteroids were used to manage pneumonitis in 9 of 26 (34.6%) subjects (all with Grade 2-3 pneumonitis).

Table 62: Summary of AEOSI – Colitis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (ApaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Colitis	4 (1.2)	7 (1.4)	5 (2.8)	16 (1.6)
Time to Onset of First Colitis (days)†				
Mean (Std)	152.8 (90.9)	140.4 (94.0)	143.2 (52.3)	144.4 (77.1)
Median	139.0	123.0	130.0	126.5
Range	70 to 263	10 to 296	95 to 223	10 to 296
Total episodes of Colitis	5	7	5	17
Average Episodes per subject	1.25	1.00	1.00	1.06
Episode duration (days)‡				
Median	50.0	41.0	28.0	42.0
Range	4 to 79	14 to 218	4 to 110	4 to 218

(%) = Number of subjects with Colitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Colitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

All but 1 case of colitis resolved, and only 1 subject reported more than 1 episode of colitis. Corticosteroids were used to manage colitis in 10 out of 16 subjects.

Table 63: Summary of AEOSI – Hypothyroidism PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Hypothyroidism	25 (7.4)	32 (6.5)	18 (10.0)	75 (7.4)
Time to Onset of First Hypothyroidism (days)†				
Mean (Std)	125.8 (103.0)	97.7 (64.2)	151.2 (114.3)	119.9 (92.9)
Median	84.0	85.5	119.5	105.0
Range	22 to 371	5 to 240	56 to 576	5 to 576
Total episodes of Hypothyroidism	25	33	19	77
Average Episodes per subject	1.00	1.03	1.06	1.03
Episode duration (days)‡				
Median	214.0	232.0	269.0	242.0
Range	14 to 574	6 to 526	31 to 740	6 to 740

(%) = Number of subjects with Hypothyroidism / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hypothyroidism.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Hypothyroidism was reported as not resolved in most patients (66 out of 75 subjects). One subject reported having 2 episodes of hypothyroidism, all other subjects were reported to have a single episode. Corticosteroids (high-dose) were used to manage hypothyroidism in only 2 subjects.

Table 64: Summary of AEOSI – Hyperthyroidism PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Hyperthyroidism	9 (2.6)	9 (1.8)	6 (3.3)	24 (2.4)
Time to Onset of First Hyperthyroidism (days)†				
Mean (Std)	69.0 (76.3)	43.9 (23.0)	172.2 (256.0)	85.4 (138.5)
Median	43.0	43.0	54.0	43.0
Range	1 to 253	15 to 84	6 to 665	1 to 665
Total episodes of Hyperthyroidism	11	9	7	27
Average Episodes per subject	1.22	1.00	1.17	1.13
Episode duration (days)‡				
Median	74.0	43.0	42.5	54.0
Range	10 to 185	28 to 390	29 to 201	10 to 390

(%) = Number of subjects with Hyperthyroidism / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hyperthyroidism.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Two subjects were reported to have 2 episodes of hyperthyroidism, and all other subjects were reported to have a single episode. The event was reported as resolved in 19 of the 24 cases. Corticosteroids were used to manage hyperthyroidism in 2 subjects, who both received high-dose (defined as ⩾40 mg/day of prednisone, or equivalent) corticosteroids. Hyperthyroidism was reported as resolved in both patients.

Table 65: Summary of AEOSI – Thyroiditis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (ApaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Thyroiditis	3 (0.9)	7 (1.4)	1 (0.6)	11 (1.1)
Time to Onset of First Thyroiditis (days)†				
Mean (Std)	37.7 (23.2)	46.0 (33.1)	71.0	46.0 (29.1)
Median	29.0	25.0	71.0	29.0
Range	20 to 64	20 to 106	71 to 71	20 to 106
Total episodes of Thyroiditis	3	7	1	11
Average Episodes per subject	1.00	1.00	1.00	1.00
Episode duration (days)‡				
Median	57.0	192.0	51.0	108.0
Range	43 to 108	22 to 262	51 to 51	22 to 262

(%) = Number of subjects with Thyroiditis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Thyroiditis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Thyroiditis was reported as resolved in 5 subjects and not resolved in 6 subjects. Three of the subjects who reported thyroiditis also reported hyperthyroidism or hypothyroidism.

Table 66: Summary of AEOSI – Hepatic PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Hepatic	5 (1.5)	3 (0.6)	0	8 (0.8)
Time to Onset of First Hepatic (days)†				
Mean (Std)	177.0 (268.4)	17.0 (7.8)	0	117.0 (219.2)
Median	63.0	21.0	0.0	22.0
Range	22 to 651	8 to 22	0 to 0	8 to 651
Total episodes of Hepatic	5	3	0	8
Average Episodes per subject	1.00	1.00	0	1.00
Episode duration (days)‡				
Median	33.0	66.5	0	39.0
Range	8 to 45	66 to 67	0 to 0	8 to 67

(%) = Number of subjects with Hepatic / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hepatic.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Hepatitis resolved in 6 of the 8 cases, was revolving in 1 case, and was ongoing in 1 case (Grade 3 hepatitis, AN 101879 in P002; 10 mg/kg Q3W). Corticosteroids were used to manage hepatitis in 5 out of 8 cases.

Table 67: Summary of AEOSI – Hypophysitis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (ApaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Hypophysitis	5 (1.5)	3 (0.6)	2 (1.1)	10 (1.0)
Time to Onset of First Hypophysitis (days)†				
Mean (Std)	89.6 (82.6)	47.0 (46.5)	106.5 (129.4)	80.2 (77.1)
Median	52.0	28.0	106.5	46.0
Range	1 to 186	13 to 100	15 to 198	1 to 198
Total episodes of Hypophysitis	5	3	2	10
Average Episodes per subject	1.00	1.00	1.00	1.00
Episode duration (days)‡				
Median	104.0	31.0	194.0	102.5
Range	29 to 385	23 to 32	142 to 246	23 to 385

(%) = Number of subjects with Hypophysitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hypophysitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

In 2 patients the event was reported as resolved, in 2 subjects hypophysitis was resolved with sequelae, while in the other 6 patients did not resolve; the ongoing events were Grade 1 or Grade 2 for all but one subject (AN 100674 in P001) at the time of the analysis. No subjects reported more than 1 episode of hypophysitis. Corticosteroids were used to manage hypophysitis in 9 out of 10 subjects.

Table 68: Summary of AEOSI – Adrenal Insufficiency PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Adrenal Insufficiency	1 (0.3)	1 (0.2)	0	2 (0.2)
Time to Onset of First Adrenal Insufficiency (days)†				
Mean (Std)	132.0	108.0	0	120.0 (17.0)
Median	132.0	108.0	0.0	120.0
Range	132 to 132	108 to 108	0 to 0	108 to 132
Total episodes of Adrenal Insufficiency	1	1	0	2
Average Episodes per subject	1.00	1.00	0	1.00
Episode duration (days)‡				
Median	4.0	16.0	0	10.0
Range	4 to 4	16 to 16	0 to 0	4 to 16

(%) = Number of subjects with Adrenal Insufficiency / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Adrenal Insufficiency.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Adrenal insufficiency was reported in 2 subjects who received pembrolizumab in the 1012-subject pooled melanoma population of P001 + P002. Both cases were treated with corticosteroid and the outcome was listed as “not resolved” for patient AN100919 (disease progression persisted, leading to death) and recovered AN101258 for patient improved with corticosteroid treatment. Improvement was registered with corticosteroid treatment.

Table 69: Summary of AEOSI – Uveitis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Uveitis	1 (0.3)	6 (1.2)	1 (0.6)	8 (0.8)
Time to Onset of First Uveitis (days)†				
Mean (Std)	107.0	73.3 (80.3)	225.0	96.5 (86.2)
Median	107.0	50.0	225.0	58.5
Range	107 to 107	13 to 233	225 to 225	13 to 233
Total episodes of Uveitis	1	7	1	9
Average Episodes per subject	1.00	1.17	1.00	1.13
Episode duration (days)‡				
Median	11.0	38.0	137.0	38.0
Range	11 to 11	20 to 265	137 to 137	11 to 265

(%) = Number of subjects with Uveitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Uveitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

All subjects reported a single episode of uveitis, except AN 101867 (P002) who had 2 events. The event resolved in all but 1 subject. Systemic corticosteroids were not used. However, a review of the narratives indicates that 5 subjects received topical corticosteroids to manage uveitis.

Table 70: Summary of AEOSI - Sponsor Assessed Nephritis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Nephritis	1 (0.3)	0	3 (1.7)	4 (0.4)
Time to Onset of First Nephritis (days)†				
Mean (Std)	62.0	0	251.0 (207.7)	203.8 (194.2)
Median	62.0	0.0	353.0	207.5
Range	62 to 62	0 to 0	12 to 388	12 to 388
Total episodes of Nephritis	1	0	3	4
Average Episodes per subject	1.00	0	1.00	1.00
Episode duration (days)‡				
Median	.	0	34.0	34.0
Range	. to .	0 to 0	15 to 99	15 to 99

(%) = Number of subjects with Nephritis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Nephritis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

All 4 events resolved, and no subjects reported more than one episode. Corticosteroids were used in all cases.

Table 71: Summary of AEOSI - Infusion Reactions PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Infusion Reactions	5 (1.5)	12 (2.4)	3 (1.7)	20 (2.0)
Time to Onset of First Infusion Reactions (days)†				
Mean (Std)	253.8 (132.6)	99.1 (147.7)	153.0 (173.2)	145.9 (154.8)
Median	216.0	42.5	98.0	91.5
Range	108 to 421	1 to 521	14 to 347	1 to 521
Total episodes of Infusion Reactions	8	12	3	23
Average Episodes per subject	1.60	1.00	1.00	1.15
Episode duration (days)‡				
Median	2.0	1.0	1.0	1.0
Range	1 to 226	1 to 255	1 to 1	1 to 255

(%) = Number of subjects with Infusion Reactions / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Infusion Reactions.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

All but 4 cases resolved, and only 1 subject (AN 100019 in P002; 2 mg/kg Q3W group) reported more than one episode of infusion reactions. High-dose corticosteroids (defined as ⩾40 mg/day of prednisone, or equivalent) were used to manage the event in only 1 case.

Table 72: Summary of AEOSI – Myositis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Myositis	1 (0.3)	2 (0.4)	1 (0.6)	4 (0.4)
Time to Onset of First Myositis (days)†				
Mean (Std)	192.0	280.0 (253.1)	258.0	252.5 (152.0)
Median	192.0	280.0	258.0	225.0
Range	192 to 192	101 to 459	258 to 258	101 to 459
Total episodes of Myositis	1	2	2	5
Average Episodes per subject	1.00	1.00	2.00	1.25
Episode duration (days)‡				
Median	381.0	86.5	108.5	92.0
Range	381 to 381	81 to 92	80 to 137	80 to 381

(%) = Number of subjects with Myositis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Myositis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Myositis was reported to have resolved in 2 subjects, while in 2 patients the events did not resolve, and were reported as continuing at the time of the analysis. No subjects received corticosteroids for myositis or related events.

Table 73: Summary of AEOSI – Skin Reaction PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

	MK-3475 2 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q3W n (%)	MK-3475 10 mg/kg Q2W n (%)	Total n (%)
Subjects in population	340	492	180	1012
Subjects with Skin	2 (0.6)	9 (1.8)	4 (2.2)	15 (1.5)
Time to Onset of First Skin (days)†				
Mean (Std)	44.5 (57.3)	165.7 (90.6)	253.8 (233.6)	173.0 (144.5)
Median	44.5	172.0	176.5	159.0
Range	4 to 85	33 to 288	71 to 591	4 to 591
Total episodes of Skin	2	9	5	16
Average Episodes per subject	1.00	1.00	1.25	1.07
Episode duration (days)‡				
Median	69.5	22.0	168.0	29.5
Range	13 to 126	4 to 451	8 to 212	4 to 451

(%) = Number of subjects with Skin / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Skin.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).

Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Severe skin AEs was reported as resolved in 11 of the 15 cases. Systemic corticosteroids were used to manage the event in 5 (33%) subjects.

Table 74: Listing of Subjects With AEOSI- Pancreatitis PN001 and PN002 Melanoma Subjects Treated with pembrolizumab (APaT Population)

Subject ID	Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W										
Trial Number=3475-002, Site Number=0088, Subject ID=101285, Gender=F, Race=White, Age=64 Years, Rel Day of Study Medication Discontinuance[1]=										
101285	Treatment Cycle 6	126	Pancreatitis	1 Weeks		2	Y	Y	Interrupted	Resolved
MK-3475 10 mg/kg Q3W										
Trial Number=3475-001, Site Number=0002, Subject ID=000395, Gender=M, Race=White, Age=68 Years, Rel Day of Study Medication Discontinuance[1]=64										
000395	Safety Follow-up	76	Pancreatitis	Continuing	Severe	3	Y	Y	Discontinued	Not Resolved

[1]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.
Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.
(MK-3475 PN001 Database Cutoff Date: 18APR2014).
(MK-3475 PN002 Database Cutoff Date: 12MAY2014).
Data Source: [Ref. 5.3.5.2: P001V02] [Ref. 5.3.5.1: P002V01]

Laboratory findings

A summary of laboratory changes from baseline for study P001 is displayed in Tables 76 and 77

Table 75: P001 Laboratory Abnormalities for Highest Toxicity Grade Parts B1, B2, and D (n=411)

Laboratory Analyte	Grade 1	Grade 2	Grade 3	Grade 4
Albumin decreased	21.7%	16.1%	0.5%	0
Glucose increased	32.4%	10.7%	3.2%	0.5%
Lymphocytes decreased	8.8%	12.9%	7.5%	0.2%
Phosphate decreased	0	12.9%	4.4%	0

Table 76: Clinical AE P001 Parts B1, B2, and D (n=411)

	Regardless of causality		Treatment-related	
Clinical AE	All grades	Grade 3-4	All grades	Grade 3-4
Hypoalbuminemia	3.6%	0.2%	0.2%	0
Hyperglycemia	4.6%	1.0%	0.7%	0.2%
Lymphopenia	1.0%	0.7%	0.5%	0
Hypophosphatemia	2.7%	0.5%	1.0%	0

A summary of laboratory changes from baseline for study P002 compared to chemotherapy is displayed in Tables 77 and 78 (cutoff:12-May-2014).

Table 77: Laboratory Abnormalities for Highest Toxicity Grade P002

	Pembrolizumab (2 mg/kg Q3W), n=178				Pembrolizumab (10 mg/kg Q3W), n=179				Chemotherapy Control arm, n=171			
Laboratory Analyte	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Albumin decreased	21.3%	16.9%	4.5%	0	26.3%	18.4%	0.6%	0	26.3%	12.3%	0.6%	0
Glucose increased	37.6%	16.9%	9.0%	0	49.7%	8.4%	4.5%	0.6%	33.9%	15.8%	5.8%	0
Lympho-cytes decreased	26.4%	18.5%	5.6%	1.1%	18.4%	18.4%	9.5%	0.6%	17.5%	22.8%	9.9%	1.2%
Phosphate decreased	1.7%	9.0%	3.4%	0	3.9%	10.1%	3.4%	0	1.8%	11.7%	1.8%	0

Table 78: Clinical Adverse Events P002

	Pembrolizumab (2 mg/kg Q3W)				Pembrolizumab (10 mg/kg Q3W)				Chemotherapy Control arm			
	Regardless of causality		Drug-related		Regardless of Causality		Drug-related		Regardless of Causality		Drug-Related	
Clinical AE	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
Hypoalbuminemia	2.8%	1.1%	0.6%	0.6%	5.6%	0.6%	0.6%	0	5.3%	0.6%	1.8%	0.6%
Hyperglycemia	5.1%	0.6%	0.6%	0	5.0%	0.6%	0.6%	0	5.8%	1.8%	0.6%	0
Lymphopenia	0	0	0	0	1.1%	0	0.6%	0	1.8	0.6%	0.6%	0
Hypophosphatemia	1.1%	0	0.6%	0	1.7%	0	0.6%	0	2.3%	0	0.6%	0

Data Source: [Ref. 5.3.5.1: P002V01]

Safety in special populations

Safety data by age class have been presented by combined pembrolizumab dose and recommended dose for studies P001 (Parts B1, B2, B3 and D), P002 and P006.

Tables below shows safety data by age in patients treated with pembrolizumab combined doses (B1, B2, B3 and D) and pembrolizumab 2 mg/kg Q3W (B1, B2 and D) on Study P001:

Table 79: Safety in Special Population pembrolizumab combined doses P001 (Parts B1, B2, B3 D)

MedDRA Terms	Age <65 number (percentage) N=397	Age 65-74 number (percentage) n=175	Age 75-84 number (percentage) n=66	Age 85+ number (percentage) n=17
Total AEs	393 (99.0)	171 (97.7)	64 (97.0)	16 (94.1)
Serious AEs – Total	133 (33.5)	57 (32.6)	28 (42.4)	8 (47.1)
- Fatal	1 (0.3)	3 (1.7)	4 (6.1)	1 (5.9)
- Hospitalization/prolong existing hospitalization	120 (30.2)	45 (25.7)	23 (34.8)	8 (47.1)
- Life-threatening	16 (4.0)	10 (5.7)	3 (4.5)	2 (11.8)
- Disability/incapacity	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
- Other (medically significant)				
AE leading to drop-out	36 (9.1)	23 (13.1)	12 (18.2)	1 (5.9)
Psychiatric disorders	86 (21.7)	38 (21.7)	8 (12.1)	7 (41.2)
Nervous system disorders	185 (46.6)	79 (45.1)	28 (42.4)	7 (41.2)
Injury, poisoning, and procedural complications	61 (15.4)	32 (18.3)	7 (10.6)	1 (5.9)
Cardiac disorders	25 (6.3)	18 (10.3)	13 (19.7)	4 (23.5)
Vascular disorders	61 (15.4)	34 (19.4)	12 (18.2)	2 (11.8)
Cerebrovascular disorders (including cerebral infarction, cerebrovascular accident, ischaemic stroke, and transient ischaemic attack)	2	2	1	1
Infections and infestations	165 (41.6)	83 (47.4)	26 (39.4)	7 (41.2)
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	61	28	17	3
<other AE appearing more frequently in older patients>				

Safety data by age class for P002 are displayed in the following tables by recommended dose, combined pembrolizumab treatment group and chemotherapy arm:

Table 80: Safety in Special Population pembrolizumab combined doses P002

MedDRA Terms	Age <65 number (percentage) N=205	Age 65-74 number (percentage) N=94	Age 75-84 number (percentage) N=54	Age 85+ number (percentage) N=4
Total AEs	200 (97.6)	94 (100.0)	52 (96.3)	4 (100.0)
Serious AEs – Total	81 (39.5)	44 (46.8)	24 (44.4)	2 (50.0)
- Fatal	10 (4.9)	8 (8.5)	3 (5.6)	0 (0.0)
- Hospitalization/prolong existing hospitalization	75 (36.6)	42 (44.7)	21 (38.9)	2 (50.0)
- Life-threatening	4 (2.0)	0 (0.0)	5 (9.3)	0 (0.0)
- Disability/incapacity	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Other (medically significant)				
AE leading to drop-out	20 (9.8)	14 (14.9)	9 (16.7)	1 (25.0)
Psychiatric disorders	31 (15.1)	11 (11.7)	11 (20.4)	0 (0.0)
Nervous system disorders	65 (31.7)	35 (37.2)	16 (29.6)	0 (0.0)
Injury, poisoning and procedural complications	24 (11.7)	12 (12.8)	8 (14.8)	0 (0.0)
Cardiac disorders	17 (8.3)	7 (7.4)	4 (7.4)	0 (0.0)
Vascular disorders	21 (10.2)	11 (11.7)	7 (13.0)	0 (0.0)
Sum of cerebral infarction, cerebrovascular accident, ischaemic stroke, and transient ischaemic attack	1	0	0	0
Infections and infestations	68 (33.2)	42 (44.7)	19 (35.2)	1 (25.0)
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	24	13	8	0
<other AE appearing more frequently in older patients>				

For Study P006, safety data are presented by combined pembrolizumab arms (10 mg/kg Q3W and Q2W).

Table 81: Safety in Special Population pembrolizumab combined treatment groups P006

MedDRA Terms	Age <65 number (percentage) N=304	Age 65-74 number (percentage) N=168	Age 75-84 number (percentage) N=70	Age 85+ number (percentage) N=13
Total AEs	294 (96.7)	165 (98.2)	68 (97.1)	12 (92.3)
Serious AEs – Total	77 (25.3)	44 (26.2)	22 (31.4)	5 (38.5)
- Fatal	5 (1.6)	5 (3.0)	1 (1.4)	1 (7.7)
- Hospitalization/prolong existing hospitalization	69 (22.7)	40 (23.8)	21 (30.0)	4 (30.8)
- Life-threatening	11 (3.6)	8 (4.8)	5 (7.1)	0 (0.0)
- Disability/incapacity	2 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)
- Other (medically significant)				
AE leading to drop-out	22 (7.2)	19 (11.3)	8 (11.4)	1 (7.7)
Psychiatric disorders	49 (16.1)	35 (20.8)	14 (20.0)	2 (15.4)
Nervous system disorders	107 (35.2)	54 (32.1)	23 (32.9)	7 (53.8)
Injury, poisoning and procedural complications	32 (10.5)	19 (11.3)	8 (11.4)	3 (23.1)
Cardiac disorders	19 (6.3)	12 (7.1)	8 (11.4)	2 (15.4)
Vascular disorders	44 (14.5)	17 (10.1)	14 (20.0)	1 (7.7)
Sum of cerebral infarction, cerebrovascular accident, ischaemic stroke, and transient ischaemic attack	0	0	1	0
Infections and infestations	121 (39.8)	75 (44.6)	30 (42.9)	2 (15.4)
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	32	21	13	3
<other AE appearing more frequently in older patients>				

The applicant did not submit safety data on different ethnic groups (see safety discussion).

Safety related to drug-drug interactions and other interactions

The applicant did not submit studies on drug-drug interactions (see clinical safety discussion).

Discontinuation due to adverse events

In the IPI-refractory melanoma patient population of study P002, 10.1%, and 14.5%, of patients in the 2 mg/kg Q3W and 10 mg/kg Q3W pembrolizumab arms, respectively, and 11.7% in the chemotherapy control arm discontinued treatment due to AEs.

In the pooled melanoma population (P001+P002), AEs leading to discontinuation were reported in 8.2% of patients in the 2 mg/kg Q3W, in 12.4% of patients in 10 mg/kg Q3W, and in 15.0% of patients in 10 mg/kg Q2W treatment arms, respectively.

With the exception of *General disorders and administration site conditions* SOC (n=24,2.4%), no SOC had an overall incidence >2.0%. However, within a dose group, the *Respiratory, thoracic and mediastinal disorders* (driven by pneumonitis, n=3, 1.7% overall) SOC and the *Nervous system disorders* SOC (n=5, spread out over 5 different AEs) had an incidence of 2.8% in the 10 mg/kg Q2W treatment arms. Also, the *Gastrointestinal disorders* SOC had an incidence of 2.2% in both the 10 mg/kg Q3W and 10 mg/kg Q2W treatment arms, which was driven by colitis (n=4, 0.8%) and diarrhoea (n=2, 1.1%), respectively.

Overall, 44 (4.3%) subjects discontinued treatment due to drug-related AEs, including 2.9% of subjects in the 2 mg/kg Q3W group, 4.5% of subjects in the 10 mg/kg Q3W group, and 6.7% of subjects in the 10 mg/kg Q2W group. Across all doses, only pneumonitis and colitis were drug-related AEs leading to discontinuation that occurred in 5 or more subjects (n=7 and n=5, respectively). Other drug-related AEs that caused discontinuation in more than 1 subject were: hyperthyroidism, hypophysitis, hypopituitarism, fatigue, generalized oedema, and autoimmune hepatitis which all occurred in 2 subjects each.

Post marketing experience

The applicant submitted data on post-marketing experience. Keytruda (pembrolizumab) was approved in the U.S. on 04-Sep-2014 for the treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

The safety reporting database was queried to retrieve all SAEs and non-serious cases spontaneously reported in the US in temporal association with pembrolizumab through 30-Nov-2014. A total of 57 cases, including 28 SAEs, were identified. The most commonly reported SAEs were the PTs of death (8 events), malignant melanoma (4 events), adverse event unspecified (3 events), disease progression (2 events), and metastatic melanoma (2 events). All other SAE terms were reported only once. Seventeen of the 57 cases reported a fatal outcome, with the vast majority associated with either disease progression and/or complications of on-going medical conditions at the time of the fatal outcome. No safety signals have been identified.

2.6.1. Discussion on clinical safety

The pembrolizumab safety database submitted to support the application consisted of safety data from 1012 patients enrolled in study P001 (Part B1, B2, B3 and D) and in study P002. This includes comparative safety data versus standard of care chemotherapy in patients with advanced melanoma refractory to ipilimumab (Study P002).

In addition, early safety results from the first interim analysis of P006 (data cutoff date 3 Sep 2014) providing comparative data versus ipilimumab in IPI-naïve advanced melanoma have also been provided. However, a pooled analysis was not feasible at the time of the interim analysis, hence section 4.8 of the SmPC includes all ADRs evaluated in 1012 patients across three doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies P001 and P002.

No major differences in the safety profile were observed between the 2 mg/kg dose and the 10 mg/kg dose when given on a Q3W schedule. Overall 340 received pembrolizumab at the recommended dose of 2 mg/kg Q3W proposed for the treatment of advanced melanoma.

In the pooled melanoma population (Studies P001 and P002) 79% of patients reported drug-related AEs, of which 13.5% were Grade 3-5. The most common adverse drug reactions observed were in the General disorders and administration site conditions (47.7%), Skin and subcutaneous tissue disorders (46.3%), Gastrointestinal disorders (31.2%), Musculoskeletal and connective tissue disorders (23.6%), Respiratory, thoracic and mediastinal disorders (14.4%), Nervous System Disorders (14.2%), Metabolism and nutrition disorders (12.2%) SOCs. Severe adverse drug reactions were more frequently reported in Gastrointestinal disorders (2.7%), General disorders and administration site conditions (1.6%) and Respiratory, thoracic and mediastinal disorders (1.6%).

A higher rate of adverse drug reactions was reported in P002 with chemotherapy (80.7%) in comparison to pembrolizumab (68% at 2 mg/kg and 74.3% at 10 mg/kg Q3W). In particular, drug-

related Grade 3-5 AEs were registered in 26.3% of patients treated with chemotherapy, while the rate in patients who received pembrolizumab was 11.2% and 14% in the 2 mg/kg Q3w and 10 mg/kg Q3W, respectively.

In both IPI-refractory patients of study P002 and IPI naïve patients of study P006, the Grade ≥3 AEs tended to occur later in the pembrolizumab arms in comparison with standard chemotherapy or ipilimumab.

An analysis of immune-related ADRs (irADRs) based on pooled data from studies P001 (cut-off 18 Apr 2014) and P002 (12 May 2014), including 1012 melanoma patients, together with a cross-program medical case review of SAEs and non-SAEs events of clinical interest from all clinical studies regardless of indication (3251 subjects) and the melanoma expanded access program (1787 subjects) has been performed. Following this safety review, Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis), Pneumonitis, Colitis and Hepatitis were confirmed as immune-related events causally associated with pembrolizumab, and the following adverse reactions: Hypophysitis, including Hypopituitarism and Secondary Adrenal Insufficiency; Uveitis; Type 1 Diabetes Mellitus, Nephritis, Pancreatitis and Infusion-Related Reaction, Myositis and Severe Skin Reaction have been added to the list of Important Identified Risk. Based on updated pooled data, the following cumulative incidences were calculated: 7.4% for hypothyroidism, 2.6% for pneumonitis, 2.4% for hyperthyroidism, 2.0% for infusion-related reaction, 1.6% for colitis, 1.5% for severe skin-reactions, 1.1% for thyroiditis, 1.0% for hypophysitis, 0.8% for hepatitis, 0.8% for uveitis, 0.4% for nephritis, 0.4% for myositis, 0.2% for adrenal insufficiency, 0.2% for pancreatitis, 0.1% for type 1 diabetes mellitus, (see section 4.4 and 4.8 of the SmPC for management of immune-related ADRs). These ADRs have been included in the RMP as important identified risks. In general, the duration of treatment seems to correlate with the occurrence of adverse events of special interest (AEOSI). In order to minimise the risks associated with these ADRs and to raise awareness to healthcare professionals and patients/carers on the early identification and detection of the signs and symptoms these ADRs, the CHMP imposed the company to provide educational material will be distributed by the MAH. This was considered by the CHMP as a condition to the market authorisation (see Annex II of the SmPC).

Since patients with severe (grade 3) irADRs on prior IPI requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior IPI were not eligible in Study P001 and P002, and data regarding AEs on prior ipilimumab treatment were not systematically collected, it is not possible to draw any conclusion on this issue at the present stage. Patients that had active systemic autoimmune disease, patients with HIV or hepatitis B or C were excluded from enrolling in the studies. These patient populations are included in the RMP as missing information. The trend observed versus a lower incidence of immune-related AEs in ipi-treated in comparison to ipi-naïve patients may be biased and driven by an unintended selection of patients. The use of pembrolizumab in patients with severe (grade 3) irADRs on prior IPI requiring corticosteroids for > 12 weeks, or life-threatening irADRs on prior IPI is considered as missing information, and the lack of data is included in the SmPC section 4.4.

A review of gastrointestinal perforation and colitis reports was performed by the Applicant involving more than 5000 patients who received pembrolizumab in clinical trials and in the Expanded Access Program. Based on the potential life-threatening nature of the event (1 fatal case was reported) and the limited information that hampers the real estimation of the events, GI perforation secondary to colitis has been added as a potential risk in the RMP and reflected in the SmPC Section 4.4.

There is no strong evidence supporting an influence of age on the safety profile, although a trend to a higher rate of drug-related AEs and discontinuations due to AEs has been reported in older patients. Based on submitted data no major differences in the pembrolizumab safety profile appear by age classes in both ipi-naïve and ipi-treated patients.

Only two patients in study 001 tested positive for ADA to pembrolizumab and the presence of these antibodies seemed to have no impact on pembrolizumab PK. However, in the majority of ADA negative samples at the screening and in the confirmatory assays (1116 out of 2058), pembrolizumab concentration was above the drug tolerance level (25 µg/mL). Drug tolerance was shown to interfere to a different degree in the two dose groups (all dose regimens and 2 mg/Kg Q3W). While 64% of patients, who received 2mg/kg, were assessable for immunogenicity, in the overall population also including 10 mg/kg dose regimens, it was only 27%. Given the low number of evaluable patients for immunogenicity and the missing validation report for ADAs, immunogenicity has been included as important potential risks.

The applicant did not submit safety data on various ethnic groups. This has been included in the RMP as missing information.

Based on the current assessment of events with fatal outcome from studies P001, P002, P006, P010, and P012, as of 31 Aug 2014, overall 15 fatal cases considered drug-related by the investigator have been reported. Pneumonitis fatal events reported in NSCLC patient has been included in section 4.8 of the SmPC and in the RMP as important identified risks. Fatal events for pembrolizumab will be monitored by routine pharmacovigilance activities.

The long term safety of pembrolizumab is unknown and has been included as missing information in the RMP. As some patients experience a relatively prolonged response to pembrolizumab, several ongoing studies in the PhV plan are being conducted which will provide further evidence on the long term safety of pembrolizumab treatment (See section 2.8 – pharmacovigilance plan).

Safety data is missing from patients who have previously had a severe hypersensitivity reaction to treatment with another mAb as the exclusion criteria from the studies excluded this patient population. Therefore, this has been included as missing information in the RMP.

There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (see SmPC section 5.1). The safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established. No data are available.

Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab (see section 4.7).

There is no information on overdose with pembrolizumab. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted (SmPC section 4.9).

The use of keytruda is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (SmPC section 4.3).

Special precautions for disposal and other handling are included in section 6.6 of the SmPC.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The ADRs reported for patients being treated with pembrolizumab appear to be mostly of low grade and manageable. It was noted that immunological ADRs include skin, gastrointestinal, endocrine, hepatic, pulmonary and renal events. These are managed appropriately with the recommendations as stated in the SmPC section 4.2, 4.4 and 4.8 and are also addressed in the RMP. However, in order to

raise the awareness of health care professionals, patients and/or their caregivers about the potential for immune-related adverse events and infusion-related reactions, which are considered important identified risks, the CHMP has imposed an educational programme for both healthcare professionals and patients to help on the identification and detection of the signs and symptoms relevant to the early recognition/identification of those ADRS.

In conclusion, the CHMP considers that the safety and tolerability of pembrolizumab has been described appropriately and is acceptable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

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

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Table 82: Summary of Safety Concerns

Important identified risks	Immune-Related Adverse Reactions • Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) • Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) • Uveitis • Colitis • Pancreatitis • Hepatitis • Type 1 diabetes mellitus • Myositis • Nephritis • Pneumonitis • Severe Skin Reactions Infusion-Related Reactions
Important potential risks	Immune-Related Adverse Events • Gastrointestinal perforation secondary to colitis

	Immunogenicity
Missing information	• Safety in patients with moderate or severe hepatic impairment • Safety in patients with severe renal impairment • Safety in patients with active systemic autoimmune disease • Safety in patients with HIV or Hepatitis B or Hepatitis C • Safety in pediatric patients • Reproductive and lactation data • Long term safety • Safety in various ethnic groups • Potential pharmacodynamic interaction with systemic immunosuppressants • Safety in patients with previous hypersensitivity to another monoclonal antibody • Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs

Pharmacovigilance plan

Table 83: Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission final reports
Clinical trial Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma (P001) (Category 3)	Primary Objectives 1. To evaluate and characterize the tolerability and safety profile of single agent MK-3475 in adult patients with unresectable advanced carcinoma (including NSCLC or MEL). 2. To evaluate anti-tumor activity of MK-3475 in MEL and NSCLC per RECIST 1.1. 3. To evaluate the extent of tumor response that correlates with the degree of biomarker positivity in the tumors of ipilimumab naïve patients treated with MK-3475 with the intent that the cut point for the PD-L1 assay will be explored and refined with tumor samples from ipilimumab-naïve MEL. 4. To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in unselected MEL	-Immune-related adverse reactions of hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), uveitis, colitis, pancreatitis, hepatitis, Type 1 diabetes mellitus, myositis, nephritis, pneumonitis, severe skin reactions, infusion-related reactions, gastrointestinal perforation secondary to colitis, immunogenicity -Long term safety	Started	Final Study Report Dec 2016

Study / activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission final reports
	refractory to ipilimumab patients and MEL patients refractory to ipilimumab with PD-L1 expressing tumors. 5. To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1.			
Clinical trial Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma (P002) (Category 3)	Primary Objectives 1. To evaluate the progression-free-survival (PFS) in patients with ipilimumab refractory advanced MEL receiving either MK-3475 or chemotherapy. 2. To evaluate the overall survival (OS) in patients with ipilimumab refractory advanced MEL receiving either MK-3475 or chemotherapy. Secondary Objectives include: To evaluate safety, tolerability and adverse experience profile of single agent MK-3475 2 mg/kg and 10 mg/kg.	-Immune-related adverse reactions of hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), uveitis, colitis, pancreatitis, hepatitis, Type 1 diabetes mellitus, myositis, nephritis, pneumonitis, severe skin reactions, infusion-related reactions, gastrointestinal perforation secondary to colitis, immunogenicity -Long term safety	Started	Final Study Report Jan 2017
Clinical trial A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to IPI in Patients with Advanced Melanoma (P006) (Category 3)	Primary Objectives 1. To evaluate progression-free-survival (PFS) in patients with advanced MEL receiving either MK-3475 or IPI. 2. To evaluate overall survival (OS) in patients with advanced MEL receiving either MK-3475 or IPI. Secondary Objectives include: To evaluate safety,	-Immune-related adverse reactions of hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), uveitis, colitis, pancreatitis, hepatitis, Type 1 diabetes mellitus, myositis, nephritis, pneumonitis, severe skin reactions, infusion-related	Started	Final Study Report Jan 2017

Study / activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission final reports
	tolerability and adverse experience profile of MK-3475 versus IPI.	reactions, gastrointestinal perforation secondary to colitis, immunogenicity -Long term safety		
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)	1.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. 2. To characterize the pharmacokinetics (PK) 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. 3. To determine the safety and tolerability of pembrolizumab based on AEs and clinical and laboratory measures in 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. 4. To evaluate anti-tumor activity of pembrolizumab in children from 6 months to <18 years of age within each tumor type including advanced melanoma or a	-Possible immune-related adverse reactions of hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), uveitis, colitis, pancreatitis, hepatitis, Type 1 diabetes mellitus, myositis, nephritis, pneumonitis, severe skin reactions, infusion-related reactions, gastrointestinal perforation secondary to colitis, immunogenicity -Safety in pediatric patients	Started	Final Study Report July 2019

Study / activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission final reports
	PDL1 positive advanced, relapsed or refractory solid tumor or lymphoma based on RECIST 1.1.			

Risk minimisation measures

Table 84: Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks: Immune-Related Adverse Reactions		
Hypophysitis (including hypopituitarism and secondary adrenal insufficiency)	The risk of the immune-related adverse reaction of hypophysitis (hypopituitarism and secondary adrenal insufficiency) 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
Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis)	The risk of the immune-related adverse reaction of thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis) 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
Uveitis	The risk of the immune-related adverse reaction ofuveitis 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.	Educational materials

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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
Pancreatitis	The risk of the immune-related adverse reaction of pancreatitis 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.	Educational materials
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
Type 1 Diabetes Mellitus	The risk of the immune-related adverse reaction of type I Diabetes Mellitus 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
Myositis	The risk of the immune-related adverse reaction of myositis 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.	Educational materials
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

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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
Severe Skin Reactions	The risk of the immune-related adverse reaction of severe skin reactions 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.	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		
Gastrointestinal perforation secondary to colitis	None	None
Important Potential Risks: Immunogenicity		
Immunogenicity	The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 5.1.	None
Missing Information		
Safety in patients with moderate or severe hepatic impairment	The missing information of safety in patients with moderate or severe hepatic impairment is described in the SmPC, Section 4.2.	None
Safety in patients with severe renal impairment	The missing information of safety in patients with severe renal impairment is described in the SmPC, Section 4.2.	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 Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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 4.5.	None
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 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.	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Pembrolizumab, an antibody that binds to PD-1 and blocks binding to the natural ligand PD-L1 and PD-L2, has shown significant treatment benefit in terms of ORR and DCR , together with preliminary data on the duration of stable disease, duration of response, PFS and OS in both IPI-refractory/treated and IPI-naïve patients, respectively, in the open label phase 1 study P001.

In IPI-refractory patients (cohort B2), ORR (25.9% and 26.3%) and there were a total of 43 confirmed objective responses, with duration ranging from 12+ to 62+ weeks at the time of the analysis. The median time to response was 12 weeks (range 7-48).

In IPI-naïve patients (cohort D), ORR (33.3% and 40.43%), and the duration of response ranged from 6+ to 61+ weeks across both arms. The median time to response was 12 weeks (range 11-39) and 83% of patients had non-PD at the time of the analysis.

Further data from study P002, a randomized controlled trial versus chemotherapy in IPI-refractory advanced melanoma patients also showed a clinically relevant result in terms of PFS of with HR: 0.57 (95%CI 0.45-0.73; p-value <0.0001). OS was not statistically significant at the time of the interim analysis (median OS 11.4 [HR:0.88; 95%CI 10.2- not reached); p-value=0.229])

Early results from the randomized, controlled, phase III study P006 comparing pembrolizumab (10 mg/kg Q3W and 10 mg/kg Q2W) to ipilimumab in IPI-naïve advanced melanoma patients showed compelling results for PFS and OS where both pembrolizumab arms met the pre-specified criteria for a positive PFS outcome at the first interim analysis, with a HR of 0.58 for both treatment arms (individually) compared to IPI (one-sided p-value <0.00001 in both comparisons, favoring pembrolizumab). Median PFS was 5.5 and 4.1 months for pembrolizumab 10 mg/kg Q2W and 10 mg/kg Q3W arms compared to 2.8 months for IPI. After 6-months, 46-47% of patients were alive and progression free on pembrolizumab, and 27% on IPI. The hazard ratio for OS is 0.63 (p=0.00052) for pembrolizumab 10 mg/kg Q2W over the control arm and 0.69 (p=0.00358) for pembrolizumab 10 mg/kg Q3W over the control arm, respectively, with no difference between the two pembrolizumab arms compared to each other (HR 0.91, p=0.51319) . The median OS has not yet been reached in all three arms, and the 12-month OS rates are 74.1% (95% CI: 68.5%, 78.9%) and 68.4% (95% CI: 62.5%, 73.6%) for pembrolizumab at Q2W and Q3W, respectively, compared to 58.2% (95% CI: 51.8%, 64.0%) in the control arm.

Uncertainty in the knowledge about the beneficial effects

There is some uncertainty in the knowledge of pembrolizumab in the long term efficacy in naïve and previously untreated patients as the efficacy data submitted for both studies P002 and P006 were based on interim analyses. Therefore, a PAES to confirm the long term efficacy of pembrolizumab were imposed as condition to the MA and reflected in the Annex II.

A numerical trend towards a lower efficacy of the 2mg/kg Q3W dose compared to 10 mg/kg Q3W dose in both PD-L1 negative and BRAFV600-mutated patients was observed in studies P001 and P002, however, no exposure-response relationship for pembrolizumab both subgroups could be demonstrated in the integrated exposure-response analysis. Although it is acknowledged that the benefit of pembrolizumab in the overall population as well as in the PD-L1 negative and BRAFV600-mutated patients subgroup analyses, has been demonstrated, this evidence is currently based on a relatively

limited number of patients at the recommended dose of 2 mg/kg Q3W. Therefore, a PAES to have the updated efficacy data for the patients is required to further characterise the magnitude of the treatment effect in these two subgroups was imposed as a condition to the MA and reflected in Annex II.

Risks

Unfavourable effects

The pembrolizumab safety database submitted consisted of safety data from 1012 patients enrolled in study P001 (Part B1, B2, B3 and D) and in study P002. In addition, early safety results from the first interim analysis of P006 (data cutoff date 3 Sep 2014) also provided further safety information for patients treated with pembrolizumab. No major differences in the safety profile were observed between the 2 mg/kg dose and the 10 mg/kg dose when given on a Q3W schedule. Overall 340 received pembrolizumab at the recommended dose of 2 mg/kg Q3W proposed for the treatment of advanced melanoma.

The most frequently reported ADRs (>10%) with the 2 mg/kg dose Q3W were fatigue, pruritus, rash, arthralgia, diarrhoea, decreased appetite, cough, and vitiligo.

Serious ADRs were more frequently reported in Gastrointestinal disorders (2.7%), General disorders and administration site conditions (1.6%) and Respiratory, thoracic and mediastinal disorders (1.6%).

On the basis of the mechanism of action, several immune-mediated AEs were identified as ADRs. Among these, those observed with an incidence $\geq$ 1% were hypothyroidism, pneumonitis, hyperthyroidism, colitis, severe skin-reactions, thyroiditis, and hypophysitis, and in addition severe skin reactions and infusion-related reaction. Other immune-related ADRs were gastrointestinal perforation, hypopituitarism, secondary adrenal insufficiency, thyroiditis, uveitis, pancreatitis,type 1 diabetes mellitus, hepatitis, nephritis, and myositis.

Uncertainty in the knowledge about the unfavourable effects

AEs of special interest will be systematically assessed within ongoing and planned studies (see RMP). Gastrointestinal perforation secondary to colitis and immunogenicity have been defined as important potential risk and are appropriately managed through the RMP and SmPC. The uncertainty in relation to the safety in the patient populations described in the missing information in the RMP will be handled through routine risk minimisation measures and/or routine pharmacovigilance activities.

Benefit-risk balance

Importance of favourable and unfavourable effects

Consistent evidence of a treatment benefit has been generated across the three main studies submitted in support of pembrolizumab in the treatment of advanced melanoma. The updated data for P001 supports the activity and benefit of pembrolizumab in ipi-refractory and ipi-naive advanced melanoma patients in terms of proportion of responders and duration of response. In addition, the interim results from P002 comparing pembrolizumab with standard chemotherapy strengthen the evidence of treatment benefit in IPI-refractory melanoma patients in terms of PFS. The top line results in IPI naïve melanoma patients from study P006 show a clinically meaningful advantage of pembrolizumab over ipilimumab in terms of PFS.

The magnitude of treatment effect is compelling and clinically relevant for both the IPI-refractory melanoma patient population, as well as in the IPI-naïve patients. Furthermore, the safety profile of pembrolizumab appears manageable and compares favorably with both chemotherapy and ipilimumab.

Benefit-risk balance

Based on the totality of the data from the interim results from studies P002 and P006 as well as the results from study P001, the benefits of pembrolizumab treatment in advanced (metastatic or unresectable) melanoma patients outweighed the risks. Therefore, the CHMP considers that the benefit-risk balance for pembrolizumab in the proposed indication is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Keytruda as monotherapy indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of KEYTRUDA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness about the potential:

- immune mediated adverse events
- infusion related reactions

associated with KEYTRUDA use, how to manage them and to enhance the awareness of patients and/or their caregivers on the signs and symptoms relevant to the early recognition/identification of those adverse events.

The MAH shall ensure that in each Member State where KEYTRUDA is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use KEYTRUDA have access to/are provided with the following educational package:

- Physician educational material
- Patient educational material

The physician educational material should contain:

- The Summary of Product Characteristics
- Healthcare Professional FAQ Brochure

The Healthcare Professional FAQ Brochure shall contain the following key elements:

- List of important immune-related adverse reactions (irARs) and their symptoms including precautions and treatment, as outlined in section 4.4 of the Summary of Product Characteristics (SmPC):
    - Immune-related hypophysitis (including hypopituitarism and secondary adrenal insufficency)
    - immune-related pneumonitis
    - Immune-related thyroid disorders (including hypothyroidism and hyperthyroidism)
    - Immune-related uveitis
    - Immune-related colitis
    - Immune-related pancreatitis
    - Immune-related hepatitis
    - Immune-related Type 1 Diabetes Mellitus
    - Immune-related myositis
    - Immune-related nephritis

- Immune-related severe skin reactions
- Infusion-related adverse reactions

- Details on how to minimise the safety concerns through appropriate monitoring and management
- Reminder to distribute the Patient Information Brochure and patient alert card

The patient educational material should contain:

- Patient Information Brochure
- The patient alert card

The Patient Information Brochure and Patient alert card shall contain the following key elements:

- Description of the main signs or symptoms of the irARs and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional first
- The importance of carrying the Patient Alert Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with Keytruda

- **Obligation to complete post-authorisation measures**

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

Description	Due date
1. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma – Final Study Report	1Q 2017
2. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P006: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma – Final Study Report	1Q 2017

3. Post-authorisation efficacy study (PAES): In order to confirm the benefit in BRAF V600 mutant and in PD-L1 negative patient subgroups at the recommended dose, the MAH should provide updated analyses from Study P001 and P002: • Updated efficacy data in subgroups comparing 2 vs 10 mg/kg Q3W from the P002 final analysis. • Efficacy data in subgroups comparing the 2 vs 10 mg/kg Q3W from P001, using the data cut-off date of 18-Oct-2014 from Parts B2 and D of P001 by dose level.	1Q 2017 3Q 2015
4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Although PD-L1 status is predictive of response in advanced melanoma patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by IHC (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing melanoma studies (P001, P002 and P006): • Comparison between PD-L1 IHC staining in archival tissue vs newly obtained • Comparison of PD-L1 IHC between pre and post treatment tumor tissues • Data on the Nanostring RNA gene signature • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling • Data on Immune cell profiling (peripheral blood)	1Q 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that pembrolizumab is qualified as a new active substance.