18 October 2018
EMA/800978/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0047

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ADA	Antidrug antibodies
AE(s)	Adverse event(s)
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ASaT	All Subjects as Treated
BICR	Blinded independent central review
BRAF	B-rapidly accelerated fibrosarcoma
CI	Confidence interval
CLND	Complete lymph node dissection
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DMFS	Distant metastasis-free survival
EC50	Half-maximal effective concentration
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D™	European Quality of Life Five-Dimensions Questionnaire EQ-5D™ is a trademark of the EuroQol Research Foundation
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastro-esophageal junction
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony stimulating factor
HL	Hodgkin lymphoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQOL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	Interferon
IgG	Immunoglobulin G
IL-2	Interleukin-2
INR	International Normalization Rate
IPI	Ipilimumab
ITT	Intent-to-treat
IV	Intravenous

KM	Kaplan-Meier
LN	Lymph node
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability − high
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung carcinoma
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRFS2	Progression/recurrence-free survival 2
PT	Preferred term
Q3W	Every 3 weeks
QLQ-C30	Quality of Life Core Questionnaire, Version 3.0
QOL	Quality of life
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-free survival
RSD	Reference Safety Dataset
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SOC	System organ class
TNM	Tumor, Node, Metastases

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 11 April 2018 an application for a variation.

The following variation was requested:

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

Extension of Indication to include (as monotherapy) adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection, based on study KEYNOTE-054; a randomized, double-blind, phase 3 study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), undertaken to evaluate adjuvant therapy with pembrolizumab compared to placebo in patients with resected high-risk melanoma (Stage IIIA [> 1 mm lymph node metastasis], IIIB and IIIC). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. An updated RMP version 17.1 was provided as part of the application.

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0043/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP on 20 November 2014 (EMEA/H/SA/2437/6/2014/II). The Scientific advice pertained to clinical aspects of the dossier. Questions related to the design element of KEYNOTE-054 such as study population, comparator, dose, endpoints and proposed analysis plan.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	11 April 2018
Start of procedure:	28 April 2018
CHMP Co-Rapporteur Assessment Report	22 June 2018
CHMP Rapporteur Assessment Report	28 June 2018
PRAC Rapporteur Assessment Report	29 June 2018
PRAC Outcome	12 July 2018
CHMP members comments	20 July 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 July 2018
Request for supplementary information (RSI)	26 July 2018
CHMP Rapporteur Assessment Report	25 September 2018
CHMP members comments	8 October 2018
Updated CHMP Rapporteur Assessment Report	12 October 2018
Opinion	18 October 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The MAH submitted a variation to the marketing authorisation to extend the indication to include (as monotherapy) adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Melanoma is a malignant tumour that originates from melanocytic cells and primarily involves the skin, causing 90% of skin cancer mortality[1]. The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12–25 in Nordic countries, and a disparity in the mortality-to-incidence ratios between Western and Eastern European countries has been observed[2] . Its incidence continues to rise worldwide. Median age at diagnosis is 59 years. However, melanoma is not

[1] Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Bastholt L, Grob JJ, Malvehy J, Newton-Bishop J, Stratigos AJ, Pehamberger H, Eggermont AM; European Dermatology Forum (EDF); European Association of Dermato-Oncology (EADO); European Organisation for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. Eur J Cancer. 2016 Aug;63:201-17

[2] Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U, et al. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.
Ann Oncol. 2015 Sep;26(Suppl 5):v126-32

uncommon among individuals younger than 30 years, being the second most commonly diagnosed cancer (after lymphomas) among adolescents and young adults[3]. The major environmental risk factor for melanoma is ultraviolet (UV) radiation. Increased UV light exposure of a genetically predisposed population seems to be, at least in part, responsible for an ongoing rise in incidence[2].

2.1.3. Biologic features, aetiology and pathogenesis

For adjuvant treatment in melanoma, surgical excision is the primary treatment for melanoma. Sentinel lymphnode biopsy (SNLB) in melanoma with a tumour thickness of >1 mm and >0.75 mm and additional risk factors such as ulceration or mitotic rate is recommended for staging[2]. A complete lymphadenectomy of regional LNs must be discussed with the patient, if the sentinel node was found positive for metastases. Among patients with a positive SLNB, additional positive non-sentinel lymphnodes are reported in about 20% of the CLND specimens (NCCN V2.2018). However, this procedure offers a relapse-free survival but did not appear to increase melanoma specific survival[2,4, 7].

After complete resection, adjuvant therapy is offered to patients without evidence of macroscopic metastases but at high risk of having microscopic metastases and higher risk of relapse.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Approximately 90% of melanomas are diagnosed as primary tumours without evidence of metastasis. The outcome of melanoma depends on the stage at presentation. For early-stage melanoma, surgical resection is the standard treatment and is associated with an excellent long-term survival prognosis for stage I (98%) and stage II (90%). However, patients with stage III disease, who have regional involvement at diagnosis, are at higher risk or recurrence after locoregional resections. Lymph node tumour burden at the time of staging, ulceration, and Breslow thickness of the primary melanoma are the most predictive independent factors for survival in patients with stage III disease.

Staging of melanoma as of January 2018 is now performed using the AJCC 8th edition TNM classification[5]; however, at the time of KEYNOTE-054 protocol development and initiation of subject enrollment, the AJCC 7th edition was in effect for TNM staging.

Table 1: AJCC Melanoma Classification - 7th and 8th editions

Stage III Category	AJCC Edition 7 (2009)	AJCC Edition 8 (2017)
IIIA	T1-4a/ N1a/ M0 T1-4a/ N2a/ M0	T1a/b-T2a/ N1a or N2a/ M0
IIIB	T1-4b/ N1a/ M0 T1-4b/ N2a/ M0 T1-4a/ N1b/ M0 T1-4a/ N2b/ M0 T1-4a/ N2c/ M0	T0/ N1b or N1c/ M0 T1a/b-T2a/ N1b/c or N2b/ M0 T2b/T3a/ N1a-N2b/ M0
IIIC	T1-4b/ N1b/ M0 T1-4b/ N2b/ M0 T1-4b/ N2c/ M0 Any T/ N3/ M0	T0/ N2b, N2c, N3b or N3c/ M0 T1a-T3a/ N2c or N3a/b/c/ M0 T3b/T4a/ Any N _N1/ M0 T4b/ N1a-N2c/ M0
IIID	-	T4b/ N3a/b/c/ M0

[3] Weir HK, Marrett LD, Cokkinides V, Barnholtz-Sloan J, Patel P, Tai E, et al. Melanoma in adolescents and young adults (ages 15-39 years): United States, 1999-2006. J Am Acad Dermatol 2011;65(5 Suppl 1):S38-S49

[4] Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, Sunderkötter C, Kaatz M, Schulte KW, Lehmann P, Vogt T, Ulrich J, Herbst R, Gehring W, Simon JC, Keim U, Martus P, Garbe C; German Dermatologic Cooperative Oncology Group (DeCOG). Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016 Jun;17(6):757-767

[5] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American joint committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 Dec;67(6):474-92

Key changes in the 8th edition of AJCC Cancer Staging Manual include:

Primary tumour status (T):

- Tumour thickness measurements to be measured to the nearest 0.1 mm, not 0.01 mm;
- Revised definitions of T1a and T1b (T1a, <0.8 mm without ulceration; T1b, 0.8-1.0 mm with or without ulceration or <0.8 mm with ulceration), with mitotic rate no longer a T1 category criterion but should be documented for all invasive melanoma;

Regional Lymph node status (N):

- N category includes regional lymph node as well as non-nodal regional disease (i.e., satellites, intransit metastasis, and microsatellites), as non-nodal regional disease was grouped together for staging purposes (because they each had a similar impact on prognosis).
- Definitions of N subcategories are revised, with the presence of microsatellites, satellites, or in-transit metastases now categorized as N1c, N2c, or N3c based on the number of tumour-involved regional lymph nodes, if any;
- The definition of a microsatellite was refined and clarified; a microsatellite is a microscopic cutaneous and/or subcutaneous metastasis adjacent or deep to, but discontinuous from, a primary melanoma detected on pathological examination of the primary tumour site.
- The N category descriptor ''microscopic'' and ''macroscopic'' have been replaced by ''clinically occult'' (i.e., detected by SLN biopsy) and ''clinical evident'' (i.e., detected by clinical examination or radiographic imaging) regional disease (corresponding to N category designations ''a'' and ''b'', respectively)

AJCC Prognostic Stage III Groups

- Stage III groupings have been redefined and increased from three to four subgroups, with the addition of a stage IIID subgroup. Stage III disease is associated with heterogeneous outcomes; five-year melanoma-specific survival rates range from 93 percent for stage IIIA disease to 32 percent for stage IIID disease.

Definition of Distant Metastatis (M)

- The site of distant metastasis remains the primary component of the M category: non-visceral (distant cutaneous, subcutaneous, nodal), M1a; lung, M1b; non-central nervous system (CNS) visceral, M1c. However, a new M1d designation was added for metastases involving the CNS. M1c no longer includes CNS metastasis.
- Although an elevated lactate dehydrogenase (LDH) is no longer an M1c criterion, LDH remains an important predictor of survival in stage IV and is now recorded for any M1 anatomic site of disease.

At the time of protocol development, 5-year survival rates reported by AJCC 7th edition for patients with stage IIIA, IIIB, and IIIC melanoma were 78%, 59%, and 40%, respectively [6]. The 5-year melanoma-specific survival rates according to the current AJCC 8th edition Staging Guidelines are 93%, 83%, 69%, and 32% for stage IIIA, IIIB, IIIC, and IIID, respectively[4].

[6] Balch CM, Gershenwald JE, Soong S-J, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27(36):6199-206

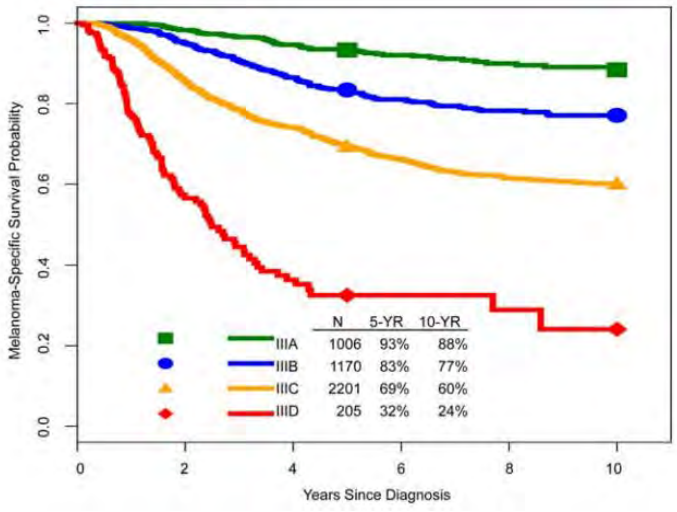


Figure 1: Kaplan-Meier melanoma-specific survival curves according to stage III subgroups from the 8th edition international melanoma database[4]

KEYNOTE 054 enrolled subjects with stage IIIA (with lymph node metastasis >1 mm), stage IIIB, or IIIC melanoma. Patients with a stage IIIA lymph node metastasis >1 mm were included because they have a significantly higher risk of relapse and death compared to patients with <1 mm nodal metastasis[7].

In addition, subjects were required to have a complete lymph node dissection; however, the benefit of lymph node dissection was recently confirmed to confer only regional disease control without a benefit for OS[8].

2.1.5. Management

According to NCCN guidelines, high-dose IFN-α is an option in stage IIB-C melanoma. For completely resected stage III melanoma, management options include observation or nivolumab for resected stage IIIb/C (category 1) or dabrafenib/trametinib for patients with BRAF V600 activating mutation and SNL metastatis >1 mm (category 1) or high-dose ipilimumab for SLN metastasis >1 mm (category 1) or interferon alfa (which can be given as high dose IFN-α for one year or as peg-IFN- α2b for up to 5 years. Among the above options, NCCN consider nivolumab the preferred adjuvant immunotherapy regimen (NCCN V2.2018).

According to the ESMO guidelines, patients with resected stage III are evaluated for IFN therapy: patients with microscopic regional nodal involvement and/or ulcerated primaries are most likely to benefit. For patients with ≥stage IIIB, clinical trials or high-dose IFN-α-2b are options. High-dose IFN-α-2b is an approved indication and offered in some European countries for high risk resected stage II or III melanoma on the basis of reduction in RFS, although not universally because of marginal OS benefit and the significant toxicity. Observation is frequently used as the standard of care in Europe[1,2,9].

Ipilimumab is approved for adjuvant treatment of melanoma in the US, but not in EU as this indication was never submitted to EMA. Nivolumab is approved as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

[7] van der Ploeg APT, van Akkooi ACJ, Haydu LE, Scolyer RA, Murali R, Verhoef C, et al. The prognostic significance of sentinel node tumour burden in melanoma patients: an international, multicenter study of 1539 sentinel node positive melanoma patients. Eur J Cancer 2014;50:111-20
[8] Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017 Jun 8;376(23):2211-22
[9] Dummer R, Keilholz U; ESMO Guidelines Committee. appendix 2: Cutaneous melanoma (2): eUpdate published online September 2016 (http://www.esmo.org/Guidelines/Melanoma). Ann Oncol. 2016 Sep;27(suppl 5):v136-v137

The combination dabrafenib/trametinib has also been approved in the EU for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Interferon-alfa: A Cochrane meta-analysis from 2013 supported the therapeutic efficacy of adjuvant interferon alpha (low, intermediate and high dosage) for the treatment of people with high-risk (AJCC TNM stage II-III) cutaneous melanoma in terms of both disease-free survival and, though to a lower extent, overall survival, compared to observation. A total of 10,499 participants from 18 RCTs published between 1995 and 2011 were eligible for the review. Of the 18 RCTs, the results from 17 trials and 15 trials were suitable to quantify the therapeutic efficacy of interferon in terms of DFS and OS, respectively. Adjuvant interferon was associated with significantly improved disease-free survival (HR = 0.83; 95% CI 0.78 to 0.87, P value < 0.00001) and overall survival (HR = 0.91; 95% CI 0.85 to 0.97; P value = 0.003)[10]. A more recent individual patient data meta-analysis showed significant event-free survival improvement with IFN-α (HR = 0.86, CI 0.81-0.91; P < 0.00001) and OS (HR = 0.90, CI 0.85-0.97; P = 0.003)[11].

Ipilimumab: Ipilimumab, a fully human IgG1 monoclonal antibody that blocks CTLA-4, was investigated in the adjuvant melanoma setting in the phase III double blind clinical trial EORTC 18071. Patients with complete resected stage III (excluding lymph node metastasis ≤1 mm or in-transit metastasis) cutaneous melanoma were randomized to receive ipilimumab 10 mg/kg (475 patients) or placebo (476) every 3 weeks for 4 doses, then every 3 months for up to 3 years or until disease recurrence or unacceptable toxicity. Recurrence-free survival was the primary end point. Median RFS was 26.1 months (95% CI 19·3–39·3) in the ipilimumab group vs 17.1 months (95% CI 13·4–21·6) in the placebo group (HR 0.75; 95% CI 0·64–0·90; p=0·0013). An updated analysis at a median follow-up of 5.3 years showed 5-year RFS rate of 40.8% vs 30.3% and a 5-years OS rate of 65.4% vs 54.4% (HR for death, 0.72; 95.1% CI, 0.58 to 0.88; P=0.001). Grade 3-4 AEs occurred in 54.1% of the patients in the ipilimumab group, with 52% of patients discontinuing ipilimumab due to AR and 5 deaths due to immune-related adverse events.[12,13]

The anti-PD1 antibody nivolumab has been evaluated in the adjuvant melanoma setting in Checkmate 238 (CA209238), a phase 3, randomized, double-blind study in subjects that had complete resection of stage IIIB/C or stage IV Melanoma. Patients were randomized to nivolumab (453 patients) 3 mg/kg (every 2 weeks) or ipilimumab (453 patients) 10 mg/kg (every 3 weeks for 4 doses followed by every 12 weeks starting at week 24) with a maximum duration of treatment of 1 year and a total follow-up of 5 years. Patients were stratified by PD-L1 status (on the basis of a 5% cutoff in tumor cells) and disease stage (Stage IIIb/c, Stage IV M1a-M1b or Stage IV M1c). With a total of 360 events (34% in nivolumab and 45.5% in ipilimumab), the primary analysis in all randomized subjects with a minimum follow-up of 18 months demonstrates a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51,0.83; stratified log-rank p<0.001). Median RFS was not reached in either arm. RFS rates were higher in the nivolumab group than in the ipilimumab group at 6- (79.8% vs 72.6%), 12- (70.5% vs 60.8%) and 18-months (66.4% vs 52.7%), showing an absolute difference in RFS rate increasing over time. A RFS advantage of nivolumab vs ipilimumab is seen in PD-L1 positive (≥ 5%) subjects (secondary endpoint) (HR=0.50, 95%CI 0.32, 0.78)[14].

Dabrafenib/trametinib combination was studied in COMBI-AD, a randomized, double-blind phase III study to evaluate the combination of dabrafenib 150 mg bid with trametinib 2 mg qd versus two placebos for 1 year as adjuvant treatment of high-risk (stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC based on the

[10] Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev. 2013 Jun 18;(6)
[11] Ives NJ, Suciu S, Eggermont AMM, Kirkwood J, Lorigan P, Markovic SN, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: an individual patient data metaanalysis. Eur J Cancer. 2017 Sep;82:171-83
[12] Eggermont AMM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015 May;16(5):522-30
[13] Eggermont AMM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med. 2016 Nov 10;375(19):1845-55
[14] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017 Nov 9;377(19):1824-35

7th edition of AJCC staging) cutaneous BRAF V600 E/K mutant melanoma after surgical resection (≤ 12 weeks prior to randomization). A total of 870 patients were randomized (438 in dabrafenib+trametinib arm and 432 patients in the placebo arm) stratified by BRAF mutation status (V600E, V600K) and disease stage (IIIA, IIIB, IIIC). Median FU was 2.8 years. With a total of 414 RFS events (38% in the dabrafenib+trametinib arm and 57% in the placebo arm), HR was 0.47 (CI95% 0.39-0.58) in favour of dabrafenib+trametinib compared to placebo (p<0.001), median RFS not reached in the dabrafenib+trametinib arm (95%CI 44.5-NR) vs 16.6 months (CI95% 12.7, 22.1 months) in the placebo arm. The estimated RFS rates at year 2 were 67% for the dabrafenib+trametinib arm and 44% in the placebo arm, at year 3 were 58% and 39%. With 153 deaths [60 (14%) in the combination-therapy group and 93 (22%) in the placebo group] at the first IA, OS HR was 0.57 (95%CI 0.42-0.79; p=0.0006) in favour of the dabrafenib+trametinib. Despite this low P value, the between-group difference was not significant because it did not cross the prespecified conservative interim boundary of P=0.000019[15].

In BRAF mutation-positive melanoma, also vemurafenib, a BRAF-inhibitor, given alone for one year, was evaluated in the BRIM8 trial versus placebo. The study enrolled 184 patients in cohort 2 (stage IIIC) and 314 patients in cohort 1 (stage IIC−IIIA−IIIB) cohort 1, showing in cohort 2 median DFS of 23.1 vs 15.4 months with vemurafenib vs placebo respectively (HR 0·80 p=0·026) and in cohort 1 median DFS NR vs 36.9 months with vemurafenib vs placebo respectively (HR 0·54, p=0·0010). The result however was not significant because of the prespecified hierarchical prerequisite for the primary DFS analysis of cohort 2 to show a significant DFS benefit[16].

[15] Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med. 2017 Nov 9;377(19):1813-23

[16] Maio M, Lewis K, Demidov L, Mandalà M, Bondarenko I, Ascierto PA, Herbert C, Mackiewicz A, Rutkowski P, Guminski A, Goodman GR, Simmons B, Ye C, Yan Y, Schadendorf D; BRIM8 Investigators. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol. 2018 Apr;19(4):510-520

Table 2: Published adjuvant stage III melanoma clinical studies in the last 3 years

Author	Study Design	Population	Treatment	Outcomes					
Ipilimumab vs Placebo				**Median RFS**	**3-year RFS**	**5-year RFS**	**5-year DMFS**	**5-year OS**	**Toxicity**
EORTC 18071 Eggermont [Ref. 5.4: 04V9YG, 04VB55][1]	Phase 3, double-blind, randomized placebo-controlled study	Patients with stage III melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis) following complete resection of primary tumor who had not received previous systemic therapy for melanoma	951 patients were assigned (1:1) to receive either: Ipilimumab 10 mg/kg IV (N=475) or Placebo (N=476) Treatment was administered every 3 weeks for 4 doses, then every 3 months for up to 3 years. Patients were stratified by disease stage and geographical region.	26.1 months 17.1 months (HR 0.75; p=0·0013)	46.5% 34.8%	40.8%[1] 30.3%[1] (HR 0.76; p<0.001)	48.3%[1] 38.9%[1] (HR 0.76; p= 0.002)	65.4%[1] 54.4%[1] (HR 0.72; p= 0.001)	All AEs 99% G3-4 AEs 54% DCAE 52% All AEs 91% G3-4 AEs 25% DCAE 4%
Nivolumab vs Ipilimumab				**1-year RFS**				**18-month RFS**	**Toxicity**
				All stages	**Stage III**	**PD-L1 <5%**	**PD-L1 ≥5%**		
Weber [Ref. 5.4: 04V9ZN]	Phase 3, double-blind, randomized active-control study	Patients with stage IIIB, IIIC, or IV melanoma who were undergoing complete lymphadenectomy or resection of the primary tumor	906 patients were assigned (1:1) to receive either: Nivolumab 3 mg/kg IV Q2W (N=453) or IV infusions of 10 mg/kg ipilimumab every 3 weeks for 4 doses and then every 12 weeks (N=453). Patients were treated for a period of up to 1 year or until disease recurrence/ unacceptable toxicity	70.5% 60.8% (HR 0.65; p<0.001)	72.3% 61.6%	64.3% 53.7%	81.9% 73.8%	66.4% 52.7%	All AEs 96.9% G3-4 AEs 25.4% DCAE 9.7% All AEs 98.5% G3-4 AEs 55.2% DCAE 42.6%

Author	Study Design	Population	Treatment	Outcomes			
Dabrafenib + Trametinib vs Placebo				**Estimated RFS**	**Median RFS**	**Estimated OS**	**Toxicity**
Long [Ref. 5.4: 04V9XV]	Phase 3, double-blind, randomized placebo-control study	Melanoma patients with BRAF V600E or V600K mutations who had undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC disease	870 patients were assigned (1:1) to receive either: oral dabrafenib at a dose of 150 mg bid + trametinib at a dose of 2 mg od (N=438) or oral matched placebo tablets (N=432) Patients were stratified according to their BRAF mutation status (V600E or K) and disease stage (IIIA, IIIB, or IIIC). Patients were treated for 12 months in the absence of disease recurrence, unacceptable toxic effects.	1 year – 88.0% 2 year – 67.0% 3 year – 58.0% 1 year – 56% 2 year – 44% 3 year – 39%	Not reached 16.6 months	1 year – 97% 2 year – 91% 3 year – 86% 1 year – 94% 2 year – 83% 3 year – 77%	All AEs 97% G3-4 AEs 41% DCAE 26% All AEs 88% G3-4 AEs 14% DCAE 3%

[1] Updated data from publication reflecting 5.3 years of follow-up compared to the original publication [Ref. 5.4: 04V9YG] of 2.74 years of follow-up.

AE=Adverse event; bid=Bis in die (twice a day); DC=Discontinued due to; DMFS=Distant metastasis–free survival; G=Grade; HR=Hazard ratio; IV=Intravenous; N=Number; od=Omne in die (once daily); OS=Overall survival; PD-L1=Programmed death ligand 1; Q2W=Every 2 weeks; RFS=Recurrence-free-survival

Treatment for metastatic or unresectable melanoma

According to ESMO guidelines, in patients with unresectable, metastatic disease with BRAF WT tumor, preferred options are clinical trials or anti-PD1 antibody. Other option is anti-CTLA4 inhibitor. For subjects with melanoma harboring BRAF mutation, options are clinical trials or BRAF+MEK inhibitors or anti-PD-1 antibody or anti-CTLA4 antibody[9]. With regard to anti-PD1 antibodies, both pembrolizumab and nivolumab are currently EU approved in the advanced (unresectable or metastatic) melanoma setting. Nivolumab is also approved in combination with ipilimumab, although, relative to nivolumab monotherapy, an increase in PFS and OS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (Opdivo SmPC, Yervoy SmPC).

About the product

Keytruda (pembrolizumab) is a humanized monoclonal anti-PD-1 antibody that blocks the interaction between programmed cell death 1 (PD-1) receptor and its ligands, programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2). The PD-1 pathway, especially the PD-1 receptor-ligand interaction, represents a major immune-control switch that may be engaged by ligands expressed in the tumour microenvironment to overcome active antitumor-specific T cell immune surveillance.

Keytruda is currently approved in EU for the treatment of advanced (unresectable or metastatic) melanoma in adults. In addition, Keytruda is approved in metastatic non-small cell lung carcinoma, refractory classical Hodgkin lymphoma and advanced/metastatic urothelial carcinoma.

Type of Application and aspects on development

The application is based on study KEYNOTE-054; a randomized, double-blind, phase 3 study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), undertaken to evaluate adjuvant therapy with pembrolizumab compared to placebo in patients with resected high-risk melanoma (Stage IIIA [> 1 mm lymph node metastasis], IIIB and IIIC).

The MAH submitted the following indication:

- KEYTRUDA as monotherapy is indicated for the adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection.

The final agreed indication was as follows:

- KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection (see section 5.1).

For the adjuvant treatment of melanoma, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The applicant did not submit an environmental risk assessment. 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 pembrolizumab is a protein and does not pose a significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

The lack of non-clinical data is acceptable as the indication is in the same disease that has been previously approved. Pembrolizumab, being a protein is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-054 [Ref. 5.3.5.1: P054V01MK 3475]	3	Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Serbia, Spain, Sweden, Switzerland, United Kingdom, United States	Adjuvant immunotherapy with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group Efficacy and safety in subjects after complete resection of Stage IIIA (>1 mm metastasis), IIIB, and IIIC melanoma	Double-blind, placebo-controlled, randomized, multicenter	Part 1: pembrolizumab 200 mg IV Q3W for 18 administrations, ~1 year Part 2: pembrolizumab 200 mg IV Q3W for up to 2 years	Male/female subjects ≥18 years of age with resected Stage III melanoma	Pembrolizumab: 509 Placebo: 502

2.3.2. Pharmacokinetics

Absorption

Keytruda (pembrolizumab) is a humanized monoclonal anti-PD-1 antibody. Keytruda is administered via IV and therefore is 100% bioavailable.

Over the course of recent clinical development, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies. While earlier population PK analyses were conducted using a two-compartment PK structural model with static clearance (CL) (i.e. no time-dependent changes in CL, referred to as a 'static model'), more recent analyses have included a time-dependent pharmacokinetic (TDPK) component for characterizing on-study changes in CL, with the intent of improving description of long-term pembrolizumab concentration-time data.

Based on the previous (Static Model) and current (TDPK Model) population PK analysis, the pembrolizumab PK profile is typical for a therapeutic mAb. Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV%]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner. Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]). Steady state is

predicted to be achieved after approximately 16 weeks (for the intended dosing regimen of 200 mg Q3W). Elimination half-life (t1/2) is 22 days (32%) at steady-state.

Pembrolizumab is approved at dosing regimens of 2 mg/kg or 200 mg Q3W for multiple advanced or metastatic indications globally, as listed below. Currently, the 200 mg Q3W dose is also being evaluated in multiple clinical studies.

- Melanoma: US (200 mg Q3W), EU and Japan (2 mg/kg Q3W), other countries (200 mg or 2 mg/kg Q3W)
- NSCLC: US, EU (only in 1L) and Japan (200 mg Q3W), other countries (200 mg or 2 mg/kg Q3W)
- HNSCC: US (200 mg Q3W)
- Classical HL: US and EU (200 mg Q3W in adults); US (2 mg/kg [up to 200 mg] Q3W in pediatrics)
- Urothelial carcinoma: US, EU, and Japan (200 mg Q3W)
- MSI-H cancer: US (200 mg Q3W in adults and 2 mg/kg [up to 200 mg] Q3W in pediatrics)
- Gastric cancer: US (200 mg Q3W)

The recommended dose of pembrolizumab for the treatment of subjects with melanoma in the adjuvant setting is 200 mg Q3W. This is based on the similarity in PK of pembrolizumab across multiple approved indications including melanoma.

No new information regarding Pharmacokinetics for pembrolizumab is available within this extension of indication.

Analytical methods

No new methods have been introduced.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Immunogenicity

The existing immunogenicity assessment for pembrolizumab monotherapy in the non-adjuvant (advanced or metastatic) setting is based on a dataset of 3727 subjects across several indications (melanoma, NSCLC, HNSCC, MSI-H, HL and UC subjects). Out of 3727 subjects, 2034 were evaluable for ADA. The observed incidence of treatment emergent ADA in these evaluable subjects was 1.8% (36 out of 2034). In the last immunogenicity dataset of the 36 treatment emergent ADA positive subjects, 9 tested positive in the neutralizing assay, accounting for a total incidence rate of treatment emergent neutralizing positive subjects of 0.4% (9 out 2043) in the overall population. Finally, pembrolizumab exposure did not change in the presence of ADAs or neutralizing antibodies as currently summarized in the USPI and EU SmPC.

This submission informs on immunogenicity potential of pembrolizumab monotherapy in subjects with melanoma treated in the adjuvant setting (KEYNOTE-054). Immunogenicity in the adjuvant setting has not been characterized previously.

Immunogenicity evaluation for study KEYNOTE-054

For pembrolizumab monotherapy in the adjuvant treatment setting, ADA samples were available from 500 subjects. A subset of the subjects was not assessable for drug-induced immunogenicity analysis, because the subjects were not treated with pembrolizumab or did not have a post-treatment ADA sample available (N=4). In total 496 subjects were included in the immunogenicity analysis. The following table shows an overview of the immunogenicity status for all 496 assessable subjects.

Table 3: Summary of subject immunogenicity status after pembrolizumab monotherapy in the adjuvant treatment setting (200 mg Q3W)

Immunogenicity status	All treatments
Assessable subjects[a]	496
Inconclusive subjects[b]	1
Evaluable subjects[c]	**495**
Negative[d]	473 (95.6%)
Non-Treatment emergent positive[d]	5 (1.0%)[e]
Neutralizing negative	5 (1.0%)[e]
Neutralizing positive	0
Treatment emergent positive[d]	17 (3.4%)[f, g]
Neutralizing negative	17 (3.4%)[f, g]
Neutralizing positive	0

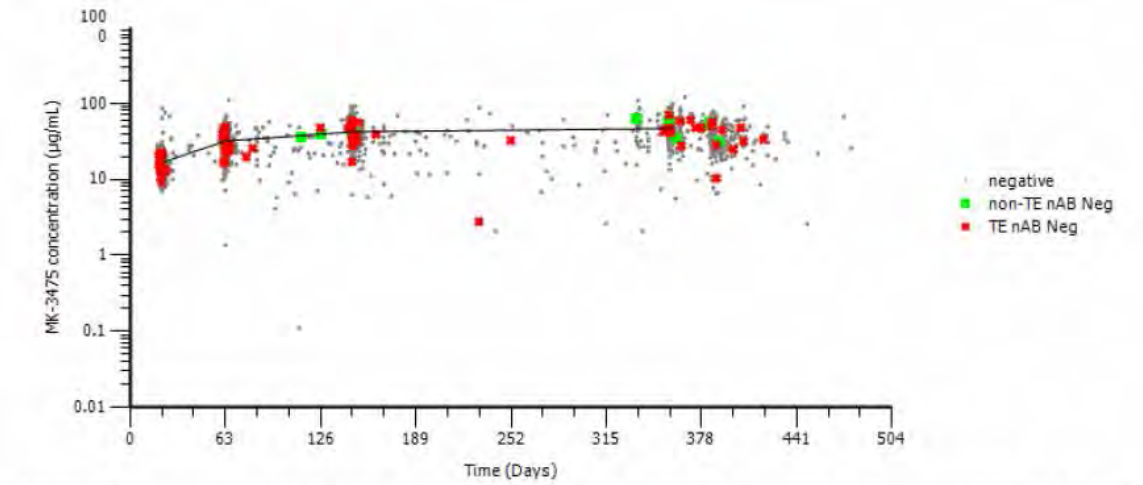
a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the DTL.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent).
d: Denominator was total number of evaluable subjects.
e: Including one subject with pre and post dose sample ADA positive, and no increase in titer.
f: Including one subject with pre and post dose sample ADA positive, and increase in titer
g: Including one subject with post dose sample ADA positive and pre dose sample missing.

The observed incidence of treatment emergent ADA in evaluable subjects treated with pembrolizumab monotherapy in the adjuvant treatment setting is 3.4% (17 out of 495), based on 17 subjects with treatment emergent positive, 5 with non-treatment emergent positive, and 473 with negative immunogenicity status. One subject was considered as inconclusive.

None of the 17 treatment emergent positive subjects had antibodies with neutralizing capacity, yielding an incidence of treatment emergent neutralizing positive subjects of 0% (0 out of 495).

Impact of ADA on Pembrolizumab Exposure

Pembrolizumab levels observed in subjects with ADA positive samples, were compared with pembrolizumab levels in subjects the ADA negative or ADA inconclusive samples subjects, all treated with the same regimen. (see figure below).



Footnote: Individual pembrolizumab concentrations for the treatment emergent positive subjects (red cross), non-treatment emergent positive subjects (green cross), negative and inconclusive subjects (grey dot) and mean value of the negative and inconclusive subjects (grey line -).

Figure 2: MK-3475 exposure for melanoma subjects (KN054) after pembrolizumab monotherapy in the adjuvant treatment setting (200 mg Q3W)

Impact of ADA on Pembrolizumab Safety

The ADA positive subjects (treatment emergent and non-treatment emergent), were evaluated for potential impact on safety.

Table 4: Overview of impact of ADA on adverse events incidence

	ADA Negative		ADA TE Nab Negative		ADA Non-TE Nab Negative	
	n	(%)	n	(%)	n	(%)
Subjects in population	478		17		5	
with one or more adverse events	446	(93.3)	17	(100.0)	4	(80.0)
with no adverse event	32	(6.7)	0	(0.0)	1	(20.0)
with drug-related† adverse events	369	(77.2)	15	(88.2)	4	(80.0)
with toxicity grade 3-5 adverse events	148	(31.0)	4	(23.5)	1	(20.0)
with toxicity grade 3-5 drug-related adverse events	68	(14.2)	2	(11.8)	1	(20.0)
with serious adverse events	118	(24.7)	4	(23.5)	1	(20.0)
with serious drug-related adverse events	59	(12.3)	3	(17.6)	1	(20.0)
who died	1	(0.2)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	65	(13.6)	2	(11.8)	1	(20.0)
discontinued drug due to a drug-related adverse event	57	(11.9)	2	(11.8)	1	(20.0)
discontinued drug due to a serious adverse event	27	(5.6)	2	(11.8)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	20	(4.2)	2	(11.8)	0	(0.0)

† Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database cutoff date: 02OCT2017).

Impact of ADA on Pembrolizumab Safety

The ADA positive subjects (treatment emergent and non-treatment emergent), were evaluated for potential impact on efficacy. Recurrence free survival (RFS) over time was visually examined to determine any potential influence of ADA on efficacy (figure below).

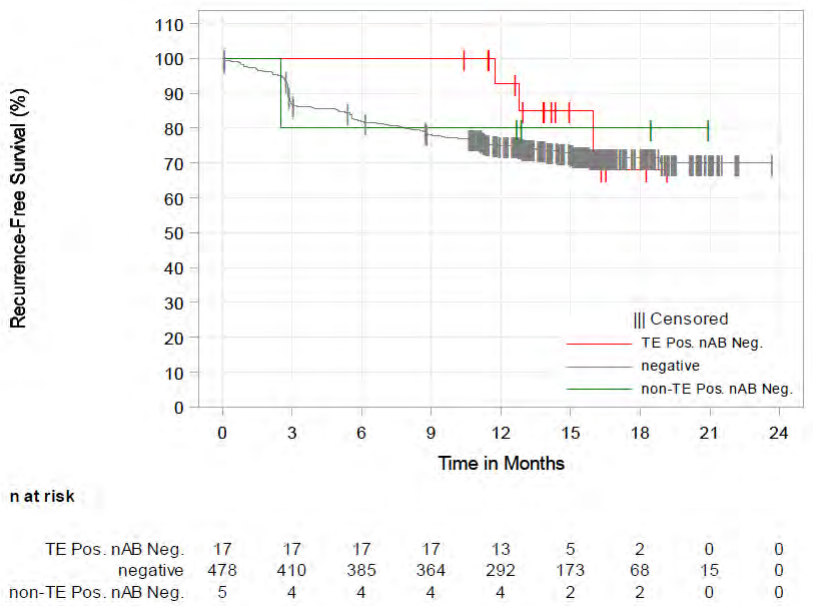


Figure 3: Recurrence free survival curves for melanoma subjects (KN054) after pembrolizumab monotherapy in the adjuvant treatment setting (200 mg Q3W)

2.3.4. Discussion on clinical pharmacology

Based on the similarity in PK of pembrolizumab across multiple approved indications including melanoma, no further evaluation of the PK profile for pembrolizumab monotherapy was considered necessary and thus no PK analysis was conducted in study KEYNOTE-054. Based on previous assessments pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]) but this decrease in CL with time is not considered clinically meaningful.

The applicant analysed the ADA formation and its impact on pembrolizumab exposure, as the information on the development of ADA is still limited in the adjuvant treatment setting. The methods used for quantitation of pembrolizumab in human serum and for the determination of ADA corresponded to the validated methods applied in previous submissions. Since the bioanalytical reports for PK and ADA assessment were interim reports, the applicant was asked to provide the final bioanalytical study reports once the study KN-054 is completed.

Pembrolizumab concentration was determined to be above the LLOQ in a total of 4 pre-treatment samples (range: 39.6 – 11600 ng/mL). The applicant was asked to comment on this unexpected finding. The applicant responded that in order to find the root cause for detectable drug concentrations at baseline in 4 pre-treat samples, a systematic investigation was triggered. No root cause for this matter has been identified, although the investigation continues and any additional findings will be included in the final bioanalytical report. Considering that drug levels in samples from this study were generated solely to aid in interpretation of immunogenicity and all 4 subjects in question were ADA negative at all time points collected, no impact to the study results is expected.

A total of 500 subjects from study KEYNOTE-054 (subjects with melanoma treated in the adjuvant setting) were included in the immunogenicity assessment, 495 subjects were evaluable.

The incidence for treatment-emergent ADA in evaluable subjects was 3.4% (17 of 495; 473 negative, 5 non-treatment-emergent positive and 17 treatment-emergent positive). None of the 17 treatment emergent positive subjects, had antibodies with neutralizing capacity, yielding an incidence of treatment

emergent neutralizing positive subjects of 0% (0 out of 495). These findings are slightly higher than the overall incidence in the non-adjuvant setting (1.8%). However, there was no incidence of treatment-emergent neutralizing positive subjects in the adjuvant treatment setting (0 out of 17), which is consistent with the low incidence seen in the non-adjuvant setting (0.4%).

For all of the ADA positive subjects (5 non-treatment emergent and 17 treatment emergent positive), the pembrolizumab exposure was comparable to that for subjects with ADA negative or ADA inconclusive samples treated with the same regimen.

Impact of neutralizing positive antibodies on exposure cannot be determined as none of the ADA positive subjects had antibodies with neutralizing capacity.

The comparison of RFS between the positive population (treatment emergent and non-treatment emergent positive subjects) and negative population (negative and inconclusive subjects) is limited by the small number of subjects in the positive populations and no conclusions can be drawn.

2.3.5. Conclusions on clinical pharmacology

The PK characteristics for pembrolizumab are considered also acceptable for the adjuvant melanoma setting. Overall, no significant difference in the incidence or characteristics of anti-pembrolizumab antibodies was detected in the adjuvant as compared to the non-adjuvant treatment setting. Furthermore, no impact of treatment-emergent ADA was observed on pembrolizumab exposure, efficacy, or safety which is consistent with the results of prior immunogenicity evaluations of pembrolizumab in the non-adjuvant monotherapy setting.

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

- The final bioanalytical reports for PK and ADA assessment from study KN-054. Due 31st December 2023.

2.4. Clinical efficacy

To support the Keytruda extension of indication in adjuvant melanoma, the efficacy data in this submission are based on the interim analysis results of a single pivotal study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), KEYNOTE-054 (EORTC1325), an ongoing, international, double-blind, placebo-controlled, randomized Phase 3 study evaluating the efficacy and safety of adjuvant therapy with pembrolizumab in subjects with completely resected stage IIIA (>1 mm LN metastasis), IIIB, and IIIC melanoma (AJCC 7th edition, 2010). Eligible subjects included those who had not received prior systemic therapy for melanoma, except adjuvant IFN for a previous melanoma without LN involvement.

The CRS is based on the results of an interim analysis from Part 1 per data cutoff date of 02-OCT-2017. Part 2 is ongoing and not included in this submission.

The MAH is seeking the following indication: *"KEYTRUDA as monotherapy is indicated for the adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection".*

2.4.1. Dose response study(ies)

The pembrolizumab dose regimen of 200 mg Q3W for this and other studies in the pembrolizumab program was selected based on population PK simulations. The PK simulations showed that a 200 mg fixed dose provides (1) adequate and similar control of PK variability relative to a weight-based regimen, and (2) exposures similar to, or slightly higher than, those obtained at 2 mg/kg dose Q3W and, therefore, well within

the established therapeutic window associated with near-maximal efficacy and acceptable tolerability in the indication.

2.4.2. Main study(ies)

Title of Study: KN-054 Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 study of the EORTC Melanoma Group

Methods

Study participants

Key inclusion criteria:

1. Had complete resection of stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as (AJCC, 2010) stage IIIA (>1 mm lymph node metastasis), any stage IIIB, or stage IIIC. No past or current intransit metastases or satellitosis.

(Patient population IIIA (> 1 mm metastasis) was capped at a maximum of 20% of the total patient population.)

2. Had tumour sample evaluable for PD-L1 expression (central laboratory testing).

4. Had disease status for the post-surgery baseline assessment documented by full chest/abdomen/pelvis CT and/or MRI with neck CT and/or MRI (for head and neck primaries) and complete clinical examination after the informed consent and prior to enrollment.

5. Post lymph node dissection radiotherapy must have been completed within the 13 week post-surgery period and prior to treatment start.

6. Had ECOG performance status of 0 or 1.

7. Had interval from surgery to first study drug treatment ≤13 weeks.

8. Had adequate organ function.

Key exclusion criteria:

1. Had mucosal or ocular melanoma.

2. Had current disease, including loco-regional relapse, distant metastasis, or clinical evidence for brain metastases.

3. Had prior therapy for melanoma except surgery for primary melanoma lesions; subjects who had previously received IFN for thick primary melanomas without evidence of lymph node involvement were eligible.

4. Had a history of another malignancy or a concurrent malignancy. Exceptions included subjects who had been disease-free for 5 years, subjects with a history of completely resected non-melanoma skin cancer, or subjects with successfully treated in situ carcinoma.

5. Had active autoimmune disease that required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

6. Had a diagnosis of immunodeficiency, systemic steroid therapy, or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.

7. Known history of human immunodeficiency virus (HIV), active Hepatitis B or Hepatitis C.

8. Received prior treatment with any anti-CTLA4 monoclonal antibody, anti-PD-1, anti- PD-L1, or anti-PD-L2 agent.

PD-L1 status: Enrollment was open to all subjects regardless of PD-L1 tumour expression but enrolled subjects were required to provide a newly obtained tumour tissue specimen for PD-L1 determination. PD-L1 tumour expression was measured using the MEL score, which counts tumour cells and associated immune cells in the tumour nests expressing PD-L1. Tumour samples were predefined using the MEL score as PD-L1-positive if the MEL score was ≥2 (i.e. staining on ≥1% of cells) or PD-L1-negative if the MEL score was 0 or 1 (i.e. staining on <1% of cells). PD-L1 expression was assessed by immunohistochemistry using the 22C3 antibody.

The following conditions require patient discontinuation from study treatment:

- Recurrence (defined as appearance of one or more new melanoma lesions: local, regional or distant). Upon recurrence, the treatment will be unblinded.
- Normal completion of the protocol treatment (one year, which is calculated from the date of the first dose)
- AE or intercurrent illness that, in the opinion of the investigator, warrants the patient's withdrawal from study treatment.
- Specific conditions described in the Management of Adverse Events.
- Investigator's decision to withdraw the patient
- Noncompliance with study treatment or procedure requirements
- Lost to follow up (at least 1 phone call and 2 certified letters before we can call a subject lost to follow up)
- Sexually active patients who refuse to use medically accepted adequate birth control methods.
- A female patient inadvertently becomes pregnant
- Request by regulatory agencies.
- Occurrence of a new malignancy (Exceptions: patients with reported SAEs of non-melanoma skin cancer or in situ carcinoma may remain in the study at the discretion of the investigator and if discussed with medical monitor).
- Patients with thin non-ulcerated primary melanoma
- The patient or legal representative withdraws consent for treatment
- Administrative reasons

Treatments

The treatment phase of the study consists of two parts:

- Part 1 (Adjuvant Therapy): pembrolizumab or placebo was administered Q3W for a total of 18 administrations (~1 year) or until disease recurrence or unacceptable toxicity
- Part 2 (Crossover or Re-challenge with pembrolizumab treatment after first recurrence).

This submission includes efficacy data from Part 1 of the study as of the data cutoff date 02-OCT-2017; Part 2 is ongoing and not included in this submission.

Treatment arms:

EXPERIMENTAL ARM: Pembrolizumab 200 mg Q3W, IV infusion.

Part 1: Day 1 of each 3 week cycle for a total of 18 administrations (~1 year)

Part 2: Day 1 of each 3 week cycle for up to 2 years

CONTROL ARM: Placebo 0 mg Q3W, IV infusion.

Part 1: Day 1 of each 3 week cycle for a total of 18 administrations (~1 year)

Objectives

Primary Objective(s):

- To prospectively assess whether postoperative adjuvant therapy with pembrolizumab improves recurrence free survival (RFS), as compared to placebo in high-risk subjects with complete resection of stage IIIA (>1 mm metastasis), IIIB, and IIIC melanoma.
- To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression, pembrolizumab improves recurrence free survival as compared to placebo.

Secondary Objective(s):

- To compare Adverse Event (AE) and Serious Adverse Event (SAE) profiles between subjects receiving pembrolizumab versus subjects in the placebo arm (CTCAE v. 4.0).
- To evaluate the pharmacokinetics (PK) of pembrolizumab when pembrolizumab is administered at 200 mg every three weeks.

Secondary Objectives (not yet analysed in this interim analysis):

- To prospectively assess whether postoperative adjuvant therapy with pembrolizumab improves distant metastasis-free survival (DMFS) as compared to placebo.
- To prospectively assess whether in the subgroup of subjects with PD-L1-positive tumor expression pembrolizumab improves DMFS as compared to placebo.
- To prospectively assess whether postoperative adjuvant therapy with pembrolizumab improves overall survival (OS), as compared to placebo.
- To prospectively assess whether in the subgroup of subjects with PD-L1-positive tumor expression pembrolizumab improves OS as compared to placebo.

Exploratory endpoints (not yet analysed in this interim analysis):

- To compare quality of life between the two arms (pembrolizumab versus placebo).
- To compare health outcomes evaluation between the two arms (pembrolizumab versus placebo).
- To evaluate predictive biomarkers (e.g., immune-related gene signatures, genetic variation, SPDL1) for treatment difference in outcome.
- Progression/recurrence-free survival 2 (PRFS2)

Outcomes/endpoints

Table 5: Description of endpoints in the populations analysed

Endpoints		Analysis Populations	Definitions
Dual Primary	RFS	ITT all-subjects	Time between the date of randomization and the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. For patients who remain alive and whose disease has not recurred, RFS will be censored on the date of last visit/contact with disease assessments. RFS will be based on the disease assessment or date of death provided by the local investigator. All imaging (radiologic) from a sample of patients will be reviewed in a blinded fashion by an Independent Review Committee (IRC) to assess recurrence.
Dual Primary	RFS	Subjects with PD-L1-positive tumors	Time between the date of randomization and the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.
Secondary	DMFS	ITT all-subjects	Time between the date of randomization and the date of 1st distant metastasis or date of death (whatever the cause), whichever occurs first. For patients who remain alive and distant metastasis-free, DMFS will be censored on the date of last visit/contact with disease assessments. DMFS will be based on the 1st date of distant metastasis assessment or date of death provided by the local investigator.
	DMFS	Subjects with PD-L1-positive tumors	Time between the date of randomization and the date of 1st distant metastasis or date of death (whatever the cause), whichever occurs first.
	OS	ITT all-subjects	Time from the date of randomization to the date of death, whatever the cause. The follow-up of patients still alive will be censored at the moment of last visit/contact.
	OS	Subjects with PD-L1-positive tumors	Time from the date of randomization to the date of death, whatever the cause
Exploratory	EORTC QLQ-C30	ITT all-subjects	Cancer-specific standard instrument for measuring HRQOL
	EuroQOL EQ-5D™	ITT all-subjects	Standardized instrument for measuring patient-reported health outcomes
	PRFS2		Progression/recurrence-free survival 2: time between the date of randomization and the earliest of the following: 1) date of 1st disease progression per RECIST 1.1 beyond the initial unresectable disease recurrence (e.g. unresectable distant metastases); 2) date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (e.g. local regional recurrences or resectable distant metastases); 3) death. For patients who remain alive and whose disease has not recurred, or disease has recurred but subsequent disease progression or recurrence has not occurred, PRFS2 will be censored on the date of last visit/contact with disease assessments or date of last follow up.

DMFS=Distant metastasis-free survival; EORTC=European Organisation for the Research and Treatment of Cancer; EuroQOL=The EuroQOL Group is an association comprising a network of international, multilingual, multidisciplinary researchers; EQ-5D™=European Quality of Life Five-Dimensions Questionnaire; HRQOL=Health-related quality of life; ITT=Intent–to-treat;

OS=Overall survival; PD-L1=Programmed cell death ligand 1; QLQ-C30=Quality of Life Core Questionnaire, Version 3.0; QOL=Quality of life; RFS=Recurrence-free survival.. EQ-5D™ is a trademark of the EuroQol Research Foundation.

Subjects were evaluated with CT and/or MRI scans to assess disease recurrence: the first imaging scan was to occur within 6 weeks prior to randomization, and subsequent imaging occurred every 12 weeks until disease recurrence. In the case of discontinuation due to disease recurrence, the recurrence scan date was used as the reference date for scheduling future imaging scans. For subjects who discontinued in the absence of disease recurrence, imaging workup was performed every 12 weeks for the first 2 years, every 6 months for Years 3 to 5, and annually thereafter.

Recurrence is defined as appearance of one or more new melanoma lesions: local, regional or distant. The first date when recurrence was observed is taken into account regardless the method of assessment. Therefore, recurrence will be declared for any lesion when:

- Only imaging was performed and progression confirmed.
- Only pathology was done and malignancy confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions).
- Both pathology and imaging were done and progression/malignancy confirmed. In this case, whatever examination came first, its date is considered to be the date of recurrence.

Progression/recurrence-free survival 2 (PRFS2) is defined as the time between the date of randomization and the earliest of the following:

- date of 1st disease progression per RECIST 1.1 (Appendix O) beyond the initial unresectable disease recurrence (e.g. unresectable distant metastases);
- date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (e.g. local regional recurrences or resectable distant metastases);
- death.

For patients who remain alive and whose disease has not recurred, or disease has recurred but subsequent disease progression or recurrence has not occurred, PRFS2 will be censored on the date of last visit/contact with disease assessments or date of last follow up.

Sample size

The study is powered for the primary endpoint, RFS. Based on data of the EORTC 18071 study, RFS hazard rates for placebo were assumed to be 0.54 pre-1 year and 0.25 post-1 year from randomization; a total of 409 events (local/regional/distant metastasis/death) for RFS were needed to provide 95% power to detect a hazard ratio (HR) of 0.70 (1-sided logrank test, alpha=2.5%) or an increase of the median RFS from 1.64 to 2.87 years (median ratio=1.75). This corresponds also to an increase of 10.2% (from 58.3% to 68.5%) in the 1-year RFS rate (see Table below).

The power could also be 92% according to the multiplicity strategy which allocates alpha=1.4% to RFS.

A total of approximately 900 eligible patients (450 patients per arm) were planned to be randomized, up to 2.5% additional patients may be enrolled in order to compensate ineligible patients and early consent withdrawal. In addition, if by the time the targeted enrollment is completed there were patients in consenting process, they were authorized to be randomized in the study.

Table 6: Estimation of RFS events

	Endpoint: RFS **Hazard ratio (HR) = 0.70 , 1-sided alpha=1.4%, power=92%** **Hazard ratio (HR) = 0.70 , 1-sided alpha=2.5%, power=95%**							
	Expected RFS rate at			**Hazard rate (lambda) per year**				**Total nb. of pts: 900**
	1-yr	3-yr	7-yr	<=1 yr	1-<3 yr	3+ yrs	Total nb. of RFS Events	100 pts/first 6 months 200 pts/month 7-12 600 pts/2nd year
Placebo	58.3%	35.3%	27.8%	0.54	0.25	0.06	409	Accrual: 2 yrs ± additional follow-up: 1 year ± total follow-up: 3 years
Pembrolizumab	68.5%	48.3%	40.8%	0.38	0.175	0.0042		
Difference/HR	10.2%	13.0%	13.0%	0.7	0.7	0.7		

The total accrual period was supposed to be approximately 2 years. Assuming that the hazard of patient drop-out for RFS evaluation would have been 0.015 per year in the placebo vs 0.03 per year in the Pembrolizumab arm, during the first year, and 0.015 subsequently in both arms, the required 409 RFS events are supposed be reached after a subsequent follow-up of approximately 12 months (i.e. approximately 3.0 years from the start of the trial). Approximately 6-9 months thereafter, once the data are complete and correct, the data-base was planned to be locked for RFS final analysis.

RFS for the PD-L1+ subgroup is the other main endpoint of the study. The power is presented for the PD-L1+ subgroup where the events in the subgroup range from 30%-60% of the 409 overall RFS events, the subgroup HR=0.55, 0.6, 0.65, or 0.7 and alpha is allocated (if the RFS hypothesis for the overall population is not rejected) or alpha=0.025 (if the hypothesis for overall population is rejected). Under these scenarios, the power for the subgroup ranges from 41% to 100%.

Randomisation

The central electronic randomization system (IVRS) assigned according to a 1:1 ratio each subject a treatment dynamically, based on the other subjects randomized in the study and the following stratification factors:

- Stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes)
- Region (North America, European countries, Australia and other countries as designated)

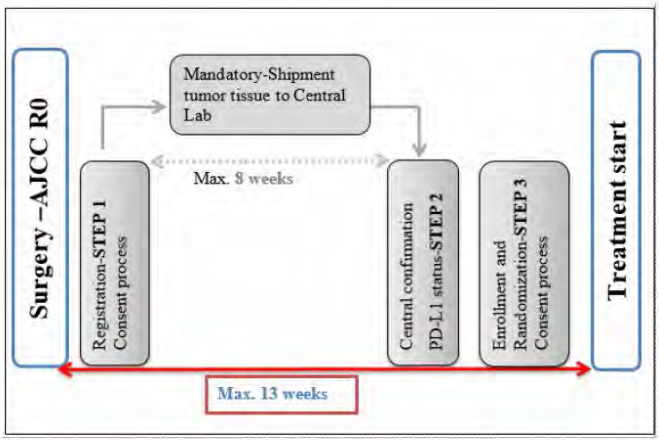


Figure 4: Multistep process for enrollment

The treatment should start no later than 13 weeks after surgery and only after complete wound healing from the surgery.

Blinding (masking)

KEYNOTE-054 was a double-blind study.

Statistical methods

All the main analyses of the efficacy endpoints for the interim analysis 1 (RFS) were performed on the ITT population (efficacy population) following the ITT principle.

The Kaplan-Meier technique was used to obtain estimates of the survival-type distributions (RFS). Medians were presented with a 95% confidence interval based on the non-parametric method of Brookmeyer and Crowley. The comparison of the time-to-event distributions (RFS) between the two treatment arms was done using the log-rank test stratified by stage, as indicated at randomization. The HR was estimated using a Cox proportional hazards (PH) model, stratified by stage, with treatment as the single covariate. The same method was stated to be applied to PRFS2.

Multiplicity adjustment

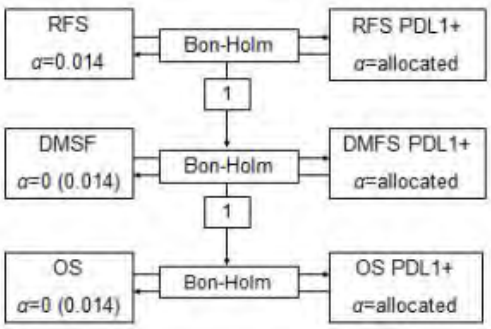
According to the multiplicity strategy (Bonferroni-Holm), the hypothesis for the overall population will first be tested at alpha=1.4%. If the hypothesis for the PD-L1+ subgroup is rejected at the allocated alpha, then the hypothesis for the overall population will be tested at alpha=2.5%.

The "graphical approach" to testing the hypotheses that the Pembrolizumab and placebo groups differ with respect to RFS, DMFS and OS is shown below. RFS, DMFS and OS are planned to be tested sequentially (initial 1-sided alpha allocation 0.025, 0 and 0, respectively). Both hypotheses (for the overall population

and for the PD-L1+ subgroup) must be rejected to proceed to the next endpoint and 100% of the alpha moves to the next endpoint.

For each endpoint, alpha allocation was determined as follows. For the overall population, 1-sided alpha=0.014. For the PD-L1+ subgroup, the allocated alpha will be calculated as a function of the event ratio (number of observed events in the PD-L1+ subgroup: total number of observed events) using a method by Spiessen and Debois.

At the time of OS final analysis, an assessment of the long term treatment impact on RFS and DMFS will be evaluated as well.



Bretz, F., Maurer, W., Brannath, W. and Posch, M. (2009), A graphical approach to sequentially rejective multiple test procedures. *Statist Med* 2009; 28: 586–604.

Spiessens and Debois. Adjusted significance levels for subgroup analysis in clinical trials. *Cont Clin Trials* 2010; 31: 647–656.

Interim analysis

One interim analysis was planned and introduced in Amendment 02 for assessing superiority of pembrolizumab over placebo with respect to the improvement of RFS in the overall population. The interim analysis was planned to occur after approximately 330 RFS events have been reported. The analysis was performed by an unblinded statistician not connected with the project. The final RFS analysis is planned to occur either immediately after the interim analysis is performed (if superiority is concluded at the time of the interim analysis) or after 409 RFS events have been observed (if superiority is not concluded at the time of the interim analysis).

The O'Brien-Fleming stopping boundaries for the interim analysis is based on the Lan-DeMets alpha spending function and derived considering the exact number of reported RFS events. The Table below displays the operating characteristics of the interim analysis, in case 330 RFS events have been reported, superiority would be concluded if the observed RFS hazard ratio is ≤0.76.

Table 7: Operating characteristics for the interim analysis

Power (%) to detect a HR=0.7 (overall 1-sided alpha=0.014)	91.4
# of events (interim)	330
p-value to show superiority (interim)	≤0.006
p-value to show superiority (final)	≤0.012
Observed HR to show superiority (interim)	≤0.76
Observed HR to show superiority (final)	≤0.8
Probability (%) of superiority (interim)	77.1
Probability (%) of superiority (final, if superiority not detected at interim analysis)	14.3
Probability (%) no superiority (final)	8.6

After the RFS final analysis, patients will continue to be followed for the efficacy endpoints: RFS (for those still alive and disease-recurrence free), DMFS (for those still alive and distant -metastasis free) and OS (for those still alive).

Sensitivity analysis

For the efficacy endpoints, the following sensitivity analyses were planned:

- a re-randomization test to ensure true randomization via minimization
- an analysis considering the stratification factor (AJCC stage) information as indicated on the CRFs, based on pathology report(s) and applying the AJCC staging rules.
- a Per Protocol Treatment (PPT) analysis.
- adjusting the treatment comparison by additional factors which appeared to be of prognostic importance (multivariate Cox model) and assessing possible interaction between a factor and treatment effect.
- applying two different set of censoring rules (table below) in order to evaluate the robustness of the RFS endpoint.

Table 8: Sensitivity analyses

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment	Recurrence at date of new anticancer treatment
Recurrence or death documented after ≤ 1 missed disease assessment	Recurrence at date of documented recurrence or death	Recurrence at date of documented recurrence or death	Recurrence at date of documented recurrence or death
Recurrence or death documented after ≥ 2 missed disease assessments	Recurrence at date of documented recurrence or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Recurrence at date of documented recurrence or death

Subgroup analysis

The following variables were considered for the efficacy endpoints (RFS, DMFS, OS):

- PD-L1 expression (negative vs positive vs undetermined).
- Variables considered in the AJCC Staging
- LN involvement: micro vs. macro- involvement
- Ulceration: absent vs. present vs. unknown
- Number of lymph-nodes positive: 1 vs. 2-3 vs. 4+
- Breslow thickness (< 2 mm vs 2-<4 mm vs ≥4 mm)

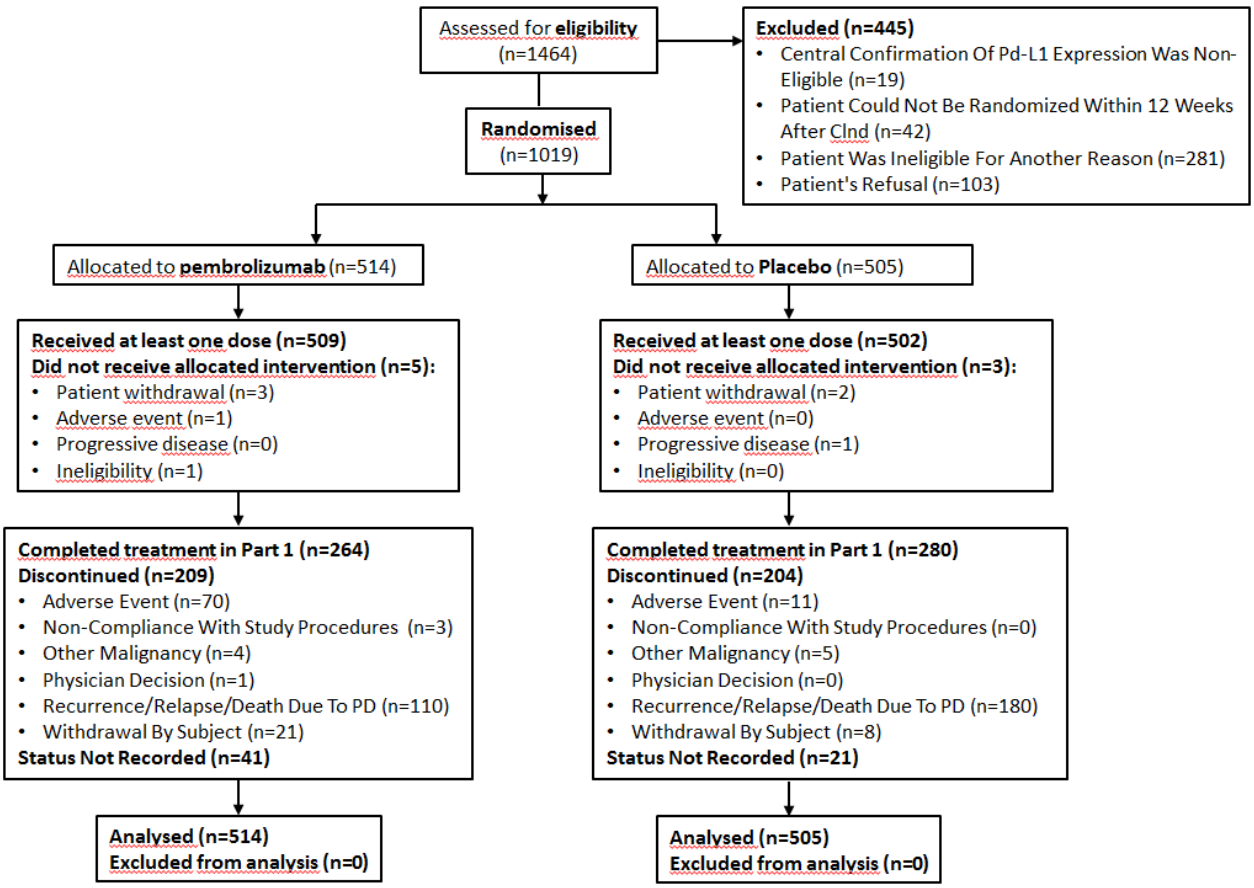
- BRAF-mutation status (negative vs positive vs unknown)
- Sex (Male vs. Female)
- Age (at randomization <65 vs. ≥65 yrs)

Changes in the Planned Analyses

Amendment 02, finalized on 02-OCT-2017, added an interim analysis after ~330 RFS events to assess whether pembrolizumab is superior to placebo with respect to RFS in the overall population.

Results

Participant flow



Recruitment

Patients were recruited between 22-July 2015 and 14 November 2016 at 134 centers in 23 countries worldwide. Study is ongoing.

Data cut-off date for this interim analysis was 2 October 2017. The median follow-up duration for all subjects was 16.0 months.

Conduct of the study

Protocol amendment:

Table 9: Summary of protocol amendments

EORTC Protocol versions	Date of EORTC PRC approval/notification	Final Protocol Version Approved by the Sponsor	EORTC Amendment reference	
			N°	Classification
Outline Amended	April 29, 2014 December 12, 2014	n/a	----	----
1.0	December 17, 2014	MK-3475-054-00	----	----
2.0	May 19, 2015	n/a	1	Scientific
2.1	June 12, 2015	n/a	4	Administrative
3.0	July 07, 2015	MK-3475-054-01	5	Scientific
4.0	January 21, 2017	n/a	8	Scientific
5.0	March 28, 2017	n/a	9	Scientific
6.0	October 02, 2017	MK-3475-054-02	12	Scientific

Main changes are summarised below:

Amendment 054-01 (07-Jul-2015)

- Added exploratory endpoint, **progression/recurrence-free survival 2 (PRFS2)**
- Eligibility criteria were revised to include in situ carcinoma and implementation of contraception guidelines based on the National recommendations for UK and Scandinavian countries.

Amendment 054-02 (02-Oct-2017)

- Implemented an **interim analysis for RFS** and updated data monitoring section. The addition of a RFS interim analysis has been justified based on newly available data released in September 2017.[17]
- Clarified eligibility section and instructions for medical monitoring of adverse events during enrolment.
- Clarified adjuvant treatment duration, withdrawal criteria, and the use of radiotherapy.

Protocol deviations

EORTC reported a total of 1914 significant protocol deviations according to their process. A clinical review of these significant protocol deviations documented as of the data cutoff date, according to the MSD process and ICH E3 guidelines, determined that only 69 met the criteria for important protocol deviations, which included subjects who:

- Were randomized but did not meet eligibility criteria that impacted safety and/or efficacy (n=14), including in-transit or satellite metastasis (resected) (n = 8), newly diagnosed hypothyroidism and not on replacement therapy at baseline (n = 2), pancreatic adenocarcinoma present on baseline imaging and diagnosed at Week 12 (n = 1), elevated bilirubin (n = 1), prior treatment with IFN-alpha after a prior

[17] Weber J., Mandala M., Del Vecchio M., et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017

diagnosis of melanoma with lymph node involvement (n = 1), and primary conjunctival (mucosal) melanoma (n = 1),

- Developed treatment discontinuation criteria but were not discontinued from the study (n=4),
- Received incorrect study treatment (n=6),
- Had a reportable SAE and/or follow up safety event information not reported per timelines outlined in the protocol due to delayed reporting by investigators of secondary malignancies (eg, SCC, BCC, and new primary melanoma) (n = 44),
- Did not comply with the study procedures which impact safety or data integrity (n=1).

No subjects were excluded from the analyses as none of the important protocol deviations were considered by the MAH to have the potential to negatively impact the integrity of the analyses.

Premature unblinding

A total of 14 subjects were unblinded during follow-up for RFS. Of the 14, 10 were unblinded due to safety concerns. Four subjects were unblinded during follow-up due to new primary melanoma.

Baseline data

Table 10: Subject Characteristics ITT Population

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	514		505		1,019	
Gender						
Male	324	(63.0)	304	(60.2)	628	(61.6)
Female	190	(37.0)	201	(39.8)	391	(38.4)
Age (Years)						
< 50	193	(37.5)	186	(36.8)	379	(37.2)
50 to 64	196	(38.1)	193	(38.2)	389	(38.2)
65 to 74	97	(18.9)	98	(19.4)	195	(19.1)
>= 75	28	(5.4)	28	(5.5)	56	(5.5)
Mean	53.9		53.7		53.8	
SD	13.6		14.2		13.9	
Median	54.0		54.0		54.0	
Range	19 to 88		19 to 83		19 to 88	
Region						
North America	38	(7.4)	37	(7.3)	75	(7.4)
Europe	341	(66.3)	336	(66.5)	677	(66.4)
Australia/New Zealand	111	(21.6)	112	(22.2)	223	(21.9)
Other	24	(4.7)	20	(4.0)	44	(4.3)
PD-L1 Status						
PD-L1 Positive	428	(83.3)	425	(84.2)	853	(83.7)
PD-L1 Negative	59	(11.5)	57	(11.3)	116	(11.4)
Unknown	27	(5.3)	23	(4.6)	50	(4.9)
BRAF-Mutation Status						
Mutation Detected	245	(47.7)	262	(51.9)	507	(49.8)
Mutation Not Detected	233	(45.3)	214	(42.4)	447	(43.9)
Unknown	36	(7.0)	29	(5.7)	65	(6.4)
ECOG						

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	514		505		1,019	
0	485	(94.4)	475	(94.1)	960	(94.2)
1	29	(5.6)	30	(5.9)	59	(5.8)
Primary Cutaneous Melanoma						
Cutaneous	455	(88.5)	460	(91.1)	915	(89.8)
Ocular	1	(0.2)	0	(0.0)	1	(0.1)
Unknown	58	(11.3)	45	(8.9)	103	(10.1)
Location of Primary Cutaneous Melanoma						
Head and Neck	53	(10.3)	66	(13.1)	119	(11.7)
Extremity	203	(39.5)	196	(38.8)	399	(39.2)
Trunk	196	(38.1)	189	(37.4)	385	(37.8)
Unknown	62	(12.1)	54	(10.7)	116	(11.4)
Breslow Thickness						
<= 1.0 mm	61	(11.9)	78	(15.4)	139	(13.6)
1.01 to 2.0 mm	99	(19.3)	103	(20.4)	202	(19.8)
2.01 to 4.0 mm	156	(30.4)	151	(29.9)	307	(30.1)
> 4.0 mm	125	(24.3)	111	(22.0)	236	(23.2)
Unknown	73	(14.2)	62	(12.3)	135	(13.2)
Cancer Stage by AJCC 2010						
Stage IIIA (> 1 mm)	80	(15.6)	80	(15.8)	160	(15.7)
Stage IIIB	237	(46.1)	230	(45.5)	467	(45.8)
Stage IIIC (1-3 LN+)	95	(18.5)	93	(18.4)	188	(18.4)
Stage IIIC (>= 4 LN+)	102	(19.8)	102	(20.2)	204	(20.0)
Number of LN+ (pathological)						
1	227	(44.2)	237	(46.9)	464	(45.5)
2-3	177	(34.4)	166	(32.9)	343	(33.7)
>= 4	110	(21.4)	102	(20.2)	212	(20.8)
Type of LN+ Involvement						
Microscopic	187	(36.4)	161	(31.9)	348	(34.2)
Macroscopic	327	(63.6)	344	(68.1)	671	(65.8)
Ulceration						
No	230	(44.7)	251	(49.7)	481	(47.2)
Yes	208	(40.5)	197	(39.0)	405	(39.7)
Unknown	76	(14.8)	57	(11.3)	133	(13.1)
Type of Surgery						
Axillary lymphadenectomy	192	(37.4)	194	(38.4)	386	(37.9)
Inguinal lymphadenectomy	137	(26.7)	130	(25.7)	267	(26.2)
Modified radical neck dissection	58	(11.3)	68	(13.5)	126	(12.4)
Other	4	(0.8)	5	(1.0)	9	(0.9)
Multiple types of surgery	123	(23.9)	108	(21.4)	231	(22.7)
Timing of First Dose of Study Therapy						
<= 13 weeks from date of surgery	500	(97.3)	490	(97.0)	990	(97.2)
> 13 weeks from date of surgery	9	(1.8)	12	(2.4)	21	(2.1)
Unknown	5	(1.0)	3	(0.6)	8	(0.8)
(Database Cutoff Date: 02OCT2017).						

The numbers of patients who received post lymph-node dissection radiotherapy were 49/514 (9.5%) and 57/505 (11.3%) in the pembrolizumab and placebo group, respectively.

Concomitant treatments: systemic antineoplastic agents were not permitted during the study; however, topical agents were permitted. Topical fluorouracil use was reported for 3 subjects (0.6%) in the pembrolizumab group and 1 subject (0.2%) in the placebo group. Systemic corticosteroids were administered to 23.0% of subjects in the pembrolizumab group and 10.5% of subjects in the placebo group.

Numbers analysed

A total of 1464 subjects were screened and 1019 randomized (ITT population), 514 in the pembrolizumab group and 505 in the placebo group.

A total of 8 subjects were randomized but not treated (5 in the pembrolizumab and 3 in the placebo group).

Table 11: Subject disposition

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	514		505	
Status for Study Medication in Trial				
Completed	264	(51.4)	280	(55.4)
Discontinued	209	(40.7)	204	(40.4)
Adverse Event	70	(13.6)	11	(2.2)
Non-Compliance With Study Procedures	3	(0.6)	0	(0.0)
Other Malignancy	4	(0.8)	5	(1.0)
Physician Decision	1	(0.2)	0	(0.0)
Recurrence/Relapse/Death Due To Pd	110	(21.4)	180	(35.6)
Withdrawal By Subject	21	(4.1)	8	(1.6)
Status Not Recorded	41	(8.0)	21	(4.2)

Each subject is counted once for Study Medication Disposition.
Status not Recorded for subjects that are continuing in trial or trial segment.
(Database Cutoff Date: 02OCT2017).

At the data cut-off date of 2-OCT-2017, for Part 2 of the study, patients from the placebo arm who crossed over to pembrolizumab were 109 (21.6%). Only one patient (0.2%) in the pembrolizumab arm was rechallenged with pembrolizumab (both crossover and rechallenge were at the discretion of the investigator).

Outcomes and estimation

Primary Endpoint – Recurrence-free Survival (RFS)

The interim analysis for RFS as of the data cut-off of 02-OCT-2017 has been presented, including a total of 351 RFS events occurred in the ITT population.

Table 12: Analysis of Recurrence-Free Survival - ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS[†] (Months) (95% CI)	RFS Rate at Month 6 in %[†] (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio[‡] (98.4% CI)[‡]	p-Value[§]
Pembrolizumab	514	135 (26.3)	6246.3	2.2	Not Reached (-, -)	82.2 (78.6, 85.3)	0.57 (0.43, 0.74)	<0.0001
Placebo	505	216 (42.8)	5566.3	3.9	20.4 (16.2, -)	73.3 (69.2, 77.0)	---	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

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

[‡] Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.

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

(Database Cutoff Date: 02OCT2017)

Table 13: Reason for Censoring in RFS Analysis Subjects Censored in RFS Analysis

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	379		289	
Reason for Censoring in RFS Analysis				
Database cutoff date	359	(94.7)	278	(96.2)
Lost to follow-up	4	(1.1)	0	(0.0)
Missing imaging	1	(0.3)	0	(0.0)
Missing scheduled follow-up visit	1	(0.3)	0	(0.0)
Subject withdrew consent	14	(3.7)	11	(3.8)
(Database Cutoff Date: 02OCT2017).				

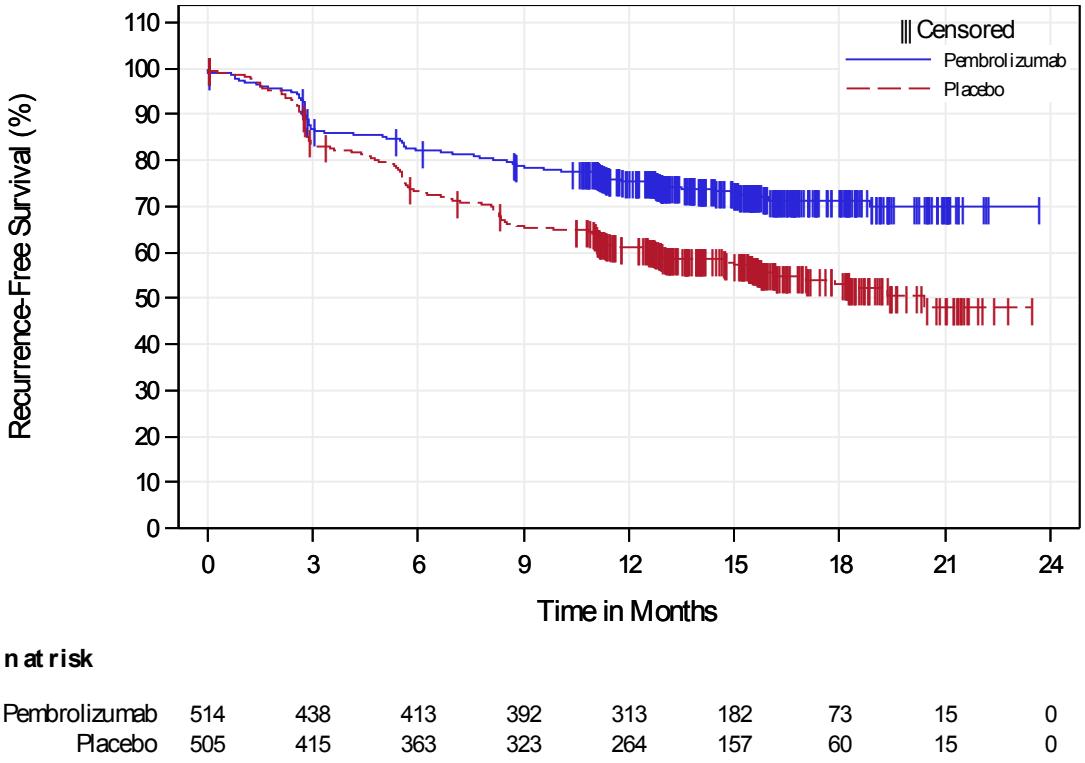


Figure 5: Kaplan-Meier Estimates of Recurrence-Free Survival - ITT Population

Table 14: Recurrence-Free Survival Rate Over Time (ITT Population)

	Pembrolizumab (N=514)	Placebo (N=505)
RFS rate at 6 Months in % (95% CI)†	82.2 (78.6, 85.3)	73.3 (69.2, 77.0)
RFS rate at 12 Months in % (95% CI)†	75.4 (71.3, 78.9)	61.0 (56.5, 65.1)
RFS rate at 18 Months in % (95% CI)†	71.4 (66.8, 75.4)	53.2 (47.9, 58.2)

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

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

(Database Cutoff Date: 02OCT2017).

Table 15: Disease Status- ITT Population

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	514	505
Type of First Event in RFS Analysis		
No event	379 (73.7)	289 (57.2)
Event	135 (26.3)	216 (42.8)
Locoregional recurrence	55 (10.7)	77 (15.2)
Distant metastasis	69 (13.4)	114 (22.6)
Both diagnosed within 30 days from each other	9 (1.8)	24 (4.8)
Death	2 (0.4)	1 (0.2)
DMFS Status		
No event	416 (80.9)	340 (67.3)
Event	98 (19.1)	165 (32.7)
Survival Status		
Alive	489 (95.1)	470 (93.1)
Dead	25 (4.9)	35 (6.9)
Database Cutoff Date: 02OCT2017		

Recurrence-free Survival (RFS) – updated analyses (cut-off date 2 May 2018)

As per CHMP request, the MAH presented updated analyses with a data cut-off date of 2 May 2018 (i.e. 7 months after the IA cut-off date of 2 Oct 2017 previously reported) for a median follow-up duration of 21.6 months. A total of **404 RFS events** occurred (vs 351 at the IA), 30.7% in the pembrolizumab vs 48.7% in the placebo arm. The number of events almost reached the planned final number of 409 RFS events.

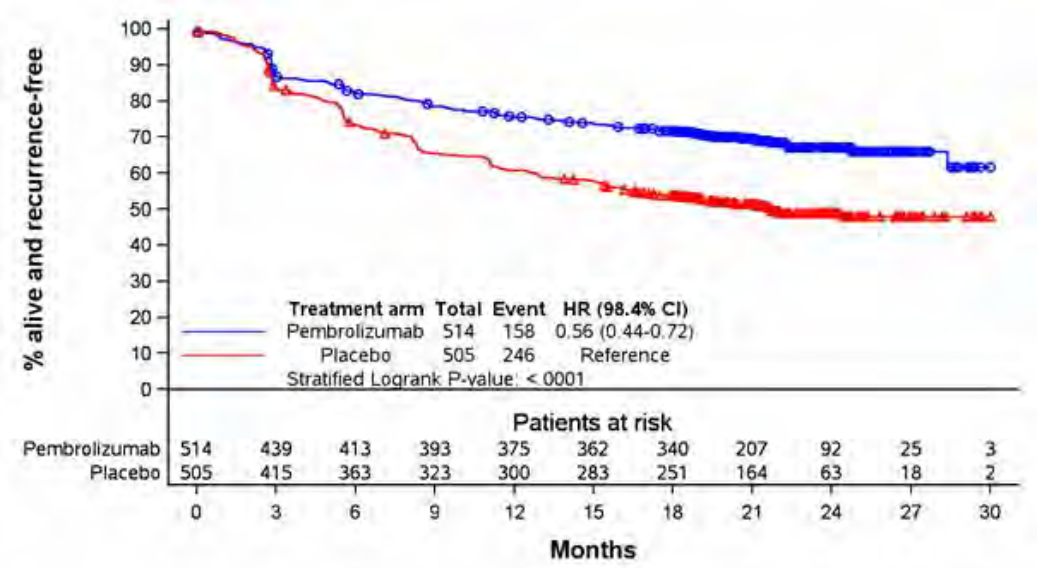


Figure 6: Recurrence-Free Survival by Treatment Arm (ITT Population) - cut-off date 2 May 2018

Table 16: Recurrence-Free Survival (ITT Population) - cut-off date 2 May 2018

	RFS event/Total	Median (95% CI)[KM]	Stratified HR (98.4%CI)[Cox]	Survival Estimates (95% CI)[KM]	P-value
Treatment arm				Month:	<.0001*
Pembrolizumab	158/514	NE (NE-NE)	0.56 (0.44-0.72)	12 :75.6 (71.6-79.1%)	
				15 :73.8 (69.7-77.4%)	
				18 :71.8 (67.6-75.5%)	
				21 :69.7 (65.5-73.6%)	
				24 :67.1 (62.5-71.4%)	
Placebo	246/505	21.7 (17.1-NE)	Reference	12 :60.8 (56.3-64.9%)	
				15 :57.7 (53.3-61.9%)	
				18 :53.8 (49.3-58.1%)	
				21 :51.5 (47.0-55.9%)	
				24 :48.8 (44.1-53.4%)	

[KM]Kaplan-Meier method; [Cox]Cox model; *Logrank test;

The curves were estimated using the Kaplan-Meier method. The circles and triangles indicate the time of censoring. The log-rank test stratified by stage at randomization is used to draw inference. The estimate of the hazard ratio is based on a Cox model stratified by stage at randomization. For the hazard ratio, 98.4% CI is presented, corresponding to a one-sided significance level of 0.008

Primary Endpoint (dual primary) – Recurrence-free Survival (RFS) in PD-L1 Positive

Table 17: Analysis of Recurrence-Free Survival - ITT Population (PD-L1 Positive)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS[†] (Months) (95% CI)	RFS Rate at Month 6 in %[†] (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab	428	102 (23.8)	5287.4	1.9	Not Reached (-, -)	83.8 (80.0, 87.0)	0.54 (0.42, 0.69)	<0.0001
Placebo	425	176 (41.4)	4830.1	3.6	Not Reached (17.1, -)	75.4 (71.0, 79.2)	---	---

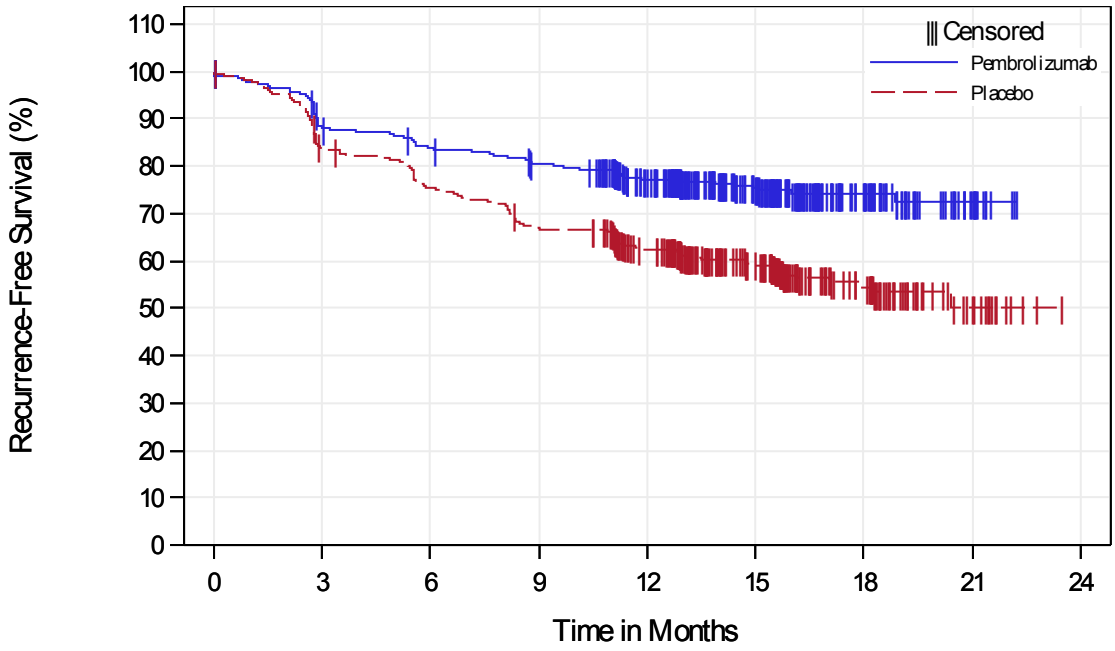
Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

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

[‡] Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.

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

(Database Cutoff Date: 02OCT2017)



n at risk

Pembrolizumab	428	370	350	333	266	156	61	13	0
Placebo	425	353	317	281	233	141	55	13	0

Figure 7: Kaplan-Meier Estimates of Recurrence-Free Survival - ITT Population (PD-L1 Positive) (cutoff Date: 02OCT2017)

RFS in PD-L1 Negative

RFS in subjects with PD-L1-negative tumours was not multiplicity controlled or pre-specified.

Table 18: Analysis of Recurrence-Free Survival- ITT Population (PD-L1 Negative)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo Hazard Ratio‡ (95% CI)‡
Pembrolizumab	59	20 (33.9)	713.4	2.8	Not Reached (15.8, -)	81.0 (68.4, 89.0)	0.47 (0.26, 0.85)
Placebo	57	27 (47.4)	545.9	4.9	19.4 (5.7, -)	63.7 (49.6, 74.9)	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

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

‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.

(Database Cutoff Date: 02OCT2017)

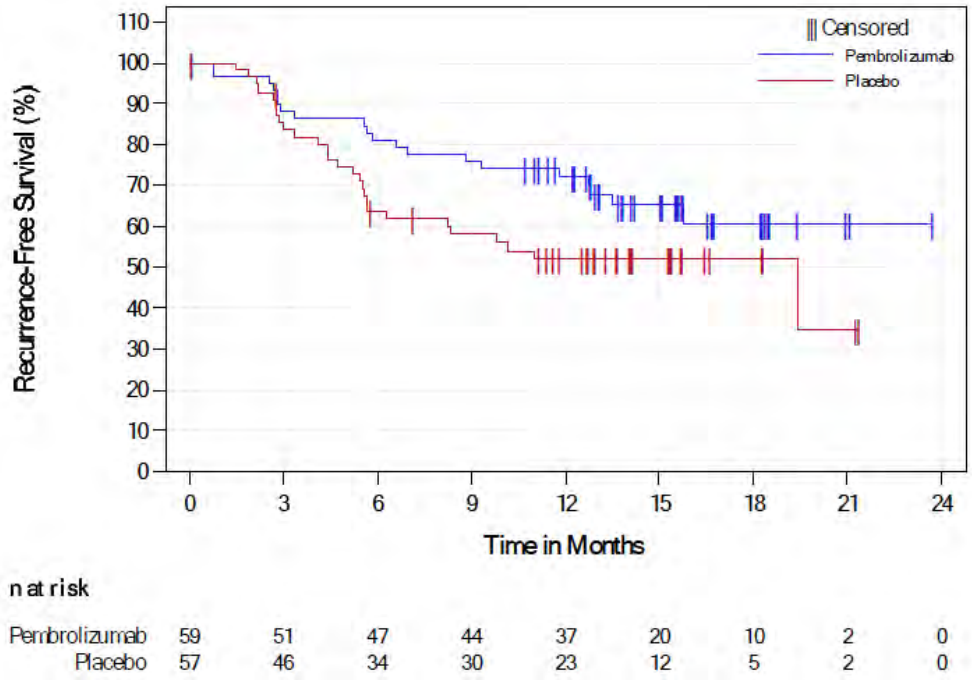


Figure 8: Kaplan-Meier Estimates of Recurrence-Free Survival - ITT Population (PD-L1 Negative) (cutoff Date: 02OCT2017)

Table 19: Subject Characteristics ITT Population PD-L1 Negative

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	59		57		116	
Gender						
Male	39	(66.1)	28	(49.1)	67	(57.8)
Female	20	(33.9)	29	(50.9)	49	(42.2)
Age (Years)						
< 50	24	(40.7)	25	(43.9)	49	(42.2)
50 to 64	20	(33.9)	22	(38.6)	42	(36.2)
65 to 74	12	(20.3)	7	(12.3)	19	(16.4)
>= 75	3	(5.1)	3	(5.3)	6	(5.2)
Mean	54.2		51.8		53.0	
SD	13.8		14.0		13.9	
Median	53.0		52.0		52.0	
Range	28 to 83		24 to 78		24 to 83	
Region						

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	59		57		116	
North America	4	(6.8)	5	(8.8)	9	(7.8)
Europe	39	(66.1)	41	(71.9)	80	(69.0)
Australia/New Zealand	14	(23.7)	9	(15.8)	23	(19.8)
Other	2	(3.4)	2	(3.5)	4	(3.4)
PD-L1 Status						
PD-L1 Negative	59	(100.0)	57	(100.0)	116	(100.0)
BRAF-Mutation Status						
Mutation Detected	19	(32.2)	28	(49.1)	47	(40.5)
Mutation Not Detected	35	(59.3)	25	(43.9)	60	(51.7)
Unknown	5	(8.5)	4	(7.0)	9	(7.8)
ECOG						
0	58	(98.3)	54	(94.7)	112	(96.6)
1	1	(1.7)	3	(5.3)	4	(3.4)
Primary Cutaneous Melanoma						
Cutaneous	58	(98.3)	54	(94.7)	112	(96.6)
Unknown	1	(1.7)	3	(5.3)	4	(3.4)
Location of Primary Cutaneous Melanoma						
Head and Neck	9	(15.3)	2	(3.5)	11	(9.5)
Extremity	28	(47.5)	21	(36.8)	49	(42.2)
Trunk	21	(35.6)	30	(52.6)	51	(44.0)
Unknown	1	(1.7)	4	(7.0)	5	(4.3)
Breslow Thickness						
<= 1.0 mm	10	(16.9)	5	(8.8)	15	(12.9)
1.01 to 2.0 mm	12	(20.3)	18	(31.6)	30	(25.9)
2.01 to 4.0 mm	25	(42.4)	15	(26.3)	40	(34.5)
> 4.0 mm	10	(16.9)	15	(26.3)	25	(21.6)
Unknown	2	(3.4)	4	(7.0)	6	(5.2)
Cancer Stage by AJCC 2010						
Stage IIIA (> 1 mm)	13	(22.0)	17	(29.8)	30	(25.9)
Stage IIIB	25	(42.4)	22	(38.6)	47	(40.5)
Stage IIIC (1-3 LN+)	9	(15.3)	9	(15.8)	18	(15.5)
Stage IIIC (>= 4 LN+)	12	(20.3)	9	(15.8)	21	(18.1)
Number of LN+ (pathological)						
1	25	(42.4)	32	(56.1)	57	(49.1)
2-3	22	(37.3)	15	(26.3)	37	(31.9)
>= 4	12	(20.3)	10	(17.5)	22	(19.0)
Type of LN+ Involvement						
Microscopic	26	(44.1)	29	(50.9)	55	(47.4)
Macroscopic	33	(55.9)	28	(49.1)	61	(52.6)
Ulceration						
No	38	(64.4)	30	(52.6)	68	(58.6)
Yes	19	(32.2)	24	(42.1)	43	(37.1)
Unknown	2	(3.4)	3	(5.3)	5	(4.3)
Type of Surgery						
Axillary lymphadenectomy	19	(32.2)	25	(43.9)	44	(37.9)
Inguinal lymphadenectomy	21	(35.6)	14	(24.6)	35	(30.2)
Modified radical neck dissection	9	(15.3)	3	(5.3)	12	(10.3)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	59		57		116	
Other	0	(0.0)	1	(1.8)	1	(0.9)
Multiple types of surgery	10	(16.9)	14	(24.6)	24	(20.7)
Timing of First Dose of Study Therapy						
<= 13 weeks from date of surgery	59	(100.0)	55	(96.5)	114	(98.3)
> 13 weeks from date of surgery	0	(0.0)	2	(3.5)	2	(1.7)
(Database Cutoff Date: 02OCT2017).						

Ancillary analyses

RFS Subgroup Analyses

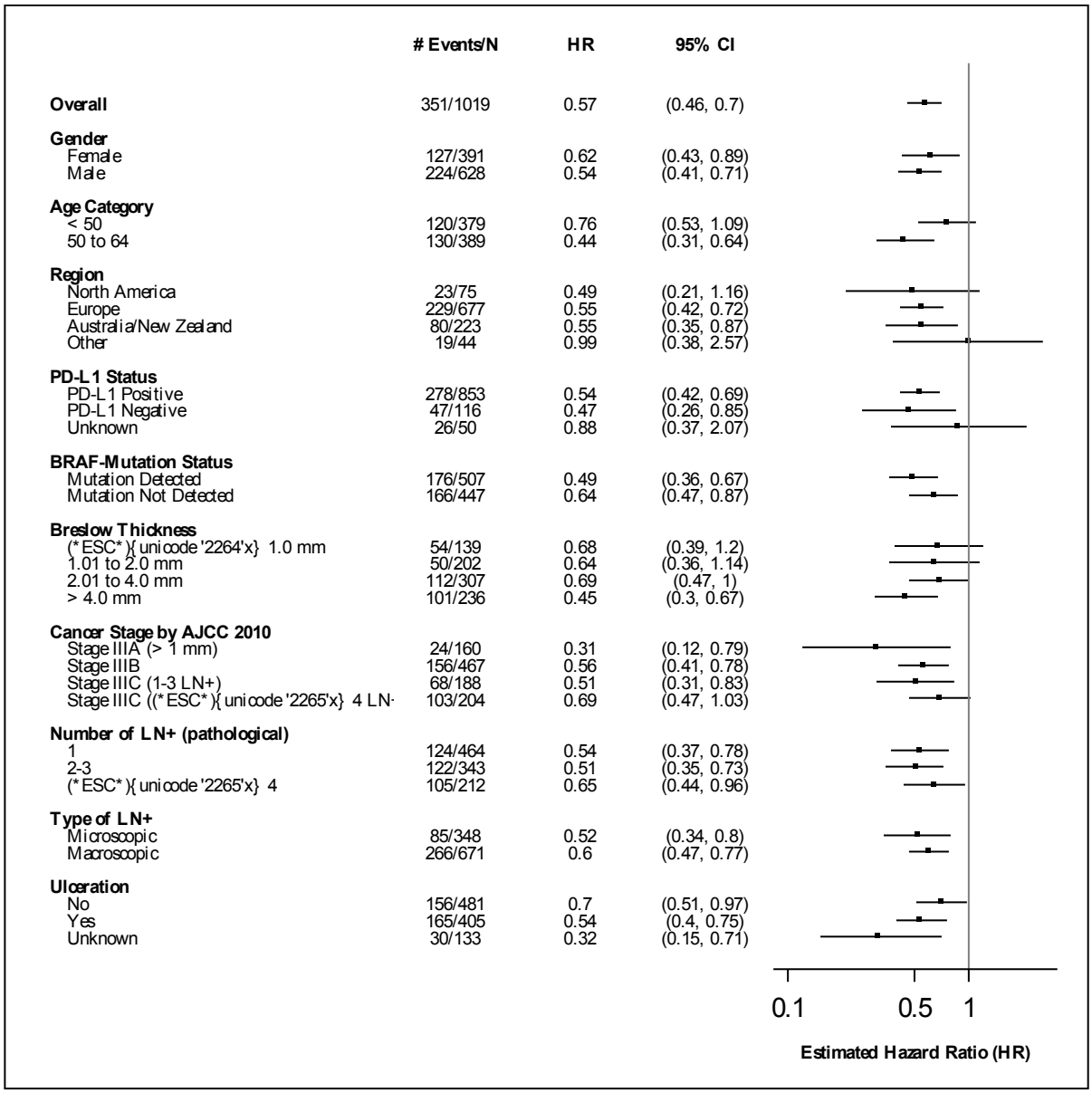


Figure 9: Forest Plot of Recurrence-Free Survival Hazard Ratio by Subgroup Factors (ITT Population) (cutoff Date: 02OCT2017)

No data have been collected regarding smoker-non smoker.

Table 20: Analysis of Recurrence-Free Survival by Age Category ITT Population

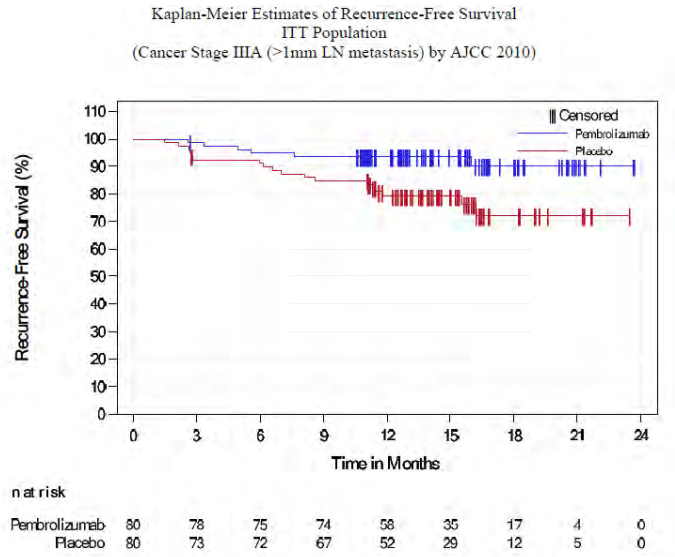
Age Category (Years)	Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo Hazard Ratio‡ (95% CI)‡
< 50	Pembrolizumab	193	52 (26.9)	2294.8	2.3	Not Reached (-, -)	80.6 (74.3, 85.6)	0.76 (0.53, 1.09)
	Placebo	186	68 (36.6)	2162.9	3.1	20.4 (17.9, -)	79.7 (73.1, 84.9)	---
50 to 64	Pembrolizumab	196	44 (22.4)	2455.6	1.8	Not Reached (-, -)	86.4 (80.7, 90.5)	0.44 (0.31, 0.64)
	Placebo	193	86 (44.6)	2109.9	4.1	19.4 (12.7, -)	71.8 (64.8, 77.6)	---
65 to 74	Pembrolizumab	97	30 (30.9)	1183.0	2.5	Not Reached (-, -)	80.2 (70.8, 86.9)	0.54 (0.34, 0.86)
	Placebo	98	49 (50.0)	1013.1	4.8	15.5 (8.3, -)	68.2 (58.0, 76.5)	---
>= 75	Pembrolizumab	28	9 (32.1)	312.9	2.9	Not Reached (6.6, -)	70.9 (50.2, 84.3)	0.50 (0.21, 1.21)
	Placebo	28	13 (46.4)	280.5	4.6	Not Reached (2.8, -)	59.3 (38.7, 75.1)	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

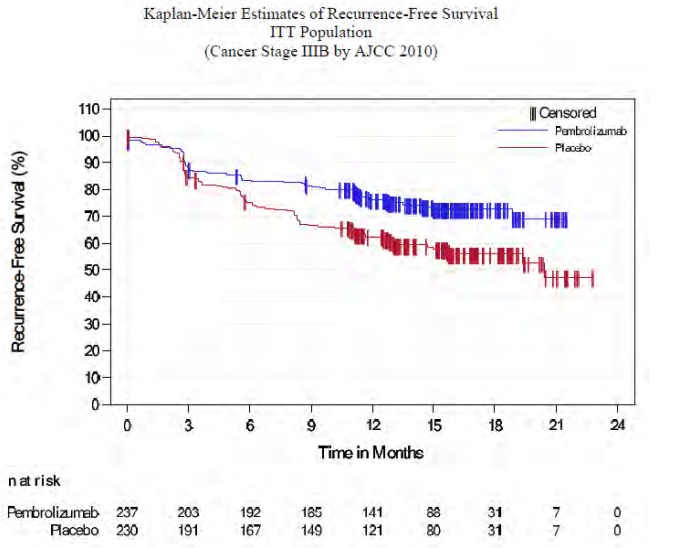
† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.

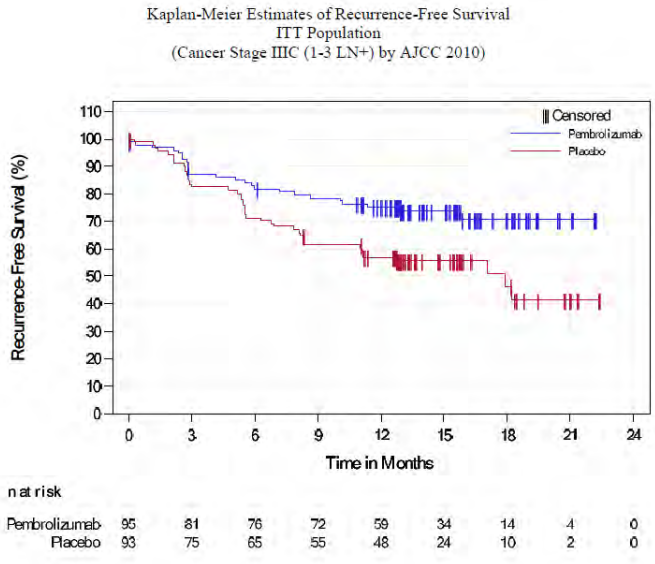
(Database Cutoff Date: 02OCT2017)



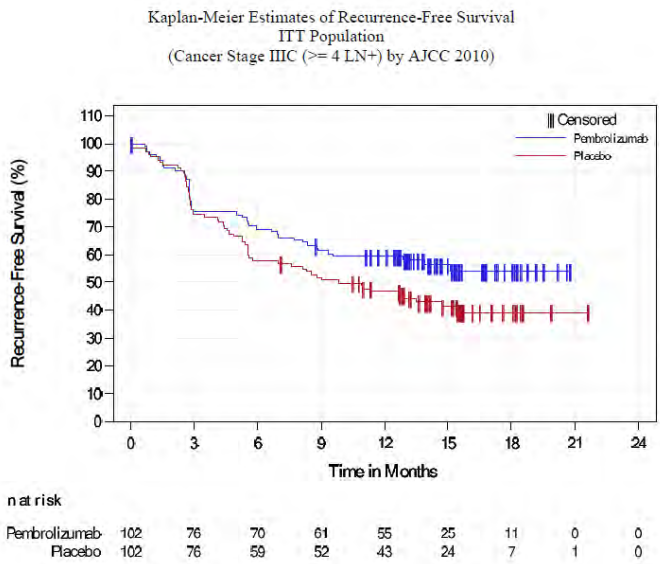
IIIA (>1mm ln mets) nb events: pembrolizumab 6 (7.5%), placebo 18 (22.5%)



IIIB nb events: pembrolizumab 60 (25.3%), placebo 96 (41.7%)



IIIC (1-3 ln) nb events: pembrolizumab 25 (26.3%), placebo 43 (46.2%)



IIIC (4+ln) nb events: pembrolizumab 44 (43.1%), placebo 59 (57.8%)

Figure 10: RFS Kaplan-Meier curves according to Stage (AJCC 7th edition, 2010)

Upon CHMP request, the MAH provided updated analyses (cut-off date 2 May 2018) of RFS by stage (AJCC 7th edition) (see table below):

Table 21: RFS by stage (AJCC 7th edition) cut-off date 2 May 2018

Stage (AJCC 7th edition)	nb patients	nb RFS events (%)	Hazard Ratio (95% CI)	p-Value
Stage IIIA (> 1 mm)	pembro 80 placebo 80	10 (12.5) 23 (28.7)	0.38 (0.14, 1.01)	0.0084
Stage IIIB	pembro 237 placebo 230	69 (29.1) 106 (46.1)	0.57 (0.38, 0.84)	0.0002
Stage IIIC (1-3 LN+)	pembro 95 placebo 93	32 (33.7) 51 (54.8)	0.53 (0.29, 0.94)	0.0038
Stage IIIC (>= 4 LN+)	pembro 102 placebo 102	47 (46.1) 66 (64.7)	0.64 (0.39, 1.05)	0.0190
Data cut-off date 02 May 2018				

KEYNOTE-054 was designed when melanoma was staged according to AJCC's manual 7th Edition, but in current clinical practice the 8th Edition is used. In the latter, a series of changes have further subdivided stage III into four categories (IIIA, IIIB, IIIC and IIID) regarding the previous three (IIIA, IIIB and IIIC) from the 7th Edition. Upon CHMP request, the MAH added a re-classification table, performed an RFS analysis stratified by stage according to AJCC 8th edition and provided subgroup analyses by cancer stage according to AJCC 8th edition.

Table 22: Distribution of Cancer Stage by AJCC 8th Edition (cut-off date 2 Oct 2017)

Cancer Stage (AJCC 7th Edition)	Cancer Stage (AJCC 8th Edition)				
	Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID	Unknown
Stage IIIA (> 1 mm)	67	61	28	0	4

Stage IIIB	14	241	192	0	20
Stage IIIC (1-3 LN+)	1	50	128	6	3
Stage IIIC (>= 4 LN+)	0	3	155	33	13

Forty subjects did not have sufficient information collected at the time of randomization to classify their cancer stage according to the AJCC 8th Edition (displayed as "Unknown").

Table 23: Analysis of Recurrence-Free Survival ITT Population Stratified by Stage According to AJCC 8th Edition

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS[†] (Months) (95% CI)	RFS Rate at Month 6 in %[†] (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio[‡] (98.4% CI)[‡]	p-Value[§]
Pembrolizumab	514	135 (26.3)	6246.3	2.2	Not Reached (-, -)	82.2 (78.6, 85.3)	0.55 (0.42, 0.71)	<0.0001
Placebo	505	216 (42.8)	5566.3	3.9	20.4 (16.2, -)	73.3 (69.2, 77.0)	---	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

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

[‡] Based on Cox regression model with treatment as a covariate stratified by stage according to AJCC 8th edition (Stage IIIA, Stage IIIB, Stage IIIC, Stage IIID).

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

(Database Cutoff Date: 02OCT2017)

Table 24: RFS according to Stage by AJCC 8th Edition

Stage (AJCC 8th edition)	nb patients	nb RFS events (%)	Hazard Ratio (95% CI)
Stage IIIA	pembro 42 placebo 40	3 (7.1) 4 (10)	0.76 (0.17, 3.39)
Stage IIIB	pembro 164 placebo 191	39 (23.8) 71 (37.2)	0.60 (0.41, 0.89)
Stage IIIC	pembro 267 placebo 236	75 (28.1) 119 (50.4)	0.48 (0.36, 0.65)
Stage IIID	pembro 19 placebo 20	10 (52.6) 15 (75)	0.62 (0.28, 1.37)
Data cut-off date 02 Oct 2017			

Table 25: RFS according to Stage by AJCC 8th Edition (updated data cut-off date 2 May 2018)

Stage (AJCC 8th edition)	nb patients	nb RFS events (%)	Hazard Ratio (99% CI)
Stage IIIA	pembro 42 placebo 40	6 (14.3) 7 (17.5)	0.84 (0.20, 3.54)
Stage IIIB	pembro 163 placebo 190	43 (26.4) 78 (41.1)	0.59 (0.36, 0.96)
Stage IIIC	pembro 267 placebo 239	87 (32.6) 141 (59.0)	0.45 (0.32, 0.64)

Stage IIID	pembro 20 placebo 18	11 (55.0) 13 (72.2)	0.69 (0.24, 1.98)
Data cut-off date 02 May 2018			

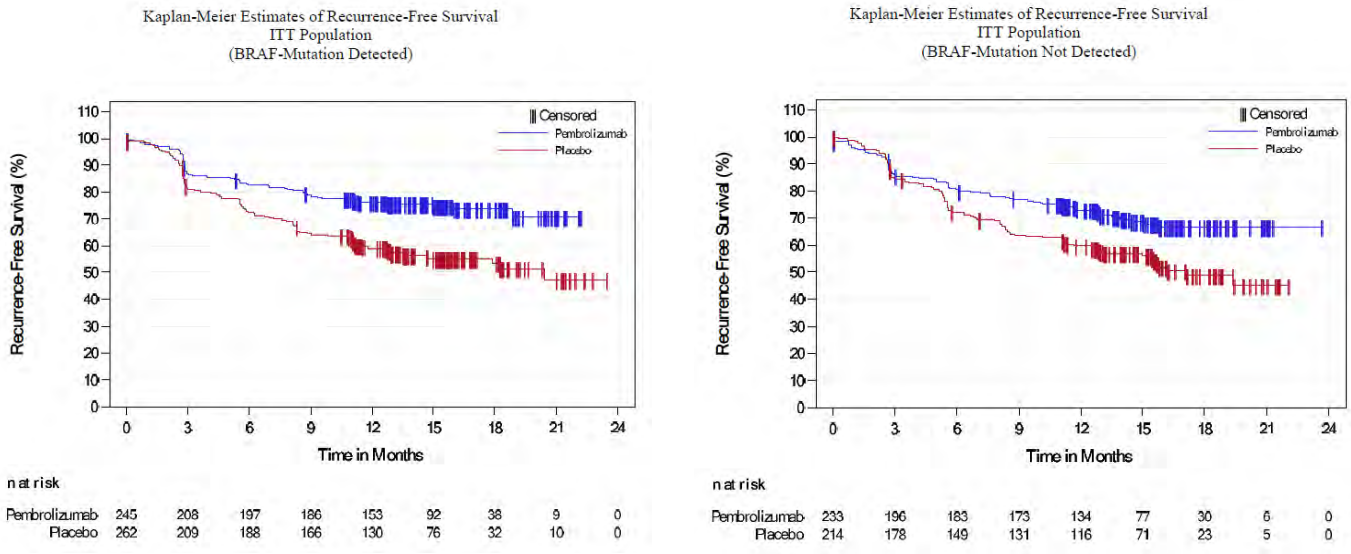


Figure 11: RFS Kaplan-Meier curves according to BRAF status

For patients with BRAF mutation "unknown" (36 patients in pembrolizumab and 29 patients in the placebo arm), 5 (13.9%) RFS events were observed in the pembrolizumab arm and 4 (13.8%) events in the placebo arm. The median RFS was not reached in both arms. The RFS rate at month 6 was 91.7% (95% CI: 76.3, 97.2) and 89.7% (95% CI: 71.3, 96.5). The HR was 0.95 (95% CI: 0.25, 3.64).

RFS Sensitivity Analyses

Table 26: Sensitivity analysis of recurrence-free survival - ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio‡ (98.4% CI)‡	p-Value§
Pembrolizumab	514	135 (26.3)	6246.3	2.2	Not Reached (-, -)	82.2 (78.6, 85.3)	0.57 (0.43, 0.74)	<0.0001
Placebo	505	216 (42.8)	5562.9	3.9	20.4 (16.2, -)	73.3 (69.2, 77.0)	---	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.
§ One-sided p-value based on log-rank test.
(Database Cutoff Date: 02OCT2017)

Table 27: Sensitivity analysis considering the start of a new anti-cancer treatment as an event - ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio‡ (98.4% CI)‡	p-Value§
Pembrolizumab	514	135 (26.3)	6246.3	2.2	Not Reached (-, -)	82.2 (78.6, 85.3)	0.56 (0.43, 0.73)	<0.0001
Placebo	505	217 (43.0)	5562.9	3.9	20.4 (16.2, -)	73.3 (69.2, 77.0)	---	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.
§ One-sided p-value based on log-rank test.
(Database Cutoff Date: 02OCT2017)

A multivariate Cox regression model was fitted as sensitivity analysis:

Table 28: Analysis of maximum likelihood estimates for parameters in the final model

Parameter	Level	Reference Level	Hazard Ratio	98.4% CI for Hazard Ratio	p-value
Treatment	Pembrolizumab	Placebo	0.55	(0.42, 0.72)	<0.001
Cancer Stage	IIIB	IIIA [>1 mm metastasis]	2.71	(1.59, 4.63)	<0.001
Cancer Stage	IIIC 1-3 nodes	IIIA [>1 mm metastasis]	2.70	(1.51, 4.85)	<0.001
Cancer Stage	IIIC ≥4 nodes	IIIA [>1 mm metastasis]	4.34	(2.49, 7.55)	<0.001
BRAF-mutation status	Mutation Detected	Mutation Not Detected	1.09	(0.83, 1.44)	0.447
BRAF-mutation status	Unknown	Mutation Not Detected	0.61	(0.39, 0.95)	0.007
Breslow thickness	> 2 mm to ≤ 4 mm	≤ 2 mm	1.16	(0.83, 1.63)	0.290
Breslow thickness	> 4 mm	≤ 2 mm	1.36	(0.97, 1.91)	0.028
Breslow thickness	Unknown	≤ 2 mm	0.73	(0.45, 1.18)	0.111
PD-L1 expression	Negative	Positive	1.50	(1.02, 2.21)	0.012
PD-L1 expression	Indeterminate	Positive	1.84	(1.11, 3.04)	0.004
Age	≥ 65 years	< 65 years	1.29	(0.97, 1.73)	0.034

Treatment after first recurrence

Table 29: Additional Treatment After First Recurrence (updated cut-off date 2 May 2018)

	Treatment arm		
	Pembrolizumab (N=156)	Placebo (N=245)	Total (N=401)
Type of additional treatment	N (%)	N (%)	N (%)
Surgery for melanoma under study			
No	84 (53.8)	150 (61.2)	234 (58.4)
Yes	72 (46.2)	95 (38.8)	167 (41.6)
Radiotherapy			
No	119 (76.3)	183 (74.7)	302 (75.3)
Yes	37 (23.7)	62 (25.3)	99 (24.7)
Chemotherapy			
No	144 (92.3)	232 (94.7)	376 (93.8)
Yes	12 (7.7)	13 (5.3)	25 (6.2)
BRAF/MEK-inhibitors			
No	112 (71.8)	181 (73.9)	293 (73.1)
Yes	44 (28.2)	64 (26.1)	108 (26.9)
Anti-CTLA4			
No	112 (71.8)	193 (78.8)	305 (76.1)
Yes	44 (28.2)	52 (21.2)	96 (23.9)
Anti-PD-1 / Anti-PD-L1			

Type of additional treatment	Treatment arm Pembrolizumab (N=156) N (%)	 Placebo (N=245) N (%)	 Total (N=401) N (%)
No	110 (70.5)	52 (21.2)	162 (40.4)
Yes	46 (29.5)	193 (78.8)	239 (59.6)
Other targeted agents			
No	155 (99.4)	240 (98.0)	395 (98.5)
Yes	1 (0.6)	5 (2.0)	6 (1.5)
Other systemic immunotherapy			
No	149 (95.5)	231 (94.3)	380 (94.8)
Yes	7 (4.5)	14 (5.7)	21 (5.2)
Other systemic therapy			
No	154 (98.7)	244 (99.6)	398 (99.3)
Yes	2 (1.3)	1 (0.4)	3 (0.7)

Other endpoints

Progression/Recurrence-free Survival 2 (PRFS2)

PRFS2 was defined as the time in days between the date of randomization and the earliest of the following: date of 1st disease progression per RECIST 1.1 after the initial unresectable disease recurrence (e.g. unresectable distant metastases); date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (e.g. local regional recurrences or resectable distant metastases); death. For patients who remain alive and whose disease has not recurred, or whose disease has recurred but subsequent disease progression or recurrence has not occurred, PRFS2 was censored on the date of last visit/contact with disease assessments or date of last follow up.

Table 30: Progression/Recurrence-free Survival 2 Status ITT Population

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	514		505	
PRFS2[†] Status				
No event	417	(81.1)	366	(72.5)
PRFS2 event	97	(18.9)	139	(27.5)
LR[‡] event, followed by a LR/DM[§]	35	(6.8)	42	(8.3)
DM event, followed by a progression	46	(8.9)	87	(17.2)
No initial recurrence, followed by death NOT due to melanoma	2	(0.4)	1	(0.2)
LR event and/or DM, followed by death (i.e., no 2nd progression reported)	14	(2.7)	9	(1.8)

[†] PRFS2 = Progression/recurrence-free survival 2.
[‡] LR = Locoregional.
[§] DM = Distant metastasis.
(Database Cutoff Date: 02MAY2018).

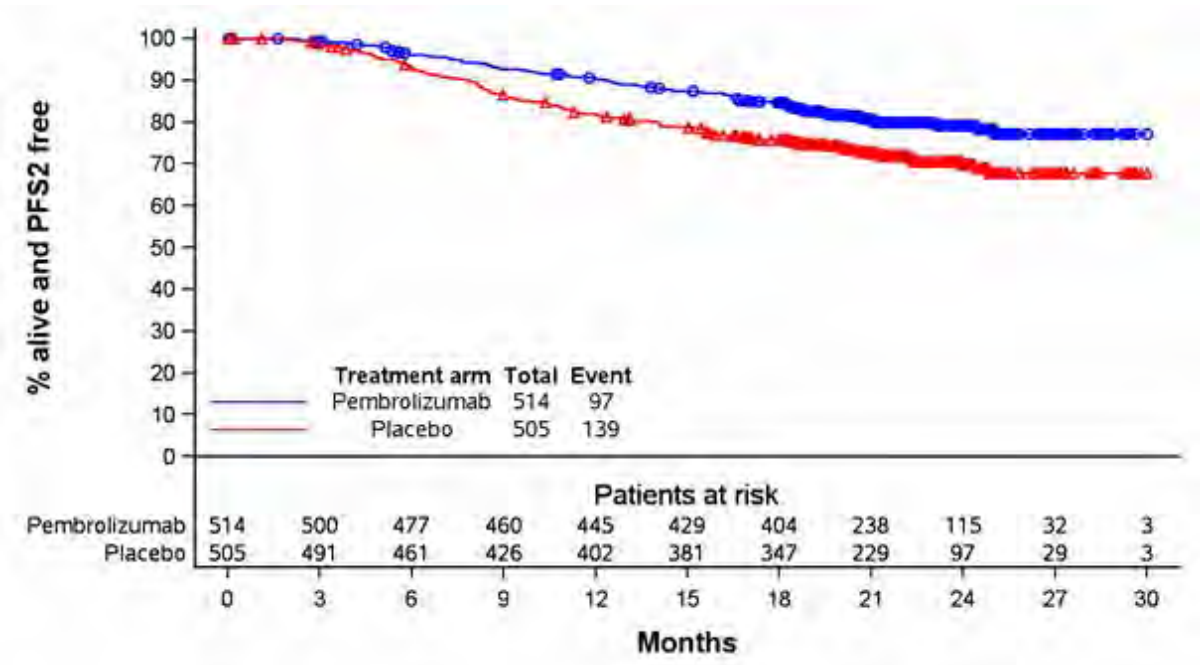


Figure 12: K-M curves for Progression/Recurrence-free Survival 2 by Treatment Arm (ITT Population)

Table 31: Progression/Recurrence-free Survival 2 by Treatment Arm (ITT Population) and Survival Estimates for 12, 15, 18, 21 and 24 months

	PFS2 /Total	events	Median (95% CI)[KM]	Stratified Hazard Ratio [Cox]	Survival Estimates (95% CI)[KM]
Treatment arm					Month:
Pembrolizumab	97/514		NE (NE-NE)	0.64	12 :90.4 (87.4-92.6%) 15 :87.5 (84.3-90.1%) 18 :84.6 (81.1-87.5%) 21 :80.6 (76.6-83.9%) 24 :79.3 (75.1-82.8%)
Placebo	139/505		NE (NE-NE)	Reference	12 :82.0 (78.3-85.1%) 15 :78.7 (74.8-82.1%) 18 :75.8 (71.7-79.3%) 21 :72.6 (68.3-76.4%) 24 :69.8 (65.1-74.1%)

[KM]Kaplan-Meier method; [Cox]Cox model

The curves were estimated using the Kaplan-Meier method. The circles and triangles indicate the time of censoring. The estimate of the hazard ratio is based on a Cox model.

Time to First Subsequent Therapy (TFST)

TFST is defined as the time between randomization and either first post-protocol systemic therapy after recurrence or death, whichever occurred first. Treatment in Part 2 of the study is considered as post-protocol systemic therapy. Patients without a record of death or post-protocol systemic therapy after recurrence are censored at the latest of the following dates: randomization, the end of treatment visit, recurrence, last disease evaluation for recurrence-free survival, last visit when information about further treatment administration was recorded. A first subsequent systemic therapy (or death) was recorded in 220 patients on the placebo arm compared to 107 on the pembrolizumab arm.

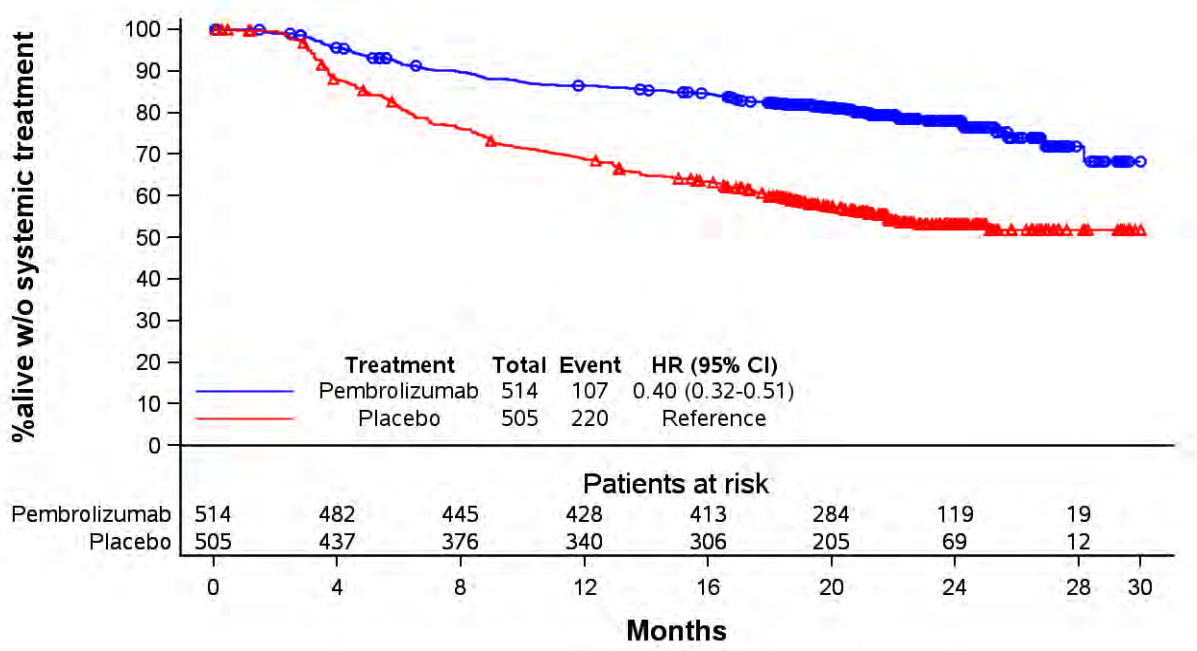


Figure 13: K-M curves for Time to First Subsequent Therapy Post-protocol Systemic Therapy-free Survival (ITT Population)

Table 32: First Subsequent Therapy Post-protocol Systemic Therapy-free Survival (ITT Population)

	Event/Total	Median (95% CI)[KM]	Hazard Ratio [Cox]	Survival Estimates (95% CI)[KM]
Treatment				Month :
Pembrolizumab	107/514	NE (NE-NE)	0.40	12 : 86.4 (83.1-89.1%) 15 : 85.0 (81.6-87.9%) 18 : 82.5 (78.9-85.6%) 21 : 80.1 (76.3-83.5%) 24 : 78.0 (73.7-81.7%)
Placebo	220/505	NE (21.8-NE)	Reference	12 : 69.0 (64.7-72.8%) 15 : 64.3 (59.9-68.3%) 18 : 59.8 (55.4-64.0%) 21 : 56.1 (51.5-60.5%) 24 : 53.2 (48.3-57.8%)

[KM]Kaplan-Meier method; [Cox]Cox model

The curves were estimated using the Kaplan-Meier method. The circles and triangles indicate the time of censoring. The estimate of the hazard ratio is based on a Cox model

Distant Metastatis free survival (DMFS) and Overall survival (OS): at the time of the data cut-off, the minimum number of events needed to analyze the endpoints of DMFS and OS had not been achieved. Therefore, KEYNOTE-054 will continue until the minimum number of protocol-specified events required to analyze each of these endpoints has been observed.

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 33: Summary of Efficacy for trial KEYNOTE-054

Title: Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 study of the EORTC Melanoma Group.			
Study identifier	MK-3475-054		
Design	Phase III international, double-blinded, placebo-controlled, randomized		
	Duration of main phase:		Part 1: Adjuvant Therapy: pembrolizumab or placebo administered Q3W for a total of 18 administrations (~1 year) or until disease recurrence or unacceptable toxicity Part 2: Crossover or Rechallenge: pembrolizumab administered Q3W for up to 2 years or until disease progression.
	Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable Study is ongoing
Hypothesis	Superiority		
Treatments groups	pembrolizumab		200 mg Q3W, IV infusion, for a total of 18 administrations (~1 year) (Part 1)
	placebo		0 mg Q3W, IV infusion, for a total of 18 administrations (~1 year) (Part 1)
Endpoints and definitions	Dual Primary endpoint	RFS in the ITT all-subjects RFS in PD-L1 positive tumors	Time between the date of randomization and the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. RFS will be based on the disease assessment or date of death provided by the local investigator.
	Secondary endpoint	DMFS in the ITT all-subjects and in PD-L1 positive tumors	Time between the date of randomization and the date of 1st distant metastasis or date of death (whatever the cause), whichever occurs first.
	Secondary endpoint	OS in the ITT all-subjects and in PD-L1 positive tumors	Time from the date of randomization to the date of death, whatever the cause
	Exploratory endpoint	HRQoL in the ITT all-subjects	EORTC QLQ-C30, EuroQOL EQ 5D™

	Exploratory endpoint	PRFS2	Progression/recurrence-free survival 2: time between the date of randomization and the earliest of the following: 1)date of 1st disease progression per RECIST 1.1 beyond the initial unresectable disease recurrence (e.g. unresectable distant metastases); 2)date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (e.g. local regional recurrences or resectable distant metastases); 3) death
Database lock	Data cut-off date: 02-OCT-2017 interim analysis		

Results and Analysis

Analysis description	**Primary Analysis (interim analysis of RFS)**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	**Pembrolizumab**	**Placebo**
	Number of subject	514	505
	RFS (ITT) nb events (%)	135 (26.3%)	216 (42.8%)
	median (95%CI)	NR (-,-)	20.4 (16.2, -)
	RFS (PD-L1+) nb events (%)	102 (23.8%)	176 (41.4%)
	median (95%CI)	NR (-, -)	Not Reached (17.1, -)
Effect estimate per comparison	Dual Primary endpoint **RFS (ITT)**	Comparison groups	pembrolizumab vs placebo
		HR	0.57
		(98.4%CI)	(0.43, 0.74)
		P-value	p<0.0001
	Dual Primary endpoint **RFS (PD-L1+)**	HR	0.54
		(95%CI)	(0.42, 0.69)
		P-value	p<0.0001
Notes	This report includes efficacy and safety results from Part 1 only. Data from the secondary endpoints are not yet mature NR= not reached		

Analysis description	**Primary Analysis (Updated analysis of RFS) - cut-off date 2 May 2018**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	**Pembrolizumab**	**Placebo**
	Number of subject	514	505
	RFS (ITT) nb events (%)	158 (30.7%)	246 (48.7%)
	median (95%CI)	NR (-,-)	21.7 (17.1, -)
Effect estimate per comparison	**RFS (ITT)**	Comparison groups	pembrolizumab vs placebo
		HR	0.56
		(98.4%CI)	(0.44, 0.72)
		P-value	p<0.0001

Notes	The updated RFS analysis provided per CHMP request included a total of 404 RFS events (the planned final number of RFS events was 409)

Clinical studies in special populations

Table 34: RFS analysis in patients aged 65-74 – ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo Hazard Ratio‡ (95% CI)‡
Pembrolizumab	97	30 (30.9)	1183.0	2.5	Not Reached (-, -)	80.2 (70.8, 86.9)	0.54 (0.34, 0.86)
Placebo	98	49 (50.0)	1013.1	4.8	15.5 (8.3, -)	68.2 (58.0, 76.5)	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.
(Database Cutoff Date: 02OCT2017)

Table 35: RFS analysis in patients aged ≥75 – ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo Hazard Ratio‡ (95% CI)‡
Pembrolizumab	28	9 (32.1)	312.9	2.9	Not Reached (6.6, -)	70.9 (50.2, 84.3)	0.50 (0.21, 1.21)
Placebo	28	13 (46.4)	280.5	4.6	Not Reached (2.8, -)	59.3 (38.7, 75.1)	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.
(Database Cutoff Date: 02OCT2017)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

KN054 is an ongoing Phase 3, randomized, double-blind clinical trial to examine pembrolizumab versus placebo as adjuvant treatment after complete resection of high-risk stage III cutaneous melanoma.

Enrolled subjects had stage IIIA (with lymph node metastasis >1 mm), stage IIIB, or IIIC cutaneous melanoma. No past or current in-transit metastases or satellitosis were allowed. Staging was performed according to AJCC 7th edition, while the classification currently in use since January 2018 is the AJCC 8th edition. This is not however considered an issue, based also on the requested indication (melanoma "with lymph node involvement"). Enrollment of stage IIIA patients was capped at 20% of the total population.

The study was designed based on experiences drawn from the EORTC 18071 study (ipilimumab vs placebo in adjuvant melanoma) where enrolled Stage IIIA (> 1 mm) were 21%. The stage IIIA (> 1 mm lymph node metastasis) patient population was capped at a maximum of 20% in order to prevent dilution of the patient population with those not at high risk for recurrence, and moreover, enriched the patient population by only enrolling patients with a high risk of recurrence. Therefore it is deemed reasonable to have a 20% cap in order to allow a timely read out of the impact of pembrolizumab on RFS and OS.

Patients were required to have had complete (R0) resection, including a complete lymph node dissection, within 13 weeks from first treatment dose; the benefit of lymph node dissection was recently confirmed to confer only regional disease control without a benefit for OS. Enrollment was open to all subjects regardless of PD-L1 tumour expression, which was centrally measured by IHC using the MEL score and measuring the number of PD-L1 positive tumour cells and associated immune cells in the tumour nests [PD-L1 positive = MEL score ≥2 (i.e. staining on ≥1% of cells); PD-L1 negative = MEL score 0-1 (i.e. staining on <1% of cells)].

The use of placebo as comparator was accepted by the CHMP in the Scientific Advice (EMEA/H/SA/2437/6/2014/II), as IFN, although approved, was not widely used in the EU and its efficacy was modest. Ipilimumab (which is not approved in EU) study results were promising but not yet mature at the time when the trial was starting (June 2015). Nevertheless, the CHMP underlined that superiority over

placebo must be convincing enough in every subgroup to exclude a posteriori that IFN would have performed similarly, with a possible inferiority of pembrolizumab.

The treatment phase of KN054 consisted of two parts: Part 1 (Adjuvant Therapy): pembrolizumab 200 mg or placebo was administered Q3W for a total of 18 administrations (~1 year) or until disease recurrence or unacceptable toxicity; Part 2 (after first recurrence): Crossover or Re-challenge with pembrolizumab treatment. This submission includes interim efficacy data from Part 1 only of the study as of the data cutoff date 02-OCT-2017; Part 2 is ongoing and was not included in this submission. The duration of Part 1 of the trial is reflected in the SmPC as the recommended treatment period (i.e. one year of adjuvant treatment). It should be noted that since a shorter or longer treatment duration was not investigated in this trial design, it is not possible to determine whether there might be a more appropriate treatment duration.

Dual primary endpoints were investigator's assessed recurrence free survival (RFS), defined as the time between the date of randomization and the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first, in the ITT population and in subjects with PD-L1-positive tumours. The primary endpoint RFS was considered acceptable by the CHMP in the context of Scientific Advice.

DMFS and OS, both in the ITT and in PD-L1-positive populations, are secondary endpoints. QoL and RPFS2 are among the exploratory endpoints. The first imaging scan was within 6 weeks prior to randomization, and subsequent imaging occurred every 12 weeks until disease recurrence. For subjects who discontinued in the absence of disease recurrence, imaging was performed every 12 weeks for the first 2 years, every 6 months for Years 3 to 5, and annually thereafter. A sample subset of imaging (the first 100 investigator-reported recurrence. i.e. 36 from the pembrolizumab arm and 64 from the placebo arm) has been reviewed independently by central reviewer in order to assess the adequacy of the site reader performance on this trial, as suggested by CHMP in the SA, showing a 91% of concordance rate (defined as the percentage of BICR-defined recurrence dates being within one consecutive scan time point of the investigator-reported recurrence date).

Subjects were randomized using a minimization technique stratifying according to stage and region. Dynamic allocation (such as minimisation) is usually not recommended and should be avoided, unless justified. The re-randomization test was provided and the p-value was <0.001 (the value of the primary analysis p<0.0001), which was reassuring on the robustness of the primary analysis.

A total of 900 subjects (approximately 450 per arm) were planned to be randomized to achieve 409 RFS events. This sample size was able to detect an HR of 0.7 (increase of the median RFS from 1.64 to 2.87 years, i.e. roughly 15 months of improvement) with power 95% and two-sided alpha 5%. A total of 1019 patients were recruited, likely due to the high number of centres involved. The sample size was powered as well to assess an RFS improvement in PD-L1+ subgroup, assuming a range of values for the event rate in the placebo group, different hypotheses on HR at two different alpha level. Under the scenario of event rate equal to 50%, HR=0.55 and alpha=0.025, that is for similar condition observed in this study, the power for the subgroup was 97%.

The statistical methods used for the analysis of the primary and secondary endpoints are considered overall adequate. Clarifications regarding several minor methodological issues have been requested and have been provided by the MAH. The RFS analysis stratified by stage and region as indicated at randomization showed no remarkable difference with the result of the primary analysis. Sensitivity analyses as per the protocol overall showed consistent results with the primary RFS analysis.

An interim analysis for RFS in the ITT population, to be conducted after 330 RFS events (i.e. ~80% of the 409 final planned RFS events), was added with Amendment 02 (final protocol version MK-3475-054-02). It is noted that this amendment was finalized on the same date of the data cut-off for the interim analysis (02-OCT-2017). The main limit of this analysis is the relatively short follow-up, with very limited information

on the outcome in the experimental arm after the end of the 12-month treatment period. The applicant provided an explanation for this interim analysis: newly available data regarding the adjuvant melanoma treatment[17] triggered an earlier RFS event cut-off than originally planned. The explanation is considered acceptable.

Efficacy data and additional analyses

The dossier is based on the RFS interim analysis with a data cut-off date of 02-OCT-2017. The median follow-up was 16 months. Patients were recruited between 22-JUL-2015 and 14-NOV-2016 at 134 centers in 23 countries worldwide. A total of 1019 patients were randomized, 514 to pembrolizumab and 505 to placebo arm. Among the 445 patients not randomized, the most frequent reason of non randomization was current disease, including locoregional relapse, distant metastasis, or clinical evidence of brain metastases.

According to MSD's review, 69 important protocol deviations have been reported. Based on the information provided, it appears unlikely that they have significantly impacted on the final results.

Subjects were primarily male (61.6%), <65 years of age (median age 54.0 years), and about 94% had ECOG PS 0. Stage IIIA comprised 15.7% of the study population in both treatment groups (below the protocol-specified cap of 20%), 45.8% were stage IIIB and 38.4% stage IIIC. The majority of subjects (83.7%) had PD-L1-positive tumours and approximately half of the overall population (49.8%) had tumours positive for a BRAF V600 mutation. Baseline characteristics appeared well balanced between arms. Post lymph-node dissection radiotherapy was used similarly in both arms was similar in both arms (9.5% in pembrolizumab and 11.3% in placebo).

Overall, approximately half the subjects completed the adjuvant treatment in both arms. More discontinuations due to AE (13.6 vs 2.2), as expected, occurred in the pembrolizumab compared to placebo arm, as well as more withdrawal by subjects (4.1 vs 1.6%).

With a total of 351 RFS events [135 (26.3%) in the pembrolizumab arm and 216 (42.8%) in the placebo arm], pembrolizumab demonstrated a statistically significant improvement in RFS versus placebo in the ITT population (HR = 0.57; 98.4% CI: 0.43, 0.74; p<0.0001). Median RFS had not yet been reached in the pembrolizumab group, but had been reached in the placebo group (20.4 months, 95%CI 16.2-NR). The 6-months RFS rate was 82.2% (95%CI 78.6, 85.3) vs 73.3% (95%CI 69.2, 77), the 1-year RFS rate was 75.4% (95% CI: 71.3, 78.9) vs 61.0% (95% CI: 56.5, 65.1) in the pembrolizumab vs the placebo group, respectively. The Kaplan-Meier curves separate after 3 months and remain separated throughout, although curves are difficult to interpret after approximately month 10 due to the high rate of censoring. In this regard, an updated RFS analysis was requested and provided by the MAH (cut-off date 2 May 2018): a total of 404 RFS events were reported (vs 351 at the prior cut-off date of 2-Oct-2017). This means that the initially defined number of 409 RFS events required to analyse this endpoint has approximately been reached. The updated analysis continues to show a benefit of pembrolizumab adjuvant therapy over placebo with a HR of 0.56 (98.4% CI: 0.44-0.72; p<0.0001) consistent with the interim RFS data. A sensitivity analysis considering the start of a new anticancer treatment as an event had comparable result to the primary RFS analysis (HR=0.56).

Distant metastases developed in 69 subjects (13.4%) in the pembrolizumab group compared with 114 subjects (22.6%) in the placebo group. Information on patients, if any, who developed new primary melanoma and how such patients were handled in the primary RFS analysis, were requested. New primary melanoma were not counted as RFS events in the primary efficacy analysis in KN054 study, differently from other recent adjuvant trials CheckMate-238 (nivolumab vs ipilimumab) and COMBI-AD (dabrafenib/trametinib vs placebo). The MAH clarified that 19 subjects (7 in the pembrolizumab group, 12 in the placebo group) had a new primary melanoma. Four of 19 subjects, all in the placebo group, had a second primary after recurrence for the current melanoma, and all remaining 15 subjects were censored in the

analysis. As the number of patients with new primary melanoma is limited and balanced between arms, and given the RFS advantage with pembrolizumab seen in the ITT population, a significant impact on the RFS result is not expected.

RFS results in subjects with PD-L1-positive tumours (dual primary) were similar to those obtained in the overall population (HR=0.54; 95% CI: 0.42, 0.69; p<0.0001). An RFS advantage with pembrolizumab over placebo was seen regardless of PD-L1 status. Indeed, HR in subjects with PD-L1 negative tumour was 0.47 (95%CI 0.26-0.85), acknowledging that the analysis was neither prespecified nor multiplicity-controlled, and the limited number of patients (59 and 57 in pembrolizumab and placebo group, respectively). A higher rate of pembrolizumab-treated patients with an RFS event is noted in the PD-L1 negative compared to PD-L1 positive subgroup (33.9% and 23.8%, respectively). It is to note that patients were not stratified by PD-L1 status. Some imbalances in baseline characteristics were noted, in particular in BRAF mutation status (BRAF mutated 32% vs 49%). According to a multivariate cox regression model, it appeared that no confounding factors have influenced the observed treatment effect on PD-L1 negative population. The results for PD-L1 "unknown" (HR 0.88) is to be interpreted with caution, given the small numbers in this subgroup. The CHMP requests that the MAH investigates biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy in adjuvant melanoma, in addition to more information regarding the pattern of expression of PD L1 (see Annex II of the SmPC).

Overall, RFS benefit of pembrolizumab over placebo appears consistent in the subgroups analysed. A more limited effect in younger patients (<50 years, HR 0.76) is noted. In an explorative Cox-regression the MAH was requested to assess the possible impact of age (as covariate) on the HR. It is noted that RFS rates differ between the separate age groups. Lower RFS rates are observed with increasing age. However, this trend is observed in both treatment groups with HRs being in favour of pembrolizumab compared to placebo regardless of age group, which is reassuring that efficacy of pembrolizumab is observed across all age groups.

As expected, the event rate for RFS is different according to stage. Although the data is immature and the number of patients with stage IIIA disease is small, it appears that there is an advantage for the use of pembrolizumab in the adjuvant setting in patients with stage IIIA that have a lower risk of recurrence (7.5% vs 22.5% of stage IIIA patients having an RFS event). In an updated analysis of RFS by stage, despite a minimal increase in HR for stages IIIA, IIIB and IIIC (1-3LN) the updated results remain to be in favour of pembrolizumab throughout all stages.

The MAH was also requested to analyse RFS according to the new melanoma staging AJCC 8th edition (2017), as at the time of the study the previous AJCC 7th edition classification was in place and used in KEYNOTE-054. An increasing RFS advantage of pembrolizumab over placebo was seen for higher stages of disease (2 May 2018 updated cut-off: IIIA 0.84, IIIB 0.59, IIIC 0.45). For stage IIID, HR was 0.69 with 95%CI 0.28-1.37, but the number of patients is limited (19 in pembrolizumab and 20 in placebo arm). With regard to stage IIIA, at lower risk of recurrence, RFS HR was 0.84 (99%CI 0.14-3.54) in stage IIIA according to the new 8th edition classification, compared to the HR=0.38 (95%CI 0.14, 1.01) in stage IIIA according to 7th edition (2 May 2018 cut-off date). Stage IIIA according to AJCC 8th edition identifies a patient population with better prognosis as compared to stage IIIA according to 7th edition, with a 5-years melanoma specific survival rate of 93%[4] . Patients according to the new stage IIIA (8th edition) are very poorly represented in the study (i.e. 42 patients with stage IIIA on pembrolizumab versus 40 patients with stage IIIA in the placebo group) and with a very small number of RFS events (6 in the pembro and 7 in the placebo arm) observed based on the updated data. Thus, the efficacy data is limited in this patient population and a statement has been included to section 5.1 of the SmPC. The treating physician should take into account the toxicity of adjuvant treatment for subjects with such a good prognosis.

Pembrolizumab improved RFS both in the BRAF mutated (HR=0.49) and BRAF wild-type (HR=0.64) tumours compared to placebo. For subgroup analyses by type and number of lymph nodes, presence of ulceration and Breslow thickness RFS results were overall consistent with those from the ITT population.

Additional preliminary data were submitted upon CHMP request and considered supportive for the conclusion (data not shown). The CHMP has requested the MAH to submit the final RFS/DMFS data by 4Q 2023 (see Annex II of the SmPC).

The OS analysisis not part of the statistical analysis plan for IA1.The CHMP has requested the MAH to submit the final OS data by 4Q 2023 (see Annex II of the SmPC).

At the data cut-off date of 2-OCT-2017, patients from the placebo arm who crossed over to pembrolizumab were 109 (21.6%). Only one patient (0.2%) in the pembrolizumab arm was rechallenged with pembrolizumab (both crossover and rechallenge were at the discretion of the investigator for Part 2 of the study). Updated analysis of systemic treatment showed, as expected, more patients in the placebo arm receiving an anti PD-1/PD-L1 agent at recurrence (approximately 80%, vs 30% in the pembrolizumab arm). A similar rate of subjects in each arm received radiotherapy, chemotherapy, BRAF/MEK inhibitors and anti-CTLA4, while surgery was more used in the pembrolizumab arm compared to control (46.2% vs 38.8%).

2.4.4. Conclusions on the clinical efficacy

The efficacy of pembrolizumab over placebo as adjuvant treatment for stage III melanoma in the ITT population has been demonstrated by statistically significant and clinically relevant increase in RFS. The results initially submitted, based on interim analyses, were confirmed by the updated efficacy analyses. It is considered that the data are stable enough to conclude on the efficacy endpoint.

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

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

   Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing NSCLC studies (P001, P010, P024 and P042), urothelial carcinoma studies (KN045, KN052), HNSCC study (KN040) and adjuvant melanoma (KN-716):
   - Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature)
   - IHC staining for PD-L2
   - Data on RNA and proteomic serum profiling

As the initial efficacy assessment is based on a surrogate endpoint, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions, the MAH is requested to submit the following:

2. Post-authorisation efficacy study (PAES): In order to investigate the long term efficacy in melanoma patients treated with adjuvant pembrolizumab, the MAH should submit the final RFS/DMFS and OS data for study KN-054: A Phase III Clinical Trial of Pembrolizumab (MK-3475) in Subjects with complete resection of high-risk Stage III melanoma.

   The clinical study report should be submitted by 4Q 2023.

2.5. Clinical safety

Introduction

The safety database in support of the current application comprises the following datasets:

- **KEYNOTE-054 Safety Dataset** (N=509): Pembrolizumab-treated subjects with resected, LN-positive, stage III melanoma comprise the KEYNOTE-054 Safety Dataset.
- **Reference Safety Dataset** (N=2799): The 2799 pembrolizumab-treated subjects in the RSD consists of 1567 subjects with advanced melanoma from studies KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, and 1232 subjects with NSCLC from studies KEYNOTE-001 and KEYNOTE-010. This dataset represents the established safety profile for pembrolizumab in the melanoma and NSCLC indications.
- **Cumulative Running Safety Dataset** (N=4993): Subjects from the KEYNOTE-054 Safety Dataset, the RSD, and subjects treated with pembrolizumab in KEYNOTE-001 (NSCLC and melanoma), KEYNOTE-002 (melanoma), KEYNOTE-006 (melanoma), KEYNOTE-010 (NSCLC), KEYNOTE-012 (HNSCC: Cohorts B and B2, urothelial tract cancer: Cohort C, and gastric cancer: Cohort D), KEYNOTE-013 (classical HL: Cohort 3; rrPMBCL: Cohort 4A), KEYNOTE-024 (NSCLC), KEYNOTE-045 (urothelial carcinoma), KEYNOTE-052 (urothelial carcinoma), KEYNOTE-059 (gastric cancer: Cohort 1), KEYNOTE-08 7 (classical HL), KEYNOTE-164 (colorectal carcinoma: Cohort A), and KEYNOTE-170 (rrPMBCL or rrRS) comprise the Cumulative Running Safety Dataset.

Patient exposure

KEYNOTE-054 is an ongoing study. As of the data cutoff 02-OCT-2017, a total of 509 subjects received at least 1 dose of pembrolizumab as Adjuvant Therapy (ASaT population for KEYNOTE-054).

Exposure in KEYNOTE-054 is summarised in the following table:

Table 36: Summary of exposure

	Pembrolizumab (N=509)	Placebo (N=502)
Study Days On-Therapy (days)		
Mean	282.0	275.3
Median	357	357
SD	120.4	123.3
Range	1 to 478	1 to 424
Number of Administrations		
Mean	14.0	13.8
Median	18	18
SD	5.6	5.8
Range	1 to 18	1 to 18
(Database Cutoff Date: 02OCT2017).		

Exposure data of study KEYNOTE-054 in comparison with the Reference and Cumulative Running datasets are shown below:

Table 37: Summary of duration of exposure data for study KN-054, the reference and cumulative running datasets

Clinical Trial Exposure to Drug by Duration
(Subjects in ASaT Population Treated with MK-3475 ‡‡)

	KN054 for MK-3475§ (N=509)			Reference Safety Dataset for MK-3475†† (N=2799)			Cumulative Running Safety Dataset for MK-3475‡‡ (N=4993)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure									
>0 m	509	(100.0)	(393.7)	2,799	(100.0)	(1,517.7)	4,993	(100.0)	(2,620.7)
>=1 m	489	(96.1)	(392.7)	2,394	(85.5)	(1,503.6)	4,250	(85.1)	(2,595.0)
>=3 m	434	(85.3)	(382.4)	1,656	(59.2)	(1,379.5)	3,000	(60.1)	(2,384.6)
>=6m	387	(76.0)	(364.9)	1,153	(41.2)	(1,197.8)	2,072	(41.5)	(2,044.5)
>=12m	67	(13.2)	(71.3)	600	(21.4)	(800.3)	823	(16.5)	(1,088.8)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
§ Includes all subjects who received at least one dose of MK-3475 in KN054.
†† Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)
MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adexsum]

Adverse events

KEYNOTE-054: Pembrolizumab vs. Placebo

Table 38: Summary of Adverse Events – Study KN-054 (ASaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more adverse events	475	(93.3)	453	(90.2)
with no adverse event	34	(6.7)	49	(9.8)
with drug-related† adverse events	396	(77.8)	332	(66.1)
with toxicity grade 3-5 adverse events	158	(31.0)	96	(19.1)
with toxicity grade 3-5 drug-related adverse events	74	(14.5)	17	(3.4)
with serious adverse events	128	(25.1)	82	(16.3)
with serious drug-related adverse events	66	(13.0)	6	(1.2)
who died	1	(0.2)	0	(0.0)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)
discontinued drug due to an adverse event	70	(13.8)	18	(3.6)
discontinued drug due to a drug-related adverse event	62	(12.2)	8	(1.6)
discontinued drug due to a serious adverse event	29	(5.7)	11	(2.2)
discontinued drug due to a serious drug-related adverse event	22	(4.3)	2	(0.4)

† Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database cutoff date: 02OCT2017).

Source: [P054V01MK3475: adam-adsl; adae]

The comparison of KEYNOTE-054 with the reference datasets is reported below:

Table 39: Comparison of the Summary of Adverse Events between the safety datasets - ASaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	475	(93.3)	2,727	(97.4)	4,812	(96.4)
with no adverse event	34	(6.7)	72	(2.6)	181	(3.6)
with drug-related[†] adverse events	396	(77.8)	2,062	(73.7)	3,517	(70.4)
with toxicity grade 3-5 adverse events	158	(31.0)	1,273	(45.5)	2,280	(45.7)
with toxicity grade 3-5 drug-related adverse events	74	(14.5)	386	(13.8)	724	(14.5)
with non-serious adverse events	473	(92.9)	2,671	(95.4)	4,723	(94.6)
with serious adverse events	128	(25.1)	1,041	(37.2)	1,810	(36.3)
with serious drug-related adverse events	66	(13.0)	281	(10.0)	515	(10.3)
with dose modification[‡] due to an adverse event	131	(25.7)	884	(31.6)	1,524	(30.5)
who died	1	(0.2)	110	(3.9)	198	(4.0)
who died due to a drug-related adverse event	1	(0.2)	10	(0.4)	19	(0.4)
discontinued drug due to an adverse event	70	(13.8)	334	(11.9)	547	(11.0)
discontinued drug due to a drug-related adverse event	62	(12.2)	146	(5.2)	281	(5.6)
discontinued drug due to a serious adverse event	29	(5.7)	253	(9.0)	397	(8.0)
discontinued drug due to a serious drug-related adverse event	22	(4.3)	101	(3.6)	177	(3.5)

[†] Determined by the investigator to be related to the drug.

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

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

[§] Includes all subjects who received at least one dose of MK-3475 in KN054.

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

[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.

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

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)

MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Overall AEs

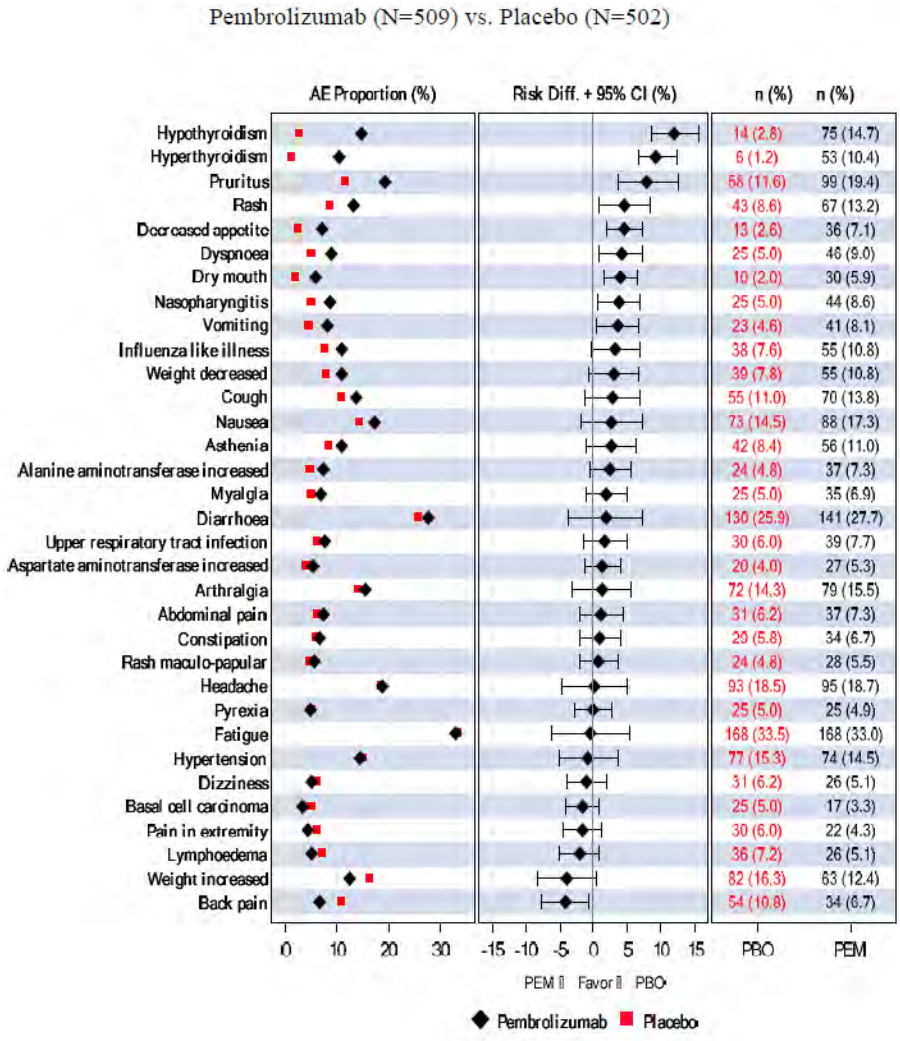


Figure 14: Rainfall plot for adverse events (≥ 5% in at least one treatment group) - Study KN-054 (ASaT population)

Drug-related AEs

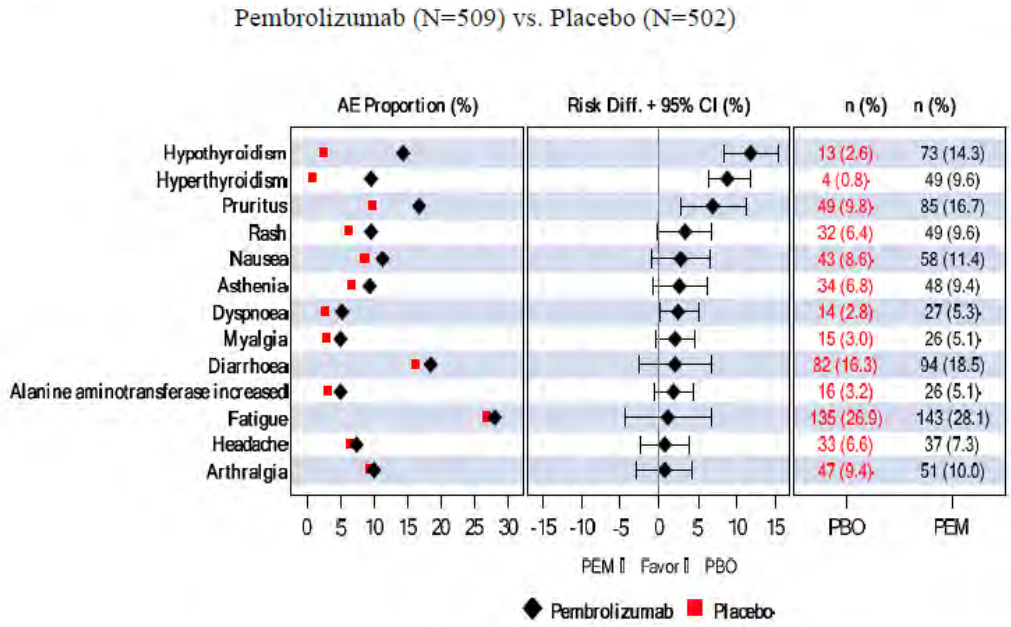


Figure 15: Rainfall plot for drug related adverse events (>5% in at least one treatment group) - Study KN-054 (ASaT population)

The comparison of KEYNOTE-054 with the reference datasets is reported below:

Table 40: Comparison of safety datasets for subjects with drug-related adverse events (>5% in at least one treatment group) - ASaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	396	(77.8)	2,062	(73.7)	3,517	(70.4)
with no adverse events	113	(22.2)	737	(26.3)	1,476	(29.6)
Fatigue	143	(28.1)	678	(24.2)	1,067	(21.4)
Diarrhoea	94	(18.5)	343	(12.3)	563	(11.3)
Pruritus	85	(16.7)	467	(16.7)	727	(14.6)
Hypothyroidism	73	(14.3)	213	(7.6)	410	(8.2)
Nausea	58	(11.4)	304	(10.9)	498	(10.0)
Arthralgia	51	(10.0)	281	(10.0)	409	(8.2)
Hyperthyroidism	49	(9.6)	82	(2.9)	181	(3.6)
Rash	49	(9.6)	386	(13.8)	563	(11.3)
Asthenia	48	(9.4)	218	(7.8)	324	(6.5)
Headache	37	(7.3)	111	(4.0)	177	(3.5)
Dyspnoea	27	(5.3)	109	(3.9)	174	(3.5)
Alanine aminotransferase increased	26	(5.1)	97	(3.5)	174	(3.5)
Myalgia	26	(5.1)	146	(5.2)	211	(4.2)
Decreased appetite	25	(4.9)	255	(9.1)	397	(8.0)

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Vitiligo	23	(4.5)	159	(5.7)	184	(3.7)

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

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

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

[§] Includes all subjects who received at least one dose of MK-3475 in KN054.

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

[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)

MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Adverse Events of Special Interest (AEOSI)

A pre-specified list of PTs was developed by the Sponsor to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. These PTs are considered to be medically equivalent to the immune-mediated events and infusion-related reactions. The list of PTs is continually updated based on emerging pembrolizumab safety data. Version 13.0 was used at the time of the database lock of 27-NOV-2017.

Table 41: Summary of Adverse Events of Special Interest (AEOSI) – Study KN-054 (ASaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more adverse events	173	(34.0)	38	(7.6)
with no adverse event	336	(66.0)	464	(92.4)
with drug-related[†] adverse events	162	(31.8)	28	(5.6)
with toxicity grade 3-5 adverse events	36	(7.1)	3	(0.6)
with toxicity grade 3-5 drug-related adverse events	32	(6.3)	3	(0.6)
with serious adverse events	42	(8.3)	3	(0.6)
with serious drug-related adverse events	38	(7.5)	2	(0.4)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	33	(6.5)	6	(1.2)
discontinued drug due to a drug-related adverse event	33	(6.5)	5	(1.0)
discontinued drug due to a serious adverse event	12	(2.4)	3	(0.6)
discontinued drug due to a serious drug-related adverse event	12	(2.4)	2	(0.4)

[†] Determined by the investigator to be related to the drug.

AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.

AEs of special interest per ECI guidance.

(Database Cutoff Date: 02OCT2017).

Source: [P054V01MK3475: adam-adsl; adae]

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more adverse events	173	(34.0)	38	(7.6)
with adverse event with maximum toxicity grade:				
Grade 1	42	(8.3)	20	(4.0)
Grade 2	95	(18.7)	15	(3.0)
Grade 3	32	(6.3)	3	(0.6)
Grade 4	4	(0.8)	0	(0.0)
Grade 5	0	(0.0)	0	(0.0)
with adverse event resolved/resolved with sequelae	125	(24.6)	26	(5.2)
who needed steroids to treat/resolve the adverse event	55	(10.8)	8	(1.6)
who needed an additional immune modulating drug to treat/resolve the adverse event	3	(0.6)	1	(0.2)

Only the highest reported grade of a given adverse event is counted for the individual subject.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
AEs of special interest per ECI guidance.
(Database cutoff date: 02OCT2017).

Source: [P054V01MK3475: adam-adsl; adae]

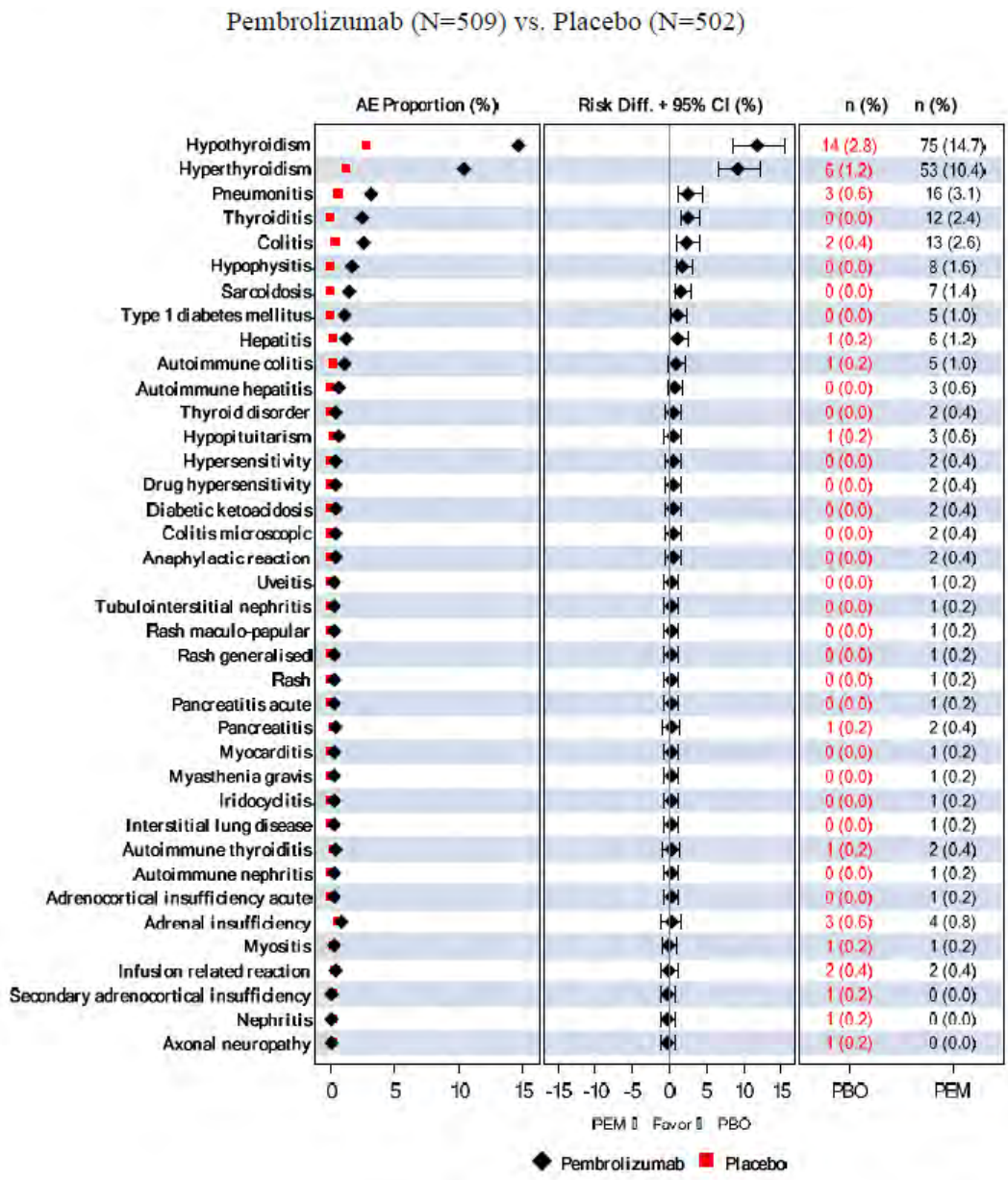


Figure 16: Rainfall plot for AEOSI - Study KN-054 (ASaT population)

The comparison of KEYNOTE-054 with the reference datasets is as follows:

Table 42: Comparison between the safety databases for AEOSI, by category and preferred term - ASaT population

	KN054 for MK-3475[1]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	173	(34.0)	594	(21.2)	1,118	(22.4)
with no adverse events	336	(66.0)	2,205	(78.8)	3,875	(77.6)
Adrenal Insufficiency	**5**	**(1.0)**	**22**	**(0.8)**	**35**	**(0.7)**
Adrenal insufficiency	4	(0.8)	20	(0.7)	32	(0.6)
Adrenocortical insufficiency acute	1	(0.2)	1	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	1	(0.0)	1	(0.0)
Colitis	**19**	**(3.7)**	**49**	**(1.8)**	**100**	**(2.0)**
Autoimmune colitis	5	(1.0)	1	(0.0)	6	(0.1)
Colitis	13	(2.6)	46	(1.6)	86	(1.7)
Colitis microscopic	2	(0.4)	2	(0.1)	4	(0.1)
Enterocolitis	0	(0.0)	1	(0.0)	6	(0.1)
Encephalitis	**0**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Encephalitis	0	(0.0)	1	(0.0)	2	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**2**	**(0.1)**	**2**	**(0.0)**
Axonal neuropathy	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	1	(0.0)	1	(0.0)
Hepatitis	**9**	**(1.8)**	**19**	**(0.7)**	**36**	**(0.7)**
Autoimmune hepatitis	3	(0.6)	12	(0.4)	16	(0.3)
Drug-induced liver injury	0	(0.0)	2	(0.1)	3	(0.1)
Hepatitis	6	(1.2)	6	(0.2)	18	(0.4)
Hyperthyroidism	**53**	**(10.4)**	**96**	**(3.4)**	**204**	**(4.1)**
Hyperthyroidism	53	(10.4)	96	(3.4)	204	(4.1)
Hypophysitis	**11**	**(2.2)**	**17**	**(0.6)**	**31**	**(0.6)**
Hypophysitis	8	(1.6)	9	(0.3)	19	(0.4)
Hypopituitarism	3	(0.6)	8	(0.3)	12	(0.2)
Hypothyroidism	**75**	**(14.7)**	**237**	**(8.5)**	**463**	**(9.3)**
Hypothyroidism	75	(14.7)	236	(8.4)	462	(9.3)
Myxoedema	0	(0.0)	1	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	1	(0.0)	1	(0.0)
Infusion Reactions	**8**	**(1.6)**	**71**	**(2.5)**	**113**	**(2.3)**
Anaphylactic reaction	2	(0.4)	3	(0.1)	5	(0.1)

	KN054 for MK-3475[1]		Reference Safety Dataset for MK-3475[77]		Cumulative Running Safety Dataset for MK-3475[22]	
	n	(%)	n	(%)	n	(%)
Infusion Reactions	**8**	**(1.6)**	**71**	**(2.5)**	**113**	**(2.3)**
Anaphylactoid reaction	0	(0.0)	1	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	2	(0.1)	8	(0.2)
Drug hypersensitivity	2	(0.4)	13	(0.5)	17	(0.3)
Hypersensitivity	2	(0.4)	22	(0.8)	34	(0.7)
Infusion related reaction	2	(0.4)	29	(1.0)	49	(1.0)
Serum sickness	0	(0.0)	1	(0.0)	1	(0.0)
Myasthenic Syndrome	**1**	**(0.2)**	**2**	**(0.1)**	**3**	**(0.1)**
Myasthenia gravis	1	(0.2)	0	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	2	(0.1)	2	(0.0)
Myocarditis	**1**	**(0.2)**	**0**	**(0.0)**	**3**	**(0.1)**
Myocarditis	1	(0.2)	0	(0.0)	3	(0.1)
Myositis	**1**	**(0.2)**	**11**	**(0.4)**	**23**	**(0.5)**
Myopathy	0	(0.0)	3	(0.1)	4	(0.1)
Myositis	1	(0.2)	7	(0.3)	17	(0.3)
Rhabdomyolysis	0	(0.0)	1	(0.0)	3	(0.1)
Nephritis	**2**	**(0.4)**	**4**	**(0.1)**	**11**	**(0.2)**
Autoimmune nephritis	1	(0.2)	0	(0.0)	2	(0.0)
Nephritis	0	(0.0)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	1	(0.0)
Tubulointerstitial nephritis	1	(0.2)	4	(0.1)	7	(0.1)
Pancreatitis	**2**	**(0.4)**	**9**	**(0.3)**	**16**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis	2	(0.4)	7	(0.3)	14	(0.3)
Pancreatitis acute	1	(0.2)	1	(0.0)	2	(0.0)
Pneumonitis	**17**	**(3.3)**	**94**	**(3.4)**	**164**	**(3.3)**
Interstitial lung disease	1	(0.2)	7	(0.3)	14	(0.3)
Organising pneumonia	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonitis	16	(3.1)	87	(3.1)	150	(3.0)
Sarcoidosis	**7**	**(1.4)**	**2**	**(0.1)**	**10**	**(0.2)**
Sarcoidosis	7	(1.4)	2	(0.1)	10	(0.2)
Severe Skin Reactions	**3**	**(0.6)**	**38**	**(1.4)**	**59**	**(1.2)**
Dermatitis bullous	0	(0.0)	2	(0.1)	3	(0.1)

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[¶]		Cumulative Running Safety Dataset for MK-3475[#]	
	n	(%)	n	(%)	n	(%)
Severe Skin Reactions	**3**	**(0.6)**	**38**	**(1.4)**	**59**	**(1.2)**
Dermatitis exfoliative	0	(0.0)	2	(0.1)	3	(0.1)
Erythema multiforme	0	(0.0)	3	(0.1)	4	(0.1)
Exfoliative rash	0	(0.0)	2	(0.1)	2	(0.0)
Pemphigoid	0	(0.0)	2	(0.1)	4	(0.1)
Pemphigus	0	(0.0)	1	(0.0)	1	(0.0)
Pruritus	0	(0.0)	4	(0.1)	5	(0.1)
Pruritus genital	0	(0.0)	1	(0.0)	1	(0.0)
Rash	1	(0.2)	9	(0.3)	17	(0.3)
Rash erythematous	0	(0.0)	1	(0.0)	1	(0.0)
Rash generalised	1	(0.2)	2	(0.1)	4	(0.1)
Rash maculo-papular	1	(0.2)	7	(0.3)	12	(0.2)
Rash pruritic	0	(0.0)	1	(0.0)	2	(0.0)
Rash pustular	0	(0.0)	1	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	1	(0.0)	1	(0.0)
Toxic skin eruption	0	(0.0)	1	(0.0)	2	(0.0)
Thyroiditis	**16**	**(3.1)**	**16**	**(0.6)**	**52**	**(1.0)**
Autoimmune thyroiditis	2	(0.4)	5	(0.2)	10	(0.2)
Thyroid disorder	2	(0.4)	0	(0.0)	4	(0.1)
Thyroiditis	12	(2.4)	11	(0.4)	39	(0.8)
Type 1 Diabetes Mellitus	**5**	**(1.0)**	**6**	**(0.2)**	**17**	**(0.3)**
Diabetic ketoacidosis	2	(0.4)	2	(0.1)	8	(0.2)
Type 1 diabetes mellitus	5	(1.0)	5	(0.2)	14	(0.3)
Uveitis	**2**	**(0.4)**	**14**	**(0.5)**	**19**	**(0.4)**
Iridocyclitis	1	(0.2)	2	(0.1)	3	(0.1)
Iritis	0	(0.0)	2	(0.1)	3	(0.1)

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[¶]		Cumulative Running Safety Dataset for MK-3475[#]	
	n	(%)	n	(%)	n	(%)
Uveitis	**2**	**(0.4)**	**14**	**(0.5)**	**19**	**(0.4)**
Uveitis	1	(0.2)	10	(0.4)	13	(0.3)

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

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

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

[§] Includes all subjects who received at least one dose of MK-3475 in KN054.

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

[#] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)

MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam.adel; adae]

Grade 3-5 AEs

Table 43: Summary of Grade 3-5 AEs (≥1% in at least one treatment group) - Study KN-054 (ASaT population)

	KN054 for MK-3475[i]		Reference Safety Dataset for MK-3475[ii]		Cumulative Running Safety Dataset for MK-3475[iii]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	158	(31.0)	1,273	(45.5)	2,280	(45.7)
with no adverse events	351	(69.0)	1,526	(54.5)	2,713	(54.3)
Hypertension	28	(5.5)	32	(1.1)	79	(1.6)
Arthralgia	6	(1.2)	17	(0.6)	29	(0.6)
Blood creatine phosphokinase increased	6	(1.2)	5	(0.2)	12	(0.2)
Colitis	6	(1.2)	32	(1.1)	54	(1.1)
Diarrhoea	6	(1.2)	36	(1.3)	65	(1.3)
Lipase increased	6	(1.2)	2	(0.1)	13	(0.3)
Basal cell carcinoma	5	(1.0)	5	(0.2)	10	(0.2)
Hyponatraemia	5	(1.0)	62	(2.2)	116	(2.3)
Pulmonary embolism	5	(1.0)	46	(1.6)	73	(1.5)
Type 1 diabetes mellitus	5	(1.0)	3	(0.1)	11	(0.2)
Fatigue	4	(0.8)	69	(2.5)	128	(2.6)
Hyperglycaemia	3	(0.6)	29	(1.0)	51	(1.0)
Pneumonitis	3	(0.6)	34	(1.2)	54	(1.1)
Hypokalaemia	2	(0.4)	25	(0.9)	48	(1.0)
Aspartate aminotransferase increased	1	(0.2)	24	(0.9)	61	(1.2)
Asthenia	1	(0.2)	34	(1.2)	56	(1.1)
Decreased appetite	1	(0.2)	26	(0.9)	51	(1.0)
Dyspnoea	1	(0.2)	78	(2.8)	116	(2.3)
Nausea	1	(0.2)	33	(1.2)	49	(1.0)
Pneumonia	1	(0.2)	75	(2.7)	117	(2.3)
Abdominal pain	0	(0.0)	27	(1.0)	54	(1.1)
Anaemia	0	(0.0)	90	(3.2)	208	(4.2)
Back pain	0	(0.0)	38	(1.4)	62	(1.2)
Blood alkaline phosphatase increased	0	(0.0)	16	(0.6)	49	(1.0)
Dehydration	0	(0.0)	28	(1.0)	55	(1.1)
Pleural effusion	0	(0.0)	37	(1.3)	58	(1.2)
Urinary tract infection	0	(0.0)	14	(0.5)	70	(1.4)

Drug-related grade 3-5 AEs

Table 44: Summary of Grade 3-5 drug-related AEs - Study KN-054 (ASaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more grade 3-5 drug-related adverse events	74	(14.5)	17	(3.4)
with no grade 3-5 drug-related adverse events	435	(85.5)	485	(96.6)
Colitis	6	(1.2)	0	(0.0)
Type 1 diabetes mellitus	5	(1.0)	0	(0.0)
Diarrhoea	4	(0.8)	3	(0.6)
Fatigue	4	(0.8)	2	(0.4)
Lipase increased	4	(0.8)	3	(0.6)
Alanine aminotransferase increased	3	(0.6)	1	(0.2)
Arthralgia	3	(0.6)	0	(0.0)
Autoimmune colitis	3	(0.6)	1	(0.2)
Autoimmune hepatitis	3	(0.6)	0	(0.0)
Hepatitis	3	(0.6)	1	(0.2)
Pneumonitis	3	(0.6)	0	(0.0)
Blood creatine phosphokinase increased	2	(0.4)	0	(0.0)
Diabetic ketoacidosis	2	(0.4)	0	(0.0)
Gamma-glutamyltransferase increased	2	(0.4)	1	(0.2)
Hyponatraemia	2	(0.4)	1	(0.2)
Hypophysitis	2	(0.4)	0	(0.0)
Pulmonary embolism	2	(0.4)	0	(0.0)
Abdominal pain upper	1	(0.2)	0	(0.0)
Adrenocortical insufficiency acute	1	(0.2)	0	(0.0)
Amylase increased	1	(0.2)	0	(0.0)
Aspartate aminotransferase increased	1	(0.2)	1	(0.2)
Autoimmune nephritis	1	(0.2)	0	(0.0)
Autoimmune pericarditis	1	(0.2)	0	(0.0)
Bronchitis	1	(0.2)	0	(0.0)
Colitis microscopic	1	(0.2)	0	(0.0)
Decreased appetite	1	(0.2)	0	(0.0)
Drug reaction with eosinophilia and systemic symptoms	1	(0.2)	0	(0.0)
Dyspnoea	1	(0.2)	0	(0.0)
Enteritis	1	(0.2)	0	(0.0)
Gastritis	1	(0.2)	0	(0.0)
Granuloma	1	(0.2)	0	(0.0)
Hyperamylasaemia	1	(0.2)	0	(0.0)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Hyperglycaemia	1	(0.2)	0	(0.0)
Hypertension	1	(0.2)	2	(0.4)
Hyperthyroidism	1	(0.2)	0	(0.0)
Hypokalaemia	1	(0.2)	0	(0.0)
Hypophosphataemia	1	(0.2)	0	(0.0)
Hypopituitarism	1	(0.2)	0	(0.0)
Hypotension	1	(0.2)	0	(0.0)
Lichen planus	1	(0.2)	0	(0.0)
Lichenification	1	(0.2)	0	(0.0)
Lichenoid keratosis	1	(0.2)	0	(0.0)
Lymphopenia	1	(0.2)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)
Myositis	1	(0.2)	0	(0.0)
Oral lichen planus	1	(0.2)	0	(0.0)
Pancreatitis acute	1	(0.2)	0	(0.0)
Peripheral sensory neuropathy	1	(0.2)	0	(0.0)
Polymyalgia rheumatica	1	(0.2)	0	(0.0)
Pyrexia	1	(0.2)	0	(0.0)
Rash maculo-papular	1	(0.2)	0	(0.0)
Systemic inflammatory response syndrome	1	(0.2)	0	(0.0)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)
Cellulitis	0	(0.0)	1	(0.2)
Headache	0	(0.0)	1	(0.2)
Pancreatitis	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database Cutoff Date: 02OCT2017).

Source: [P054V01MK3475: adam-adsl; adae]

The comparison of KEYNOTE-054 with the reference datasets is reported below:

Table 45: Comparison of drug-related AEs in the safety datasets (≥1% for at least one treatment group - ASaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	74	(14.5)	386	(13.8)	724	(14.5)
with no adverse events	435	(85.5)	2,413	(86.2)	4,269	(85.5)
Colitis	6	(1.2)	27	(1.0)	46	(0.9)
Type 1 diabetes mellitus	5	(1.0)	3	(0.1)	11	(0.2)
Fatigue	4	(0.8)	30	(1.1)	60	(1.2)
Pneumonitis	3	(0.6)	32	(1.1)	50	(1.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[§] Includes all subjects who received at least one dose of MK-3475 in KN054.
[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.
Grades are based on NCI CTCAE version 4.0.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)
MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Serious adverse event/deaths/other significant events

Table 46: Summary of serious adverse events (≥1% in at least on treatment group) - Study KN-054 (ASaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more serious adverse events	128	(25.1)	82	(16.3)
with no serious adverse events	381	(74.9)	420	(83.7)
Basal cell carcinoma	17	(3.3)	25	(5.0)
Colitis	8	(1.6)	0	(0.0)
Pneumonitis	7	(1.4)	0	(0.0)
Squamous cell carcinoma	6	(1.2)	3	(0.6)
Diarrhoea	5	(1.0)	2	(0.4)
Cellulitis	3	(0.6)	7	(1.4)
Malignant melanoma in situ	1	(0.2)	6	(1.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database Cutoff Date: 02OCT2017).

Source: [P054V01MK3475: adam-adsl; adae]

The comparison of KEYNOTE-054 with the reference datasets is reported below:

Table 47: Comparison between safety datasets for SAEs up to 90 days of last dose (≥1% in at least one treatment group) - ASaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	128	(25.1)	1,041	(37.2)	1,810	(36.3)
with no adverse events	381	(74.9)	1,758	(62.8)	3,183	(63.7)
Basal cell carcinoma	17	(3.3)	18	(0.6)	36	(0.7)
Colitis	8	(1.6)	31	(1.1)	53	(1.1)
Pneumonitis	7	(1.4)	46	(1.6)	79	(1.6)
Squamous cell carcinoma	6	(1.2)	15	(0.5)	22	(0.4)
Diarrhoea	5	(1.0)	26	(0.9)	47	(0.9)
Pyrexia	4	(0.8)	35	(1.3)	63	(1.3)
Pulmonary embolism	2	(0.4)	41	(1.5)	59	(1.2)
Pleural effusion	1	(0.2)	48	(1.7)	73	(1.5)
Pneumonia	1	(0.2)	85	(3.0)	128	(2.6)
Anaemia	0	(0.0)	31	(1.1)	58	(1.2)
Dyspnoea	0	(0.0)	45	(1.6)	63	(1.3)
Urinary tract infection	0	(0.0)	15	(0.5)	56	(1.1)

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

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

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

[§] Includes all subjects who received at least one dose of MK-3475 in KN054.

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

[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)

MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Drug-related SAE

Table 48: Summary of drug-related SAEs - Study KN-054 (ASaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more drug-related serious adverse events	66	(13.0)	6	(1.2)
with no drug-related serious adverse events	443	(87.0)	496	(98.8)
Colitis	8	(1.6)	0	(0.0)
Pneumonitis	7	(1.4)	0	(0.0)
Diarrhoea	4	(0.8)	1	(0.2)
Aspartate aminotransferase increased	3	(0.6)	0	(0.0)
Autoimmune colitis	3	(0.6)	0	(0.0)
Hypophysitis	3	(0.6)	0	(0.0)
Type 1 diabetes mellitus	3	(0.6)	0	(0.0)
Alanine aminotransferase increased	2	(0.4)	0	(0.0)
Autoimmune hepatitis	2	(0.4)	0	(0.0)
Decreased appetite	2	(0.4)	0	(0.0)
Diabetic ketoacidosis	2	(0.4)	0	(0.0)
Fatigue	2	(0.4)	0	(0.0)
Pulmonary embolism	2	(0.4)	0	(0.0)
Sarcoidosis	2	(0.4)	0	(0.0)
Thyroiditis	2	(0.4)	0	(0.0)
Abdominal pain upper	1	(0.2)	0	(0.0)
Adrenocortical insufficiency acute	1	(0.2)	0	(0.0)
Aptyalism	1	(0.2)	0	(0.0)
Arthralgia	1	(0.2)	0	(0.0)
Autoimmune nephritis	1	(0.2)	0	(0.0)
Autoimmune pericarditis	1	(0.2)	0	(0.0)
Bronchitis	1	(0.2)	0	(0.0)
Conjunctivitis allergic	1	(0.2)	0	(0.0)
Drug reaction with eosinophilia and systemic symptoms	1	(0.2)	0	(0.0)
Enteritis	1	(0.2)	0	(0.0)
Gamma-glutamyltransferase increased	1	(0.2)	0	(0.0)
Gastritis	1	(0.2)	0	(0.0)
Granuloma	1	(0.2)	0	(0.0)
Hepatitis	1	(0.2)	0	(0.0)
Hypercreatininaemia	1	(0.2)	0	(0.0)
Hyperglycaemia	1	(0.2)	0	(0.0)
Hyperthyroidism	1	(0.2)	0	(0.0)
Hyponatraemia	1	(0.2)	1	(0.2)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Hypopituitarism	1	(0.2)	0	(0.0)
Lichenoid keratosis	1	(0.2)	0	(0.0)
Myasthenia gravis	1	(0.2)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)
Myositis	1	(0.2)	0	(0.0)
Nausea	1	(0.2)	0	(0.0)
Oedema	1	(0.2)	0	(0.0)
Oral lichen planus	1	(0.2)	0	(0.0)
Pancreatitis acute	1	(0.2)	0	(0.0)
Papillitis	1	(0.2)	0	(0.0)
Peripheral sensory neuropathy	1	(0.2)	0	(0.0)
Psoriasis	1	(0.2)	0	(0.0)
Pyrexia	1	(0.2)	0	(0.0)
Rash maculo-papular	1	(0.2)	0	(0.0)
Rheumatoid arthritis	1	(0.2)	0	(0.0)
Small intestinal perforation	1	(0.2)	0	(0.0)
Systemic inflammatory response syndrome	1	(0.2)	0	(0.0)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)
Vomiting	1	(0.2)	0	(0.0)
Cellulitis	0	(0.0)	1	(0.2)
Pancreatitis	0	(0.0)	1	(0.2)
Respiratory tract infection viral	0	(0.0)	1	(0.2)
Secondary adrenocortical insufficiency	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database Cutoff Date: 02OCT2017).

The comparison of KEYNOTE-054 with the reference datasets is reported below:

Table 49: Comparison between safety datasets for drug-related SAEs up to 90 days of last dose (≥1% in at least one treatment group) - ASaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	66	(13.0)	281	(10.0)	515	(10.3)
with no adverse events	443	(87.0)	2,518	(90.0)	4,478	(89.7)
Colitis	8	(1.6)	25	(0.9)	44	(0.9)
Pneumonitis	7	(1.4)	44	(1.6)	74	(1.5)

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.
[§] Includes all subjects who received at least one dose of MK-3475 in KN054.
[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)
MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Source: [ISS: adam-adsl; adae]

Deaths

Table 50: Summary of AEs resulting in death - Study KN-054 (ASaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more adverse events resulting in death	1	(0.2)	0	(0.0)
with no adverse events resulting in death	508	(99.8)	502	(100.0)
Drug reaction with eosinophilia and systemic symptoms	1	(0.2)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database Cutoff Date: 02OCT2017).

Laboratory findings

Table 51: Summary of laboratory findings in patients with increases in laboratory toxicity grade from baseline - Study KN-054 (ASaT population)

Laboratory Test	Pembrolizumab (N=509) n	(%)	Placebo (N=502) n	(%)
Bilirubin Increased (Blood bilirubin increased)				
Subjects with Baseline and Post-baseline Measurements	507		498	
Grade 1	35	(6.9)	36	(7.2)
Grade 2	18	(3.6)	16	(3.2)
Grade 3	1	(0.2)	1	(0.2)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	1	(0.2)	1	(0.2)
All Grades	54	(10.7)	53	(10.6)
Calcium Decreased (Hypocalcemia)				
Subjects with Baseline and Post-baseline Measurements	503		491	
Grade 1	60	(11.9)	34	(6.9)
Grade 2	6	(1.2)	2	(0.4)
Grade 3	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	1	(0.2)
Grade 3-4	0	(0.0)	1	(0.2)
All Grades	66	(13.1)	37	(7.5)
Calcium Increased (Hypercalcemia)				
Subjects with Baseline and Post-baseline Measurements	503		491	
Grade 1	16	(3.2)	23	(4.7)
Grade 2	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	1	(0.2)
Grade 3-4	0	(0.0)	1	(0.2)
All Grades	16	(3.2)	24	(4.9)
Creatinine Increased (Creatinine increased)				
Subjects with Baseline and Post-baseline Measurements	506		498	
Grade 1	65	(12.8)	49	(9.8)
Grade 2	9	(1.8)	1	(0.2)
Grade 3	3	(0.6)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	3	(0.6)	0	(0.0)
All Grades	77	(15.2)	50	(10.0)

Laboratory Test	Pembrolizumab (N=509) n	(%)	Placebo (N=502) n	(%)
Leukocytes Decreased (White blood cell decreased)				
Subjects with Baseline and Post-baseline Measurements	507		498	
Grade 1	47	(9.3)	65	(13.1)
Grade 2	6	(1.2)	11	(2.2)
Grade 3	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)
All Grades	53	(10.5)	76	(15.3)
Lymphocytes Decreased (Lymphocyte count decreased)				
Subjects with Baseline and Post-baseline Measurements	503		492	
Grade 1	70	(13.9)	49	(10.0)
Grade 2	43	(8.5)	24	(4.9)
Grade 3	4	(0.8)	6	(1.2)
Grade 4	1	(0.2)	0	(0.0)
Grade 3-4	5	(1.0)	6	(1.2)
All Grades	118	(23.5)	79	(16.1)
Neutrophils Decreased (Neutrophil count decreased)				
Subjects with Baseline and Post-baseline Measurements	504		491	
Grade 1	32	(6.3)	35	(7.1)
Grade 2	16	(3.2)	15	(3.1)
Grade 3	0	(0.0)	3	(0.6)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	3	(0.6)
All Grades	48	(9.5)	53	(10.8)
Platelets Decreased (Platelet count decreased)				
Subjects with Baseline and Post-baseline Measurements	507		498	
Grade 1	33	(6.5)	22	(4.4)
Grade 2	0	(0.0)	2	(0.4)
Grade 3	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)
All Grades	33	(6.5)	24	(4.8)

Laboratory Test	Pembrolizumab (N=509) n	(%)	Placebo (N=502) n	(%)
Potassium Decreased (Hypokalemia)				
Subjects with Baseline and Post-baseline Measurements	505		493	
Grade 1	34	(6.7)	27	(5.5)
Grade 2	0	(0.0)	0	(0.0)
Grade 3	6	(1.2)	2	(0.4)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	6	(1.2)	2	(0.4)
All Grades	40	(7.9)	29	(5.9)
Potassium Increased (Hyperkalemia)				
Subjects with Baseline and Post-baseline Measurements	505		493	
Grade 1	55	(10.9)	43	(8.7)
Grade 2	10	(2.0)	17	(3.4)
Grade 3	2	(0.4)	1	(0.2)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	2	(0.4)	1	(0.2)
All Grades	67	(13.3)	61	(12.4)
Sodium Decreased (Hyponatremia)				
Subjects with Baseline and Post-baseline Measurements	506		497	
Grade 1	62	(12.3)	57	(11.5)
Grade 2	0	(0.0)	0	(0.0)
Grade 3	10	(2.0)	3	(0.6)
Grade 4	0	(0.0)	1	(0.2)
Grade 3-4	10	(2.0)	4	(0.8)
All Grades	72	(14.2)	61	(12.3)
Sodium Increased (Hypernatremia)				
Subjects with Baseline and Post-baseline Measurements	506		497	
Grade 1	29	(5.7)	29	(5.8)
Grade 2	1	(0.2)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)

Laboratory Test	Pembrolizumab (N=509) n	(%)	Placebo (N=502) n	(%)
Sodium Increased (Hypernatremia)				
All Grades	30	(5.9)	29	(5.8)

If a subject had more than one toxicity grade for a laboratory test, only the highest grade is counted.
Number of subjects with at least one baseline and post-baseline laboratory measurement is used as the denominator in percentage calculation.
Grades are based on NCI CTCAE version 4.03.
(Database Cutoff Date: 02OCT2017).

Table 52: Summary of liver function tests - Study KN-054 (ASaT population)

Criteria	Pembrolizumab		Placebo	
	n/m	(%)	n/m	(%)
Subjects in population	509		502	
Alanine Aminotransferase				
≥3 x ULN	21/507	(4.1)	6/498	(1.2)
≥5 x ULN	12/507	(2.4)	1/498	(0.2)
≥10 x ULN	4/507	(0.8)	1/498	(0.2)
≥20 x ULN	1/507	(0.2)	0/498	(0.0)
Aspartate Aminotransferase				
≥3 x ULN	21/507	(4.1)	6/496	(1.2)
≥5 x ULN	9/507	(1.8)	2/496	(0.4)
≥10 x ULN	1/507	(0.2)	0/496	(0.0)
≥20 x ULN	1/507	(0.2)	0/496	(0.0)
Aminotransferase (ALT or AST)				
≥3 x ULN	28/507	(5.5)	9/496	(1.8)
≥5 x ULN	14/507	(2.8)	2/496	(0.4)
≥10 x ULN	4/507	(0.8)	1/496	(0.2)
≥20 x ULN	1/507	(0.2)	0/496	(0.0)

Criteria	Pembrolizumab		Placebo	
	n/m	(%)	n/m	(%)
Bilirubin				
≥2 x ULN	6/507	(1.2)	8/498	(1.6)
Alkaline Phosphatase				
≥1.5 x ULN	20/506	(4.0)	7/494	(1.4)
Aminotransferase (ALT or AST) and Bilirubin				
AT ≥3 x ULN and BILI ≥1.5 x ULN	3/507	(0.6)	0/498	(0.0)
AT ≥3 x ULN and BILI ≥2 x ULN	1/507	(0.2)	0/498	(0.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	1/507	(0.2)	0/498	(0.0)

n = Number of Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
(Database cutoff date: 02OCT2017).

Laboratory abnormalities

In patients treated with pembrolizumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 10.8% for lymphocytes decreased, 7.6% for sodium decreased, 6.5% for haemoglobin decreased, 5.2% for phosphate decreased, 5.2% for glucose increased, 2.9% for alkaline phosphatase increased, 2.6% for AST increased, 2.3% for ALT increased, 2% for potassium decreased, 1.8% for bilirubin increased, 1.6% for potassium increased, 1.5% for albumin decreased, 1.5% for calcium increased, 1.4% for creatinine increased, 1.4% for platelets decreased, 1.4% for neutrophils decreased, 1.2% for calcium decreased, 0.8% for magnesium increased, 0.6% for leucocytes decreased, 0.5% for glucose decreased, 0.2% for magnesium decreased, and 0.2% for sodium increased.

Safety in special populations

Age

Table 53: Summary of AEs by age category - Study KN-054 (ASaT population)

	< 50				50 to 64				65 to 74				>= 75			
	Pembrolizumab		Placebo		Pembrolizumab		Placebo		Pembrolizumab		Placebo		Pembrolizumab		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	192		185		193		193		96		97		28		27	
with one or more adverse events	178	(92.7)	170	(91.9)	181	(93.8)	177	(91.7)	91	(94.8)	83	(85.6)	25	(89.3)	23	(85.2)
with no adverse event	14	(7.3)	15	(8.1)	12	(6.2)	16	(8.3)	5	(5.2)	14	(14.4)	3	(10.7)	4	(14.8)
with drug-related[†] adverse events	146	(76.0)	125	(67.6)	154	(79.8)	136	(70.5)	75	(78.1)	56	(57.7)	21	(75.0)	15	(55.6)
with toxicity grade 3-5 adverse events	45	(23.4)	33	(17.8)	62	(32.1)	39	(20.2)	36	(37.5)	18	(18.6)	15	(53.6)	6	(22.2)
with toxicity grade 3-5 drug-related adverse events	23	(12.0)	8	(4.3)	28	(14.5)	6	(3.1)	15	(15.6)	2	(2.1)	8	(28.6)	1	(3.7)
with serious adverse events	40	(20.8)	24	(13.0)	45	(23.3)	35	(18.1)	30	(31.3)	18	(18.6)	13	(46.4)	5	(18.5)
with serious drug-related adverse events	24	(12.5)	1	(0.5)	25	(13.0)	4	(2.1)	11	(11.5)	1	(1.0)	6	(21.4)	0	(0.0)
who died	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	27	(14.1)	7	(3.8)	27	(14.0)	7	(3.6)	9	(9.4)	3	(3.1)	7	(25.0)	1	(3.7)
discontinued drug due to a drug-related adverse event	26	(13.5)	5	(2.7)	23	(11.9)	2	(1.0)	8	(8.3)	1	(1.0)	5	(17.9)	0	(0.0)
discontinued drug due to a serious adverse event	13	(6.8)	2	(1.1)	9	(4.7)	5	(2.6)	3	(3.1)	3	(3.1)	4	(14.3)	1	(3.7)
discontinued drug due to a serious drug-related adverse event	12	(6.3)	0	(0.0)	6	(3.1)	1	(0.5)	2	(2.1)	1	(1.0)	2	(7.1)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database cutoff date: 02OCT2017).

Source: [P054V01MK3475: adam-adsl; adae]

Table 54: Summary of AEs by age category for elderly patients - Study KN-054 (ASaT population)

	Age (Years)															
	Pembrolizumab								Placebo							
	< 65		65 to 74		75 to 84		>= 85		< 65		65 to 74		75 to 84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	385		96		26		2		378		97		27		0	
with one or more adverse events	364	(94.5)	92	(95.8)	23	(88.5)	2	(100.0)	355	(93.9)	90	(92.8)	25	(92.6)	0	(0.0)
who died	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
with serious adverse events	87	(22.6)	31	(32.3)	11	(42.3)	2	(100.0)	68	(18.0)	27	(27.8)	7	(25.9)	0	(0.0)
discontinued[†] due to an adverse event	58	(15.1)	11	(11.5)	6	(23.1)	1	(50.0)	16	(4.2)	5	(5.2)	4	(14.8)	0	(0.0)
CNS (confusion/extrapyramidal)	17	(4.4)	6	(6.3)	0	(0.0)	0	(0.0)	14	(3.7)	5	(5.2)	0	(0.0)	0	(0.0)
AE related to falling	17	(4.4)	5	(5.2)	1	(3.8)	0	(0.0)	25	(6.6)	9	(9.3)	2	(7.4)	0	(0.0)
CV events	121	(31.4)	32	(33.3)	9	(34.6)	0	(0.0)	122	(32.3)	33	(34.0)	9	(33.3)	0	(0.0)
Cerebrovascular events	2	(0.5)	2	(2.1)	0	(0.0)	0	(0.0)	4	(1.1)	0	(0.0)	1	(3.7)	0	(0.0)
Infections	188	(48.8)	34	(35.4)	17	(65.4)	1	(50.0)	161	(42.6)	36	(37.1)	14	(51.9)	0	(0.0)

MedDRA V20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment, SAEs were followed 90 days after last dose of study treatment.
Database Cutoff Date: 02OCT2017

Gender

Table 55: Summary of AEs by gender - Study KN-054 (ASaT population)

	Male				Female			
	Pembrolizumab		Placebo		Pembrolizumab		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	320		302		189		200	
with one or more adverse events	299	(93.4)	270	(89.4)	176	(93.1)	183	(91.5)
with no adverse event	21	(6.6)	32	(10.6)	13	(6.9)	17	(8.5)
with drug-related† adverse events	240	(75.0)	186	(61.6)	156	(82.5)	146	(73.0)
with toxicity grade 3-5 adverse events	100	(31.3)	55	(18.2)	58	(30.7)	41	(20.5)
with toxicity grade 3-5 drug-related adverse events	45	(14.1)	11	(3.6)	29	(15.3)	6	(3.0)
with serious adverse events	75	(23.4)	43	(14.2)	53	(28.0)	39	(19.5)
with serious drug-related adverse events	35	(10.9)	4	(1.3)	31	(16.4)	2	(1.0)
who died	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	38	(11.9)	12	(4.0)	32	(16.9)	6	(3.0)
discontinued drug due to a drug-related adverse event	32	(10.0)	7	(2.3)	30	(15.9)	1	(0.5)
discontinued drug due to a serious adverse event	14	(4.4)	7	(2.3)	15	(7.9)	4	(2.0)
discontinued drug due to a serious drug-related adverse event	9	(2.8)	2	(0.7)	13	(6.9)	0	(0.0)

† Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database cutoff date: 02OCT2017).

ECOG

Table 56: Summary of AEs by performance status (ECOG) - Study KN-054 (ASaT population)

	KN054 for MK-3475[‡]				Reference Safety Dataset for MK-3475[‡†]				Cumulative Running Safety Dataset for MK-3475[‡‡]			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	459		31		1,488		1,347		2,521		2,282	
with one or more adverse events	437	(95.0)	30	(96.8)	1,417	(98.0)	1,305	(96.9)	2,432	(96.5)	2,202	(96.5)
with no adverse event	32	(7.0)	1	(3.2)	29	(2.0)	42	(3.1)	89	(3.5)	80	(3.5)
with drug-related† adverse events	359	(78.2)	24	(77.4)	1,149	(79.5)	911	(67.6)	1,907	(75.6)	1,507	(66.0)
with toxicity grade 3-5 adverse events	144	(31.4)	9	(29.0)	588	(40.7)	682	(50.6)	979	(38.8)	1,207	(52.9)
with toxicity grade 3-5 drug-related adverse events	69	(15.0)	2	(6.5)	201	(13.9)	184	(13.7)	343	(13.6)	354	(15.5)
with non-serious adverse events	425	(92.6)	30	(96.8)	1,404	(97.1)	1,263	(93.8)	2,409	(95.6)	2,142	(93.9)
with serious adverse events	116	(25.3)	6	(19.4)	466	(32.2)	572	(42.5)	760	(30.1)	975	(42.6)
with serious drug-related adverse events	61	(13.3)	2	(6.5)	148	(10.2)	133	(9.9)	252	(10.0)	245	(10.7)
with dose modification† due to an adverse event	116	(25.3)	5	(16.1)	423	(29.3)	459	(34.1)	687	(27.3)	774	(33.9)
who died	1	(0.2)	0	(0.0)	38	(2.6)	73	(5.5)	57	(2.3)	131	(5.7)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	4	(0.3)	6	(0.4)	7	(0.3)	12	(0.5)
discontinued drug due to an adverse event	61	(13.3)	4	(12.9)	148	(10.2)	185	(13.7)	239	(9.5)	284	(12.4)
discontinued drug due to a drug-related adverse event	54	(11.8)	4	(12.9)	82	(5.7)	64	(4.8)	133	(6.1)	116	(5.1)
discontinued drug due to a serious adverse event	25	(5.4)	1	(3.2)	104	(7.2)	148	(11.0)	151	(6.0)	228	(10.0)

	KN054 for MK-3475[‡]				Reference Safety Dataset for MK-3475[‡‡]				Cumulative Running Safety Dataset for MK-3475[‡‡]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	16	(4.7)	8	(3.5)	43	(4.6)	58	(3.1)	72	(3.8)	105	(3.4)

† Determined by the investigator to be related to the drug
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡ Includes all subjects who received at least one dose of MK-3475 in KN054.
‡† Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase); KN006; and KN010
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase); KN006; KN010; KN012 Cohorts B, B2, C and D; KN013 Cohorts 3 and 4A; KN024; KN045; KN052; KN059 Cohort 1; KN054; KN087; KN164 Cohort A; and KN170
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014; KN002: 28FEB2015; KN006: 03MAR2015; KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015; KN010: 30SEP2015; KN024: 09MAY2016;)
MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)
MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016; KN059- Cohort 1: 16JAN2017; KN061: 17FEB2017)
MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016; KN087: 27JUN2016)
MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015; KN045: 07SEP2016; KN052: 01SEP2016)
MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)
MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017; KN170: 14APR2017)
Source: [SS: adam.adsl, adae]

Region

Table 57: Summary of AEs by region - Study KN-054 (ASaT population)

	EU				Ex-EU			
	Pembrolizumab		Placebo		Pembrolizumab		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	339		334		170		168	
with one or more adverse events	316	(93.2)	296	(88.6)	159	(93.5)	157	(93.5)
with no adverse event	23	(6.8)	38	(11.4)	11	(6.5)	11	(6.5)
with drug-related[†] adverse events	264	(77.9)	211	(63.2)	132	(77.6)	121	(72.0)
with toxicity grade 3-5 adverse events	101	(29.8)	57	(17.1)	57	(33.5)	39	(23.2)
with toxicity grade 3-5 drug-related adverse events	49	(14.5)	13	(3.9)	25	(14.7)	4	(2.4)
with serious adverse events	70	(20.6)	45	(13.5)	58	(34.1)	37	(22.0)
with serious drug-related adverse events	41	(12.1)	4	(1.2)	25	(14.7)	2	(1.2)
who died	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	45	(13.3)	13	(3.9)	25	(14.7)	5	(3.0)
discontinued drug due to a drug-related adverse event	42	(12.4)	6	(1.8)	20	(11.8)	2	(1.2)
discontinued drug due to a serious adverse event	19	(5.6)	8	(2.4)	10	(5.9)	3	(1.8)
discontinued drug due to a serious drug-related adverse event	16	(4.7)	2	(0.6)	6	(3.5)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database cutoff date: 02OCT2017).

Discontinuation due to adverse events

Table 58: Comparison between the safety datasets on AEs resulting in treatment discontinuation – AsaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	70	(13.8)	334	(11.9)	547	(11.0)
with no adverse events	439	(86.2)	2,465	(88.1)	4,446	(89.0)

Table 59: Comparison between the safety datasets on drug-related AEs resulting in treatment discontinuation (≥1% in at least on treatment group)– AsaT population

	KN054 for MK-3475[§]		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	509		2,799		4,993	
with one or more adverse events	72	(14.1)	351	(12.5)	619	(12.4)
with no adverse events	437	(85.9)	2,448	(87.5)	4,374	(87.6)
Diarrhoea	10	(2.0)	35	(1.3)	64	(1.3)
Pneumonitis	9	(1.8)	21	(0.8)	44	(0.9)
Arthralgia	7	(1.4)	18	(0.6)	30	(0.6)
Alanine aminotransferase increased	5	(1.0)	19	(0.7)	39	(0.8)
Aspartate aminotransferase increased	5	(1.0)	21	(0.8)	38	(0.8)

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.

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

[§] Includes all subjects who received at least one dose of MK-3475 in KN054.

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

[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B, B2, C and D, KN013 Cohorts 3 and 4A, KN024, KN045, KN052, KN059 Cohort 1, KN054, KN087, KN164 Cohort A, and KN170.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-Lung: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 19FEB2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059- Cohort 1: 16JAN2017, KN061: 17FEB2017)

MK-3475 Database Cutoff Date for Hodgkin Lymphoma (KN013 Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial Tract Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164 Cohort A: 03JUN2016)

MK-3475 Database Cutoff Date for Mediastinal Large B-Cell Lymphoma (KN013 Cohort 4A: 03APR2017, KN170: 14APR2017)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-MAR-2017 through 03-SEP-2017. There is no post-marketing data of pembrolizumab in the indication of adjuvant melanoma.

2.5.1. Discussion on clinical safety

The randomised, double-blind, Phase III study KEYNOTE-054 provides safety information in support of the current application, with a total population of 509 stage III melanoma patients treated with pembrolizumab 200 mg Q3W as adjuvant therapy (ASaT population), in comparison with a control arm (placebo) of 502 patients (1:1 randomisation scheme). Additional safety comparative data are provided based on the prior clinical experience of pembrolizumab monotherapy in the non-adjuvant treatment setting, with a pooled dataset comprising melanoma and NSCLC patients (Reference Dataset; N=2799), as well as the totality of clinical trials conducted so far (Cumulative Running Safety Dataset; N=4993).

The comparable length of exposure between treatment arms (375 days in median in both the pembrolizumab and placebo group) in study KEYNOTE-054, enables a controlled long-term safety evaluation of the proposed therapy. As expected, the comparison with placebo showed an unfavourable safety profile of pembrolizumab in the adjuvant setting of resectable melanoma; even though a rather high proportion of drug-related AEs was reported in placebo-treated patients (66.1% vs 77.8% in pembrolizumab group), the incidence of drug-related grade 3-5 AEs (14.5 % vs 3.4%), drug-related SAEs (13% vs 1.2%), drug

discontinuations due to either drug-related AEs (12.2% vs 5.2%) or drug-related SAEs (4.3% vs 3.6%) were all more frequent in the experimental group compared to control. Moreover, two pembrolizumab-related fatalities were found between tabled results and subject narratives (discrepancies in the number of deaths across the dossier have been clarified by the MAH), while one death unrelated to the study medication was reported in the placebo group.

The safety profile of pembrolizumab is consistent with prior experience, although it must be acknowledged that a lower incidence of grade 3-5 AEs, SAEs and drug-modifications due to AEs were reported in KEYNOTE-054 compared to the reference datasets. This is likely to be explained by the younger age and better clinical performance as well as the nature of cancer disease in the KEYNOTE-054 study population, which recruited patients with localised and resected melanoma but otherwise healthy, compared with the advanced stage of metastatic disease of the reference database.

The very commonly reported ADRs of KEYTRUDA including rash, diarrhea, nausea, pruritus and fatigue were also among the main overall AEs in KEYNOTE-054. However, with the exception of rash (13.2% vs 8.6% in pembrolizumab and placebo, respectively) and pruritus (19.4% vs 11.6%), no major differences were observed in the frequency of the other events between treatment arms (nausea: 17.3% vs 14.5%; diarrhea: 27.7% vs 25.9%; fatigue: 33% vs 33.5% in pembrolizumab and placebo, respectively). Other common ADRs such as decreased appetite, dyspnoea, influenza-like syndrome, dry mouth and vomiting were observed more often in pembrolizumab-treated patients than controls, although with a similar frequency than the reference database. Notably, pembrolizumab-treated patients presented with a significantly increased rate of thyroid dysfunction than controls (14.7% vs 2.8% and 10.4% vs 1.2 for hypo and hyperthyroidism, respectively), even more common than in previous trials. Relevant info is reflected in section 4.8 of the SmPC.

Drug-related AEs showed a preponderance of endocrine disturbances in the comparison between pembrolizumab and placebo, their incidence in the experimental group being higher than previously reported (24% in KEYNOTE-054 vs 10.5% in the RSD and 11.8% in the Cumulative Running RDS, including both hypo and hyperthyroidism). Asthenia, headache, dyspnoea and alanine aminotransferase that also were among the most frequently reported drug-related AEs in KEYNOTE-054, occurred with a higher incidence than previously observed. With the exception of infusion-related reactions, anaphylactic reaction, skin reactions and myositis, all the remaining AEOSI were more frequent in KEYNOTE-054 than prior trials.

The majority of drug-related AEOSI in the pembrolizumab group were of grade 2 in severity (95/173; 55%), required therapy in 32% of cases, and 72.2% of events resolved (with or without sequelae). In the placebo group, AEOSI that were related to treatment by Investigators occurred at a significantly lower rate (7.6% vs 34% in the experimental arm), were mostly of Grade 1 (20/38; 53%), and required immunosuppressive therapy in 21% of cases; 68% of AEOSI resolved (with or without sequelae). Duration of AEOSI were similar in both groups (43 days in median). Hypothyroidism (14.7% vs 2.8%) and hyperthyroidism (10.4% vs 1.2% in pembrolizumab and control group, respectively) were the prevailing AEOSI reported in the study.

AEOSI were also among the leading causes of drug-related Grade 3-5 AEs. Colitis and Type 1 diabetes mellitus were the most commonly reported AEs within this category. Differences compared to the prior clinical experience mainly relate to the incidence of type 1 diabetes, whose higher rate in pembrolizumab-treated patients in KEYNOTE-054 is likely to have been triggered by their longer time on treatment (time-to-onset was 64 days in median, range:43-315). Colitis and pneumonitis were also the main pembrolizumab-related SAEs in KEYNOTE-054, with colitis, but not pneumonitis, being more frequently reported than in the reference datasets (1.6% vs 0.9%). Neither colitis nor pneumonitis were observed in the placebo group.

The increased risk of drug-related AEs and AEOSI is likely to be attributed to the longer exposure in KEYNOTE-054 (375 days in median) compared to the reference datasets (127 and 135 days in the RSD and Cumulative Running dataset), with an overall AEOSI time-to-onset of 85 days in median, ranging between

1 and 423 days. Out of a total of 509 subjects in the pembrolizumab arm receiving at least one dose of study treatment, 173 (34%) experienced at least one AEOSI. As more than 60% of AEOSI were reported as not resolved, given the long survival expected in the adjuvant setting, more details have been requested, showing that most common not-resolved AEOSI were attributable to thyroid disorders which can be managed with hormone replacement therapy. However, although less commonly, severe AEOSIs also with serious long term consequences can occur. It is underlined that pembrolizumab SmPC has been recently modified (II/58 procedure) to include a clearer warning in 4.4 that "Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab.".

A summary of the laboratory abnormalities based on the cumulative safety dataset has been added to the SmPC in section 4.8.

Two deaths were reported in the pembrolizumab arm, including a drug-reaction with eosinophilia and systemic symptoms, and a case of immune-mediated myositis considered related to pembrolizumab by the Investigator. In the placebo group, one death due myocardial infarction was observed (unrelated to study treatment).

There was an age-dependent increase in drug-related AEs of Grade 3-5 in severity and SAEs in the pembrolizumab arm. Tolerability to pembrolizumab was particularly reduced in patients aged ≥75 years compared to younger subgroups (28.6% vs 12% in patients <50 years for drug-related grade 3-5 AEs; 21.4% vs 12.5% in patients <50 years for drug-related SAEs). Therefore, a warning has been included in section 4.4 of the SmPC that a trend toward increased frequency of severe and serious adverse reactions in patients ≥ 75 years was observed. Safety data of pembrolizumab in the adjuvant melanoma setting in patients ≥ 75 years are limited. With regard to gender subgroup analyses, more drug-related AEs (82.5% versus 75%) and drug-related SAEs (16.4% versus 10.9%) were observed in the female ASaT population treated with pembrolizumab. Overall, female subjects tended to tolerate treatment with pembrolizumab less well than male subjects. This differs from the so far available AE profile by gender observed in the RSD and in the Cumulative Running Safety Dataset, where no distinct difference was observed between male and female subjects. Since these observations from the KEYNOTE-054 data set are based on 189 female subjects (compared to 320 male subjects), this finding cannot be attributed to a low number of female subjects in the KN054 population. The Applicant was therefore requested to comment on the increased SAE and study drug discontinuation rates in female subjects. There were higher frequencies in females versus males for different AE categories also observed not only in the pembrolizumab arm but also in the placebo cohort, (e.g., drug-related AEs were observed in 73.0% of female subjects in the placebo arm vs. 61.6% of male subjects; and SAEs were observed in 19.5% of females vs. 14.2% of males in the placebo arm). This is indicative that the differences observed may be the result of random variability within the patient population.

As regards immunogenicity, the incidence of treatment-emergent ADA to pembrolizumab in subjects with melanoma treated in the adjuvant setting is higher than the overall incidence in the non-adjuvant setting (3.4% versus 2%). However, there was no incidence of treatment-emergent neutralizing positive subjects in the adjuvant treatment setting (0 out of 17), which is consistent with the low incidence seen in the non-adjuvant setting. Furthermore, similar to the non-adjuvant setting, there was no impact of treatment-emergent ADA observed on pembrolizumab exposure, efficacy, or safety.

2.5.2. Conclusions on clinical safety

There were no new safety signals observed in study KN-054 in the pembrolizumab treatment arm in the adjuvant setting of completely resected stage III melanoma. The ADRs observed were generally manageable as the severity was mainly of Grade 1-2. Drug-related grade 3-5 AEs, drug-related SAEs and drug-related fatalities occurred more often in the experimental arm than placebo, which is expected, and frequencies were generally comparable to what has been observed with pembrolizumab monotherapy in the non-adjuvant setting. However, an increased rate of AEOSI mainly related to endocrine disturbances

(thyroid dysfunction and type 1 diabetes) occurred, likely due to the longer exposure of patients in KEYNOTE-054 than in prior trials. No specific warning has been included in the PI as the risks of hypothyroidism (myxoedema), hypophysitis (hypopituitarism) thyroiditis (autoimmune thyroiditis and thyroid disorder) and diabetes type 1 have already been reflected in the PI previously. Therefore, for the adjuvant treatment of melanoma, Keytruda should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year (see SmPC 4.2).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 22 is acceptable.

There are no changes to the list of safety concerns, to the pharmacovigilance plan or to the risk minimisation measures as a result of this extension of indication.

The CHMP endorsed the Risk Management Plan version 22 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-Related Adverse Reactions • Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis • Immune-related nephritis • Immune-related endocrinopathies - Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) - Type 1 diabetes mellitus • Severe skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) Other Immune-Related Adverse Reactions • Uveitis • Myositis • Pancreatitis • Myocarditis • Guillain-Barre Syndrome • Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients • Encephalitis • Sarcoidosis Infusion-Related Reactions
Important potential risks	Immune-Related Adverse Events • Gastrointestinal perforation secondary to colitis Other Immune-Related Adverse Events

Summary of safety concerns	
	• For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab • Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT) 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

On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities					
Started	Clinical trial A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (KN010)	To examine the overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and long term efficacy and safety of MK-3475 in previously treated subjects with NSCLC whose tumors express PD-L1.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety	Final Study Report	Aug 2019

On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (KN024)	To evaluate the overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) and the safety and tolerability profile of pembrolizumab in subjects with 1L metastatic NSCLC, whose tumors express PD-L1, treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT; Immunogenicity) -Long term safety	Final Study Report	Sep 2018
Started	Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (KN042)	To evaluate the overall survival (OS) and progression free survival (PFS) and to examine the safety and tolerability profile of pembrolizumab in subjects with PD-L1 positive 1L advanced/metastatic NSCLC, treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity) -Long term safety	Final Study Report	Dec 2019
Started	Clinical Trial A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies (KN013)	To examine the safety and tolerability of pembrolizumab in subjects with hematologic malignancies including, Hodgkin lymphoma, mediastinal large B cell lymphoma (MLBCL), relapsed/refractory non-Hodgkin lymphoma (NHL), myelodysplastic syndrome (MDS) and multiple myeloma .	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in	Final Study Report	Mar 2019

On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
			patients with a history of allogeneic SCT;Immunogenicity)		
Started	Clinical Trial A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (KN087)	To determine the safety and tolerability of pembrolizumab in subjects with relapsed or refractory classical Hodgkin Lymphoma (cHL) and to evaluate overall response rate (ORR), progression free survival (PFS), duration of response (DOR) and overall survival (OS) of pembrolizumab in study subjects.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Aug 2021
Started	Clinical Trial A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204)	To compare overall survival (OS), progression free survival (PFS) and overall response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Apr 2021

On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	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 (KN051)	To define the toxicities and maximum tolerated, maximum administered dose of pembrolizumab when administered as monotherapy to children between 6 months to 18 years of age with advanced melanoma, advanced, relapsed or refractory solid tumors or lymphoma. Study is designed to determine the safety and tolerability of pembrolizumab in all children between 6 months to 18 years of age.	Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis); GVHD after pembrolizumab administration in patients with a history of allogeneic SCT; -Safety in pediatric patients	Final Study Report	July 2019
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risks of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT.	Important identified risks of encephalitis, sarcoidosis; potential risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	PSUR	2019
Started	Clinical trial A Phase I/II Study of MK-3475 in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma (KN021)	To determine the recommended Phase II dose for MK-3475 in combination with chemotherapy or immunotherapy in subjects with unresectable or metastatic NSCLC.	Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety	Final Study Report	Apr 2020

On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical Trial A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KN189)	To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy and to evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using OS.	Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety	Final Study Report	Jun 2021
Started	Clinical Trial A randomized, active-controlled, multicenter, open-label Phase III clinical trial to examine the efficacy and safety of Pembrolizumab versus the choice of 3 different standard treatment options in subjects with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) whose disease has progressed on or after prior platinum-containing chemotherapy (KN040)	To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, Immunogenicity) -Long term safety	Final Study Report	May 2020

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related Pneumonitis	Routine risk minimisation measures: • 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. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Colitis	Routine risk minimisation measures: • 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. Additional risk minimisation measures: • Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Hepatitis	Routine risk minimisation measures: • 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. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immune-related Nephritis	Routine risk Minimisation measures: • 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. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Target questionnaire for spontaneous postmarketing reports of all adverse events. Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Endocrinopathies -Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis) - Type 1 Diabetes Mellitus	Routine risk Minimisation measures: • The risk of the immune-related endocrinopathies [Hypophysitis (including hypopituitarism and secondary adrenal insufficiency); Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis); Type 1 Diabetes Mellitus] associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4 and 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in the Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Severe Skin Reactions including SJS and TEN	Routine risk Minimisation measures: • The risk of severe skin reactions including SJS and TEN associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire for spontaneous postmarketing reports of all adverse events

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • Educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Other Immune-related adverse reactions -Uveitis, Myositis, Pancreatitis, Myocarditis, Guillain-Barre Syndrome, Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients, Encephalitis, Sarcoidosis	Routine risk Minimisation measures: • The risk of other immune-related adverse reactions (uveitis, myositis, pancreatitis, myocarditis, Guillain-Barre syndrome, Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients, encephalitis, sarcoidosis) associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 (Guillain-Barre Syndrome, Myocarditis, Encephalitis are also described in Section 4.2) and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types • Cumulative review of literature, clinical trial and post-marketing cases of encephalitis and sarcoidosis to be included with PSUR submission in 2019.

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Infusion-Related Reactions		
Infusion-Related Reactions	Routine risk Minimisation measures: • 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 Additional risk minimisation measures: Educational materials.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks: Immune-Related Adverse Events		
Gastrointestinal perforation secondary to colitis	Routine risk Minimisation measures: • The risk of the immune-related adverse event of gastrointestinal perforation secondary to colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire for spontaneous postmarketing reports of all adverse events Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Other Immune-related adverse events- For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk Minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trials (KN013, KN087, KN204).
Other Immune-related adverse events- GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk Minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: • Educational materials	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types • Cumulative review of literature, clinical trial and post-marketing cases of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT with PSUR submission in 2019.
Important Potential Risks: Immunogenicity		
Immunogenicity	Routine risk Minimisation measures: • The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 4.8.	Routine pharmacovigilance activities Additional pharmacovigilance including: • Conducting anti-drug antibody (ADA) assessments in multiple MAH- sponsored clinical trials in different tumor types in the pembrolizumab program.

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	Routine risk Minimisation measures: • The missing information of safety in these patients is described in the SmPC, Section 4.2, 4.4.	Routine pharmacovigilance activities
Safety in patients with active systemic autoimmune disease	Routine risk Minimisation measures: • The missing information of safety in patients with active systemic autoimmune disease is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities
Safety in patients with HIV or Hepatitis B or Hepatitis C	Routine risk Minimisation measures: • 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.	Routine pharmacovigilance activities
Safety in Pediatric patients	Routine risk Minimisation measures: • The missing information of safety in pediatric patients is described in the SmPC, Section 4.2.	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in the paediatric investigation plan (PIP): 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 (KN051)
Reproductive and lactation data	Routine risk Minimisation measures: • Use during pregnancy and use in nursing mothers is described in the SmPC, Section 4.6, 5.3.	Routine pharmacovigilance activities
Long term safety	No risk Minimisation warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Safety in various ethnic groups	No risk Minimisation warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in ongoing global MAH-sponsored clinical trials for pembrolizumab
Potential pharmacodynamic interaction with systemic immunosuppressants	Routine risk Minimisation measures: • The missing information of potential pharmacodynamic interaction with systemic immunosuppressants is described in the SmPC, Section 4.4, 4.5.	Routine pharmacovigilance activities
Safety in patients with previous hypersensitivity to another monoclonal antibody	Routine risk Minimisation measures: • The missing information of safety in patients with previous hypersensitivity to another monoclonal antibody is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities
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	Routine risk Minimisation measures: • The missing information of safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs is described in the SmPC, Section 4.4, 5.1.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • T questionnaire for spontaneous postmarketing reports of all adverse events

2.7. Update of the Product information

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

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the product information are considered minor and in relation to the new indication, hence, the changes do not affect the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH is seeking an extension of indication for KEYTRUDA monotherapy as adjuvant treatment of adult melanoma patients with lymph node involvement who have undergone complete resection, based on the interim results of study KEYNOTE-054.

3.1.1. Disease or condition

Melanoma is a malignant tumour that originates from melanocytic cells and primarily involves the skin, causing 90% of skin cancer mortality[1]. The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12−25 in Nordic countries, and a disparity in the mortality-to-incidence ratios between Western and Eastern European countries has been observed[2]. Its incidence continues to rise worldwide. Median age at diagnosis is 59 years. However, melanoma is not uncommon among individuals younger than 30 years, being the second most commonly diagnosed cancer (after lymphomas) among adolescents and young adults[3].

The major environmental risk factor for melanoma is ultraviolet (UV) radiation. Increased UV light exposure of a genetically predisposed population seems to be, at least in part, responsible for an ongoing rise in incidence[2].

Approximately 90% of melanomas are diagnosed as primary tumors without evidence of metastasis. The outcome of melanoma depends on the stage at presentation. For early-stage melanoma, surgical resection is the standard treatment and is associated with an excellent long-term survival prognosis for stage I (98%) and stage II (90%). However, patients with stage III disease, who have regional involvement at diagnosis, are at higher risk or recurrence after locoregional resections. Lymph node tumour burden at the time of staging, ulceration, and Breslow thickness of the primary melanoma are the most predictive independent factors for survival in patients with stage III disease.

Staging of melanoma as of January 2018 is now performed using the AJCC 8th edition TNM classification[4]; however, at the time of KEYNOTE-054 protocol development and initiation of subject enrollment, the AJCC 7th edition was in effect for TNM staging.

At the time of protocol development, 5-year survival rates reported by AJCC 7th edition for patients with stage IIIA, IIIB, and IIIC melanoma were 78%, 59%, and 40%, respectively[5]. The 5-year melanoma-specific survival rates according to the current AJCC 8th edition Staging Guidelines are 93%, 83%, 69%, and 32% for stage IIIA, IIIB, IIIC, and IIID, respectively[4].

3.1.2. Available therapies and unmet medical need

Surgical excision is the primary treatment for melanoma. Adjuvant therapy is offered to patients who present without evidence of macroscopic metastases but are at high risk of having microscopic metastases and relapse.

According to the ESMO guidelines, patients with resected stage III are evaluated for IFN therapy: patients with microscopic regional nodal involvement and/or ulcerated primaries are most likely to benefit. For patients with ≥stage IIIB, clinical trials or high-dose IFN-α-2b are options. High-dose IFN-α-2b is an approved indication and offered in some European countries for high risk resected stage II or III melanoma on the basis of reduction in RFS, although not universally because of marginal OS benefit and the significant toxicity. Observation is frequently used as the standard of care in Europe[1,2,9].

Nivolumab and the combination dabrafenib/trametinib (for BRAF mutated tumors) have been recently approved for the adjuvant treatment of melanoma. The approved indication for nivolumab is as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1). The approved indication for dabrafenib in combination with trametinib is for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Pembrolizumab is currently EU approved in the advanced (unresectable or metastatic) melanoma setting.

3.1.3. Main clinical studies

The current application is based upon results of the Phase III KEYNOTE-054 trial, a Randomized, Double-Blind, Study of the EORTC Melanoma Group testing Pembrolizumab versus placebo after complete resection of high-risk Stage III (stage III [lymph node metastasis >1 mm], IIIB, IIIC) cutaneous melanoma. This is an ongoing study currently at its first RFS interim analysis (data cut-off date: 02-OCT-2017).

Updated data with a cut-off date of 2 May 2018 has been submitted per CHMP request.

Investigator's assessed RFS, in the ITT and in PD-L1-positive population, were dual primary endpoints.

3.2. Favourable effects

- Statistically significant improvement in RFS of pembrolizumab versus placebo in the ITT population (HR = 0.57; p<0.0001). Median RFS not yet reached in the pembrolizumab group, 20.4 months in the placebo group. An updated RFS analysis (data cut-off date 2 May 2018) reaching almost the final planned number of RFS events (404 vs 409) confirmed the interim results (HR=0.56, 98.4%CI 0.44-0.72, p<0.0001).
- Advantage of pembrolizumab over placebo seen in the 6-months and 1-year rates. The Kaplan-Meier curves separate after 3 months and remain separated throughout.
- Available sensitivity analyses are supportive of the primary analysis.
- RFS benefit of pembrolizumab over placebo appears consistent in the subgroups analysed. This include subgroups according to PD-L1 expression (positive and negative), BRAF mutation status and tumor stage (according to AJCC 7th edition).
- Fewer distant metastases and locoregional recurrences (as RFS event) were reported in the pembrolizumab arm compared to placebo (13.4% vs 22.6% and 15.2% vs 10.7%, respectively).
- Within the limits of immature analyses, PRFS2 and TFST showed overall consistent estimated hazard ratios with RFS and are supporting the benefit of pembrolizumab with regard to delaying the occurrence of distant metastasis and the use of subsequent systemic therapy. In addition, at visual inspection, Kaplan Maier curves for RFS, PRFS2 and TFST appear to divide and maintain separated over time.
- Additional preliminary data were submitted upon CHMP request and considered supportive for the conclusion (data not shown).

3.3. Uncertainties and limitations about favourable effects

- The CHMP requests that the MAH submits the final results for RFS/DMFS and OS for study KN-054 to confirm the efficacy observed with the interim analyses provided.
- PD-L1 was not shown to be a predictive marker for responses in adjuvant melanoma. Nevertheless, The CHMP requests that the MAH investigates biomarkers other than PD-L1 expression status by

Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy in adjuvant melanoma, in addition to more information regarding the pattern of expression of PD L1.

3.4. Unfavourable effects

- The incidence of drug-related AEs (77.8% vs 66.1%), drug-related grade 3-5 AEs (14.5 % vs 3.4%), drug-related SAEs (13% vs 1.2%), drug discontinuations due to either drug-related AEs (12.2% vs 5.2%) or drug-related SAEs (4.3% vs 3.6%) were all more frequent in the pembrolizumab group compared to control.
- Asthenia, headache, dyspnoea and alanine aminotransferase that also were among the most frequently reported drug-related AEs in KEYNOTE-054, occurred with a higher incidence than previously observed. With the exception of infusion-related reactions, anaphylactic reaction, skin reactions and myositis, all the remaining AEOSI were more frequent in KEYNOTE-054 than prior trials.
- Two pembrolizumab-related fatalities were found while one death unrelated to the study medication was reported in the placebo group.
- Drug-related AEs showed a preponderance of endocrine disturbances in the comparison between pembrolizumab and placebo, their incidence in the experimental group being higher than previously reported (24% in KEYNOTE-054 vs 10.5% in the RSD and 11.8% in the Cumulative Running RDS, including both hypo and hyperthyroidism)
- Colitis and Type 1 diabetes mellitus were the most commonly reported AEs within the category of Grade 3-5 AEs; colitis and pneumonitis were also the main pembrolizumab-related SAEs in KEYNOTE-054, with colitis, but not pneumonitis, being more frequently reported than in the reference datasets (1.6% vs 0.9%). Neither colitis nor pneumonitis were observed in the placebo group.

3.5. Uncertainties and limitations about unfavourable effects

There were no new safety concerns identified during the conduct of the clinical trial. Hence, there are no uncertainties on the unfavourable effects.

3.6. Effects Table

Table 60: Effects Table for Keytruda for the adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection (KEYNOTE-054, data cut-off: 02-OCT-2017, RFS Interim Analysis)

Effect	Short description	Unit	Pembro 200 mg Q3W	Placebo	Uncertainties / Strength of evidence	Ref.
Favourable Effects						
RFS (ITT) *dual primary*	Time of first recurrence (local, regional, distant metastasis) or death (whatever the cause) from randomisation	months (95% CI)	Not Reached (--, --)	20.4 (16.2, --)	limited follow-up/statistically significant results, consistent results in subgroups. Updated RFS results (cut-off 02 May 2018) supported interim data (median RFS NR (-,-) vs 21.7 (17.1, -); HR 0.56, 98.4%CI (0.44,	CSR
		HR (98.4%CI)	0.57 (0.43, 0.74) p<0.0001			
RFS (PD-L1 positive) *dual primary*	As above	months (95% CI)	Not Reached (-, -)	Not Reached (17.1, -)		

Effect	Short description	Unit	Pembro 200 mg Q3W	Placebo	Uncertainties / Strength of evidence	Ref.
					0.72) p<0.0001)	
Unfavourable Effects						
Tolerability						
	drug related AEs	%	77.8	66.1		CSR
	drug related Gr≥3 AE	%	14.5	3.4		
	drug related SAEs	%	13.0	1.2		
	drug related deaths	%	0.2%	0.0		
	discontinuation drug related AEs	%	12.2	1.6		
	discontinuation drug related SAEs	%	4.3	0.4		
Drug-related AEs						
	Fatigue	%	28.1	26.9	Higher rate of AEOSIs were reported in KN-054 compared to the reference datasets, including colitis (<2%), hepatitis (<1%), and endocrine disturbances (thyroid dysfunction [<10%] and type I diabetes mellitus [<1%])	
	Diarrhoea	%	18.5	16.3		
	Pruritus	%	16.7	9.8		
	Hypothyroidism	%	14.7	2.8		
	Nausea	%	11.4	8.6		
	Arthralgia	%	10.0	9.4		
	Hyperthyroidism	%	9.6	0.8		
	Rash	%	9.6	6.4		
	Asthenia	%	9.4	6.8		
	Headache	%	7.3	6.6		
	Dyspnoea	%	5.3	2.8		
	ALT increase	%	5.1	3.2		
	Myalgia	%	5.1	3.0		
	Colitis	%	3.7	0.4		
	Pneumonitis	%	2.9	0.6		
	Hepatitis	%	1.8	0.2		
	Type 1 diabetes mellitus	%	1.0	0.0		

Abbreviations: CSR: Clinical Study report; RFS: Recurrence Free Survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pembrolizumab demonstrated a statistically significant improvement in RFS compared to placebo in the ITT population and in the PD-L1 positive patients when used as adjuvant treatment in lymph-node positive cutaneous melanoma after complete resection. The data was supported by subgroup analyses and sensitivity analyses which reflected the RFS benefit observed in the overall population. The updated RFS analysis, reaching almost the final planned number of RFS events, confirmed the interim RFS result of a statistically significant RFS benefit of pembrolizumab over placebo and provides robustness to the conclusion that the effect is maintained in the long term.

Within the limits of immature analyses, PRFS2 and TFST showed overall consistent estimated hazard ratios with RFS and are supporting the benefit of pembrolizumab with regard to delaying the occurrence of distant metastasis and the use of subsequent systemic therapy. In addition, at visual inspection, Kaplan Maier curves for RFS, PRFS2 and TFST appear to divide and maintain separated over time. Additional preliminary data submitted upon CHMP request were considered supportive for the conclusion (data not shown).

In terms of safety, there were no new safety risks identified in the trial KN-054 and the safety is similar to what is already known for pembrolizumab. There was an increased incidence of immune-mediated reactions including thyroid dysfunctions, type 1 diabetes mellitus and colitis among the most frequently reported ones. However, these are considered tolerable and manageable with the recommendations as stated in the SmPC as well as additional risk minimisation activities. Of note, the incidence of these pembrolizumab-related AEs was higher than previously observed, most likely in view of a longer exposure to treatment in the KEYNOTE-054 than prior trials. Moreover, although the majority was of Grade 2 in severity, immunological disturbances gave rise to AEs resolving with sequelae as well as to serious events, including fatalities, in otherwise healthy individuals. AEOSI with a not-resolved outcome were 63%, most commonly attributable to thyroid disorders which can be managed with hormone replacement therapy. Although less commonly, severe AEOSIs also with serious long term consequences can occur. A clearer warning regarding the occurrence of severe and fatal cases of immune-related adverse reaction following pembrolizumab has been recently introduced in the SmPC. There were too few patients aged ≥75 years to draw conclusion on the safety in older age and a warning has been included to this effect in the SmPC.

3.7.2. Balance of benefits and risks

The CHMP considers that efficacy has been established for pembrolizumab over placebo in the treatment of adjuvant melanoma in adult patients with lymph node involvement who have undergone complete resection. Additionally, there were no new safety signals observed. Therefore, the benefit-risk balance was concluded to be positive.

3.7.3. Additional considerations on the benefit-risk balance

RFS benefit for pembrolizumab over placebo was apparent across all stage subgroups according to the AJCC 7th edition classification, which was the one used in KEYNOTE-054 trial. In order to evaluate the study results in light of the currently used AJCC 8th edition staging system, post-hoc RFS subgroup analyses by cancer stage according to AJCC 8th Edition were requested. In the new AJCC classification, Stage IIIA identifies a patient population with better prognosis as compared to the same stage in 7th edition, with a 5-years melanoma specific survival rate of 93%. There are few patients with stage IIIA according to the new AJCC 8th edition classification in the study and the number of events is very limited. Therefore, although the benefit risk is considered positive in these patients with earlier disease stage, the efficacy data is limited in this patient population and a statement has been included to section 5.1 of the SmPC. For subjects with such a good prognosis, the treating physician should consider the toxicity of adjuvant treatment with one year of pembrolizumab in determining the best course of treatment for the patient.

3.8. Conclusions

The overall B/R of Keytruda is positive.

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

- The final bioanalytical reports for PK and ADA assessment from study KN-054. Due 31st December 2023.

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

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

   Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing NSCLC studies (P001, P010, P024 and P042), urothelial carcinoma studies (KN045, KN052), HNSCC study (KN040) and resected Stage II melanoma adjuvant study (KN-716):
   - Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature)
   - IHC staining for PD-L2
   - Data on RNA and proteomic serum profiling

As the initial efficacy assessment is based on a surrogate endpoint, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions, the MAH is requested to submit the following:

2. Post-authorisation efficacy study (PAES): In order to investigate the long term efficacy in melanoma patients treated with adjuvant pembrolizumab, the MAH should submit the final RFS/DMFS and OS data for study KN-054: A Phase III Clinical Trial of Pembrolizumab (MK-3475) in Subjects with complete resection of high-risk Stage III melanoma.

   The clinical study report should be submitted by 4Q 2023 .

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 22 out of 32 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include (as monotherapy) adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection, based on study KEYNOTE-054; a randomized, double-blind, phase 3 study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), undertaken to evaluate adjuvant therapy with pembrolizumab compared to placebo in patients with resected high-risk melanoma (Stage IIIA [> 1 mm lymph node metastasis], IIIB and IIIC). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. The RMP version 22.0 was agreed.

This CHMP recommendation is subject to the following amended condition:

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

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

Description	Due date
The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing NSCLC studies (P001, P010, P024 and P042) and urothelial carcinoma studies (KN045, KN052), HNSCC study (KN040) and resected Stage II melanoma adjuvant study (KN716): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling	 2Q 2020 2Q 2019 4Q 2021 4Q 2024
Post-authorization efficacy study (PAES) the MAH should submit the final study report of RFS/DMFS and OS data for study KN054: a Phase III Clinical Trial of Pembrolizumab (MK-3475 in Subjects with complete resection of high-risk Stage III melanoma – Final Study Report	4Q 2023

Divergent position to the majority recommendation is appended to this report.

5. Appendix

1. Divergent positions dated 18 October 2018.

APPENDIX

DIVERGENT POSITION DATED 18 October 2018

DIVERGENT POSITION DATED 18 October 2018

Keytruda EMEA/H/C/003820/II/47

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the extension of the indication for Keytruda to add the following:

'Keytruda as monotherapy is indicated for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection (see section 5.1)'.

The reason for divergent opinion was the following:

According to the natural course of melanoma in patients with lymph node involvement following complete resection, the great majority of recurrences will occur within 3 years. The current follow-up of the Phase III KEYNOTE-054 with interpretable results up to 15 months, is not considered sufficient to establish therapeutic efficacy, precluding a positive B/R for Keytruda in the proposed indication.

Bart Van Der Schueren

Jorge Camarero Jimenez

Jayne Crowe

Johann Lodewijk Hillege

Katarina Vucic

Koenraad Norga

Kristina Dunder

Outi Maki-Ikola

Robert James Hemmings

Sol Ruiz