19 May 2022
EMA/574905/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0111

Note

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

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List of abbreviations

Abbreviation	Definition
2L+	Second-line therapy or later
ADA	Antidrug antibodies
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AEOSI	Adverse event(s) of special interest
AJCC	American Joint Committee on Cancer
APaT	All Participants as Treated
cHL	Classical Hodgkin Lymphoma
CI	Confidence interval
CRC	Colorectal cancer
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical Study Report
DCO	Data cutoff
DMFS	Distant metastasis-free survival
dMMR	Mismatch repair deficient
EC	Endometrial carcinoma
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GEJ	Gastro-esophageal junction
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IFN	Interferon
IgG	Immunoglobulin G
IL-2	Interleukin-2
ITT	Intent-to-treat
KM	Kaplan-Meier
LN+	Lymph node positive
mAb	Monoclonal antibody
MCC	Merkel cell carcinoma

Abbreviation	Definition
MSI-H	Microsatellite instability-high
MSS	Melanoma-specific survival
NCCN	National Comprehensive Cancer Network
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
PK	Pharmacokinetic(s)
PMBCL	Primary mediastinal large B-cell lymphoma
PRFS2	Progression/recurrence-free survival 2
Q3W	Every 3 weeks
RCC	Renal cell carcinoma
RFS	Recurrence-free survival
RSD	Reference Safety Dataset
SAE(s)	Serious adverse event(s)
SCLC	Small cell lung carcinoma
SLN	Sentinel lymph node
TMB-H	Tumour mutational burden-high
UC	Urothelial carcinoma
US	United States

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 27 July 2021 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 the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, Stage IIC or stage III melanoma and to include the treatment of adolescents aged 12 years and older with advanced melanoma for Keytruda; as a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 36.1 of the RMP has also been submitted.

The variation requested 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 completed.

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 MAH 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 18 October 2018 (EMEA/H/SA/2437/26/2018/II). The Scientific Advice pertained to clinical aspects and in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	27 July 2021
Start of procedure	14 August 2021
CHMP Rapporteur's preliminary assessment report circulated on	8 October 2021
PRAC Rapporteur's preliminary assessment report circulated on	12 October 2021
CHMP Co-Rapporteur's Critique circulated on	20 October 2021
PRAC RMP advice and assessment overview adopted by PRAC	28 October 2021
Updated CHMP Rapporteur's assessment report circulated on	4 November 2021
Request for supplementary information adopted by the CHMP on	11 November 2021
MAH's responses submitted to the CHMP on	15 December 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 February 2022
2nd request for supplementary information adopted by the CHMP on	24 February 2022
MAH's responses submitted to the CHMP on	17 March 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 April 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	13 May 2022
CHMP opinion adopted on	19 May 2022

2. Scientific discussion

2.1. Introduction

Within the remit of the current type II variation, the MAH is seeking extension of indication for Keytruda in the adjuvant setting of stage IIB and IIC melanoma for both adolescents aged 12 years and older and adults, and is pursuing a paediatric indication encompassing adolescents aged 12 years and older for the already licensed use of Keytruda as adjuvant therapy in stage III melanoma and as treatment of advanced melanoma.

2.1.1. Problem statement

Disease or condition

The current application pertains to the treatment of melanoma in both adults (stage IIB and IIC) and adolescents aged 12 years and older (stage IIB, IIC, III and advanced stage):

- KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults **and adolescents aged 12 years and older with Stage IIB, Stage IIC or** ~~with~~ Stage III melanoma and ~~lymph node involvement~~ who have undergone complete resection.

- KEYTRUDA as monotherapy is indicated for the treatment of **adults and adolescents aged 12 years and older with** advanced (unresectable or metastatic) melanoma~~ in adults~~.

Epidemiology and risk factors, screening tools/prevention

The worldwide incidence of melanoma has increased rapidly over last decades among white populations, especially in people older than 60 years of age. In Europe, the incidence rate is < 10-25 new cases over 100,000 habitants. In the paediatric population melanoma occurs with rare frequency especially in youngest children but the incidence of disease increases by age with an estimated rate of 10.4 per million in the 15-19 year olds. While cases are expected to substantially augment in the older population, the most recent epidemiology data indicate a stabilisation of melanoma incidence in the youngest, possibly due to the favourable influence of public campaigns to promote healthy sun exposure behaviours. Indeed, the main exogenous risk factor for melanoma is UV exposure, while inherited conditions including melanocortin-1 receptor (MC1R) variants or phenotypes characterised by high numbers of common naevi or presence of congenital naevi are recognised predisposing factors. Similar considerations apply to the majority of paediatric melanoma that are sporadic and mostly related to UV-mediated DNA damage.

Biologic features, aetiology and pathogenesis

Melanoma is a malignant tumour that arises from melanocytes and primarily involves the skin. It is classified as melanoma in situ when confined within the epidermis, or invasive when atypical melanocytes progressively invade into the dermis.

The 4th edition, 2018 of the WHO classification of skin tumours distinguishes melanoma subtypes based on the pathway concept of melanoma pathogenesis and its association with sun-exposed skin that consequently determines the genetic hallmark of lesions.

Classification of melanomas, including epidemiological, clinical, pathological, and common genomic features. Adapted from [29].

Type of UVR exposure/CSD	Subtype of melanoma	Affected genes
Low-CSD melanoma	SSM	BRAF V600 E/K or NRAS CDKN2A TP53 SWI/SNF TERT
High-CSD melanoma	LMM Desmoplastic melanoma	NF1, NRAS, BRAF, KIT CDKN2A TP53 SWI/SNF TERT
Low to no UVR exposure (or variable/ incidental)	Spitz melanoma	HRAS, ROS1, NTRK1, NTRK3, ALK, RET, MET, BRAF, CDKN2A, TERT
	Acral melanoma Mucosal melanoma (genital, oral, sinonasal)	NRAS, KIT, NF1, SPRED1, BRAF, CCND1, ALK, ROS1, RET, NTRK1, CDKN2A, CDK4, TP53, SWI/SNF, TERT
	Uveal melanoma	GNAQ, GNA11, CYSLTR2, PLCB4, BAP1, SF3B1, EIF1AX
	Melanoma arising in congenital naevus	NRAS
	Melanoma arising in blue naevus	GNAQ, GNA11, CYSLTR2, BAP1, SF3B1, EIF1AX

CSD = Cumulative sun damage.

Four histology-based melanoma subtypes are also described, including superficial spreading melanoma (SSM, 41%), nodular melanoma (NM, 16%), lentigo malignant melanoma (LMM, 2.7-14%) and acral lentiginous melanoma (ALM, 1-5%). Of note, distinction of different subtypes, either based on UV-exposure relationship or pure histology features does not provide prognostic indications and is not considered in the current tumour staging system. Indeed, the eighth edition AJCC Cancer Staging Manual offers a clinical and pathological classification of lesions based on thickness, ulceration, and level of metastization as these features have been identified as major prognostic factors.

Paediatric melanoma is conventionally distinguished into three main categories, including conventional melanoma (CM), melanoma arising in congenital nevi (CNM), and spitzoid melanoma.

CMs show a high rate of single nucleotide variations (SNVs) that are characteristic of UV damage and displays a high rate of genetic similarities with adult melanoma. On the contrarily, there is evidence that melanoma arising in CNMs shows a lower frequency of UV-related mutations, possibly due to a higher baseline risk. Spitzoid melanoma refers to malignant nature of spitz tumours, as defined by

large epithelioid melanocytes resembling those found in Spitz nevi. They may be challenging to classify since the histopathologic features that are commonly taken as indicators of malignancy, such as nuclear atypia, scatter of melanocytes in the upper epidermis, poor maturation within the dermis, deep extension, and deep dermal mitoses, are not uncommonly seen in Spitz tumours with benign biologic behavior [4]. The 2018 WHO classification of skin tumours introduced the concept of Spitz melanoma (malignant Spitz tumour) as a melanoma subtype that not only has the morphologic features of Spitz tumours, but also has their genetic hallmarks. The 8th Edition AJCC Cancer Staging Manual also applies to paediatric melanoma.

The comparison between adult and paediatric melanoma is challenging given the poorly investigated biology and pathogenesis of disease in the paediatric setting. Controversial findings have been reported in terms of prognostic values in the young age categories for histopathological hallmarks such as ulceration and thickness (see below section), differences in primary site of lesions between adults and adolescents have been described, as well as stage at diagnosis and tumour subtypes. Overall, a distinct biological behaviour of melanoma in adults and young has been described that need to be accounted for. Nevertheless, it should be considered that clinical features associated to the youngest age including the different reactivity of the immune system and consequent cancer surveillance are considered to favourably impact on clinical prognosis and survival.

Clinical presentation, diagnosis <and stage/prognosis

About 90% of melanomas are diagnosed as primary tumours without metastasis, with a 10-year-survival rate of 75-95%. Site of lesions in adults more often involves the head and neck.

Stratification of patients into classes of risks as based on the eighth edition AJCC Cancer Staging guides melanoma clinical management. Stage IIB and IIC, which the current application refers to for the adult indication, identifies high-risk primary tumours (N0, M0) with lesions >2-4 mm of thickness and ulcerated (T3b), or > 4 mm thickness either with or without ulceration (T4a and T4b). Stage IIC is considered more aggressive than IIB and displays a prognosis similar to Stage IIIB. Their prognosis is illustrated in the figures below:

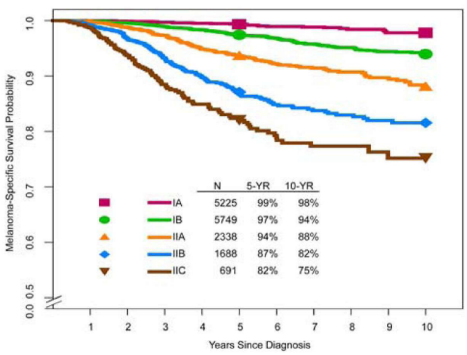

FIGURE 6.
Kaplan-Meier Melanoma-Specific Survival Curves According to T Category Stage Group for Patients With Stage I and II Melanoma From the Eighth Edition International Melanoma Database. Patients with N0 melanoma were filtered, so that patients with T2+ melanoma were included only if they had negative sentinel lymph nodes, whereas those with T1N0 melanoma were included regardless of whether they underwent sentinel lymph node biopsy.

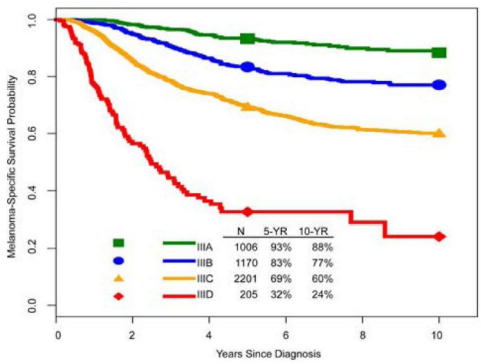

FIGURE 7.
Kaplan-Meier Melanoma-Specific Survival Curves According to Stage III Subgroups From the Eighth Edition International Melanoma Database.

Similar to adults, primary lesions are the most frequent clinical presentation of melanoma in adolescent patients aged 12 years and older; however, sites of lesions are different since they more often involve the trunk, especially in males, and extremity in females.

The prognostic role of age, gender, tumour thickness, ulceration, and sentinel lymph node status is less

characterised than in adult disease. Specifically, the association between thickness and survival is controversial. Tumour thickness and ulceration are strong predictors of sentinel lymph node metastases among children. Similar to adults, a positive sentinel lymph node is associated with poorer prognosis. A diagnosis of spitzoid melanoma confers a better prognosis than conventional melanoma due to a lower frequency of recurrence and metastatization with lethal outcomes than adult-like lesions.

In addition to the melanoma-specific differences in terms of cancer behaviour, it should be considered that the immune system reactivity diminishes with age, thus accounting for an immune system surveillance that is reduced in older populations compared to youngest individuals. The immunological response represents a biological factor that is believed to contribute to a better prognosis of melanoma in paediatric ages. This is an important aspect to consider in the context of a treatment that aims at boosting immune-mediated responses against tumour progression.

Management

Systemic therapies licensed for the treatment of cutaneous melanoma are summarised in the following table:

Currently Approved Therapies for Adjuvant Treatment of Melanoma

Drug	FDA-approved Indication	EU-approved Indications
Pembrolizumab	Adjuvant treatment of patients with melanoma with involvement of lymph node(s), after complete resection	As monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
Nivolumab	Adjuvant treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection[a]	As monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. [e]
Ipilimumab	Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy[b]	Not approved for adjuvant treatment of melanoma [f]
Dabrafenib/trametinib	Adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), after complete resection[c]	Adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection [g, h]
Interferon-alfa-2b	Adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease, but at high-risk for systemic recurrence, within 56 days of surgery[d]	As adjuvant therapy in patients who are free of disease after surgery, but are at high-risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement [i]

With particular reference to the treatment of primary melanoma Stage IIB and IIC, surgical resection with a sentinel lymph node biopsy (SNB) represents the first-line approach. In the event of a negative SNB, follow-up with active surveillance for recurrence is the solely recommended action to be undertaken accordingly with the most recent guidelines. It is estimated that 90% of relapse occurs during the first 5 years post-surgery, which is therefore considered the most critical period for monitoring. Adjuvant systemic therapy is contemplated at relapse.

Treatment in adolescents relies upon surgical strategies. Adjuvant systemic therapies are currently not licensed in Europe. For the treatment of the advanced (unresectable or metastatic) stage, the only approved drug concerns ipilimumab as monotherapy. It is however noted that this treatment in the respective adult disease has been replaced by the available PD-1 inhibitors owning a better efficacy and safety profile.

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2.1.2. About the product

Keytruda (pembrolizumab) is a humanized mAb IgG4/kappa isotype with a PD-1 blocking activity. The resulting prevention of interaction between PD-1 and its ligands PD-L1/2, leads to a stimulation of the immune-mediated anti-tumour activity mediated by T cell lymphocytes. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not non-specifically activate T cells.

Pembrolizumab is currently approved in EU as monotherapy and in combination with chemotherapy for the treatment of different cancer types (i.e. melanoma, NSCLC, RCC, HNSCC, urothelial cancer, cHL and MSI-H mCRC). With particular reference to the management of melanoma, the granted license reads as follows:

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

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 SmPC section 5.1).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice (SA) was received pertaining to the clinical development of Keytruda as adjuvant treatment in Stage II melanoma, including the paediatric indication.

The CHMP recommended an application based on IA2 of Study Keynote-716 to allow for sufficient data maturity. RFS was noted to be an acceptable endpoint in the adjuvant setting. However, in order to

support sound conclusions on efficacy and to address the strategic aspect of early therapy (adjuvant) versus late treatment (at recurrence), inclusion of PRFS2 data was also advised.

Regarding the paediatric indication, the CHMP emphasised the concern on long-term safety sequaelae related to pembrolizumab toxicity profile, and the limited data on efficacy available in adolescents with advanced melanoma at the time of SA application. In the current submission, the numerosity of the paediatric sample size remains limited to 2 patients in the pivotal KEYNOTE-716 (one patient in each treatment arm) and 8 subjects enrolled in study KEYNOTE-051, which is described in the agreed PIP for which a positive compliant report has been issued (PIP decision number: P/0043/2018).

2.1.4. General comments on compliance with GCP

The MAH stated that all studies were conducted according to current standard research approaches and following appropriate GCP standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed

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

Keytruda is a protein and is therefore exempt from the ERA requirements. This is compliant to the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Clinical Development Program for Pembrolizumab for Adjuvant and Combination Studies in Melanoma: Ongoing Studies

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-555 Ongoing, enrollment complete	Phase 1, open-label, randomized, crossover, bioavailability and safety study	Participants with advanced melanoma	Cohort A (6 treatment groups): *Cycles 1-3* 200 mg IV Q3W, 130 mg/mL SC Q3W, and 165 mg/mL SC Q3W for pembrolizumab, given in different sequences over 3 cycles (6 possible treatment sequences) *Cycles 4-35* 200 mg IV Q3W for pembrolizumab Cohort B: *Cycles 1-18* 400 mg IV Q6W for pembrolizumab	ORR (Cohort B only)
MK-1308-001 Ongoing	Phase 1/2, open-label, nonrandomized, combination dose-escalation + dose confirmation + efficacy expansion study	Participants with Dose-escalation, Cohorts 1, 2, and 3: advanced/metastatic solid tumour (except NSCLC for Cohorts 2 and 3) Dose confirmation, Arms A, B, C, and E: 1L, advanced/metastatic NSCLC Dose confirmation, Arm D: 2L+ advanced/metastatic SCLC Efficacy expansion, Arms F and G: PD-1-refractory, Stage III/IV melanoma	Cohorts 1, 2, 3: Cycle 1: single dose of 25, 75, or 200 mg for MK-1308 C2-C5: 25, 75, or 200 mg Q3W for MK-1308 + 200 mg Q3W for pembrolizumab C6 and thereafter: 200 mg Q3W for pembrolizumab Arms A, B, C, D, E: 25, 75, or 200 mg Q3W or Q6W for MK-1308 200 mg Q3W for pembrolizumab Cohorts F, G: Cohort F: 25 mg Q6W for MK-1308 + 400 mg Q6W for pembrolizumab Cohort G: 25 mg Q6W for MK-1308	ORR (efficacy expansion only)
MK-7902-004 / E7080-G000-225 (LEAP-004) Ongoing, enrollment complete	Phase 2, open-label, single-arm study	Participants with unresectable Stage III or Stage IV melanoma previously exposed to an anti-PD-1/L1 agent	200 mg/kg Q3W for pembrolizumab 20 mg qd for lenvatinib	ORR
KEYNOTE-053 (SWOG 1404) Ongoing, enrollment complete	Phase 3, multicenter, randomized study	Participants with complete resection of Stage IIIA (N2A), IIIB, IIIC, or IV melanoma	Pembrolizumab 200 mg IV Q3W for up to 1 year or physician/participant choice of either high-dose IFN-alfa-2b or IPI 10 mg/kg	OS RFS OS in PD-L1-positive subgroup

Study Number/ Status	Design	Population		Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-054/EORTC protocol 1325-MG Ongoing, enrollment complete	Phase 3, double-blinded, placebo-controlled, randomized study, with crossover or rechallenge	Participants with completely resected, Stage III (IIIA, IIIB, or IIIC) metastatic cutaneous melanoma		Part 1, adjuvant therapy: 200 mg Q3W for pembrolizumab Matching placebo (saline solution) Q3W Part 2, crossover to or rechallenge with pembrolizumab: 200 mg Q3W for pembrolizumab	RFS RFS in PD-L1-positive subgroup
MK-7902-003/E7080-G000-312 (LEAP-003) Ongoing enrollment complete	Phase 3, randomized, placebo-controlled, parallel-group, double-blinded, efficacy and safety study, with extension portion of study in China	Participants with unresectable Stage III or Stage IV melanoma, no prior systemic therapy, not amenable to local therapy		200 mg Q3W for pembrolizumab 20 mg qd for lenvatinib or matching placebo	PFS, OS
KEYNOTE-716 Ongoing enrollment complete	Phase 3, double-blinded (Part 1) and unblinded (Part 2), placebo-controlled, randomized, parallel-group study, with crossover or re-challenge.	Participants with surgically resected, high-risk, Stage II melanoma One stratum for paediatric participants (aged 12-17 years) and 3 strata for adult participants (aged 18 years and older) defined by T-stage (T3b, T4a, and T4b)		Part 1, adjuvant treatment: 200 mg Q3W (adult) or 2 mg/kg Q3W up to a maximum of 200 mg Q3W (paediatric) for pembrolizumab placebo (saline solution) Q3W Part 2, crossover to or re-challenge with pembrolizumab 200 mg Q3W (adult) or 2 mg/kg Q3W up to a maximum of 200 mg Q3W (paediatric) for pembrolizumab	RFS
KEYMAKER-U02 Ongoing	Phase1/2, open-label, rolling-arm, umbrella platform design of investigational agents with or without pembrolizumab or pembrolizumab alone in participants with melanoma:	Substudies 02 A	PD-1 refractory melanoma	Arm 1: MK-7684 200 mg Q3W+ pembrolizumab 200 mg Q3W Arm 1 and Arm 2: Arm 1: MK-1308 25 mg Q6W + pembrolizumab 400 mg Q6W Arm 2: lenvatinib 20 mg qd + 400 mg Q6W Arm 2: lenvatinib 20 mg qd + pembrolizumab 400 mg Q6W	Adverse Events, Study-intervention discontinuations due to AEs. Objective response: CR or PR
		Substudies 02B	1L advanced melanoma	Arm 1: MK-7684 200 mg Q3W + pembrolizumab 200 mg Q3W Arm 3 and Arm 4: MK-1308A, which is the coformulation of pembrolizumab + MK-1308 Q6W: MK-1308 25 mg + pembrolizumab 400 mg Arm 4: lenvatinib 20 mg qd	Adverse Events, Study-intervention discontinuations due to AEs. Objective response: CR or PR

Study Number/ Status	Design	Population		Dosage, Regimen	Primary Endpoint(s)
		Substudy 02C	Participants with Stage III melanoma who are candidates for neoadjuvant therapy	Arm 1: MK-7684 200 mg Q3W + pembrolizumab 200 mg Q3W Arm 2: V937, 3 × 10^8 TCID50 + pembrolizumab 200 mg Q3W	Adverse Events, Study-intervention discontinuations due to AEs. pCR
		Substudy 02D	Cohort 1: PD-1 naïve Cohort 2: PD-1 exposed	Arm 1: Cohort 1, Cohort 2: MK-1308A, which is the coformulation of pembrolizumab + MK-1308 Q6W: MK-1308 25 mg + pembrolizumab 400 mg Arm 1 and Arm 2: Cohort 1, Cohort 2 lenvatinib 20 mg qd	Adverse Events, Study-intervention discontinuations due to AEs. Objective response: CR or PR
1L=first-line therapy; 2L+=second-line therapy or later; AEs=adverse events; AJCC=American Joint Committee on Cancer; AUC=area under the concentration-time curve; BRAF=proto oncogene BRAF; CR=complete response; DCR=disease control rate; DOR=duration of response; DLT=dose-limiting toxicity; RFS=distant metastasis-free survival; ECOG=Eastern Oncology Cooperative Group; EORTC=European Organisation for Research and Treatment of Cancer; IFN=interferon; IHC=immunohistochemistry; IPI=ipilimumab; irPFS=immune-related progression-free survival; irRECIST=immune-related Response Evaluation Criteria in Solid Tumours; IV=intravenous; LDH=lactate dehydrogenase; MEL=melanoma; MTD=maximum tolerated dose; NSCLC=non–small cell lung cancer; ORR=objective response rate; OS=overall survival; pCR=pathological complete response; PD-1=programmed cell death 1; PD L1=programmed cell death ligand 1; PEG-IFN=pegylated interferon; PFS=progression-free survival; PO=per os (orally); PR=partial response; PS=performance status; qd=once daily; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; Q12W=every 12 weeks; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumours; RFS=recurrence-free survival; RP2D=recommended Phase 2 dose; RR=response rate; SC=subcutaneous; SD=stable disease; TCID50=median tissue culture infectious dose; TTR=time to response.					

2.3.2. Pharmacokinetics

KEYNOTE-716 is an ongoing, randomized, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of pembrolizumab for the adjuvant treatment of adult and paediatric (12 years and older) patients with completely resected Stage IIB and IIC melanoma, and a negative SLN biopsy.

A total of 976 participants, 12 years and older (including 2 paediatric participants, one in the placebo arm), were randomized to pembrolizumab or placebo q3w in a 1:1 ratio.

This application is supported by the results of KEYNOTE-054 to provide context for understanding the efficacy and safety of adjuvant pembrolizumab therapy and by extrapolation from adult to paediatric (>12 years of age) melanoma based on similar biology and treatment paradigm to adult melanoma as well as PK and safety data from KEYNOTE-051 for paediatric participants with advanced melanoma.

KEYNOTE-051 is a nonrandomized, open-label, single-arm, combined Phase 1 and Phase 2 (Part I and Part II) study to evaluate the PK, PD, toxicity, safety, and antitumour activity of pembrolizumab in paediatric participants aged 6 months to less than 18 years with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumour or lymphoma.

Part I (dose finding and dose confirmation) has been completed. Part I also evaluated the safety, PK, PD, toxicity, and preliminary efficacy of pembrolizumab. Part II (tumour cohort expansion at the RP2D) is ongoing and further evaluates the safety and efficacy at the established RP2D. The study has been conducted at 51 centres in 12 countries for approximately 6 years.

In KEYNOTE-716 participants with resected, Stage IIB and IIC melanoma received adjuvant pembrolizumab 200 mg q3w (adult dose) or 2 mg/kg up to a maximum of 200 mg q3w (paediatric dose).

Pembrolizumab PK in adults has been characterised within the previous applications, therefore in the present variation only the extrapolation to paediatric patients (>12 years old) has been discussed.

Paediatric populations

As novel therapies for adults with melanoma have led to dramatically improved outcomes, treatment options for paediatric patients with high-risk and advanced melanoma are still limited. Due to the rarity of melanoma in younger age groups, recruitment into clinical trials is often hampered and relevant data are scarce. KEYNOTE-716 was open to recruitment of patients aged 12 years and older and 2 adolescent participants were enrolled.

This application is supported by the extrapolation from adult to adolescent melanoma based on the following:

(a) similarity of melanoma disease biology between adults and paediatric patients aged 12 to 17 years, and (b) similar pharmacology of drug effect and similar exposure-response for efficacy and safety.

The paediatric dose of pembrolizumab is well-established and is approved in the EU for treatment of paediatric patients aged 3 years and older with relapsed or refractory cHL.

Based on available PK data in KEYNOTE-051, the paediatric clinical study of pembrolizumab, and extrapolation of adult PK data, it was determined that 2 mg/kg (up to a maximum of 200 mg) q3w dosing provides appropriate exposure in paediatric patients. KEYNOTE-051 has resulted in the first approval for KEYTRUDA in the EU for paediatric patients with cHL. Apart from a cohort of 22 patients aged 11 years to 17 years with cHL, this approval was also based on extrapolation of pharmacology and PK data.

a) Similarity of Melanoma Disease Biology Between Adults and Paediatric Patients Aged 12 to 17 Years

The continuity of melanoma disease across patients ~12 to 17 years of age and >18 years of age confirms that it is essentially the same disease in adolescents and adults. This is underscored by shared predisposing factors such as exposure to UV sunlight, red hair, blue eyes, poor tanning ability, freckling, dysplastic nevi, and a family history. Many genetic abnormalities are shared between adult and paediatric melanoma, and germline variants in several genes (eg, MC1R, CDKN2A) have been associated with the development of familial melanoma in children and adults. Melanoma in adolescents has many genomic similarities to adult melanoma, including an enrichment of UV-induced mutations, a high prevalence of TERT-promoter mutations, and involvement of similar oncogenes (such as BRAF) and tumour suppressor genes. The clinical presentation of melanoma in adolescence is similar to that of adults; most tumours arise in previously healthy skin. The most common subtype of melanoma in both adolescents and adults is superficial spreading melanoma.

Treatment of melanoma in childhood and adults generally uses a similar strategy. Surgery is the mainstay of treatment for localized disease. For adult patients with clinically node negative disease and a primary tumour with Breslow depth ≥1 mm, examination of regional lymph nodes using SLN biopsy is the standard of care and has become routine as well in many paediatric centres. Surgical resection of cutaneous melanoma in paediatric patients includes full-thickness biopsy for diagnosis, WLE with margins based on lesion depth, and selective use of SLN biopsy and CLND. The use of CLND in paediatric patients should weigh the risk of morbidity against the risk of recurrence over their longer life span compared with adults, as well as taking into account evolving standards of care for SLN biopsy and CLND.

KEYNOTE-716 is the first Phase 3 study to report results for the adjuvant treatment of Stage IIB and IIC melanoma in participants aged 12 years and older. Given the rarity of the disease, only 2 adolescent participants were enrolled in approximately 2 years, although many sites were open to enrollment in this age group.

b) Similar Pharmacology of Drug Effect and Similar Exposure-Response for Efficacy and Safety

As part of procedure EMEA/H/C/3820/II/090 for pembrolizumab for cHL, which obtained approval for an extension of the indication in adults to an earlier line of therapy and resulted in an approval for paediatric patients aged 3 years and older on 09-MAR-2021, it was shown that a similar exposure-response relation for pembrolizumab exists across indications. It is expected that these data obtained in cHL are also relevant for melanoma.

Data presented in the cHL submission showed that the exposure-response relationship and PK profile are similar in adult and paediatric patients (6 years of age and older). No information can be provided on the exposure-response relationship between adult and paediatric patients in melanoma. However, since consistent flat exposure-response relationships are seen for pembrolizumab in multiple tumour types and since clearance is not meaningfully different across tumour types, this suggests that saturation of the target in circulation is achieved at the clinical dose across all tumour types. This further supports that PK/exposures and exposure-response relationships are consistent across indications.

During KEYNOTE-716 only 2 female adolescents of 16 and 17 years of age were enrolled, of these just one adolescent received pembrolizumab 2 mg/kg IV q3w. Considering that, no conclusion can be drawn on PK and immunogenicity in adolescents with data from KEYNOTE-716.

An extrapolation from adult to adolescent melanoma was made based on the following:
(1) similarity of melanoma disease biology between adults and paediatric patients aged 12 to17 years, and

(2) similar pharmacology of drug effect and similar exposure-response for efficacy and safety. The paediatric dose of pembrolizumab is well-established and is approved in the EU for treatment of paediatric patients aged 3 years and older with relapsed or refractory cHL.

The similarity of the disease between adolescent and adults is evaluated and commented in the efficacy section, please refer to the relative one.

Regarding the pharmacology similarity, the MAH states that the PK profile and exposure-response relationship in paediatric patients with advanced cancers are similar to those in adults, supporting these conclusions with the data from KEYNOTE-051 (EMEA/H/C/3820/II/090). During that procedure, figures at Cycle 1 and steady state are generated for KEYNOTE-051 paediatric participants and KEYNOTE-204 adult cHL participants, based on the updated popPK model including adult cHL participants and paediatric participants with solid tumours and cHL.

The PK model parameter estimates (CL and Vc) are lower for paediatric patients compared to adults. This was expected, since the parameters have been shown to be correlated to body weight. Exposure parameters following the weight-based regimen of 2 mg/kg Q3W are largely similar between the paediatric age groups and between paediatrics and adults.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

A description of the immunogenicity of pembrolizumab in the adjuvant melanoma setting was included in the KEYNOTE-054 application to support approval of pembrolizumab monotherapy in the adjuvant setting for Stage III melanoma participants [variation II/47]. The immunogenicity evaluation confirmed that pembrolizumab has a limited potential to elicit the information of ADA in the adjuvant

monotherapy setting, which is consistent with the results of prior immunogenicity evaluations of pembrolizumab in the non-adjuvant monotherapy setting

No updated analysis was performed on immunogenicity in paediatrics within the variation II/90 (KEYNOTE-051); details of the immunogenicity analysis are available in the prior version of the CSR of study KN051 in which out of the 133 paediatric subjects included in the immunogenicity assessment, 125 subjects were evaluable. The evaluable subject group contains 2 subjects with non-treatment emergent positive status (1.6%), and 123 with negative immunogenicity status (98.4%). There were no subjects with a treatment emergent positive status observed.

2.3.4. PK/PD modelling

No new PK/PD modelling was included in this application.

2.3.5. Discussion on clinical pharmacology

An extrapolation from adult to adolescent melanoma (>12 years of age) was made by the MAH assuming the similarity of melanoma disease biology between adults and paediatric patients aged 12 to 17 years, and similar pharmacology of drug effect and similar exposure-response for efficacy and safety.

The proposed paediatric dose of pembrolizumab is the one already approved in the EU for treatment of paediatric patients aged 3 years and older with relapsed or refractory cHL (2 mg/kg Q3W).

Regarding the pharmacology similarity, the MAH states that the PK profile and exposure-response relationship in paediatric patients with advanced cancers are similar to those in adults, supporting these conclusions with the data from KEYNOTE-051 (EMEA/H/C/3820/II/090). Exposure parameters following the weight-based regimen of 2 mg/kg Q3W are largely similar between the paediatric age groups and between paediatrics and adults.

As of the data cutoff date for the II/90 variation submitted report (10-JAN-2020), 162 participants (N=22 rrcHL patients) were enrolled out of a total of up to 310 participants that were planned to be enrolled, in total, there were 151 participants in KEYNOTE-051 with evaluable PK samples. Since the last DCO (10-JAN-2020), only 5 new subjects, most with r/r cHL, and no new subject with melanoma, were enrolled; therefore additional analyses were not considered meaningful and not expected to alter any conclusions on dosing recommendations.

No additional analysis has been conducted, neither for PK or exposure-response relationship.

A discussion on exposure/response in melanoma in order to better substantiate and complete the bridging strategy was requested, however the MAH stated that due to limited number of paediatric melanoma patients, no information have been provided on the exposure-response relationship between adult and paediatric patients in melanoma.

Therefore the conclusion on similar pharmacology between adults and adolescents in melanoma relies only on data data from KEYNOTE-051 (EMEA/H/C/3820/II/090). In which, observed plasma concentrations were consistent with predicted plasma concentrations derived from the reference popPK model, further supporting a flat exposure-response relationships across multiple tumour types, suggesting that saturation of the target in circulation is achieved at the clinical dose across all tumour types.

IL-2 biomarker data in paediatric participants are limited, observed IL-2 simulation ratio data were collected and analysed for KEYNOTE-051. During EMEA/H/C/3820/II/090 variation assessment the IL-2

stimulation ratio curves in paediatric participants were found to be consistent with those in adults; even if only 8 melanoma patients were enrolled in the study and it is not possible to establish if the HL paediatric data are well captured by the model.

As reported by the MAH, the EU Reflection Paper on extrapolation for paediatrics foresees similar exposure-response for efficacy and safety in the extrapolation approach, however, no specific conclusion can be drawn on similar exposure-response for efficacy and safety in adolescent melanoma.

An indirect conclusion on E-R is drawn: data in cHL presented in the submission for KEYNOTE-051 showed that the E-R relationship and PK profile are similar in adult and paediatric patients. Since in adults consistent flat exposure-response relationships are seen for pembrolizumab in multiple tumour types and PK is not meaningfully different among tumour types, the exposure of pembrolizumab is also expected to be similar across all indications in paediatrics (similar to adults).

Overall, the conclusions on similar pharmacology of drug effect are based only on data from KEYNOTE-051 (EMEA/H/C/3820/II/090) and no specific conclusion can be drawn on similar exposure-response in adolescent melanoma. PK data supporting the bridging can be considered only as supportive.

No updated analysis was performed on immunogenicity in paediatrics within the variation II/90 (KEYNOTE-051); considering the small number of new subjects enrolled, it is not considered as meaningful additional analysis.

As reported in the EPAR of variation II/47 (Extension of Indication to include as monotherapy the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection, based on study KEYNOTE-054) the incidence for treatment-emergent ADA in evaluable subjects with melanoma treated in the adjuvant setting 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 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%).

As immunogenicity has not been characterized in the adjuvant setting, the MAH was recommended in 2017 to assess the immunogenicity of pembrolizumab in the adjuvant setting in studies KN054 and KN091 (comprising more than 1000 subjects). Immunogenicity data for KEYNOTE 054 were submitted in 2018 with 495 evaluable subjects. The current projection for the availability of data from KEYNOTE-091 based on IA2 is late 1Q2022 with the target completion for the comprehensive immunogenicity assessment in 2Q2022.

2.3.6. Conclusions on clinical pharmacology

Overall, the conclusions on similar pharmacology of drug effect are based on data from KEYNOTE-051 (EMEA/H/C/3820/II/090). An indirect conclusion on E-R can be drawn based on the demonstrated similarity in E-R relationship and PK profile between adult and paediatric patients in cHL, and the assumption that the flat exposure-response relationship seen in adults across multiple tumour types is preserved in paediatric patients across indications. PK data supporting the bridging can be considered only as supportive.

2.4. Clinical efficacy

The current application relies upon a single pivotal trial, study KEYNOTE-716. KEYNOTE-716 is a randomized, placebo-controlled, parallel-group, crossover/rechallenge, multicentre, Phase 3 study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma. Participants must have had newly diagnosed, pathologically confirmed, and completely resected melanoma with negative margins, and could not have received prior systemic therapy for Stage II melanoma.

The MAH also refers to the already submitted and reviewed study KEYNOTE-054 as supportive data for the efficacy of pembrolizumab after complete resection of high-risk Stage III melanoma. A claim for extrapolation of data from adult to paediatric melanoma is made, based on similar biology and treatment. The PK and safety profile of pembrolizumab as derived in study KEYNOTE-051 for paediatric participants with advanced melanoma is also presented in support of the claimed indication.

2.4.1. Dose response study(ies)

Pembrolizumab is approved at the 2 mg/kg or 200 mg q3w dosing regimen for multiple indications across the globe. Currently, the 200 mg q3w dose is being evaluated in multiple clinical studies. An additional dosing regimen of 400 mg q6w has been approved in the EU on 28-MAR-2019 for all monotherapy indications approved at the time. This approval was supported by a modelling and simulation-based approach, bridging PK and E-R data between the 200 mg q3w and 400 mg q6w dosing regimens for approved indications in the monotherapy setting. Pediatric participants in KEYNOTE-716 with resected stage IIB and IIC melanoma received adjuvant pembrolizumab 2 mg/kg q3w up to a maximum of 200 mg q3w (paediatric dose). The 200 mg q3w dose is recommended as the appropriate adult dose based on prior indications. The 400 mg q6w regimen is considered a suitable dosing option for pembrolizumab based on the expected similarity of PK exposures, target saturation, and efficacy and safety profile with those for the approved dosing regimens of 200 mg q3w or 2 mg/kg q3w. For the paediatric indication, KEYNOTE-051, the paediatric clinical study of pembrolizumab, together with extrapolation of adult PK data, it was determined that 2 mg/kg (up to a maximum of 200 mg) q3w dosing provides appropriate exposure in paediatric patients.

2.4.2. Main study(ies)

Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)

Methods

KEYNOTE-716 is a randomized, placebo-controlled, parallel-group, crossover/rechallenge, multicentre, Phase 3 study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma. Stage IIB and IIC cutaneous melanoma are defined as T category T3b, T4a, or T4b, with no regional nodal metastases (N0) confirmed by a negative SLN biopsy and no evidence of distant metastasis (M0) per AJCC eighth edition guidelines. Stage IIB is T3b or, M0 T4a, N0; Stage IIC is T4a, N0, M0. Participants must have had newly diagnosed, pathologically

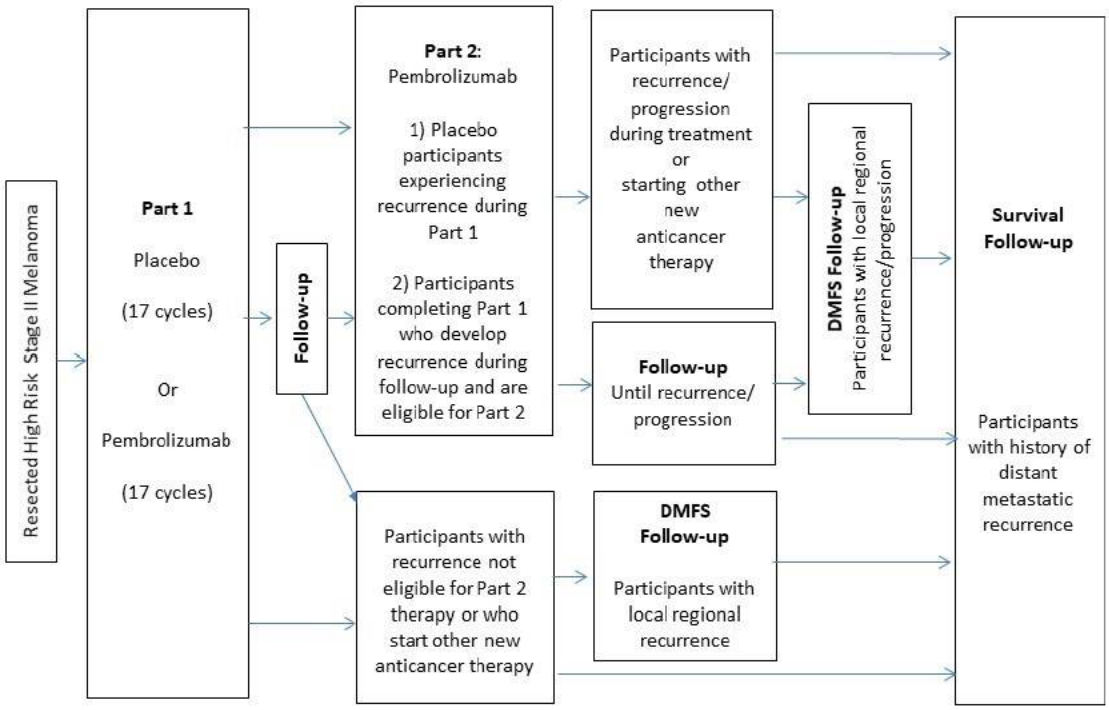
confirmed, and completely resected melanoma with negative margins, and could not have received prior systemic therapy for Stage II melanoma.

Participants in Part 1 were stratified into 3 strata for adults based on T-stage tumour thickness and ulceration and there was a separate stratum for paediatric participants (≥12 years of age and <18 years of age).

Participants under 18 years of age who were randomized to receive pembrolizumab at the beginning of Part 1 remained on the paediatric dose of pembrolizumab throughout Part 1.

Participants who begin Part 2 as an adult will receive the fixed adult dose of pembrolizumab (200 mg Q3W) regardless of their Part 1 dosing regimen.

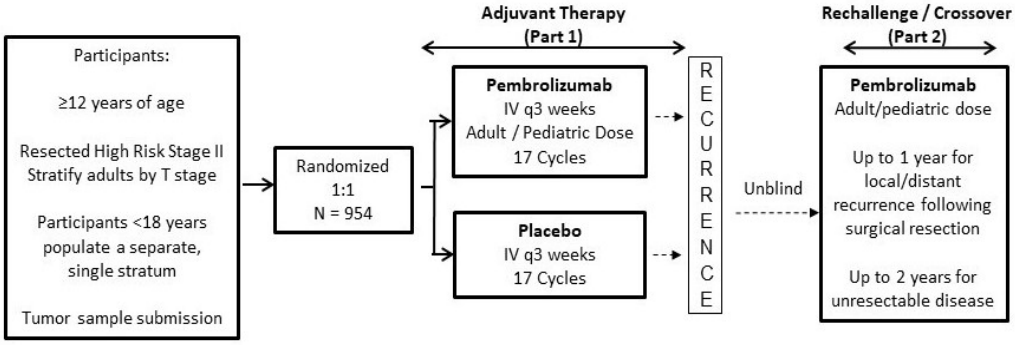
Study Design



All participants complete the Safety Follow-up visit prior to entering long-term follow up.
See protocol Section 4.1 for details.

Source [16.1.1]

In In the current application, only data from Part 1 are presented.



Study participants

Inclusion Criteria

Key inclusion criteria included the following:

1. Male or female participants who were ≥12 years of age with surgically resected and histologically/pathologically confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma (T-stage of T3b, T4a, or T4b with pathologically confirmed negative SLN biopsy, and no evidence of regional [N0] or distant metastatic [M0] disease) per AJCC eighth edition guidelines.

2. Not previously treated for melanoma beyond complete surgical resection.

3. No more than 12 weeks between final surgical resection and randomization, with complete surgical wound healing.

4. No evidence of metastatic disease on imaging as determined by investigator assessment; suspicious lesions amenable to biopsy confirmed negative for malignancy.

5. Performance status of 0 or 1 on the ECOG Performance Scale at the time of enrollment, LPS score ≥50 (for participants ≤16 years old.), or a KPS score ≥50 (for participants >16 years and <18 years of age).

Exclusion Criteria

Key exclusion criteria included the following:

1. Has a known additional malignancy that is progressing or has required active antineoplastic therapy (including hormonal) within the past 5 years.

2. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment.

3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137).

4. Has received prior systemic anticancer therapy for melanoma including investigational agents.

Treatments

The treatment phase of the study consists of 2 parts:

• Part 1 (Adjuvant Treatment): Pembrolizumab or placebo administered every 3 weeks (Q3W) for 17 cycles.

• Part 2 (Crossover/Rechallenge after First Recurrence): Pembrolizumab administered Q3W for 17 cycles after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis) or up to 35 cycles of pembrolizumab Q3W for unresectable disease recurrence (unresectable local [regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases] or unresectable distant recurrence).

This report includes efficacy and safety results from Part 1 only.

Study Treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	Solution for infusion	25 mg/mL vial	2 mg/kg (maximum 200 mg) Q3W for pediatric participants (≥12 and <18 years old); 200 mg Q3W for adults (≥18 years of age)	Intravenous (IV) infusion via infusion pump	Part 1: 17 cycles Part 2: 17 or 35 cycles	Experimental
Saline placebo	Solution for infusion	None	None	IV infusion via infusion pump	Part 1: 17 cycles	Placebo

Objectives

Outcomes/endpoints

Primary Objective	Primary Endpoint
Objective: To compare recurrence-free survival (RFS) between treatment groups Hypothesis (H1): Pembrolizumab is superior to placebo with respect to RFS as assessed by the site investigator.	RFS: time from randomization to (1) any recurrence (local or regional [including invasive ipsilateral tumor and invasive locoregional tumor], or distant) as assessed by the investigator, or (2) death due to any cause (both cancer and noncancer causes of death)
Secondary Objectives	**Secondary Endpoints**
Objective: To compare distant metastasis-free survival (DMFS) between treatment groups Hypothesis (H2): Pembrolizumab is superior to placebo with respect to DMFS as assessed by the site investigator.	DMFS: The time from randomization to appearance of a distant metastasis as assessed by the investigator. A distant metastasis refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes
Objective: To compare overall survival (OS) between treatment groups Hypothesis (H3): Pembrolizumab is superior to placebo with respect to OS.	OS: The time from randomization to death due to any cause
Objective: To assess the safety and tolerability of pembrolizumab compared to placebo in the proportion of AEs	▪ AEs ▪ Discontinuation of study treatment due to AEs

Of note, new cases of melanoma were not counted as events for recurrence-free-survival. Disease recurrence was confirmed by investigator radiographically and/or by exam/biopsy and, when clinically appropriate, pathologically confirmed by the site.

Exploratory Endpoints

Time to Subsequent Therapy (TTST)

Time to subsequent therapy is defined as time from randomization to the date of first subsequent therapy (eg, surgery, radiation therapy, antineoplastic therapy) or death (whatever the cause) whichever occurs first.

Progression/recurrence-free Survival 2 (PRFS2)

Progression/recurrence-free Survival 2 is defined as the time between the date of randomization and the earliest of the following:

- date of 1st disease progression per RECIST1.1 beyond the initial unresectable disease recurrence (unresectable local-regional disease recurrence or unresectable distant metastatic disease recurrence);

- date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (resectable local regional recurrences or resectable distant metastatic disease recurrence);

- date of death.

Sample size

In this study, approximately 954 participants were to be randomized in a 1:1 ratio into the pembrolizumab and placebo adjuvant treatment arms. RFS is the primary endpoint for the study, with DMFS and OS as the key secondary endpoints.

For RFS endpoint, the final analysis is event-driven and will be conducted after approximately 179 events have been observed, unless the study is terminated early. It may occur at ~ 48 months after the first participant is randomized (depending on enrolment rate and event accumulation rate). Based on a target number of 179 events at the final analysis and 1 interim analysis at approximately 71% of the target number of events, the study has ~92% power for detecting a hazard ratio of 0.6 at 2.5% (1-sided) significance level.

The above sample size and power calculations are based on the following assumptions: RFS follows a "cure" model with a long-term RFS of 50%; the 60-month RFS estimated to be 68% for the control group; an annual drop-out rate of 4.7%; enrollment period of 16 months; a follow-up period of 32 months after the last participant is randomized.

Randomisation

Treatment allocation/randomization was centrally determined using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants were assigned randomly in a 1:1 ratio to pembrolizumab study treatment or saline placebo study treatment in Part 1.

Treatment allocation/randomization was stratified according to the following factors:

1. Melanoma T Stage (Table 3) for adults only

2. A separate stratum for paediatric (age 12-17) participants

Table 3 Melanoma Stage Stratification Table

Melanoma Stage	T Stage	T Stage Definition (thickness and ulceration status)
IIB	T3b	>2.0-4.0 mm with ulceration
IIB	T4a	>4.0 mm without ulceration
IIC	T4b	>4.0 mm with ulceration

T stage of disease as defined by thickness and ulceration status per AJCC guidelines 8th edition

Blinding (masking)

In Part 1 of this study a double-blinding technique was used.

Statistical methods

The intention-to-treat (ITT) population was used for the analysis of efficacy data.

The nonparametric Kaplan-Meier method was used to estimate the RFS curve in each treatment group. The treatment comparison in RFS was evaluated using a stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (ie, HR and its 95% CI) between the treatment arms. Kaplan-Meier estimates and the corresponding 95% CIs at specific follow-up time-points were provided for RFS. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.

In the event that there are small strata, for the purpose of analysis, strata were combined to ensure sufficient number of participants, responses and events in each stratum.

Due to the small number of paediatric participants enrolled (2 participants), stratum 1 (paediatric participants) was combined with other strata according to the T-stage level.

Since disease assessment was performed periodically, events such as disease recurrence and metastatic disease recurrence can occur any time in the time interval between the last assessment where the event was not documented and the assessment when the event is documented. For the primary analysis, the true date of the event was approximated by the date of the first assessment at which event is objectively documented. Participants who do not experience a first recurrence event were censored at the last disease assessment date.

In order to evaluate the robustness of the RFS endpoint, a sensitivity analysis with a different set of censoring rules was performed. For the sensitivity analysis, the true date of the event was approximated by the date of the first assessment at which event is objectively documented, after ≤1 missed disease assessment and before new anti-cancer therapy is initiated, if any. Participants who experience a first recurrence immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy is initiated were censored at the last disease assessment prior to the earlier date of the ≥2 consecutive missed disease assessment or date the new anti-cancer therapy is initiated. Participants who do not experience a first recurrence event were censored at the last disease

assessment before new anti-cancer therapy is initiated, if any. The censoring rules for primary and sensitivity analyses of RFS are summarized in Table 8.

Table 8 Censoring Rules for Primary and Sensitivity Analyses of RFS

Situation	Primary Analysis	Sensitivity Analysis
Recurrence or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Event at earliest date of documented recurrence or death	Event at earliest date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Event at earliest date of documented recurrence or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any
No recurrence and no death; and new anticancer treatment is not initiated	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

The proportional hazards assumption on RFS were examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for RFS may be plotted for the comparison between the pembrolizumab and placebo arms. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies using, for example, the Restricted Mean Survival Time method [Uno, H., et al 2014] or a parametric method [Odell, P. M., et al 1994].

One assumption for the stratified Cox proportional hazard model is that the treatment HR is constant across the strata. If strong departures from this assumption are observed (which can result in a notably biased and/or less powerful analysis), a sensitivity analysis may be performed based on a two-step weighted Cox model approach, in which the treatment effect is first estimated for each stratum, and then the stratum specific estimates are combined for overall inference using sample size weights [Mehrotra, D. V., et al 2012].

New primary melanomas were not counted as RFS events for the primary RFS analysis. A sensitivity analysis to include new primary melanomas as RFS events were performed to assess the robustness of the RFS endpoint.

Multiplicity

The multiplicity strategy specified in this section will be applied to the primary hypothesis and 2 secondary hypotheses. The primary hypothesis tests the superiority of pembrolizumab to placebo with respect to RFS. The 2 secondary hypotheses test the superiority of pembrolizumab to placebo with respect to DMFS and OS. The overall Type-I error among the 3 hypotheses is strongly controlled at 2.5% (one-sided), with 2.5% initially allocated to the RFS hypothesis. The study was considered a success if RFS is demonstrated to be statistically significant at either an interim analysis or the final analysis under multiplicity control.

The study uses the graphical method of Maurer and Bretz [Maurer, W. 2013] to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 4 shows that the initial one-sided α allocation is assigned to the RFS hypothesis. Should the RFS comparison be statistically significant, the 2.5% alpha will be reallocated to the DMFS comparison. Should the DMFS comparison be statistically significant, the 2.5% alpha will be reallocated to the OS comparison.

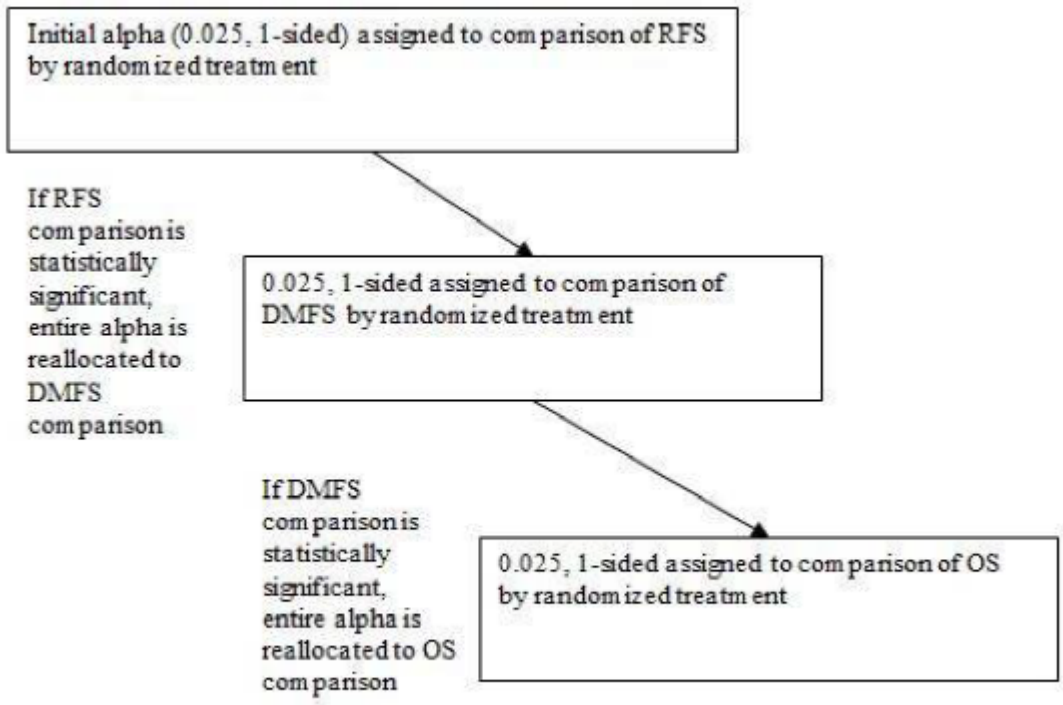


Figure 4 Multiplicity Graph for Type I Error Control of Study Hypotheses

The trial initially allocates α = 2.5%, one-sided to test RFS. Table 12 shows the boundary properties for the interim analyses, which were derived using a Lan-DeMets O'Brien- Fleming approximation spending function. Note that the final row indicates the total power to reject the null hypothesis for

RFS.

Table 12 Boundary Properties for Planned Analyses of the RFS Analyses Based on α = 0.025

Analysis	Value	Efficacy
IA 1: 71%[1]	Z[2]	2.4115
N: 954	p (1-sided)[2]	0.0079
Events: 128	HR[3] at bound	0.6522
Month: 33	P(Cross)[4] if HR=1	0.0079
	P(Cross)[4] if HR=0.6	0.6717
Final (IA2)	Z	2.0029
N: 954	p (1-sided)	0.0226
Events: 179	HR at bound	0.7410
Month: 48	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.6	0.9190

[1] Percentage of total number of events expected at final analysis
[2] Boundary values for statistical significance
[3] HR= hazard ratio
[4] Probability of crossing boundary for statistical significance

Subgroup Analyses

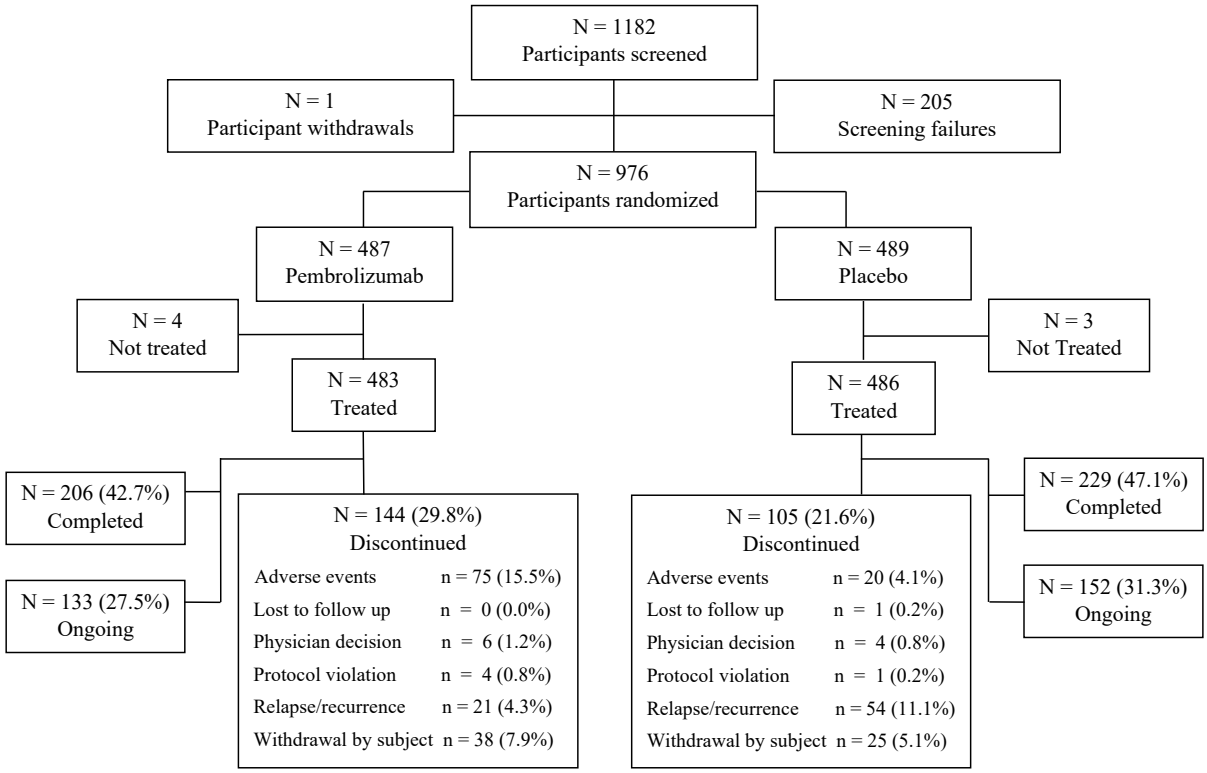
To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints were estimated and plotted within each category of the following classification variables:

- T-Stage (T3b versus T4a versus T4b)
- Age (<65 years versus ⩾65 years)
- Sex (male versus female)
- Race (white versus nonwhite)
- ECOG performance status (0 versus 1) or equivalent KPS or LPS status
- Region (US vs. Ex-US)

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis was not to be performed for this category of the subgroup variable, and this subgroup variable may not be displayed in the forest plot. The subgroup analyses were conducted using an unstratified Cox model.

Results

Participant flow



Recruitment

This study was conducted at 152 centers in 16 countries. The planned enrollment total was 954 participants. As of the data cutoff (DCO) date for this report, 976 participants were randomized (487 in the pembrolizumab group and 489 in the placebo group).

Data cut-off date for this interim analysis was 04 December 2020. The median follow-up duration for all subjects was 14.3 months.

Summary of Follow-up Duration
(ITT Population)

	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Follow-up duration (months)[a]			
Median (Range)	14.4 (1.5 - 26.4)	14.2 (1.0 - 26.2)	14.3 (1.0 - 26.4)
Mean (SD)	14.4 (5.6)	14.2 (5.7)	14.3 (5.6)

[a]Follow-up duration is defined as the time from randomization date to the date of death or the database cutoff date if the patient was still alive.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adintdt]

Conduct of the study

Changes in the planned conduct of the study implemented by protocol amendments are shown below>

Amendment	Date of Issue	Overall Rationale
Amendment 3	28-SEP-2020	Clarify imaging schedule
Amendment 2 – Country Specific	05-AUG-2019	Alignment with UK-specific requirements
Amendment 1	18-MAR-2019	Conformation with FDA and other country-specific requirements

Measures implemented by the Sponsor to manage key aspects of study conduct during the pandemic are summarized below (implementation date shown in parentheses). Not all measures were implemented at all study sites due to differences in local conditions and impact of the pandemic.

Process	Measure (Date Implemented)
Study site monitoring	▪ Modifications to the frequency of on-site and remote monitoring were allowed due to national and local travel restrictions and/or study site restrictions to on-site monitoring (21-MAR-2020). ▪ Alternate methods for source data review and verification for critical data points in absence of remote access to electronic medical records were allowed under documented circumstances (06-MAR-2020). ▪ Source data review and/or verification before database lock was/were waived for this study where remote access to the site electronic medical records was not available and per risk assessment (13-MAR-2020). ▪ Critical data points for source document verification were reassessed and the study management plan updated without the usual approval workflow for resumption of on-site monitoring (01-MAY-2020).
Protocol deviations	▪ Study sites were queried as to the relationship of reported deviations to the COVID-19 pandemic. The responses were documented (20-MAR-2020).
AE reporting	▪ COVID-19 infection was to be reported following the protocol's AE and SAE reporting instructions, as well as the standard COVID-19 Data Entry Guidelines.
Clinical supplies (including study treatment)	▪ Clinical supply shipments were carefully monitored to ensure timely delivery (15-MAR-2020). ▪ An alternate location (eg, primary care center, pharmacy) for infusion administration of study treatment/other clinical supplies was allowed when participant travel was impacted, and administration could not be postponed (21-APR-2020).
Data management	▪ Alternative procedures were allowed for study sites using shared electronic devices to complete clinical outcome assessments (08-APR-2020). ▪ Study sites were queried, and responses documented about the relationship of the following to the COVID-19 pandemic (08-APR-2020): - Missing participant study visits and data - Participants who discontinued study treatment and/or the study

Process	Measure (Date Implemented)
Clinical laboratory and other facilities	▪ Alternate clinical laboratory facilities were allowed for collection of samples for study participants unable to visit the study site, where supported by the clinical site processes, HA and/or IRB/IEC guidance (16-APR-2020). ▪ Alternate imaging facilities and delayed schedules for study site and alternate facility imaging were allowed for protocol-required imaging (each to be reported as a protocol deviation) (24-MAR-2020).
Informed consent	▪ Oral confirmation of participant consent (eg, via telephone) was allowed when in-person discussion and signature was not possible (30-MAR-2020).
Home health care services	▪ Home health services could be used to perform protocol-specified activities (eg, physical examination, completion of participant questionnaires, sample collection) for study participants unable to visit the study site (31-MAR-2020). ▪ For participants who only completed telemedicine visits, a complete physical examination was required to ensure AE and disease recurrence evaluations were completed (06-NOV-2020).
EQ-5D-5L and EORTC QLQ-C30	▪ Participants were permitted to complete paper QoL questionnaires with IRB/IEC approval if they did not want to use the shared electronic device on site (15-APR-2020).

Protocol deviations

Summary of Important Protocol Deviations Considered to be Clinically Important (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	487		489		976	
with one or more clinically important protocol deviations	12	(2.5)	8	(1.6)	20	(2.0)
with no clinically important protocol deviations	475	(97.5)	481	(98.4)	956	(98.0)
Inclusion/ Exclusion Criteria	**7**	**(1.4)**	**5**	**(1.0)**	**12**	**(1.2)**
Participant did not meet inclusion criteria 01. (Male/female participants who are ≥ 12 years of age on the day of signing informed consent/assent [unless local regulations and/or institutional policies do not allow for participants < 18 years of age to participate; for those sites, the eligible population is ≥ 18 years of age] with surgically resected and histologically/pathologically confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma per AJCC 8th edition guidelines.)	4	(0.8)	2	(0.4)	6	(0.6)
Participants entered into the trial, i.e. progressed beyond screening, who did not meet key inclusion/exclusion criteria.	3	(0.6)	3	(0.6)	6	(0.6)
Safety Reporting	**3**	**(0.6)**	**3**	**(0.6)**	**6**	**(0.6)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	3	(0.6)	3	(0.6)	6	(0.6)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Study Intervention	**2**	**(0.4)**	**0**	**(0.0)**	**2**	**(0.2)**
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	2	(0.4)	0	(0.0)	2	(0.2)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 04DEC2020.						

Source: [P716V01MK3475: adam-adsl] [P716V01MK3475: sdtm-dv; suppdv]

Changes to SAP

With Amendment 03, Censoring Rules for Primary and Sensitivity Analyses of RFS were updated as shown below:

Situation	Primary Analysis	Sensitivity Analysis
Recurrence or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Event at earliest date of documented recurrence or death	Event at earliest date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Event at earliest date of documented recurrence or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any
No recurrence and no death; and new anticancer treatment is not initiated	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

Censoring Rules for Primary and Sensitivity Analyses of RFS before Amendment 3 are detailed in the following table:

Situation	Primary Analysis	Sensitivity Analysis
Progression of disease that precludes surgery or recurrence or second primary malignancy or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented progression or recurrence or second primary malignancy or death	Progressed at date of documented progression or recurrence or second primary malignancy or death
Progression of disease that precludes surgery or recurrence or second primary malignancy or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented progression or recurrence or second primary malignancy or death
No progression of disease that precludes surgery, no recurrence, no second primary malignancy, and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No progression of disease that precludes surgery, no recurrence, no second primary malignancy, and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment

Baseline data

Participant Characteristics
(ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	487		489		976	
Sex						
Male	300	(61.6)	289	(59.1)	589	(60.3)
Female	187	(38.4)	200	(40.9)	387	(39.7)
Age (Years)						
12 - 17	1	(0.2)	1	(0.2)	2	(0.2)
18 - 64	302	(62.0)	294	(60.1)	596	(61.1)
≥ 65	184	(37.8)	194	(39.7)	378	(38.7)
Mean	59.0		59.6		59.3	
SD	12.6		13.3		12.9	
Median	60.0		61.0		61.0	
Range	16 to 84		17 to 87		16 to 87	
Race						
American Indian Or Alaska Native	1	(0.2)	0	(0.0)	1	(0.1)
Asian	4	(0.8)	1	(0.2)	5	(0.5)
Black Or African American	4	(0.8)	4	(0.8)	8	(0.8)
Multiple	1	(0.2)	0	(0.0)	1	(0.1)
Black Or African American White	1	(0.2)	0	(0.0)	1	(0.1)
White	435	(89.3)	439	(89.8)	874	(89.5)
Missing	42	(8.6)	45	(9.2)	87	(8.9)
Ethnicity						
Hispanic Or Latino	49	(10.1)	30	(6.1)	79	(8.1)
Not Hispanic Or Latino	390	(80.1)	409	(83.6)	799	(81.9)
Not Reported	42	(8.6)	45	(9.2)	87	(8.9)
Unknown	6	(1.2)	5	(1.0)	11	(1.1)
Geographic Region						
US	95	(19.5)	80	(16.4)	175	(17.9)
Non-US	392	(80.5)	409	(83.6)	801	(82.1)
ECOG						
0	454	(93.2)	452	(92.4)	906	(92.8)
1	32	(6.6)	35	(7.2)	67	(6.9)
2	0	(0.0)	1	(0.2)	1	(0.1)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Not Applicable	1	(0.2)	1	(0.2)	2	(0.2)
KPS Status						
100 - Normal. No complaints. No evidence of disease.	1	(0.2)	1	(0.2)	2	(0.2)
Not Applicable	486	(99.8)	488	(99.8)	974	(99.8)
T-Stage						
T3a	2	(0.4)	0	(0.0)	2	(0.2)
T3b	200	(41.1)	201	(41.1)	401	(41.1)
T4a	113	(23.2)	116	(23.7)	229	(23.5)
T4b	172	(35.3)	172	(35.2)	344	(35.2)
Nodal Involvement						
NX	2	(0.4)	1	(0.2)	3	(0.3)
N0	481	(98.8)	487	(99.6)	968	(99.2)
N1C	4	(0.8)	1	(0.2)	5	(0.5)
Metastatic Staging						
M0	487	(100.0)	487	(99.6)	974	(99.8)
M1C	0	(0.0)	1	(0.2)	1	(0.1)
M1D	0	(0.0)	1	(0.2)	1	(0.1)
Overall Cancer Stage						
IIA	1	(0.2)	0	(0.0)	1	(0.1)
IIB	309	(63.4)	316	(64.6)	625	(64.0)
IIC	171	(35.1)	169	(34.6)	340	(34.8)
IIIC	4	(0.8)	1	(0.2)	5	(0.5)
IV	0	(0.0)	2	(0.4)	2	(0.2)
Missing	2	(0.4)	1	(0.2)	3	(0.3)
Stratification						
Pediatric Age 12 to 17	1	(0.2)	1	(0.2)	2	(0.2)
IIB T3b >2.0-4.0 mm with ulceration	199	(40.9)	198	(40.5)	397	(40.7)
IIB T4a >4.0 mm without ulceration	112	(23.0)	114	(23.3)	226	(23.2)
IIC T4b >4.0 mm with ulceration	175	(35.9)	176	(36.0)	351	(36.0)

ECOG is not applicable for pediatric participants. KPS is not applicable for adult participants.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl]

Numbers analysed

Efficacy analyses were based on the ITT population, which consisted of all 976 randomized participants. Participants were analyzed according to the treatment group assigned at randomization.

Study Population

	Pembrolizumab	Placebo	Total
Number of Participants Screened			1182
Number of Participants Randomized (Planned Treatment) (ITT)	487	489	976
Number of Participants Received Treatment (Actual Treatment) (APaT)	483	486	969
Number of Participants Randomized and Did not Receive Treatment	4	3	7
Database Cutoff Date: 04DEC2020.			

Source: [P716V01MK3475: adam-adsl]

No participants were excluded from the efficacy analysis population.

Disposition of Participants (ITT Population)

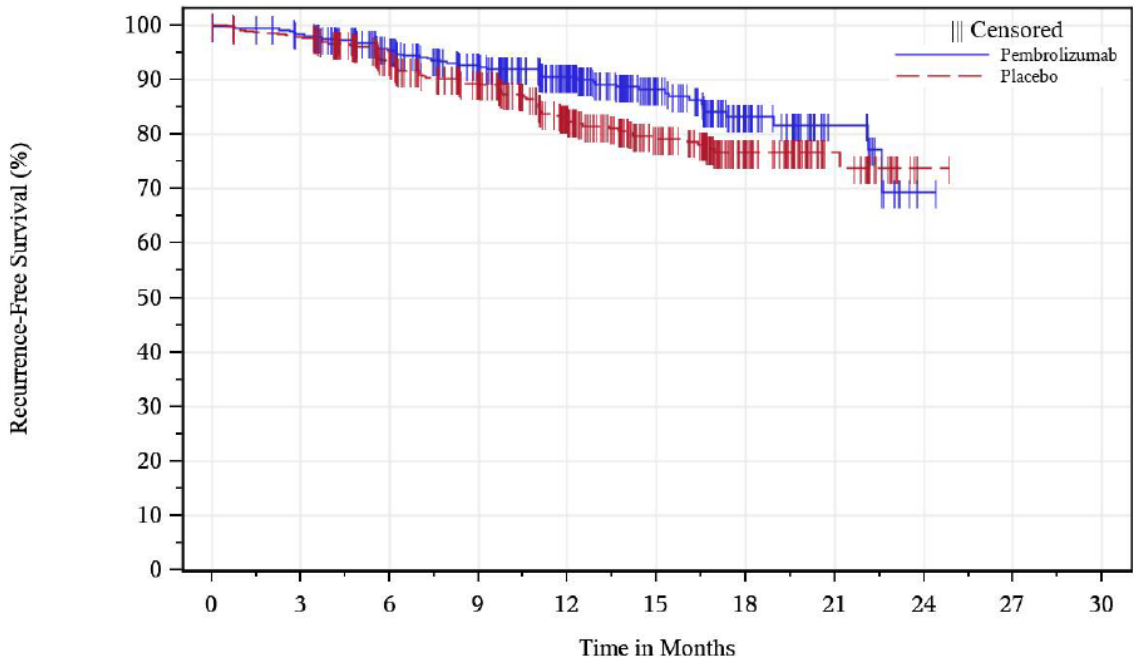
	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	487		489		976	
Participant Study Medication Disposition						
Started	483		486		969	
Completed	206	(42.7)	229	(47.1)	435	(44.9)
Discontinued	144	(29.8)	105	(21.6)	249	(25.7)
Adverse Event	75	(15.5)	20	(4.1)	95	(9.8)
Lost To Follow-Up	0	(0.0)	1	(0.2)	1	(0.1)
Physician Decision	6	(1.2)	4	(0.8)	10	(1.0)
Associated With Covid-19	0	(0.0)	3	(0.6)	3	(0.3)
Protocol Violation	4	(0.8)	1	(0.2)	5	(0.5)
Relapse/Recurrence	21	(4.3)	54	(11.1)	75	(7.7)
Withdrawal By Subject	38	(7.9)	25	(5.1)	63	(6.5)
Associated With Covid-19	3	(0.6)	5	(1.0)	8	(0.8)
Participants Ongoing	133	(27.5)	152	(31.3)	285	(29.4)
Trial Disposition						
Discontinued	12	(2.5)	15	(3.1)	27	(2.8)
Death	6	(1.2)	9	(1.8)	15	(1.5)
Lost To Follow-Up	0	(0.0)	1	(0.2)	1	(0.1)
Not Associated With Covid-19, No Further Information	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal By Subject	6	(1.2)	5	(1.0)	11	(1.1)
Not Associated With Covid-19, No Further Information	6	(1.2)	5	(1.0)	11	(1.1)
Participants Ongoing	475	(97.5)	474	(96.9)	949	(97.2)
If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.						
Database Cutoff Date: 04DEC2020.						

Source: [P716V01MK3475: adam-adsl]

Outcomes and estimation

Primary Efficacy Endpoint: Recurrence-free Survival

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
(ITT Population)



At Risk

Pembrolizumab	487	465	401	340	249	149	71	21	1	0	0
Placebo	489	475	400	336	229	149	77	27	1	0	0

Database Cutoff Date: 04DEC2020.
Source: [P716V01MK3475: adam-adsl; adtte]

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	487	54 (11.1)	5807.1	0.9	NR (22.6, NR)	95.4 (93.0, 97.0)
Placebo	489	82 (16.8)	5815.5	1.4	NR (NR, NR)	93.5 (90.9, 95.4)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.65 (0.46, 0.92)	0.00658[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
[c] One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

Recurrence-Free Survival Rate Over Time
(ITT Population)

	Pembrolizumab (N=487) % (95% CI)[a]	Placebo (N=489) % (95% CI)[a]
Recurrence-Free Survival rate at time point		
6 months	95.4 (93.0, 97.0)	93.5 (90.9, 95.4)
12 months	90.5 (87.1, 93.0)	83.1 (79.0, 86.5)
18 months	83.3 (77.8, 87.5)	76.6 (71.2, 81.1)
24 months	69.4 (49.0, 83.0)	73.8 (65.7, 80.2)

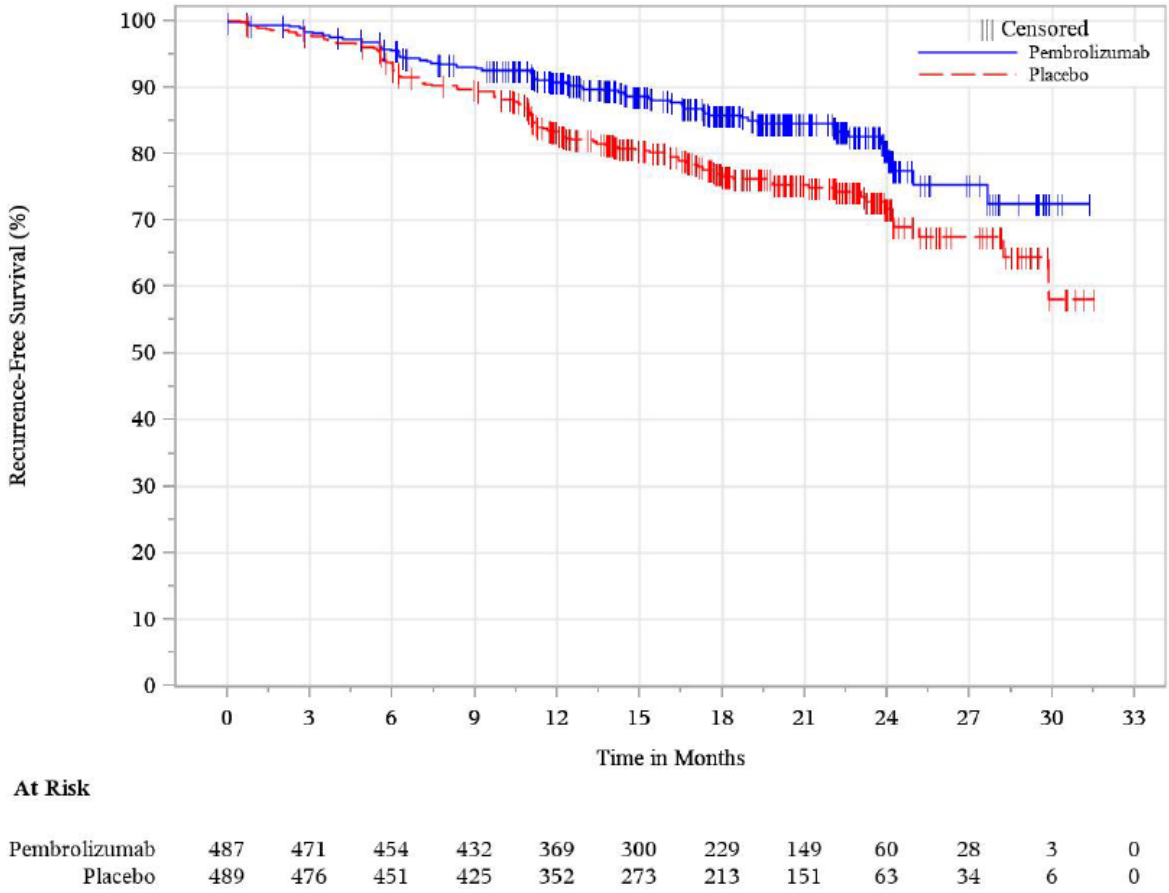
[a] From product-limit (Kaplan-Meier) method for censored data.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

Updated analysis of the primary endpoint

Results refer to the per protocol final analysis of RFS at IA2 with date cut-off of 21-JUN-2021. Data are reported below:

Figure 11-2
Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
(ITT Population - IA2)



Analysis of Recurrence-Free Survival (Primary Censoring Rule)
(ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 18 months in % [a] (95% CI)
Pembrolizumab	487	72 (14.8)	8282.2	0.9	NR (NR, NR)	85.8 (82.0, 88.9)
Placebo	489	115 (23.5)	8105.5	1.4	NR (29.9, NR)	77.0 (72.6, 80.7)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.61 (0.45, 0.82)	0.00046[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
[c] One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 21JUN2021.

Source: [P716V02MK3475: adam-adsl; adtte]

Table 11-4
Disease Status
(ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	487		489		976	
Type of First Event in RFS Analysis						
No event	415	(85.22)	374	(76.48)	789	(80.84)
Event	72	(14.78)	115	(23.52)	187	(19.16)
Local/Regional/LocoRegional	38	(7.80)	50	(10.22)	88	(9.02)
Distant[a]	31	(6.37)	60	(12.27)	91	(9.32)
Death	3	(0.62)	5	(1.02)	8	(0.82)

[a] Includes Distant event diagnosed within 30 days from Local/Regional/Locoregional event.
Database Cutoff Date: 21JUN2021.

Source: [P716V02MK3475: adam-adsl; adintdt]

Subsequent therapies after first recurrence:

Table 11-5
Subsequent Surgical Procedure in Part 1 Post First Recurrence
(ITT Population - Participants with RFS events)

	Pembrolizumab n (%)	Placebo n (%)	Total n (%)
Participants with RFS events	72	115	187
Participants with Surgical Procedure in Part 1 Post First Recurrence[a]	**38 (52.8)**	**56 (48.7)**	**94 (50.3)**
Skin Excisional Biopsy	8 (11.1)	11 (9.6)	19 (10.2)
Lymph Node Biopsy	1 (1.4)	2 (1.7)	3 (1.6)
Skin Metastasis Resection	8 (11.1)	12 (10.4)	20 (10.7)
Lymphadenectomy	13 (18.1)	22 (19.1)	35 (18.7)
Distant Metastasis Resection	10 (13.9)	13 (11.3)	23 (12.3)
Lung Metastasis Resection	4 (5.6)	11 (9.6)	15 (8.0)
Parotidectomy	0 (0.0)	1 (0.9)	1 (0.5)
Tonsillectomy	1 (1.4)	0 (0.0)	1 (0.5)
Craniotomy	2 (2.8)	0 (0.0)	2 (1.1)
Amputation	2 (2.8)	0 (0.0)	2 (1.1)
Intestinal Metastasis Resection	1 (1.4)	1 (0.9)	2 (1.1)

[a] Participants with multiple surgeries are counted in multiple categories.
Database Cutoff Date: 21JUN2021.

Source: [P716V02MK3475: adam-adsl; adtte; adsubtrt]

Table 11-6
Subsequent Radiation in Part 1 Post First Recurrence
(ITT Population - Participants with RFS events)

	Pembrolizumab n (%)	Placebo n (%)	Total n (%)
Participants with RFS events	72	115	187
Participants with Radiation in Part 1 Post First Recurrence	**13 (18.1)**	**11 (9.6)**	**24 (12.8)**
Control of Brain Metastases	4 (5.6)	2 (1.7)	6 (3.2)
Control of Recurrent Disease	6 (8.3)	5 (4.3)	11 (5.9)
Palliative Treatment or Symptom Control	0 (0.0)	1 (0.9)	1 (0.5)
Palliative Treatment or Symptom Control of Metastatic Disease	3 (4.2)	3 (2.6)	6 (3.2)

Database Cutoff Date: 21JUN2021.

Source: [P716V02MK3475: adam-adsl; adtte; adsubtrt]

Table 11-7
Subsequent Therapy in Part 1 Post First Recurrence
(ITT Population - Participants with RFS events)

	Pembrolizumab n (%)	Placebo n (%)	Total n (%)
Participants with RFS events	72	115	187
Participants with Subsequent Therapy in Part 1 Post First Recurrence	**42 (58.3)**	**44 (38.3)**	**86 (46.0)**
Anti PD-1 Therapy	7 (9.7)	19 (16.5)	26 (13.9)
Anti CTLA-4 Therapy	3 (4.2)	1 (0.9)	4 (2.1)
Immunotherapy	2 (2.8)	0 (0.0)	2 (1.1)
Protein Kinase Inhibitor	2 (2.8)	0 (0.0)	2 (1.1)
BRAF/MEK Targeted Therapy	15 (20.8)	9 (7.8)	24 (12.8)
Anti PD-1/Anti CTLA-4 Combination Therapy	12 (16.7)	9 (7.8)	21 (11.2)
Anti PD-1/Immunotherapy Combination Therapy	1 (1.4)	1 (0.9)	2 (1.1)
Anti PD-1/Anti CTLA-4 /Immunotherapy Combination Therapy	0 (0.0)	1 (0.9)	1 (0.5)
Anti PD-1/Cancer Vaccine Combination Therapy	0 (0.0)	2 (1.7)	2 (1.1)
Anti PD-1/TKI Combination Therapy	0 (0.0)	2 (1.7)	2 (1.1)
Database Cutoff Date: 21JUN2021.			

Source: [P716V02MK3475: adam-adsl; adtte; adsubtrt]

Results from IA3 with a median (range) duration of follow-up of 26.9 (4.6 to 39.2) months, were also provided for the DMFS and updated RFS.

Table: Analysis of Distant Metastases-Free Survival (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median DMFS [a] (months) (95% CI)	DMFS Rate at 18 months in % [a] (95% CI)
Pembrolizumab	487	63 (12.9)	11100.8	0.6	NR (NR, NR)	92.7 (89.9, 94.7)
Placebo	489	95 (19.4)	10870.0	0.9	NR (NR, NR)	86.5 (83.1, 89.3)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.64 (0.47, 0.88)	0.00292[c]

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).

[c] One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).

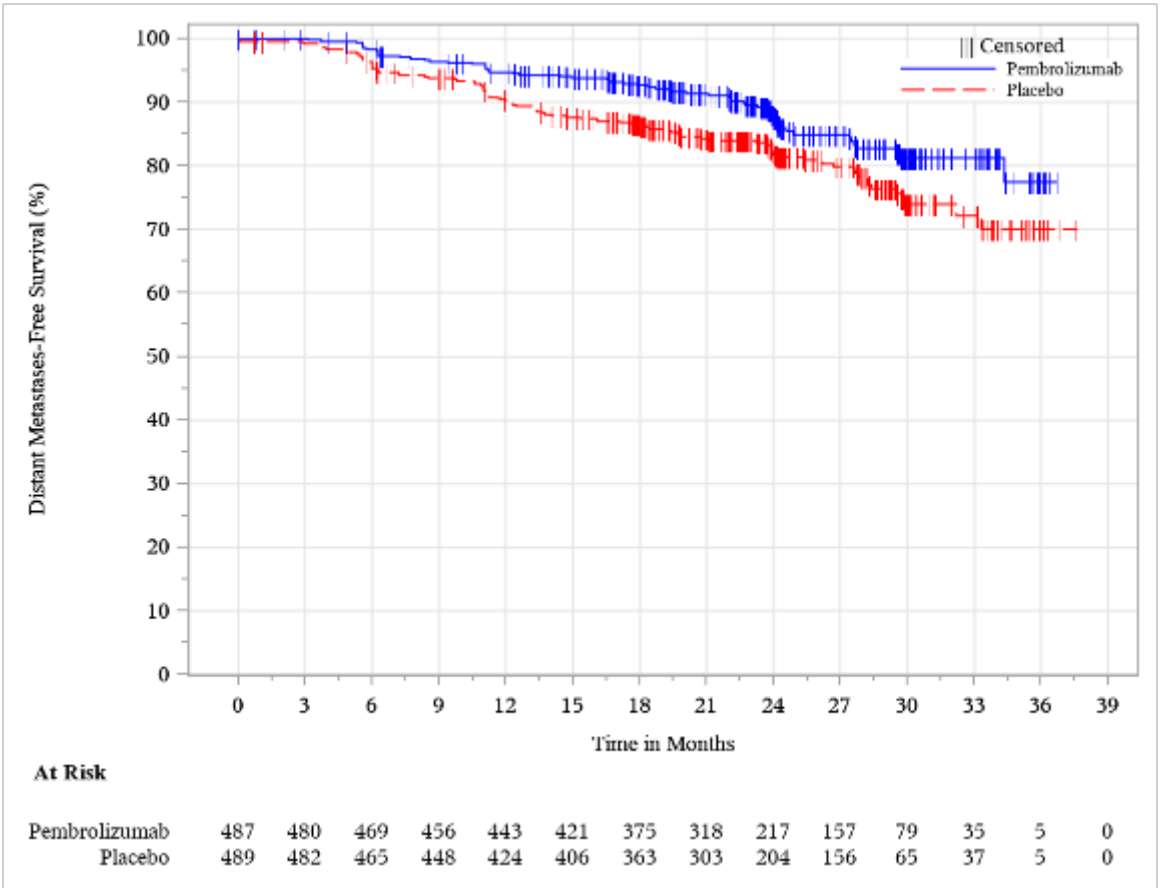
NR = Not reached.

Distant metastasis-free survival is defined as the time from randomization to the first diagnosis of a distant metastasis.

Database Cutoff Date: 04JAN2022.

Source: [P716V03MK3475: adam-adsl; adtte]

Figure: Kaplan-Meier Estimates of Distant Metastases-Free Survival (ITT Population)



Database Cutoff Date: 04JAN2022.
Source: [P716V03MK3475: adam-adsl; adtte]

Table: Analysis of Recurrence-Free Survival (Primary Censoring Rule) (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 18 months in % [a] (95% CI)
Pembrolizumab	487	95 (19.5)	10653.6	0.9	37.2 (NR, NR)	86.1 (82.6, 88.9)
Placebo	489	139 (28.4)	10200.7	1.4	NR (NR, NR)	77.8 (73.7, 81.2)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	
Pembrolizumab vs. Placebo					0.64 (0.50, 0.84)	

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).

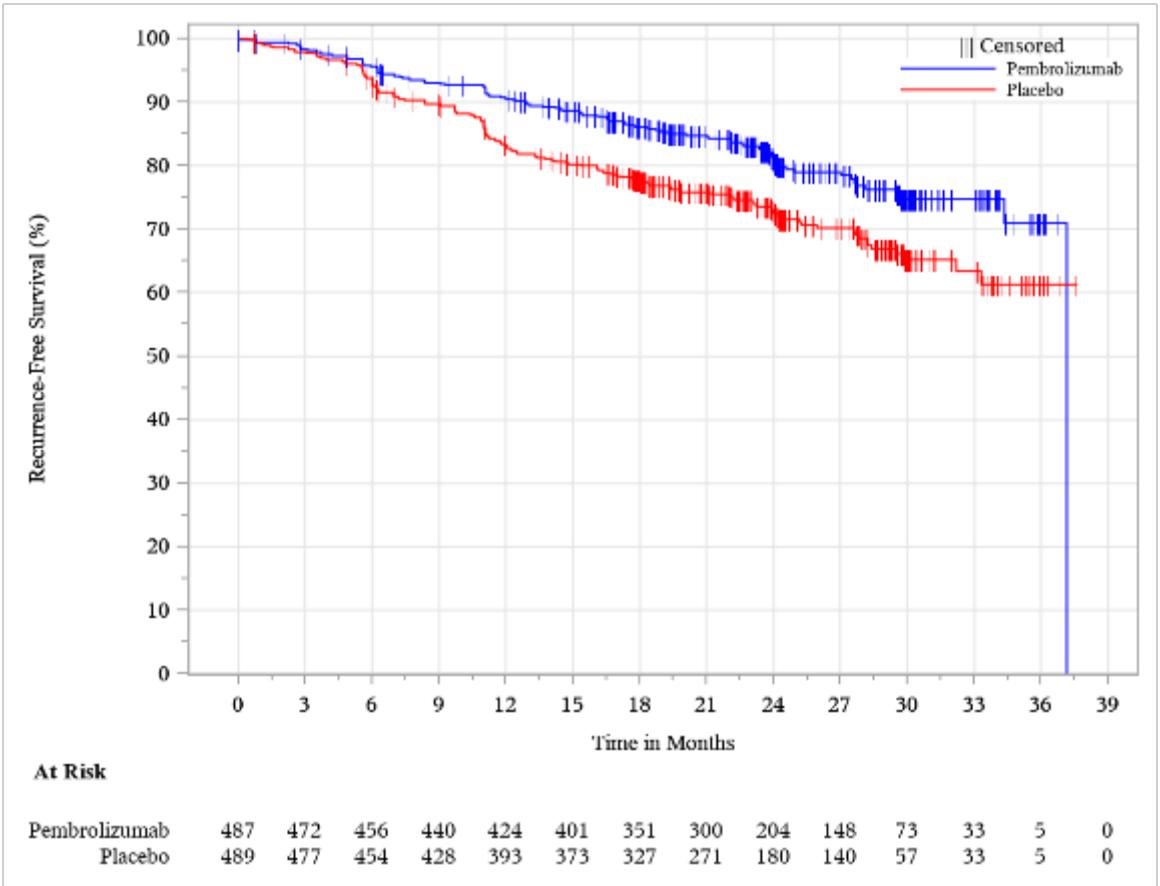
NR = Not reached.

Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.

Database Cutoff Date: 04JAN2022.

Source: [P716V03MK3475: adam-adsl; adtte]

Figure: Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule) (ITT Population)



Database Cutoff Date: 04JAN2022.
Source: [P716V03MK3475: adam-adsl; adtte]

Patient-reported Outcomes

EORTC QLQ-C30

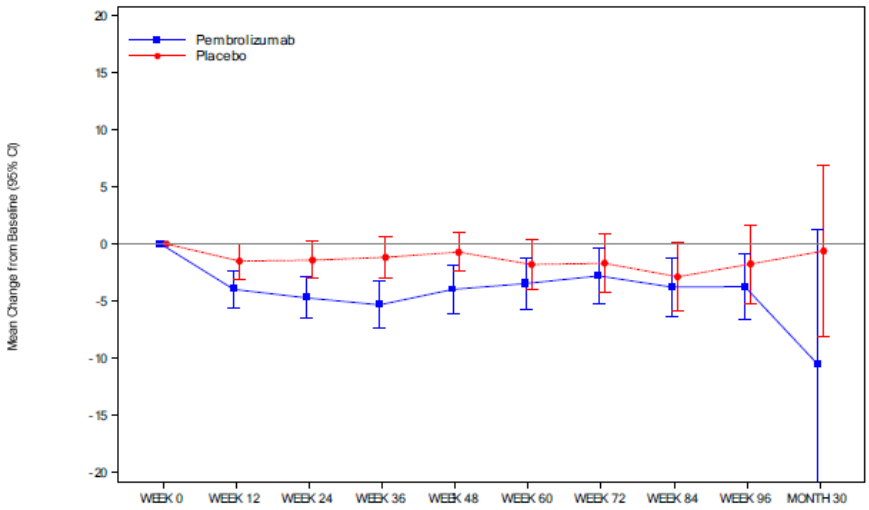
Based on completion and compliance rates, Week 12 was selected as the time point for analysing changes from baseline for the EORTC QLQ-C30. At Week 12 the completion rates in the pembrolizumab and placebo groups were 84.6% and 90.5%, respectively; the compliance rates were 84.8% and 90.5%, respectively.

Adjuvant pembrolizumab treatment resulted in a difference in LS means of -2.18 [95% CI: -4.19, -0.17] in global health status QoL at Week 12 compared with placebo. The change from baseline to Week 12 in physical functioning was similar in the treatment groups.

The proportions of participants for whom the change from baseline in the global health status score and physical functioning score had improved, remained stable, or deteriorated were similar in the pembrolizumab and placebo groups (data not shown).

The mean changes from baseline in the EORTC QLQ-C30 QoL and physical functioning scores over time are presented below.

Figure 11-6
Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (PRO FAS Population)



Number of Participants

Pembrolizumab	449	387	359	327	317	255	200	163	116	19
Placebo	459	418	372	351	350	247	198	148	124	27

Database Cutoff Date: 21JUN2021
Source: [P716V02MK3475: adam-adsl; adpro]

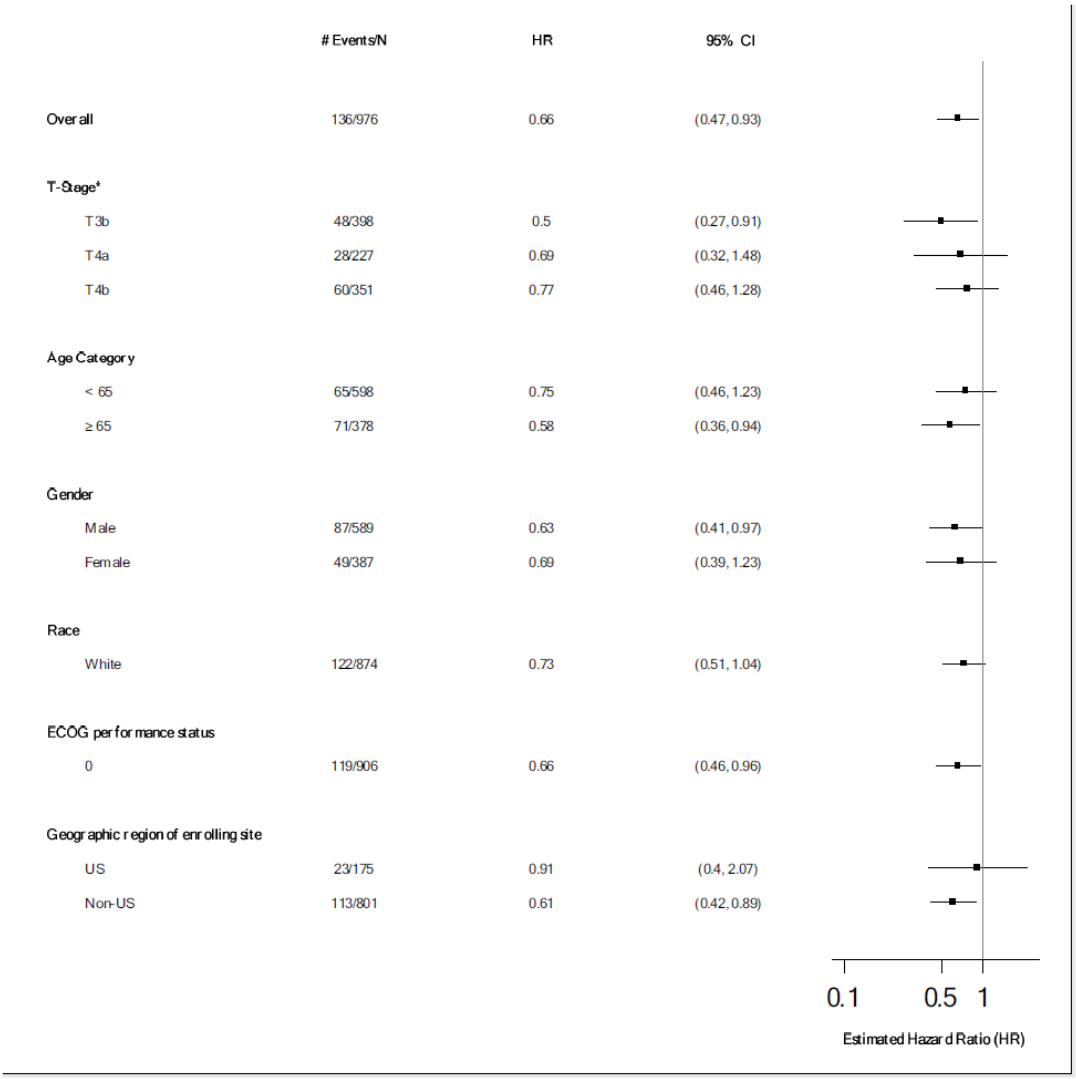
EQ-5D-5L

Based on completion and compliance rates, Week 36 was selected as the time point for analyzing change from baseline for the EQ-5D-5L. At Week 36 the completion rates in the pembrolizumab and placebo groups were 61.0% and 64.4%, respectively; the compliance rates were 78.4% and 82.8%, respectively. Analysis of the EQ-5D-5L score at Week 36 showed no difference between the treatment groups.

Ancillary analyses

Recurrence-free Survival by Subgroup

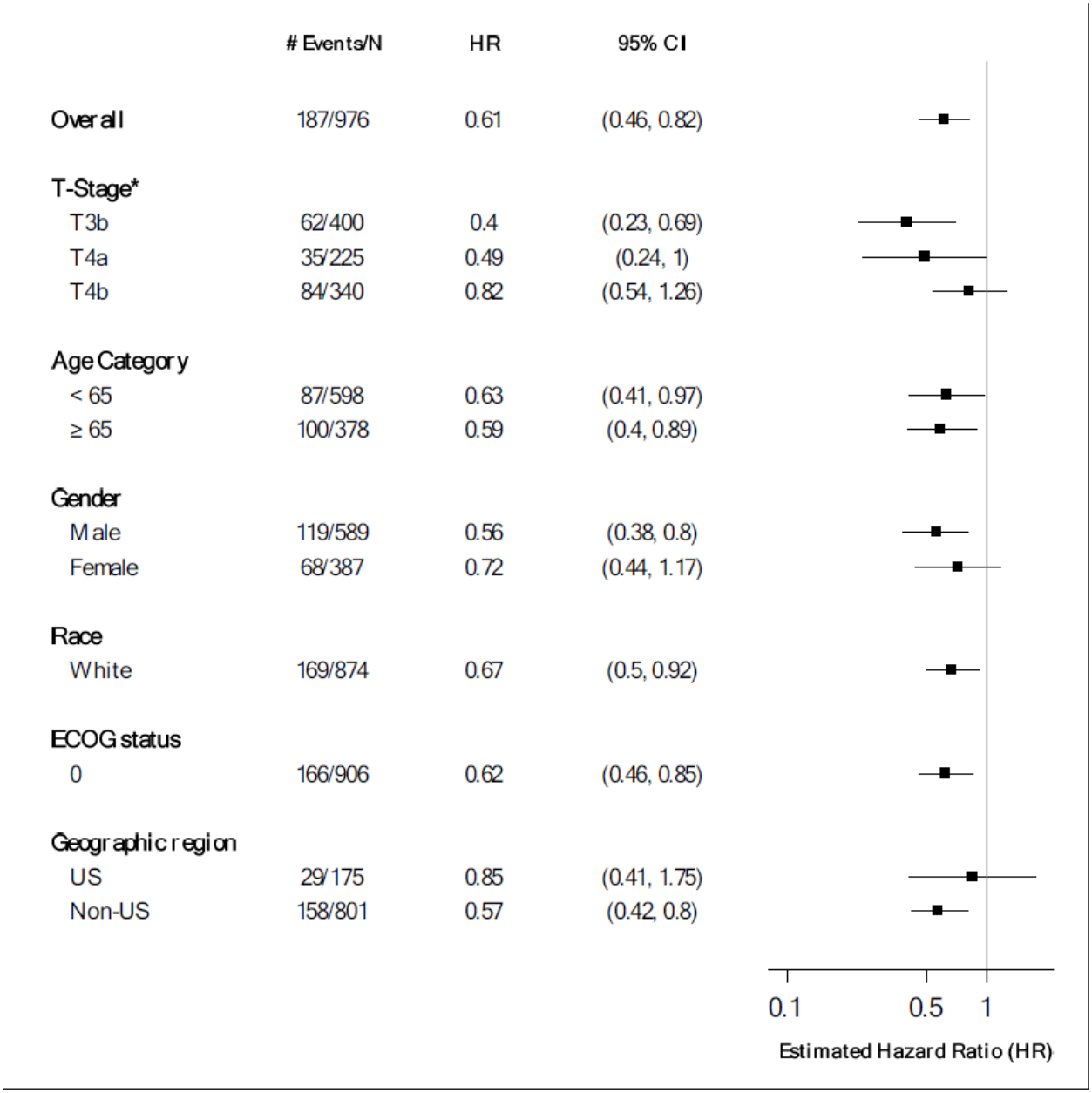
Forest Plot of Recurrence-Free Survival Hazard Ratio by Subgroup Factors (ITT Population)



A subgroup with number of participants < 10% ITT population is not displayed on the plot.
*Based on stratification at randomization.
Database Cutoff Date: 04DEC2020.
Source: [P716V01MK3475: adam-adsl; adtte]

An updated analysis at IA2 was provided for RFS by subgroups:

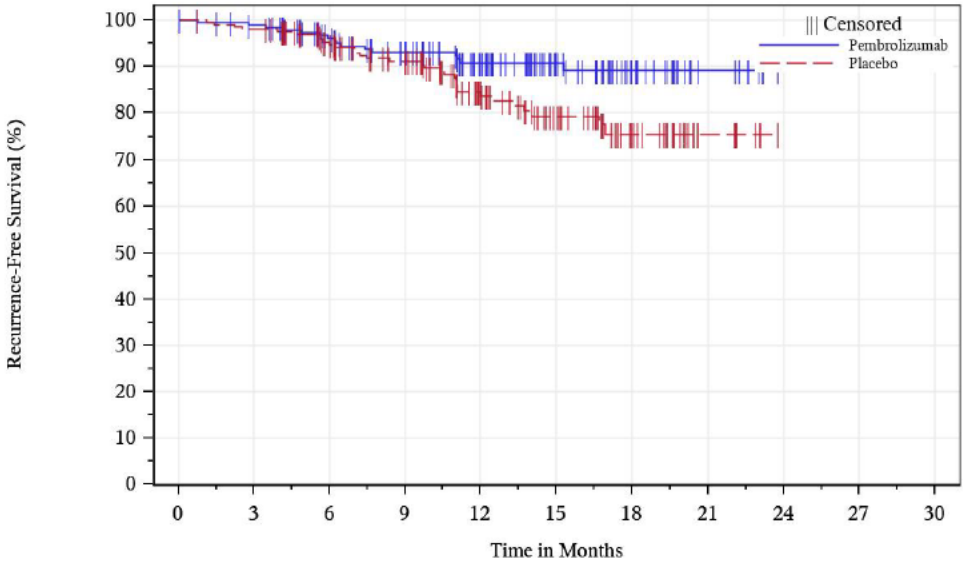
Figure 11-3
Forest Plot of Recurrence-Free Survival Hazard Ratio by Subgroup Factors
(ITT Population – IA2)



A subgroup with number of participants < 10% ITT population is not displayed on the plot.
*Based on actual baseline tumor stage collected on eCRF.
Database Cutoff Date: 21JUN2021.
Source: [P716V02MK3475: adam-adsl; adtte]

Recurrence-free Survival by T stage

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
for Participants with Baseline Tumor Stage T3b
(ITT Population)



At Risk

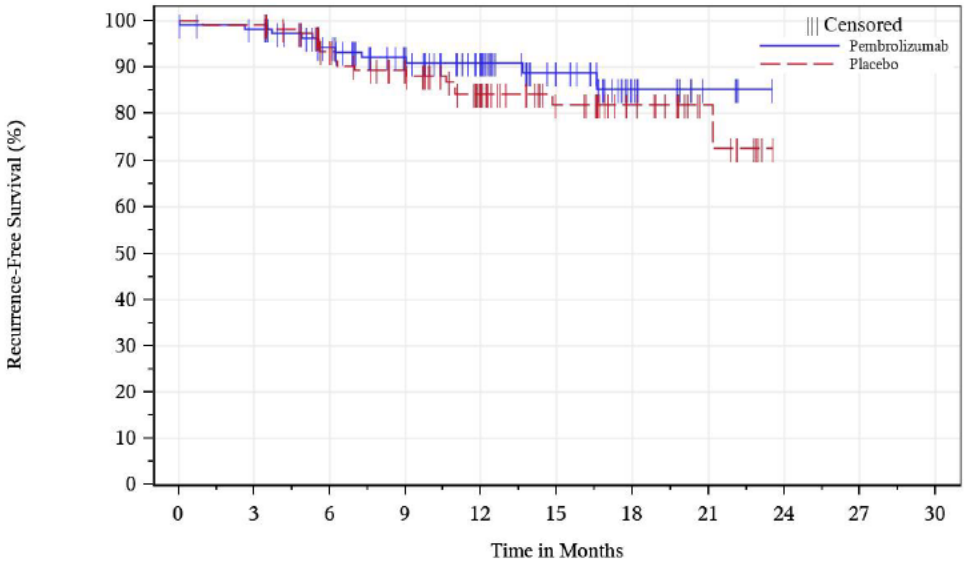
Pembrolizumab	199	190	162	141	102	58	31	8	0	0	0
Placebo	199	194	168	144	91	60	30	9	0	0	0

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	199	16 (8.0)	2367.3	0.7	NR (NR, NR)	96.2 (92.1, 98.2)
Placebo	199	32 (16.1)	2393.5	1.3	NR (NR, NR)	95.3 (91.1, 97.5)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.50 (0.27, 0.91)	0.01041[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
for Participants with Baseline Tumor Stage T4a
(ITT Population)



At Risk

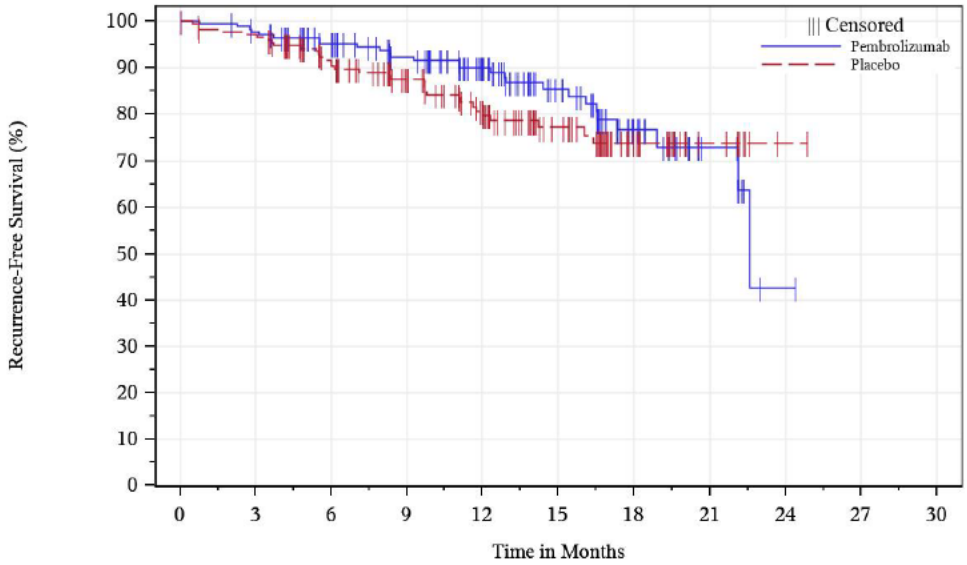
Pembrolizumab	113	108	92	75	52	33	12	4	0	0	0
Placebo	114	113	92	79	54	35	20	9	0	0	0

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	113	11 (9.7)	1296.4	0.8	NR (NR, NR)	94.3 (87.7, 97.4)
Placebo	114	17 (14.9)	1387.6	1.2	NR (21.2, NR)	93.4 (86.6, 96.8)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.69 (0.32, 1.48)	0.16850[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
for Participants with Baseline Tumor Stage T4b
(ITT Population)



At Risk

Pembrolizumab	175	167	147	124	95	58	28	9	1	0	0
Placebo	176	168	140	113	84	54	27	9	1	0	0

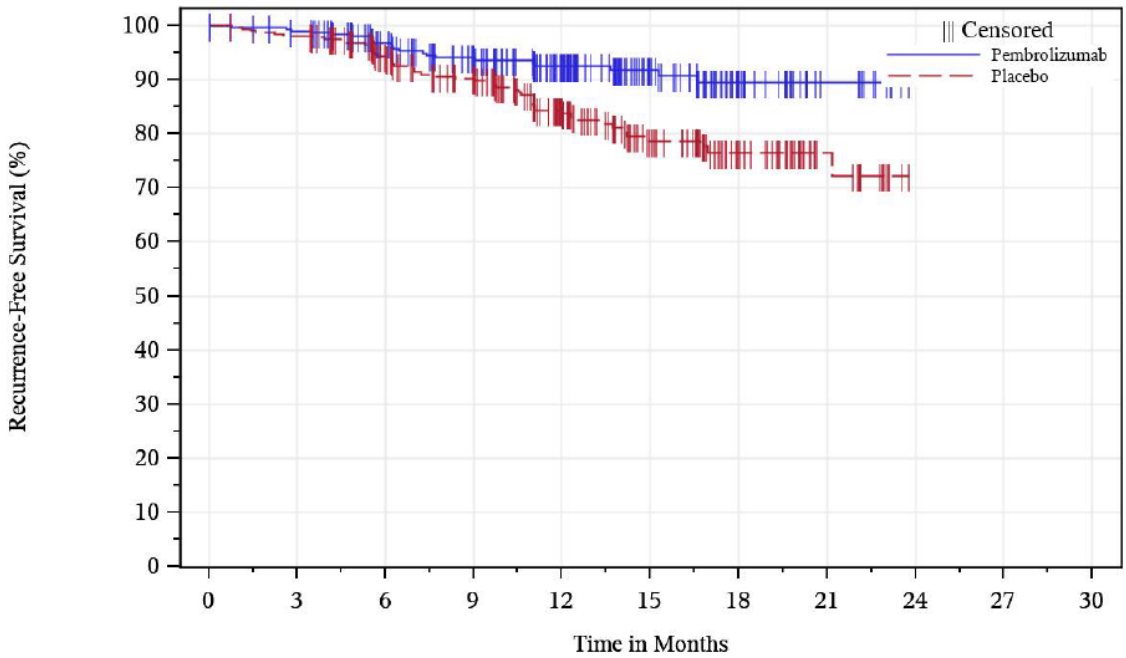
Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	175	27 (15.4)	2143.4	1.3	22.6 (22.1, NR)	95.2 (90.6, 97.6)
Placebo	176	33 (18.8)	2034.4	1.6	NR (NR, NR)	91.6 (86.2, 95.0)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.77 (0.46, 1.28)	0.15649[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

Recurrence-free Survival by Cancer Stage

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
for Participants with Baseline Cancer Stage IIB
(ITT Population)



At Risk

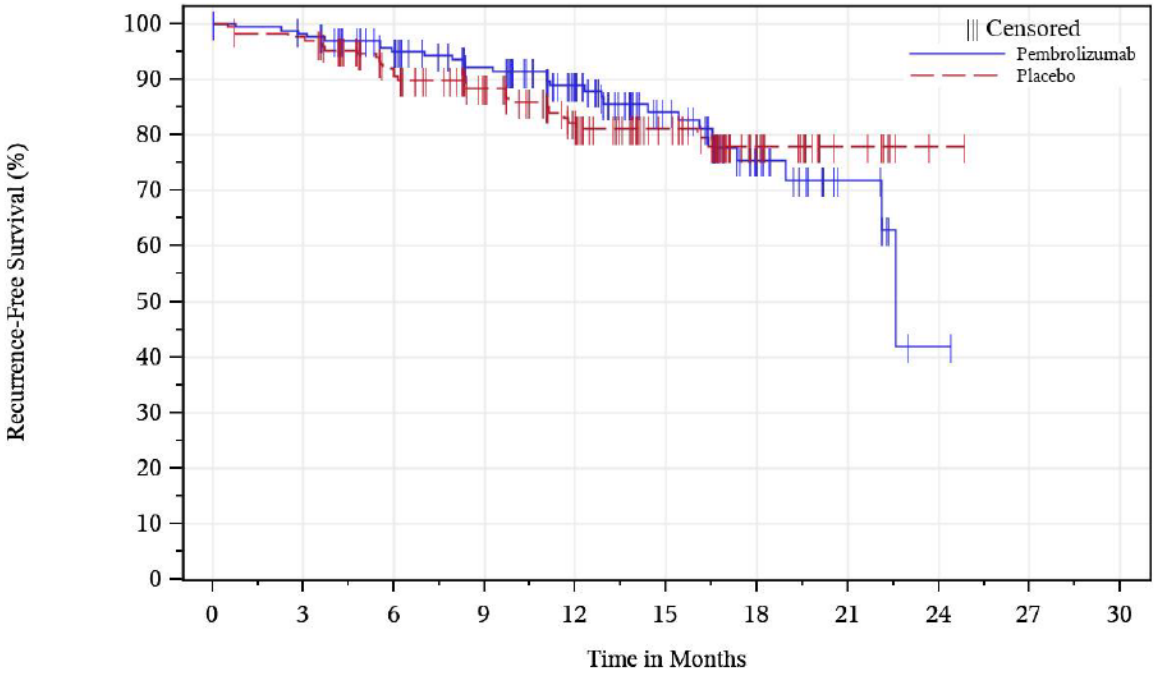
Pembrolizumab	309	295	254	216	154	91	43	12	0	0	0
Placebo	316	309	262	225	146	93	50	18	0	0	0

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	309	22 (7.1)	3651.8	0.6	NR (NR, NR)	96.8 (94.0, 98.3)
Placebo	316	52 (16.5)	3799.3	1.4	NR (NR, NR)	94.3 (91.0, 96.4)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	
Pembrolizumab vs. Placebo					0.44 (0.27, 0.72)	

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
for Participants with Baseline Cancer Stage IIC
(ITT Population)



At Risk

Pembrolizumab	171	165	145	122	93	56	27	9	1	0	0
Placebo	169	164	136	110	83	56	27	9	1	0	0

Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.
Database Cutoff Date: 04DEC2020.
Source: [P716V01MK3475: adam-adsl; adtte]

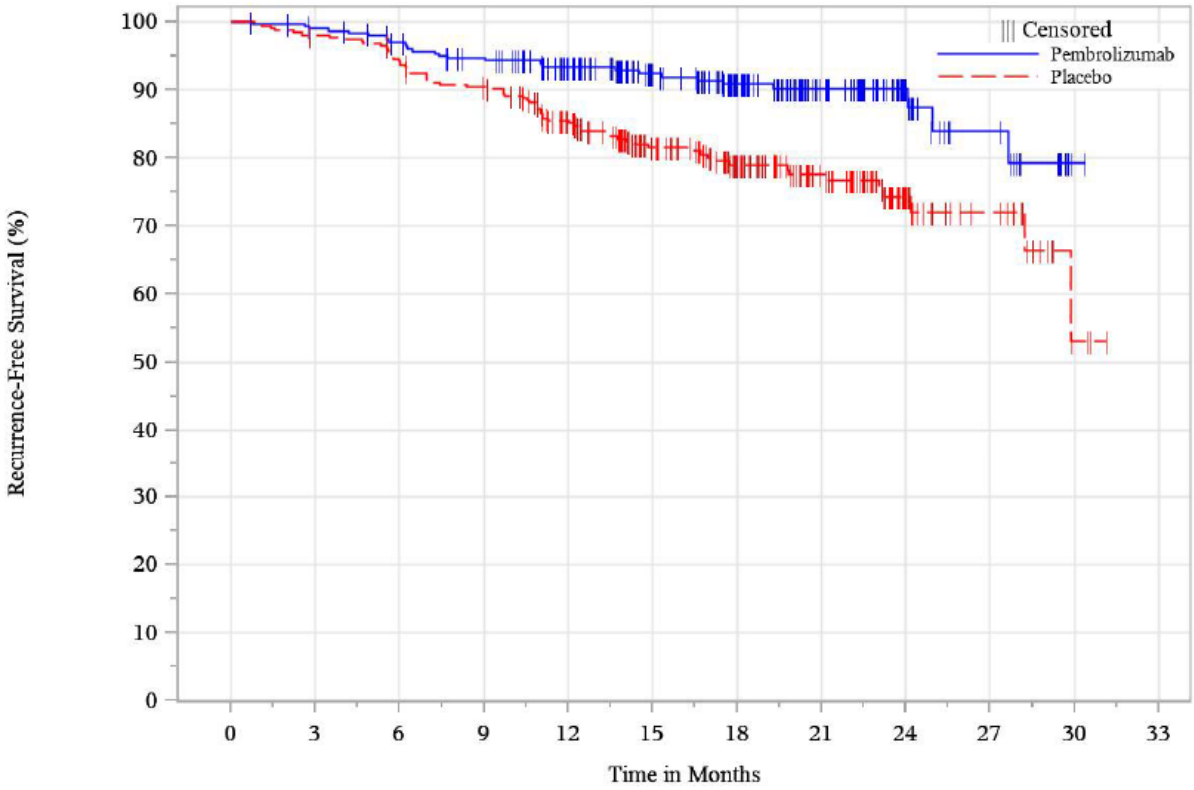
Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	171	28 (16.4)	2106.6	1.3	22.6 (22.1, NR)	95.1 (90.4, 97.5)
Placebo	169	28 (16.6)	1997.4	1.4	NR (NR, NR)	91.9 (86.5, 95.2)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	
Pembrolizumab vs. Placebo					0.94 (0.56, 1.59)	

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

An updated analysis (IA2) was provided for results by cancer stage:

Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule)
for Participants with Baseline Cancer Stage IIB
(ITT Population)

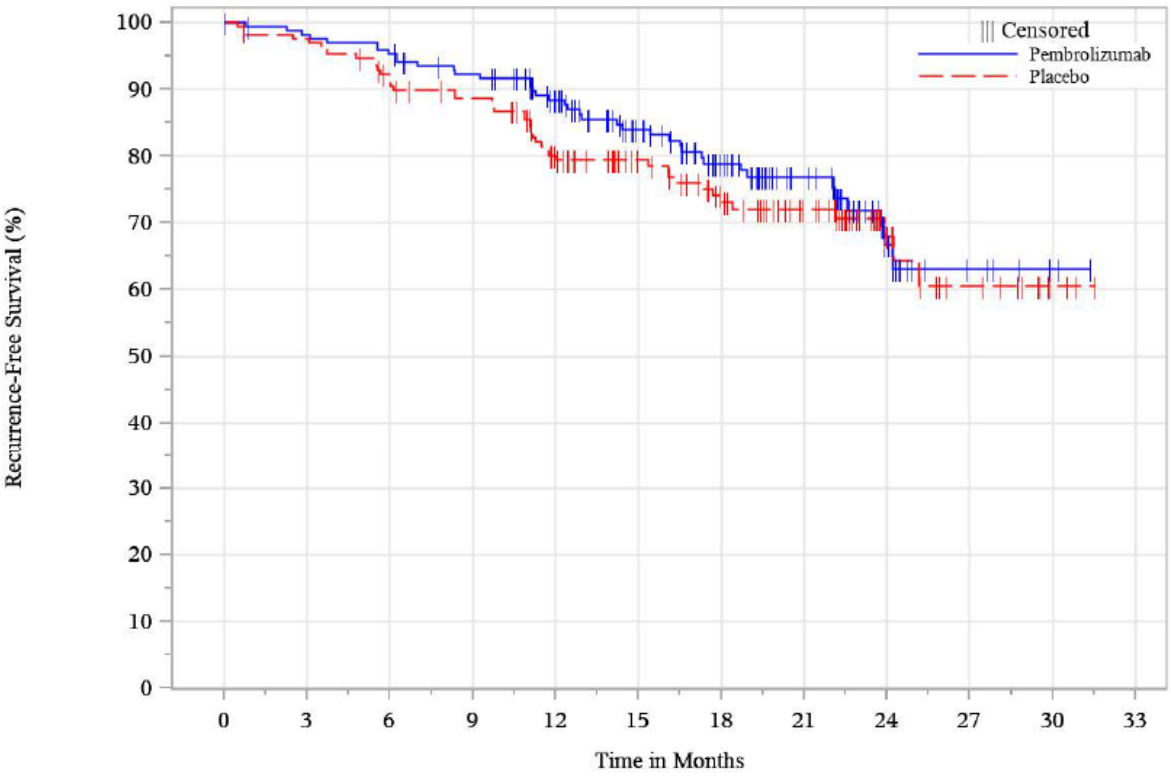


At Risk

Pembrolizumab	309	300	290	278	237	193	146	94	38	19	1	0
Placebo	316	309	296	281	236	180	138	96	39	22	3	0

Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.
Database Cutoff Date: 21JUN2021.
Source: [P716V02MK3475: adam-adsl; adtte]

Figure 11-5
Kaplan-Meier Estimates of Recurrence-Free Survival (Primary Censoring Rule) for Participants with Baseline Cancer Stage IIC (ITT Population)



At Risk

Pembrolizumab	171	166	161	152	130	105	81	54	21	8	2	0
Placebo	169	164	152	143	116	93	75	55	24	12	3	0

Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.
Database Cutoff Date: 21JUN2021.
Source: [P716V02MK3475: adam-adsl; adtte]

The MAH also provided available data on **Progression/Recurrence-free Survival 2:**

Table: Type of First Event in Progression/Recurrence-free Survival 2 Analysis (Intention-to-Treat Population)

Study: KEYNOTE 716[a]	**Pembrolizumab N[b]=487**	**Placebo N[b]=489**
Type of first event in PRFS2, n (%)		
No Event	450 (92.4)	448 (91.6)
No adequate post-baseline disease assessment	0 (0.0)	0 (0.0)
No progression/second recurrence/death as of the data cutoff date	450 (92.4)	448 (91.6)
Event	37 (7.6)	41 (8.4)
Documented progression/second recurrence	29 (6.0)	30 (6.1)
Death	8 (1.6)	11 (2.2)
a: Database Cutoff Date: 21JUN2021		
b: Number of participants: intention-to-treat population		

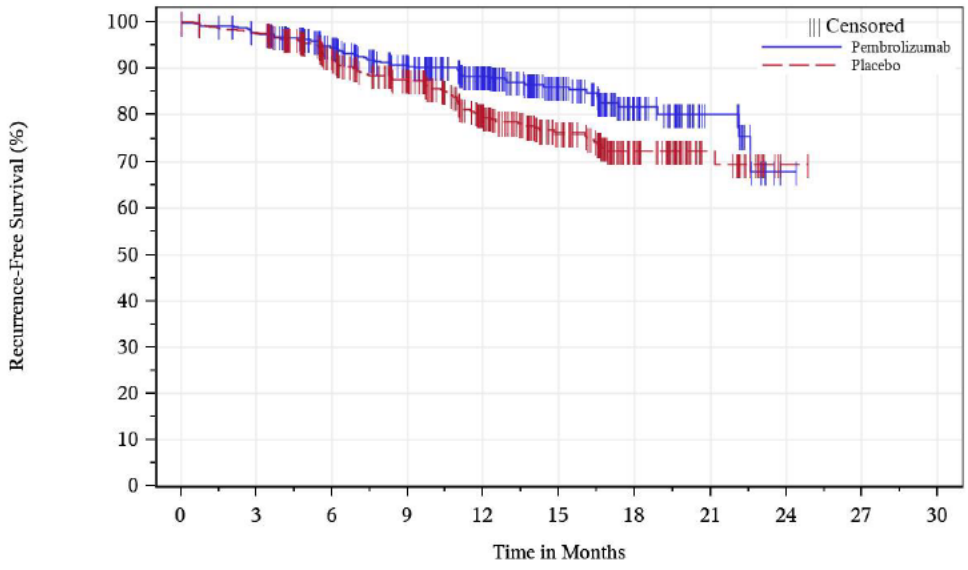
Table: Summary of Progression/Recurrence-free Survival 2 Rate Over Time (Primary Censoring Rule) (Intention-to-Treat Population)

Progression/Recurrence-Free Survival 2	**Study: KEYNOTE 716[a]**	
	Pembrolizumab (N[b]=487)	**Placebo (N[b]=489)**
Kaplan-Meier Rate at Specified Timepoint,% [95% CI][c]		
Month 3	100 [100; 100]	100 [100; 100]
Month 6	99.6 [98.3; 99.9]	99.6 [98.4; 99.9]
Month 9	97.9 [96.1; 98.8]	97.0 [95.1; 98.2]
Month 12	96.3 [94.1; 97.7]	95.1 [92.6; 96.7]
Month 18	93.4 [90.4; 95.5]	91.0 [87.8; 93.4]
Month 24	88.8 [83.7; 92.3]	88.5 [84.0; 91.8]
Month 30	80.9 [70.5; 87.9]	88.5 [84.0; 91.8]
a: Database Cutoff Date: 21JUN2021		
b: Number of participants: intention-to-treat population		
c: From product-limit (Kaplan-Meier) method for censored data		
CI: Confidence Interval		

Sensitivity Analyses

A sensitivity analysis that included new primary melanomas as part of the RFS analysis was performed to evaluate the robustness of the RFS endpoint. The results were consistent with the primary analysis, with an improvement in RFS in the pembrolizumab group compared with the placebo group (HR=0.64 [95% CI: 0.46, 0.88; nominal p=0.00274]).

Kaplan-Meier Estimates of Recurrence-Free Survival (Sensitivity Analysis Including New Primary Melanoma) (Primary Censoring Rule)
(ITT Population)



At Risk

Pembrolizumab	487	461	397	332	242	144	68	20	1	0	0
Placebo	489	474	396	330	219	142	73	25	1	0	0

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	487	62 (12.7)	5711.7	1.1	NR (22.6, NR)	94.5 (92.0, 96.3)
Placebo	489	96 (19.6)	5714.3	1.7	NR (NR, NR)	92.5 (89.6, 94.5)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab vs. Placebo					0.64 (0.46, 0.88)	0.00274[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
[c] One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adtte]

A second sensitivity analysis, in which a different censoring rule was applied, was also performed to evaluate the robustness of the RFS endpoint. The results were consistent with the primary analysis.

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).

Summary of Efficacy for trial KEYNOTE 716

Title: Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)	
Study identifier	IND: 110,080; EudraCT: 2018- 000669-35; NCT03553836

Design	Randomized, Double-blind		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12SEP2018-04DEC2020 not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab		Adult dose: 200 mg IV QW3, 17 cycles, n=487 Paediatric dose: 2 mg/kg IV (⩾12 years and <18 years of age) up to a maximum of 200 mg Q3W, 17 cycles, n=1
	Placebo		IV infusion QW3, 17 cycles, n=489 Paediatric: IV infusion QW3, 17 cycles, n=1
Endpoints and definitions	Primary endpoint	RFS	time from randomization to (1) any recurrence (local or regional [including invasive ipsilateral tumour and invasive locoregional tumour], or distant) as assessed by the investigator, or (2) death due to any cause (both cancer and noncancer causes of death)
	Secondary endpoint	DMFS	The time from randomization to appearance of a distant metastasis as assessed by the investigator
	Secondary endpoint	OS	The time from randomization to death due to any cause
Database lock	04 DEC 2020		

Results and Analysis

Analysis description	**Primary Analysis (IA1 of RFS)**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subject	487	489
	RFS (n events, %)	54 (11.1%)	82 (16.8%)
	Median months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Effect estimate per comparison	Primary endpoint RFS	Comparison groups	Pembrolizumab vs Placebo
		HR	0.65
		95% CI	0.46,0.92
		P-value	0.00658
Notes	RFS: recurrence free survival		

Clinical studies in special populations

The MAH submitted an efficacy analysis by age (<65, 65 to 74, and 75 to 84) based on IA1 DCO.

The analysis for age >85-year category was not provided due to a very limited size in this subgroup (2 participants, both in the placebo group). The trend observed is generally comparable across different age sub-categories and consistent with the primary analysis in the ITT population.

Table: Analysis of Recurrence-free Survival (Primary Censoring Rule) for Participants with Age <65 (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	303	28 (9.2)	3665.0	0.8	NR (NR, NR)	95.1 (91.9, 97.1)
Placebo	295	37 (12.5)	3644.8	1.0	NR (NR, NR)	95.5 (92.4, 97.4)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	
Pembrolizumab vs. Placebo					0.75 (0.46, 1.23)	

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.
Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.
Database Cutoff Date: 04DEC2020.

Table: Analysis of Recurrence-free Survival (Primary Censoring Rule) for Participants with Age 65 to 74 (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	132	20 (15.2)	1532.0	1.3	22.1 (22.1, NR)	96.0 (90.7, 98.3)
Placebo	135	33 (24.4)	1533.3	2.2	NR (NR, NR)	88.1 (81.0, 92.6)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	
Pembrolizumab vs. Placebo					0.61 (0.35, 1.06)	

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

NR = Not reached.

Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.

Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.

Database Cutoff Date: 04DEC2020.

Table: Analysis of Recurrence-free Survival (Primary Censoring Rule) for Participants with Age 75 to 84 (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median RFS [a] (months) (95% CI)	RFS Rate at 6 months in % [a] (95% CI)
Pembrolizumab	52	6 (11.5)	610.0	1.0	NR (NR, NR)	95.7 (83.9, 98.9)
Placebo	57	11 (19.3)	609.9	1.8	NR (16.1, NR)	96.1 (85.2, 99.0)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	
Pembrolizumab vs. Placebo					0.52 (0.19, 1.41)	

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

NR = Not reached.

Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first.

Baseline cancer stage is based on the actual cancer stage recorded on the eCRF.

Database Cutoff Date: 04DEC2020.

Supportive study(ies)

KEYNOTE-054 is an ongoing, randomized, double-blind, Phase 3 study investigating adjuvant therapy with pembrolizumab versus placebo after complete resection of high-risk Stage III melanoma.

The results of KEYNOTE-054 showed that adjuvant pembrolizumab provided a significant and clinically meaningful benefit in RFS and DMFS compared with placebo and established PD-1 inhibition as an active adjuvant therapy for patients with resected, high-risk, Stage III melanoma regardless of PD-L1 status, cancer substage, and BRAF mutation status.

Key results include the following:

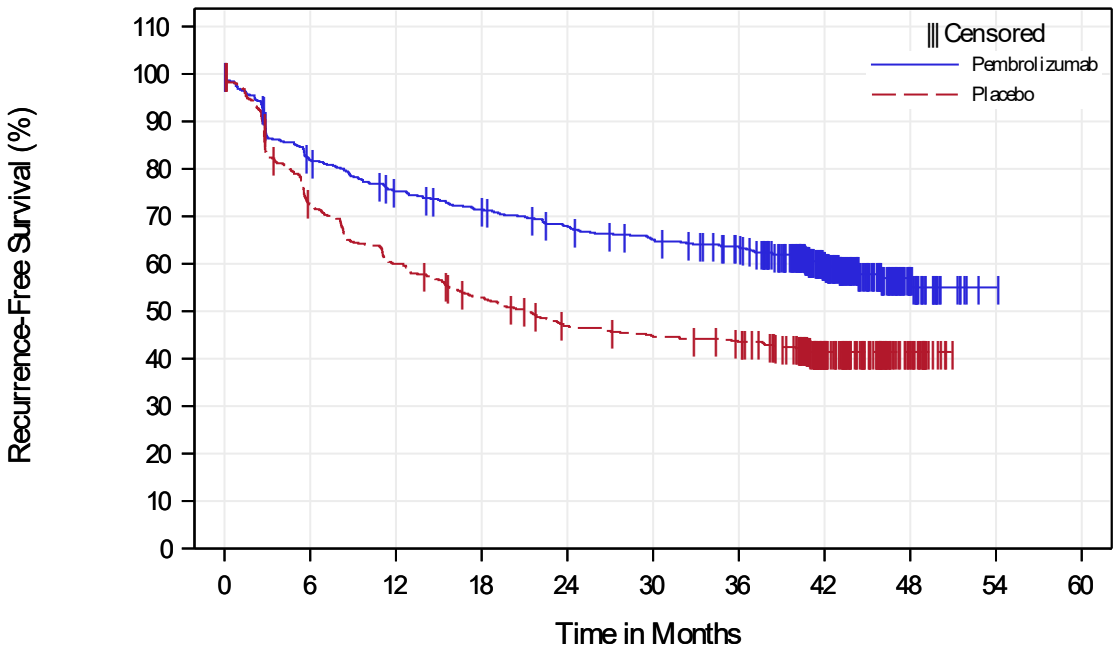
• With a median duration of follow-up of 15 months:

- Adjuvant pembrolizumab therapy resulted in a significantly longer RFS compared with placebo in the ITT population (HR=0.57 [98.4% CI: 0.43, 0.74]; p<0.0001). The 1-year RFS rate was 75.4% (95% CI: 71.3, 78.9) in the pembrolizumab group versus 61.0% (95% CI: 56.5, 65.1) in the placebo group.

• With a median duration of follow-up of 45.5 months:

- Adjuvant pembrolizumab therapy resulted in a sustained **RFS** benefit in the ITT population compared with placebo (descriptive analyses, 203 vs 288 RFS events, respectively; HR=0.59 [95% CI: 0.49, 0.70]) [Sec. 2.7.3-melanoma9: 3.1]. The 3-year RFS rate was 63.7% and 43.5% in the pembrolizumab and placebo groups, respectively. Pembrolizumab also provided a sustained RFS benefit in the PD-L1-positive tumour subgroup (HR=0.59 [95% CI: 0.49, 0.73]).

Kaplan-Meier Estimates of Recurrence-Free Survival ITT Population



n at risk

Pembrolizumab	514	412	375	353	333	316	300	163	30	1	0
Placebo	505	359	297	258	225	213	205	115	26	0	0

Database Cutoff Date: 03APR2020

Improvements in RFS were observed across all cancer substages analyzed (AJCC seventh edition criteria) [Ref. 5.4: 06D4VV]:

- Stage IIIA (>1 mm): HR=0.5 (95% CI: 0.28, 0.89; [51 events/160 participants])

- Stage IIIB: HR=0.58 (95% CI: 0.44, 0.76; [214 events/467 participants])

- Stage IIIC: 1 to 3 LN+, HR=0.55 (95% CI: 0.37, 0.83; [96 events/188 participants]); ≥4 LN+, HR=0.67 (95% CI: 0.48, 0.95; [130 events/204 participants])

- Adjuvant pembrolizumab therapy provided a statistically significant and clinically meaningful improvement in DMFS compared with placebo in adults with Stage III melanoma who have undergone

complete resection regardless of PD-L1 status, cancer substage, and BRAF mutation status (HR=0.60 [95% CI: 0.49, 0.73]; p<0.0001) [Ref. 5.4: 06D4VV].

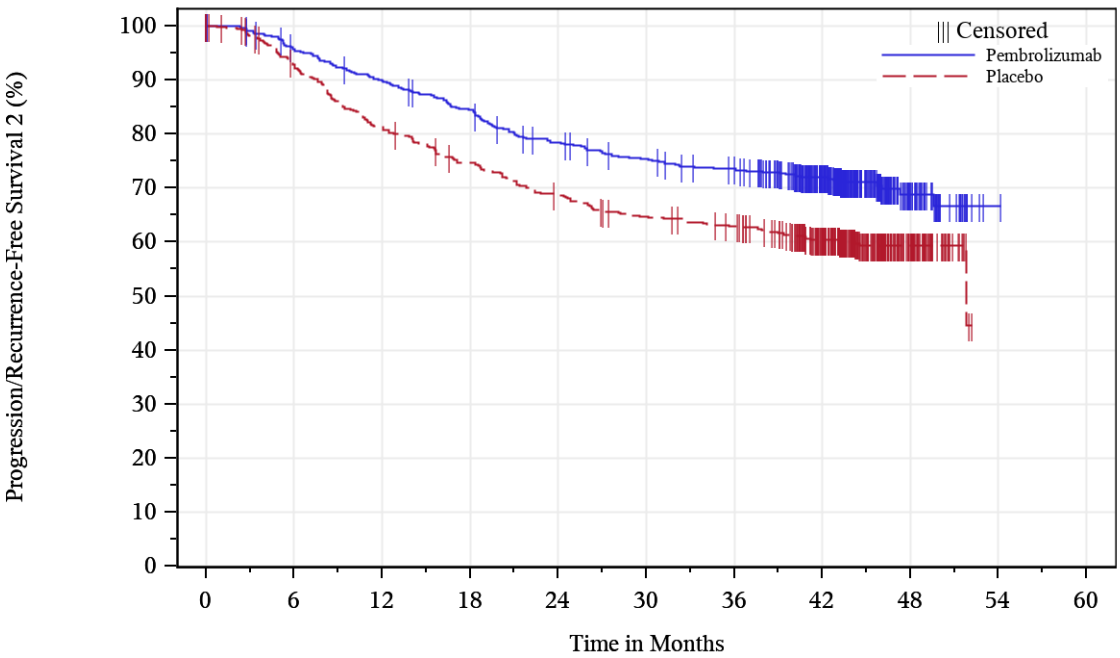
Improvements in DMFS were observed across all cancer stages analyzed (AJCC seventh edition criteria):

- Stage IIIA: HR=0.56 (95% CI: 0.3, 1.05)
- Stage IIIB: HR=0.58 (95% CI: 0.43, 0.78)
- Stage IIIC: 1 to 3 LN+, HR=0.6 (95% CI: 0.39, 0.94); ≥4 LN+, HR=0.65 (95% CI: 0.45, 0.95)

-PRFS2

Analysis of PRFS2, an exploratory objective in KEYNOTE-054, showed an apparent improvement in PRFS2 of a magnitude consistent with the improvements in RFS observed in the study.

Kaplan-Meier Estimates of Progression/Recurrence-Free Survival 2
(ITT Population)



At Risk

Pembrolizumab	514	481	451	422	388	369	355	259	55	1	0
Placebo	505	460	402	367	336	314	301	233	59	0	0

As of the DCO date (03-APR-2020) of the PRFS2 analysis for KEYNOTE-054, there were 146 second progression/recurrence events (including deaths) in the pembrolizumab group and 198 in the placebo group. Treatment with pembrolizumab resulted in longer PRFS2 than placebo (HR=0.66 [95% CI: 0.53, 0.82]). Median PRFS2 was not yet reached in the pembrolizumab group and was 51.8 months in the placebo group. Although the superiority of pembrolizumab compared with placebo cannot be formally declared, the point estimate for the HR and the shape of the KM curve show that pembrolizumab provided an apparent improvement in PRFS2.

Pembrolizumab for Adjuvant Therapy in Paediatric Participants With Melanoma

Efficacy in paediatric patients with melanoma is supported by extrapolation of efficacy data from adults (KEYNOTE-006, KEYNOTE-054, KEYNOTE-716), by using specific arguments from the EU 'Reflection paper on the use of extrapolation in the development of medicines for paediatrics' October 2018. In addition, KEYNOTE-051 provides supportive efficacy data in cHL paediatric patients and safety data in paediatric patients with different tumour types.

The MAH claims that due to a high medical need and lack of relevant efficacy data currently available for melanoma, an extrapolation from adult to adolescent melanoma can be made based on the following: (1) similarity of melanoma disease biology between adults and paediatric patients aged 12 to 17 years, and (2) similar pharmacology of drug effect and similar exposure-response for efficacy and safety. Based on available PK data in KEYNOTE-051, the paediatric clinical study of pembrolizumab, and extrapolation of adult PK data, it was determined that 2 mg/kg (up to a maximum of 200 mg) q3w dosing provides appropriate exposure in paediatric patients. KEYNOTE-051 has resulted in the first approval for KEYTRUDA in the EU for paediatric patients with cHL. Apart from a cohort of 22 patients aged 11 years to 17 years with cHL, this approval was also based on extrapolation of pharmacology and PK data. Similar extrapolation approaches have resulted in approvals in other regions such as the US not only for cHL but also for PMBCL, MCC, MSI-H or dMMR cancer, and TMB-H cancers in the paediatric population.

Adolescent Participants in KEYNOTE-716

A summary of information about the 2 adolescent participants enrolled in KEYNOTE-716 is provided in the table below. Both participants were alive at the last contact before the DCO.

KEYNOTE-716 Adolescent Participants – Brief Summary

Age (Years)	Sex	Disease Characteristics	Treatment Assignment	Number of Treatment Cycles Completed Before DCO	Study Medication Disposition Before DCO	Adverse Events Before DCO	Last Assessment of Treatment Response Before DCO
PPD		Stage IIB cutaneous melanoma	Pembrolizumab 2 mg/kg IV q3w	17	Completed	Grade 1 hidradenitis (2 episodes) and Grade 2 decreased lymphocyte count: reported as not related to pembrolizumab by investigator	No recurrence
		Stage IIB cutaneous melanoma	Placebo (saline solution) IV q3w	14	Ongoing	None	No recurrence

DCO=data cutoff; IV=intravenous; q3w=every 3 weeks.

Source: [Ref. 5.3.5.1: P716V01MK3475: Table 14.1-1, 14.1-3] [Ref. 5.3.5.1: P716V01MK3475: 16.2.6, 16.2.7.1.20]

Pembrolizumab for the Treatment of Paediatric Participants With Advanced Cancers in KEYNOTE-051

KEYNOTE-051 is an ongoing, combined Phase 1 and Phase 2 (Part I and Part II), non-randomized, open-label, single-arm, multicenter study to evaluate the PK, PD, toxicity, safety, and antitumour activity of pembrolizumab in paediatric participants (aged 6 months to less than 18 years) with advanced cancers, including melanoma. Part I has been completed and established pembrolizumab 2 mg/kg q3w as the paediatric RP2D for Part II of the study.

The currently available results of KEYNOTE-051 show that the safety profile of pembrolizumab monotherapy in paediatric patients with advanced cancers is similar to that in adults. The presence or absence of efficacy in the small cohort of participants with advanced melanoma could not be definitively assessed as of the DCO date of 10-JAN-2020 for IA9, and as the cohort was open for additional enrolment.

Safety Results from IA9 for Parts I and II of KEYNOTE-051 for the APaT Population

The results of the safety analysis for KEYNOTE-051 at IA9 show that the safety profile of pembrolizumab monotherapy in paediatric participants with advanced cancers is consistent with the known safety profile of pembrolizumab monotherapy in adults for the different indications currently approved for adult patients in the EU. Although 57.8% of the 161 participants in the APaT population had one or more treatment-related AEs, pembrolizumab was well tolerated as shown by the small percentages of participants with Grade 3 to 5 treatment-related AEs (8.7%), treatment-related SAEs (9.9%), and treatment-related AEs leading to discontinuation of study treatment (3.7%). The most frequently reported treatment-related AEs (fatigue, anemia, pyrexia, AST increased, lymphocyte count decreased, diarrhea, ALT increased, and hypothyroidism, each in >5% of participants) were consistent with a heavily pretreated paediatric population with advanced cancers and with the established safety profile of pembrolizumab in adults.

Efficacy Results from IA9 for Parts I and II of KEYNOTE-051 for the Melanoma Cohort

By the time of the DCO for IA9, the median duration of follow-up in the APaT population was 8.3 months for 139 participants with advanced cancers other than Hodgkin lymphoma. Nine (5.6%) of the 161 participants in the APaT population had advanced melanoma. Of these, 4 participants were <12 years of age, and 5 participants were ≥12 years of age. All participants had histologically confirmed melanoma. There were no responders per RECIST 1.1 in the melanoma cohort. One participant had a best overall response of stable disease.

The number of adolescent melanoma patients in KEYNOTE-051 was low, reflective of its rarity, and the disease in the patients studied was highly aggressive and rapidly progressive. Therefore KEYNOTE-051 does not allow efficacy assessment of pembrolizumab in adolescent melanoma. The purpose of including KEYNOTE-051 in the current submission is to provide safety data in paediatric patients. Additionally, this study has shown efficacy in a cohort of cHL paediatric patients, which has resulted in approval for the paediatric age group of 3 years and older for patients with relapsed or refractory classical Hodgkin lymphoma who have failed ASCT or after at least 2 prior therapies when ASCT is not a treatment option. Due to similarity in disease between adults and adolescents, efficacy in patients 12 years and older with melanoma is supported by extrapolation of efficacy data in adults (KEYNOTE-006, KEYNOTE-054, KEYNOTE-716).

KEYNOTE-051 Melanoma Cohort – Summary of Individual Efficacy Response Data
(APaT Population - Parts I and II)

Age (Years)	Sex	Histology	Site	Treatment Assessment Visit(s)	Treatment Response at Visit(s)	Reason for Treatment Discontinuation
PPD		Melanoma (spitzoid) BRAFmut	Skin, liver, lung	Cycle 3 Day 1	PD	PD
		Melanoma (cutaneous) BRAFwt	Skin, lung, LNs	Cycle 3 Day 1 Cycle 5 Day 1 Discontinuation visit	PD PD PD	PD
		Melanoma (nodular)	CNS	Cycle 1 Day 15 through Cycle 3 Day 1	PD	PD
		Melanoma (ulcerated nodular) BRAFmut	Lung, LNs, bone, liver	Cycle 1 Day 1 through Cycle 1 Day 15	No data	Clinical progression
		Melanoma (nodular) BRAFwt	LNs	Cycle 3 Day 1 through Cycle 8 Day 1	SD	Physician decision
		Melanoma (nodular): metastatic melanoma - primary lesion on natal cleft (intergluteal region)	LNs	Cycle 3 Day 1 through Cycle 28 Day 1	PD	PD
		Melanoma: melanocytic neoplasm (cutaneous origin of melanoma)	Bone, LNs	Discontinuation visit	PD	PD
		Melanoma: epithelioid cell melanoma - disease arose from a preexisting congenital nevus (cutaneous)	Lung, liver, LNs	Discontinuation visit	PD	PD
		Melanoma (nodular) BRAFwt	Lung, LNs	Cycle 1 Day 1 through Cycle 3 Day 8	No data	Withdrawal by parent/guardian (Clinical PD noted)

BRAFmut=BRAF mutant; BRAFwt=BRAF wild type; CNS=central nervous system; LN=lymph node; PD=progressive disease; SD=stable disease.
Database Cutoff Date: 04DEC2020

Source: [P051V02MK3475: adam-adsl; adex] [P051V02MK3475: sdtm-cm; suppcm; sdtm-ds; suppds; sdtm-lb; supplb; sdtm-rs; supprs; vs; suppvs; suppdm; dm; suppmh; mh]

2.4.3. Discussion on clinical efficacy

The MAH is seeking an extension of indication for pembrolizumab in the adjuvant setting of Stage II melanoma for both adults and adolescents aged >12 years, and is proposing a paediatric indication as adjuvant therapy of Stage III and treatment of Stage IV melanoma, for which pembrolizumab is currently licensed to adults only.

The application is based on the pivotal study KEYNOTE-716 for the Stage II melanoma indication. In support of the paediatric indication the MAH presents a discussion on the efficacy data of study KEYNOTE-054 (i.e. the registrative study for the Stage III adjuvant therapy, recently reviewed as part of procedure EMEA/H/C/003820/II/0100) and a claim of similarity between the adult and paediatric disease in terms of biology and pharmacology of drug effect. Study KEYNOTE-051, which supported the recently approved indication of pembrolizumab in paediatric cHL, is referred to as ground for the paediatric dose.

Design and conduct of clinical studies

Study KEYNOTE-716 is a Phase 3 randomized, placebo-controlled, parallel-group, crossover/rechallenge, multicentre study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma. The study consists of Part 1 where patients were assigned to either pembrolizumab or placebo for a 17-cycle length of treatment, followed by Part 2 in which participants who completed Part 1 and experienced a recurrence were started on pembrolizumab regardless of the treatment received in Part 1. In the current application, only data from Part 1 are presented.

Study KEYNOTE-716 was the subject of a Scientific Advice pertaining clinical aspects of the trial including the strategy adopted to support the paediatric indication (procedure n. EMEA/H/SA/2437/26/2018/II).

The study enrolled subjects with Stage IIB and IIC cutaneous melanoma based on the AJCC eighth edition guidelines, to include T category T3b, T4a, or T4b, with no regional nodal metastases (N0) confirmed by a negative SLN biopsy and no evidence of distant metastasis (M0). Participants must have had newly diagnosed, pathologically confirmed, and completely resected melanoma with negative margins, and could not have received prior systemic therapy for Stage II melanoma.

Adult participants were stratified based on T cancer staging (T3b, T4a, or T4b); this was deemed adequate by the CHMP in the provided Scientific Advice. It is however noted that centre effect was not considered, contrary to the directives of ICH E3 and ICH E9 guidelines for multicentre trials. The MAH argued that enrolment size in each centre was small; because of this, the 140 centres were classified into 3 world regions: Europe, North America and Rest of the World.

It is noted that PD-1 expression as well as BRAF mutation status were not contemplated among stratification factors. Although measurement of these markers is not routinary performed in clinical practice for Stage II melanoma due to the current lack of licensed adjuvant therapies in this clinical setting (either immunological or targeted), collecting information on these biomarkers would have provided a characterisation of effect of treatment in the target population across relevant patient subgroups. Unfortunately, due to the limited availability of tissue samples in study KEYNOTE-716, the MAH did not consider it valuable collecting data on this aspect on the basis of the prior experience with KEYNOTE-054, which reported comparable responses to treatment in terms of RFS and DMFS across participants regardless of the BRAF mutations and PD-L1 expression status.

The choice of the comparator (placebo) is in line with current standard-of-care considering that active surveillance is generally adopted in the post-surgery. Indeed, adjuvant IFN that is the only licensed treatment for Stage II melanoma, has been proven to reduce RFS but is not universally recommended owning the marginal benefit on OS despite significant toxicity.

The administrated dose of study medication was 200 mg Q3W as licensed in other indications. For paediatric participants, it was determined that 2 mg/kg (up to a maximum of 200 mg) q3w dosing provides appropriate exposure based on study KEYNOTE-051 together with extrapolation of adult PK data. Follow-up of patients recruited in the study included imaging every 6 months until year 4 and annually thereafter. A central revision of imaging was not contemplated by the study protocol; however, the double blinding nature of the trial mitigates the risk of bias.

Treatment allocation/randomization was centrally determined using an interactive response technology (IRT) system and the participants were assigned randomly in a 1:1 ratio to pembrolizumab or placebo. Details regarding the randomization method (e.g. type of randomization method, if appropriate block length, etc.) were provided and deemed adequate.

The primary objective of the study was the evaluation of recurrence-free-survival (RFS) assessed by the investigator, which can be considered appropriate for the adjuvant setting. This was also confirmed by the CHMP in the prior Scientific Advice. It has been emphasized, however, that sufficient maturity of data and additional endpoints enabling a sound conclusion on efficacy and a proper evaluation of the benefit of early intervention (adjuvant) versus late treatment (at recurrence), were expected at the time of type II variation submission. The MAH initially submitted IA1 of the RFS that only provides a very early overview of inference of treatment. Indeed, this was an event driven trial where the IA1 should have required 128 RFS events (~71% information fraction). Amount of information fraction required to trigger IA1 has been fully respected because the IA1 included 136 observed RFS events (~76% information fraction). Based on a target number of 179 events at the final analysis and 1

interim analysis at approximately 71% of the target number of events, the study was estimated to provide a ~92% power for detecting a hazard ratio of 0.6 at 2.5% (1-sided) significance level. Progression/recurrence-free Survival 2 (PRFS2) and distant-metastasis free survival (DMFS) were included later in the submission. Overall survival (OS) data are not yet available.

The sample size was calculated based on the following assumptions: i) RFS follows a "cure" model with a long-term RFS of 50%; ii) the 60-month RFS is estimated to be 68% for the control group; iii) 4.7% annual drop-out rate; enrolment period of 16 months; a follow-up period of 32 months after the last participant is randomized. Definition of the first two assumptions was based upon discussion with KOLs. The observed data revealed a higher rate of recurrences relatively to the protocol assumption. The poisson Mixture model was run to analyse long-term survivors.

The initial efficacy data were based on results from IA1 and included 136 observed RFS events (~76% information fraction). The IA1 was triggered by prespecified protocol criteria of 128 RFS events observed (~71% information fraction). A sensitivity analysis excluding these overrunning patients was provided and confirmed IA1.

Overall, the statistical methods are considered adequate. In particular, multiplicity strategy, censoring rules and sensitivity analyses are correctly specified. However, concerns arise around the validity of the proposed Cox model of RFS data: considering the underlying hypothesis of the sample size calculation, a "cure model" was expected to be used. Moreover, the Cox model relies upon a proportional hazard assumption that does not seem to have been satisfied, judging by a visual inspection of the RFS curves. Further analyses were conducted that confirmed proportionality, including the Grambsch and Therneau test.

Regarding the paediatric indication, the CHMP emphasised the concern on long-term safety sequaelae related to pembrolizumab toxicity profile, and the limited data on efficacy available in adolescents with advanced melanoma at the time of Scientific Advice application. In the current submission, the numerosity of the paediatric sample size remains limited to 2 patients in the pivotal KEYNOTE-716 (one patient in each treatment arm). With Amendment 03 the originally planned separate stratum analysis for paediatric (age 12-17) participants was combined with the remaining population, which is reasonable. The only implication is that results for the paediatric population are not available.

Efficacy data and additional analyses

KEYNOTE-716

The MAH initially presented results from IA1 (date cut-off 04 DEC 2020) on a total of 976 participants (487 vs 489 allocated to pembrolizumab and placebo, respectively) with 14 month length of follow-up in median, equally achieved between treatment arms. While 42.7% and 47.1% of subjects completed treatment in the pembrolizumab and control group, respectively, 27.5% and 31.3% of patients were still receiving study medication at the time of analysis. More discontinuations due to AE (15.5% vs 4.1%), as expected, occurred in the pembrolizumab compared to the placebo arm, as well as more withdrawal by subjects (7.9% vs 5.1%). **Protocol violations** occurred equally in the groups with a low incidence, and do not appear to have compromised study conduct and analyses.

The **study population** is representative of the target indication and comprises participants with Stage IIB and IIC cutaneous melanoma as defined by the AJCC eighth edition guidelines on cancer staging (i.e. T category T3b, T4a, or T4b, with no regional nodal metastases (N0) confirmed by a negative SLN biopsy and no evidence of distant metastasis (M0)). Participants were recruited within 12 weeks from complete cancer surgical removal and were treatment naïve for prior systemic therapies. Only two

subjects aged between 12-17 years were included, thus restricting the availability of efficacy data to the adult setting.

Baseline demographic characteristics were balanced between groups. The majority of patients were males (60.3%), aged 61 years in median, white (89.5%) with ECOG score 0 (92.8%). The different T stages were well represented in the study population (T3b 41.1%; T4a 23.5%; T4b 35.2%) although there was a predominance of Stage IIB (64% vs 34.8% for Stage IIC). This, however, counterbalanced the distribution of events between the two groups so that similar contribution to the disease recurrence rate was observable regardless of prognosis. Levels of **PD-L1** expression as well as **BRAF** mutation status were not characterised in the study population. This is an important limiting aspect of the current trial in verifying homogeneity of treatment effect in the target population, especially considering the rapidly evolving therapeutic landscape of the adjuvant setting where targeted therapies are currently under scrutiny and might become available. On the other side, it is acknowledged that response to treatment is expected to be independent from these markers considering that results of study KEYNOTE-054 showed similar effect regardless of PD-L1 phenotype or BRAF hallmark.

Within the limit of a highly immature **RFS** analysis due to the low number of events (16.8% in the control vs 11.1% in active treatment) and elevated censoring rate from month 3 ongoing, a statistically significant advantage of pembrolizumab relative to placebo emerged from IA1s (HR=0.65; 95% CI: 0.46, 0.92; p=0.00658). A sensitivity analysis that included new primary melanomas as part of the RFS analysis confirmed this. Despite statistical significance was reached, results were difficult to interpret in order to establish benefit of treatment, since 95% CI of RFS rate overlapped at all time points and at 24 months the rate of events turned even unfavourable in the pembrolizumab group compared to placebo (69.4% vs 73.8% in RFS). Moreover, one third of total patients were still receiving study medication, thus implying a lack of sufficient observation time in the study population to disentangle the cure effect from a delayed effect.

The **analysis of disease status** revealed a slightly high incidence of events for all recurrence categories in the placebo arm (local: 4.9% vs 4.1%, lymph node: 3.5% vs 2.3%, distant: 7.8% vs 4.7% and death:0.6% vs 0% in the control and pembrolizumab arm, respectively). However, in those experiencing recurrent events who were previously exposed to pembrolizumab, the use of surgical procedures (50% vs 43.9%), radiations (14.8% vs 4.9%) and subsequent systemic therapy (48.1% vs 36.6%) including combined immunological treatments (18.5% vs 9.8%) and BRAF/MEK targeted therapies (14.8% vs 8.5%) was more frequent than in the placebo group. Results indicate that a more aggressive immunological approach is adopted following pembrolizumab as adjuvant therapy and the effect by BRAF mutation status may vary. The MAH provided an updated IA2 with final RFS results, for an additional 6-month follow-up and a total length of observation of 20.5 months in median. With a recurrence rate of 23.5% in the placebo group (previously registered event rate was 16.8%), which was reduced to 14.8% in the pembrolizumab arm (HR=0.61; 95% CI: 0.45, 0.82; p=0.00046), the updated results confirmed IA1; moreover, reduction in recurrence was observed for both the local-regional (7.80% vs 10.22%) and distant (6.37% vs 12.27%) relapse of disease confirming the originally submitted data. A subsequent IA3 was performed with 26.9 months of follow-up, in median. Although immature, results from the first DMFS analysis were provided and showed a significant reduction of events in the pembrolizumab arm relative to placebo (HR=0.64; 95% CI 0.47, 0.88; p=0.00292). An updated RFS analysis was also submitted, further consolidating the initial available data HR=0.64; 95% CI: 0.50, 0.84).

The OS was not available at the time of this procedure and this were proposed to be included in Annex II to obtain the analysis of other clinically relevant outcomes as soon as available.

The MAH will provide the per-protocol specified final analysis for DMFS and interim analysis for OS as follows:

- IA4 – Q2 2023 (DMFS)
- IA5 – Q4 2028 (OS)

IA5 – Q4 2028 (OS) is the first IA for OS, and the results would only be provided if OS reaches statistical significance. If not statistically significant, the team will remain blinded until the FA currently planned for Q4 2033. Therefore, the IA5 is included in Annex IID, recognising that if OS is not statistical significance, the Annex II will be updated to reflect the FA. In general, the IAs are event-driven and the current projected timings listed above are subject to change.

PROs were comparable between groups. The proportions of participants for whom the change from baseline in the global health status score and physical functioning score had improved, remained stable, or deteriorated were similar in the pembrolizumab and placebo groups. Analysis of the EQ-5D-5L score at Week 36 showed no difference between the treatment groups. As part of IA2, the MAH also reassessed PRO at week 48, demonstrating consistency with IA1 results (data not shown).

Subgroup analyses showed similar effects across prespecified strata that are consistent with the ITT population. However, there is a trend for more attenuated treatment effect by increasing T stage (T3b HR:0.5; T4a HR:0.69; T4b HR:0.77) that more clearly emerges in the efficacy results by cancer stage (Stage IIB HR:0.44; 95% CI 0.27, 0.72; Stage IIC HR:0.94; 95% CI 0.56,1.59), demonstrating no benefit for patients expected to have a worse prognosis. The lower numerosity of the Stage IIC group (340 vs 625 patients in Stage IIB) might have limited detection of inference of treatment, bearing in mind that all subgroups lack statical power and ultimately a similar rate of events occurred in the two groups (around 16% in both placebo arms of Stage IIB and IIC at IA1). Results from IA2 showed a more numerous rate of events registered during the follow-up that brought the HR of RFS in Stage IIC toward a slight reduction (from HR=0.94, 95% CI 0.56,1.59 to HR=0.82; 95% CI 0.54, 1.26). There remained a divergence of effect compared to Stage IIB, for which RFS estimation is more convincingly in favour of pembrolizumab (HR=0.43;95% CI 0.28, 0.67). It is likely that additional updated analyses in RFS would consolidate the data, rather than abolishing the lack of consistency, due to the limitations related to the small sample size, and very few at-risk patients particularly in the final tail of the KM curves of stage IIC.

Supportive studies

KEYNOTE-054 concerns Stage III melanoma and the presented data have been the subject of a recently assessed procedure confirming the benefit of treatment for pembrolizumab at this stage of disease. Although the indication supported by the trial falls within the adjuvant setting, study KEYNOTE-054 does not provide efficacy data applicable to more early stages of disease and it is therefore of limited value. It provides, however, a comparative evaluation of clinical outcomes available at the time of approval of pembrolizumab as adjuvant for Stage III melanoma that further underlines the immaturity of Study KEYNOTE-716 in the current application. Indeed, although a similar length of follow-up was achieved by the two studies (15 months in KEYNOTE-054 and 14 months in KEYNOTE-716) at the time of first submission, study KEYNOTE-054 has registered a higher number of events that reflects the worse prognosis of the specific disease stage (42.8% in the placebo arm vs 16% in the placebo arm of KN716) and results of PRFS2 were available, thus supporting the surrogate endpoint. It should be considered that also for study KEYNOTE-054 an updated analysis was requested at the time of initial submission, and those initial data found correspondence in the recently submitted variation (EMEA/H/C/003820/II/0100) pertaining to an update of the trial with additional 30 months of follow-up obtained since the first interim analysis for RFS. Of particular relevance to the current

application is the evidence deriving from study KEYNOTE-054 demonstrating lack of a "rebound" effect for pembrolizumab in the post-treatment phase of the adjuvant setting.

Study **KEYNOTE-051** provides support for the paediatric dose. Although the MAH underlines that efficacy data are not retrievable from this study, it should be considered that 9 paediatric cases of advanced melanoma were recruited (see section below).

Assessment of paediatric data on clinical efficacy

There are no efficacy data in the paediatric setting since only 2 subjects aged between 12-17 years were enrolled in the pivotal study KEYNOTE-716. The MAH claims similarity on the biological aspects of disease and pharmacokinetic of pembrolizumab between adults and children as a ground to a bridging strategy that aims at extending the use of pembrolizumab to adolescents aged >12 years in both the adjuvant setting of Stage II and Stage III and as treatment for advanced melanoma (Stage IV).

The MAH discussed the scientific basis in support of disease similarity, by making references to the histology (the majority of adolescent cases are superficially spreading melanoma) and genetic alterations that are common in the two age groups. Regarding prognostic factors in the adjuvant setting, for completely resected melanoma in adolescent patients, it has been underlined by the MAH that prognostic factors are shared with adult melanoma. Similarity in therapeutic response to treatments was also mentioned to support the extrapolation concept, on the basis of a demonstrated poor performance of chemotherapy for the treatment of advanced disease in both age groups, as well as the use of ipilimumab that has provided proof for immunotherapy in adolescent melanoma.

The MAH also considered Stage II and III melanoma in adults and adolescents to be the same disease, sharing the same prognostic factors and the high risk of recurrence and death, despite locoregional recurrence may occur more frequently for Stage IIB disease and systemic recurrence manifests more frequently for Stage IIC disease. It is acknowledged that similarity based upon biological factors applies to melanoma regardless of stages. There are, however, suggestions that tumour-unrelated clinical characteristics and the obvious better clinical conditions of the youngest patients, including their more active immunosurveillance status, might influence clinical outcomes. In the setting of a metastatic disease, these differences are not relevant due to the advanced status of melanoma but for earliest stages of disease, they should be factored into the equation to better define prognosis and the consequent weight of benefit against risks associated to treatment. Clinical observations on efficacy are currently very limited and inconclusive (9 participants, only 5 in the adolescent age range), and actually show a negative trend in terms of response. However, the biological similarity of disease is recognised and provides support to the proposed extrapolation.

Due to limited number of paediatric melanoma patients, the MAH did not provide information on the exposure-response relationship between adult and paediatric patients in melanoma. No additional analysis has been conducted, neither for PK or exposure-response relationship. Therefore, the conclusion on similar pharmacology of drug effect is based on data from KEYNOTE-051 (EMEA/H/C/3820/II/090) and during the II/90 variation assessment it was concluded that "*since consistent flat exposure-response relationships are seen for pembrolizumab in multiple tumour types and since clearance is not meaningfully different across tumour types, this can suggest that saturation of the target in circulation is achieved at the clinical dose across all tumour types*".

2.4.4. Conclusions on the clinical efficacy

Pembrolizumab-induced reduction of disease recurrence (including both loco-regional and distant patterns) during the limited and initial period of follow-up as demonstrated in study KEYNOTE-716 can

be regarded as clinically relevant. It remains to be excluded that anticipation of pembrolizumab as adjuvant therapy merely produces a delaying effect on disease relapse with no benefit on the overall survival compared to a delayed treatment at recurrence. The behaviour of disease cannot be predicted in the post-treatment phase on the basis of the current K-M curves, not only because of the immature analysis but also in consideration of the fact that immunosurveillance might be influenced by cessation of therapy, thus concurring to delineate a different progression of disease. In this context, the prior experience with KEYNOYE-054 can be considered supportive, and show lack of a "rebound" effect upon therapy cessation, thus providing reassurance on the maintenance of treatment benefit at later time points in the adjuvant setting. Although efficacy can be considered substantiated in this new indication, results require confirmation through a longer follow-up and additional clinically relevant outcomes.

The MAH will provide the per-protocol specified final analysis for DMFS and IA for OS as follows:

- IA4 – Q2 2023 (DMFS) [included in Annex IID]
- IA5 – Q4 2028 (OS) [included in Annex IID]

The proposed bridging strategy in support of a paediatric indication currently lacks direct evidence of exposure-response relationships in adolescent melanoma. Clinical observations on efficacy are also very limited. The biological similarity of disease, however, is recognised and provides support to the proposed extrapolation. As regards pharmacology, only an indirect conclusion on E-R can be drawn based on the demonstrated similarity in E-R relationship and PK profile between adult and paediatric patients in cHL, and the assumption that the flat exposure-response relationship seen in adults across multiple tumour types is preserved in paediatric patients across indications. Even though carrying all these limitations, the bridging strategy adopted by the MAH could be deemed acceptable within the specific tumour-type, considering the historically recognised immunoresponsive nature of melanoma, and taking into account that extrapolation is limited to adolescents. Indeed, in this clinical setting, no factors potentially affecting response to therapy are foreseen. A commitment, however, is requested to the MAH for prospectively collecting as much post-authorisation data as possible (on efficacy and safety outcomes) on paediatric/adolescent treated patients in the approved indication(s), e.g., in a study (or registry) post marketing authorisation and, regarding the melanoma indications, making the distinction between adjuvant and advanced setting.

The following measures are considered necessary to address issues related to clinical efficacy:

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of pembrolizumab as adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma, the MAH should submit the per-protocol specified final analysis of DMFS and the interim analysis of OS for study KN716: A Phase III Clinical Trial of Pembrolizumab (MK-3475) in Subjects with complete resection of high-risk Stage II melanoma.

2.5. Clinical safety

Introduction

The safety results of pembrolizumab for the adjuvant treatment of adult and paediatric patients aged 12 years and older with Stage IIB and IIC melanoma who have undergone complete resection, are presented for the following 3 datasets:

- **KEYNOTE-716 Safety Dataset** (N= 969), including pembrolizumab-treated participants (n=483) and participants who received placebo (n=486) with resected Stage IIB and IIC melanoma in KEYNOTE-716 (DCO date 04 DEC 2020);

- **KEYNOTE-054 Safety Dataset** (N=509), including pembrolizumab-treated participants with resected, lymph node -positive, Stage III melanoma who participated in KEYNOTE-054 (DCO date 03-APR-2020);
- **Pembrolizumab Monotherapy RSD** (N=6185), including 6185 pembrolizumab-treated participants with advanced melanoma from studies KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, and KEYNOTE-054 and participants with NSCLC from studies KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042. In addition, this dataset includes participants from KEYNOTE-013 Cohort 3, KEYNOTE-087, and KEYNOTE-204 (cHL), KEYNOTE-012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055 (HNSCC), KEYNOTE-045 and KEYNOTE-052 (urothelial cancer), and KEYNOTE-177 (CRC). This dataset represents the established safety profile for pembrolizumab.

Patient exposure

KEYNOTE-716 is the first study of adjuvant treatment with pembrolizumab in participants with resected Stage IIB and IIC melanoma. The treatment phase of the study consists of 2 parts:

Part 1: Adjuvant therapy with pembrolizumab or placebo administered IV Q3W (200 mg for participants ≥18 years of age or 2 mg/kg up to a maximum of 200 mg for participants ≥12 years and <18 years of age) for a total of 17 administrations (~1 year) or until disease recurrence or unacceptable toxicity.

Part 2: For participants who developed disease recurrence during Part 1, optional crossover or rechallenge treatment with pembrolizumab administered IV Q3W for 17 administrations (~1 year) after resection of recurrent disease or up to 35 administrations (~2 years) for unresectable disease recurrence or unresectable distant recurrence, or until disease recurrence or unacceptable toxicity.

The safety analyses were conducted using the APaT population, which included all participants who were enrolled in Part 1 of KEYNOTE-716 and who received at least 1 dose of pembrolizumab or placebo as of the DCO date of 04-DEC-2020. The median duration of follow-up as of the DCO was 14.3 months (range: 1.0 to 26.4 months). The median duration of exposure to pembrolizumab in KEYNOTE-716 was similar to KEYNOTE-054 and was more than twice as long as the duration of exposure in the RSD (9.9 months, 11.8 months, and 4.9 months, respectively) (Table 1).

Table 1. Summary of Drug Exposure (APaT Population)

	KN716 Data for Pembrolizumab[k] (N=483)	KN716 Data for Placebo[l] (N=486)	KN054 Data for Pembrolizumab[m] (N=509)	EU Reference Safety Dataset for Pembrolizumab[n] (N=6185)
Study Days On-Therapy (Months)				
Mean	8.26	9.05	9.29	7.52
Median	9.9	11.0	11.8	4.9
SD	3.76	3.19	3.97	7.03
Range	0.0 to 15.4	0.0 to 15.2	0.0 to 15.7	0.0 to 32.5
Number of Administrations				
Mean	12.38	13.60	14.01	11.97
Median	15.0	16.0	18.0	8.0
SD	5.21	4.40	5.62	10.43
Range	1.0 to 17.0	1.0 to 17.0	1.0 to 18.0	1.0 to 59.0

Each participant is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

In KEYNOTE-716, 88.6% of participants remained on treatment for ≥3 months and 69.8% remained on treatment for ≥6 months. These results are similar to KEYNOTE-054, but higher than the RSD (Table 2).

Table 2. Drug Exposure by Duration (APaT Population)

	KN716 Data for Pembrolizumab[k] (N=483)			KN716 Data for Placebo[l] (N=486)			KN054 Data for Pembrolizumab[m] (N=509)			EU Reference Safety Dataset for Pembrolizumab[n] (N=6185)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	483	(100.0)	(332.4)	486	(100.0)	(366.7)	509	(100.0)	(394.1)	6,185	(100.0)	(3,876.2)
>=1 m	455	(94.2)	(331.5)	472	(97.1)	(366.2)	489	(96.1)	(393.1)	5,314	(85.9)	(3,847.5)
>=3 m	428	(88.6)	(327.0)	461	(94.9)	(364.1)	434	(85.3)	(382.8)	3,860	(62.4)	(3,605.3)
>=6 m	337	(69.8)	(292.4)	382	(78.6)	(333.4)	387	(76.0)	(365.3)	2,808	(45.4)	(3,222.9)
>=12 m	32	(6.6)	(34.6)	29	(6.0)	(31.4)	72	(14.1)	(76.2)	1,431	(23.1)	(2,180.6)

Each participant is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adexsum]

Demographic and other characteristics of Study Population in the different Safety Datasets are reported in Table 3.

Table 3. Participant Characteristics (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
Gender								
Male	297	(61.5)	287	(59.1)	320	(62.9)	4,039	(65.3)
Female	186	(38.5)	199	(40.9)	189	(37.1)	2,146	(34.7)
Age (Years)								
<65	299	(61.9)	295	(60.7)	385	(75.6)	3,587	(58.0)
>=65	184	(38.1)	191	(39.3)	124	(24.4)	2,598	(42.0)
Mean	59.1		59.5		53.9		60.2	
SD	12.6		13.2		13.6		13.6	
Median	60.0		61.0		54.0		62.0	
Range	16 to 84		17 to 87		19 to 88		15 to 94	
Race								
American Indian Or Alaska Native	1	(0.2)	0	(0.0)	0	(0.0)	30	(0.5)
Asian	4	(0.8)	0	(0.0)	0	(0.0)	695	(11.2)
Black Or African American	3	(0.6)	4	(0.8)	0	(0.0)	121	(2.0)
Multiracial	1	(0.2)	0	(0.0)	0	(0.0)	70	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
White	432	(89.4)	438	(90.1)	0	(0.0)	4,673	(75.6)
Missing	42	(8.7)	44	(9.1)	509	(100.0)	591	(9.6)
Ethnicity								
Hispanic Or Latino	49	(10.1)	30	(6.2)	0	(0.0)	424	(6.9)
Not Hispanic Or Latino	386	(79.9)	407	(83.7)	0	(0.0)	4,927	(79.7)
Not Reported	42	(8.7)	44	(9.1)	0	(0.0)	199	(3.2)
Unknown	6	(1.2)	5	(1.0)	0	(0.0)	117	(1.9)
Missing	0	(0.0)	0	(0.0)	509	(100.0)	518	(8.4)
Age Class (Years)								
<65	299	(61.9)	295	(60.7)	385	(75.6)	3,587	(58.0)
65-74	132	(27.3)	134	(27.6)	96	(18.9)	1,797	(29.1)
75-84	52	(10.8)	55	(11.3)	26	(5.1)	694	(11.2)
>=85	0	(0.0)	2	(0.4)	2	(0.4)	107	(1.7)
ECOG Performance Scale								
[0] Normal Activity	450	(93.2)	449	(92.4)	481	(94.5)	2,942	(47.6)
[1] Symptoms, but ambulatory	32	(6.6)	35	(7.2)	28	(5.5)	3,069	(49.6)

Other/Missing	1	(0.2)	2	(0.4)	0	(0.0)	174	(2.8)
Geographic Region								
EU	250	(51.8)	302	(62.1)	319	(62.7)	2,217	(35.8)
Ex-EU	233	(48.2)	184	(37.9)	190	(37.3)	3,968	(64.2)

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Race and ethnicity data were not collected for KN054.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Adverse events

Summary of adverse events

A comparison of safety parameters between the pembrolizumab and placebo groups of KEYNOTE-716 Safety Dataset, the RSD, and the consistency with KEYNOTE-054 are the focus of this summary. AEs were coded using MedDRA (Version 23.1) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. In Table 4 the summary of adverse event is reported.

Table 4. Adverse Event Summary (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	449	(93.0)	433	(89.1)	480	(94.3)	5,989	(96.8)
with no adverse event	34	(7.0)	53	(10.9)	29	(5.7)	196	(3.2)
with drug-related[a] adverse events	386	(79.9)	296	(60.9)	398	(78.2)	4,366	(70.6)
with toxicity grade 3-5 adverse events	125	(25.9)	83	(17.1)	162	(31.8)	2,984	(48.2)
with toxicity grade 3-5 drug-related adverse events	78	(16.1)	21	(4.3)	74	(14.5)	975	(15.8)
with serious adverse events	91	(18.8)	85	(17.5)	127	(25.0)	2,371	(38.3)
with serious drug-related adverse events	44	(9.1)	9	(1.9)	62	(12.2)	701	(11.3)
who died	0	(0.0)	4	(0.8)	1	(0.2)	321	(5.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	39	(0.6)
discontinued drug due to an adverse event	77	(15.9)	22	(4.5)	71	(13.9)	832	(13.5)
discontinued drug due to a drug-related adverse event	74	(15.3)	12	(2.5)	62	(12.2)	444	(7.2)
discontinued drug due to a serious adverse event	33	(6.8)	12	(2.5)	29	(5.7)	598	(9.7)
discontinued drug due to a serious drug-related adverse event	30	(6.2)	4	(0.8)	22	(4.3)	265	(4.3)

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

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.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

As provided, the exposure-adjusted incidence of AE category was either consistent or lower in the pembrolizumab group of KEYNOTE-716 compared with the RSD, except for drug-related AEs and AEs resulting in treatment discontinuation (Table 5).

Table 5. Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN716 Data for Pembrolizumab[k]	KN716 Data for Placebo[l]	KN054 Data for Pembrolizumab[m]	EU Reference Safety Dataset for Pembrolizumab[n]
Number of participants exposed	483	486	509	6185
Total exposure[b] in person-months	4376.85	4776.40	5230.95	52032.15
Total events (rate)				
adverse events	3744 (85.54)	2838 (59.42)	4924 (94.13)	65352 (125.60)
drug-related[c] adverse events	1738 (39.71)	983 (20.58)	2285 (43.68)	20469 (39.34)
toxicity grade 3-5 adverse events	181 (4.14)	121 (2.53)	286 (5.47)	6514 (12.52)
toxicity grade 3-5 drug-related adverse events	107 (2.44)	26 (0.54)	124 (2.37)	1469 (2.82)
serious adverse events	137 (3.13)	124 (2.60)	244 (4.66)	4283 (8.23)
serious drug-related adverse events	54 (1.23)	9 (0.19)	117 (2.24)	976 (1.88)
adverse events leading to death	0 (0.00)	4 (0.08)	1 (0.02)	328 (0.63)
drug-related adverse events leading to death	0 (0.00)	0 (0.00)	0 (0.00)	39 (0.07)
adverse events resulting in drug discontinuation	85 (1.94)	27 (0.57)	81 (1.55)	904 (1.74)
drug-related adverse events resulting in drug discontinuation	82 (1.87)	16 (0.33)	70 (1.34)	481 (0.92)
serious adverse events resulting in drug discontinuation	33 (0.75)	12 (0.25)	31 (0.59)	635 (1.22)
serious drug-related adverse events resulting in drug discontinuation	30 (0.69)	4 (0.08)	23 (0.44)	279 (0.54)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[b] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
For participants who received second course treatment, adverse events which occurred in second course phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae] [Table 5.3.5.3.3-melanoma9: 5]

Common adverse events

The overall incidences of AEs in KEYNOTE-716 were similar in the pembrolizumab and placebo groups. AEs that occurred at a higher incidence in the pembrolizumab group than in the placebo group, and with the greatest difference in incidence (≥8 percentage points) between the treatment groups, were *diarrhoea*, *pruritus, rash*, *hypothyroidism*, and *hyperthyroidism* (Fig. 1). The most frequently reported AEs (incidence >20%) in KEYNOTE-716, *fatigue*, *diarrhoea*, *pruritus*, and *arthralgia*, were similar to the most frequently reported AEs in KEYNOTE-054 and were generally consistent with the RSD (Table 6).

Fig. 1. Rainfall Plot for Specific Adverse Event Preferred Terms Sorted by Risk Difference (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

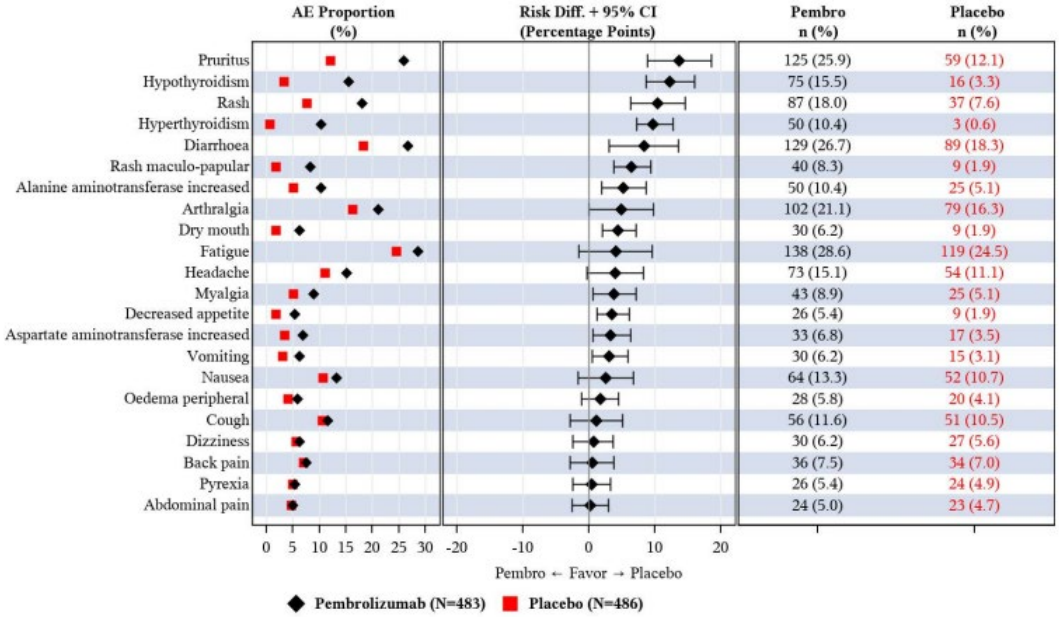


Table 6. Participants with Adverse Events (Incidence ≥ 10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	449	(93.0)	433	(89.1)	480	(94.3)	5,989	(96.8)
with no adverse events	34	(7.0)	53	(10.9)	29	(5.7)	196	(3.2)
Fatigue	138	(28.6)	119	(24.5)	170	(33.4)	1,967	(31.8)
Diarrhoea	129	(26.7)	89	(18.3)	139	(27.3)	1,295	(20.9)
Pruritus	125	(25.9)	59	(12.1)	103	(20.2)	1,111	(18.0)
Arthralgia	102	(21.1)	79	(16.3)	90	(17.7)	1,149	(18.6)
Rash	87	(18.0)	37	(7.6)	67	(13.2)	936	(15.1)
Hypothyroidism	75	(15.5)	16	(3.3)	76	(14.9)	699	(11.3)
Headache	73	(15.1)	54	(11.1)	95	(18.7)	747	(12.1)
Nausea	64	(13.3)	52	(10.7)	89	(17.5)	1,282	(20.7)
Cough	56	(11.6)	51	(10.5)	71	(13.9)	1,200	(19.4)
Asthenia	51	(10.6)	53	(10.9)	55	(10.8)	692	(11.2)
Alanine aminotransferase increased	50	(10.4)	25	(5.1)	38	(7.5)	429	(6.9)
Hyperthyroidism	50	(10.4)	3	(0.6)	53	(10.4)	261	(4.2)
Constipation	37	(7.7)	38	(7.8)	34	(6.7)	1,032	(16.7)
Hypertension	37	(7.7)	41	(8.4)	76	(14.9)	318	(5.1)
Back pain	36	(7.5)	34	(7.0)	36	(7.1)	709	(11.5)
Vomiting	30	(6.2)	15	(3.1)	40	(7.9)	784	(12.7)
Decreased appetite	26	(5.4)	9	(1.9)	36	(7.1)	1,181	(19.1)
Pyrexia	26	(5.4)	24	(4.9)	24	(4.7)	802	(13.0)
Dyspnoea	20	(4.1)	23	(4.7)	45	(8.8)	1,020	(16.5)
Anaemia	15	(3.1)	11	(2.3)	7	(1.4)	872	(14.1)
Weight decreased	12	(2.5)	5	(1.0)	56	(11.0)	574	(9.3)
Influenza like illness	10	(2.1)	11	(2.3)	56	(11.0)	245	(4.0)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Weight increased	3	(0.6)	6	(1.2)	65	(12.8)	209	(3.4)

Every participant 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.

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

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Drug-related Adverse Events

The treatment-related AEs of *pruritus, rash*, *hypothyroidism*, and *hyperthyroidism* were reported at higher incidences in the pembrolizumab group than in the placebo group. The incidence and types of drug-related AEs in the different datasets are reported in Table 5. The most frequently reported drug-related AEs (incidence >10%) in KEYNOTE-716, *pruritus*, *fatigue*, *diarrhoea*, *rash*, *hypothyroidism*, and *arthralgia*, were consistent with the most frequently reported drug-related AEs in KEYNOTE-054 (Table 7).

Table 7. Participants with Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	386	(79.9)	296	(60.9)	398	(78.2)	4,366	(70.6)
with no adverse events	97	(20.1)	190	(39.1)	111	(21.8)	1,819	(29.4)
Pruritus	112	(23.2)	48	(9.9)	87	(17.1)	871	(14.1)
Fatigue	98	(20.3)	87	(17.9)	144	(28.3)	1,216	(19.7)
Diarrhoea	85	(17.6)	51	(10.5)	93	(18.3)	681	(11.0)
Rash	75	(15.5)	29	(6.0)	50	(9.8)	702	(11.4)
Hypothyroidism	70	(14.5)	12	(2.5)	74	(14.5)	605	(9.8)
Arthralgia	69	(14.3)	35	(7.2)	52	(10.2)	490	(7.9)
Hyperthyroidism	48	(9.9)	3	(0.6)	49	(9.6)	231	(3.7)
Asthenia	43	(8.9)	40	(8.2)	47	(9.2)	376	(6.1)
Nausea	38	(7.9)	31	(6.4)	59	(11.6)	561	(9.1)
Alanine aminotransferase increased	34	(7.0)	18	(3.7)	26	(5.1)	254	(4.1)
Rash maculo-papular	34	(7.0)	8	(1.6)	24	(4.7)	166	(2.7)
Aspartate aminotransferase increased	28	(5.8)	8	(1.6)	20	(3.9)	244	(3.9)
Myalgia	27	(5.6)	14	(2.9)	26	(5.1)	236	(3.8)
Headache	19	(3.9)	13	(2.7)	37	(7.3)	199	(3.2)
Decreased appetite	16	(3.3)	4	(0.8)	25	(4.9)	479	(7.7)
Dyspnoea	6	(1.2)	2	(0.4)	27	(5.3)	204	(3.3)

Every participant 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.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Grade 3 to 5 Adverse Events

The overall incidence of Grade 3 to 5 AEs was higher in the pembrolizumab group compared with the placebo group. The most frequently reported Grade 3 to 5 AEs (in ≥1.0% of participants in either

treatment group) were *hypertension*, *diarrhoea*, *rash*, *autoimmune hepatitis*, *ALT increased*, *colitis*, and *lipase increased* but no clinically meaningful difference was observed between the pembrolizumab and placebo groups in the incidences of these Grade 3 to 5 AEs (Fig. 2)

Table 8 displays the number and percentage of subjects with Grade 3 to 5 AEs (incidence ≥1%) in different datasets. No Grade 5 AEs occurred in the pembrolizumab group.

Fig. 2. Rainfall Plot for Grade 3-5 Adverse Event Preferred Terms Sorted by Risk Difference (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

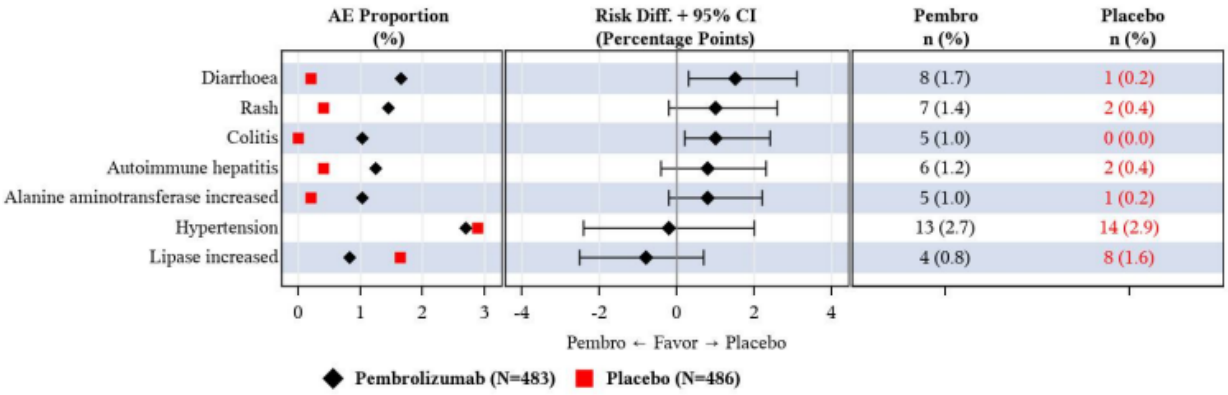


Table 8. Participants With Grade 3-5 Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	125	(25.9)	83	(17.1)	162	(31.8)	2,984	(48.2)
with no adverse events	358	(74.1)	403	(82.9)	347	(68.2)	3,201	(51.8)
Hypertension	13	(2.7)	14	(2.9)	28	(5.5)	113	(1.8)
Diarrhoea	8	(1.7)	1	(0.2)	6	(1.2)	91	(1.5)
Rash	7	(1.4)	2	(0.4)	2	(0.4)	31	(0.5)
Autoimmune hepatitis	6	(1.2)	2	(0.4)	3	(0.6)	21	(0.3)
Alanine aminotransferase increased	5	(1.0)	1	(0.2)	3	(0.6)	67	(1.1)
Colitis	5	(1.0)	0	(0.0)	7	(1.4)	64	(1.0)
Blood creatine phosphokinase increased	4	(0.8)	2	(0.4)	6	(1.2)	15	(0.2)
Lipase increased	4	(0.8)	8	(1.6)	6	(1.2)	17	(0.3)
Aspartate aminotransferase increased	3	(0.6)	2	(0.4)	1	(0.2)	70	(1.1)
Back pain	2	(0.4)	0	(0.0)	0	(0.0)	66	(1.1)
Decreased appetite	2	(0.4)	0	(0.0)	1	(0.2)	74	(1.2)
Fatigue	2	(0.4)	0	(0.0)	4	(0.8)	150	(2.4)
Hyperglycaemia	2	(0.4)	1	(0.2)	3	(0.6)	67	(1.1)
Type 1 diabetes mellitus	2	(0.4)	0	(0.0)	5	(1.0)	14	(0.2)
Arthralgia	1	(0.2)	2	(0.4)	7	(1.4)	59	(1.0)
Asthenia	1	(0.2)	0	(0.0)	1	(0.2)	61	(1.0)
Dehydration	1	(0.2)	0	(0.0)	0	(0.0)	64	(1.0)
Hypokalaemia	1	(0.2)	0	(0.0)	3	(0.6)	62	(1.0)
Pleural effusion	1	(0.2)	0	(0.0)	0	(0.0)	69	(1.1)
Pneumonia	1	(0.2)	1	(0.2)	2	(0.4)	255	(4.1)
Pneumonitis	1	(0.2)	0	(0.0)	3	(0.6)	89	(1.4)
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	247	(4.0)
Basal cell carcinoma	0	(0.0)	0	(0.0)	5	(1.0)	11	(0.2)
Dyspnoea	0	(0.0)	0	(0.0)	1	(0.2)	133	(2.2)
Hyponatraemia	0	(0.0)	0	(0.0)	5	(1.0)	161	(2.6)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Pulmonary embolism	0	(0.0)	2	(0.4)	5	(1.0)	94	(1.5)
Urinary tract infection	0	(0.0)	1	(0.2)	0	(0.0)	74	(1.2)

Every participant 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.

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

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Table 9. Participants with Grade 3-5 Drug-Related Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	78	(16.1)	21	(4.3)	74	(14.5)	975	(15.8)
with no adverse events	405	(83.9)	465	(95.7)	435	(85.5)	5,210	(84.2)
Rash	7	(1.4)	1	(0.2)	0	(0.0)	24	(0.4)
Autoimmune hepatitis	6	(1.2)	2	(0.4)	3	(0.6)	21	(0.3)
Colitis	5	(1.0)	0	(0.0)	7	(1.4)	57	(0.9)
Diarrhoea	5	(1.0)	1	(0.2)	4	(0.8)	60	(1.0)
Lipase increased	4	(0.8)	8	(1.6)	4	(0.8)	12	(0.2)
Type 1 diabetes mellitus	2	(0.4)	0	(0.0)	5	(1.0)	13	(0.2)
Fatigue	1	(0.2)	0	(0.0)	4	(0.8)	66	(1.1)
Pneumonitis	1	(0.2)	0	(0.0)	3	(0.6)	84	(1.4)

Every participant 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.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Serious adverse event/deaths/other significant events

Deaths Due to Adverse Events

No participants in the KEYNOTE-716 pembrolizumab group and 4 participants in the placebo group had an AE that resulted in death during the study or follow-up period. None of the deaths were reported as drug related.

All Serious Adverse Events

The overall incidence of SAEs was similar in the pembrolizumab and placebo groups (18.8% and 17.5%, respectively). *Basal cell carcinoma*, *malignant melanoma in situ*, and *squamous cell carcinoma* were the most frequently reported SAEs (in >1.0% of participants in either treatment group) (Fig. 3). Table 10 displays the number and percentage of subjects with SAEs (incidence ≥1%) in different safety datasets.

Fig. 3. Rainfall Plot for Serious Adverse Event Preferred Terms Sorted by Risk Difference (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

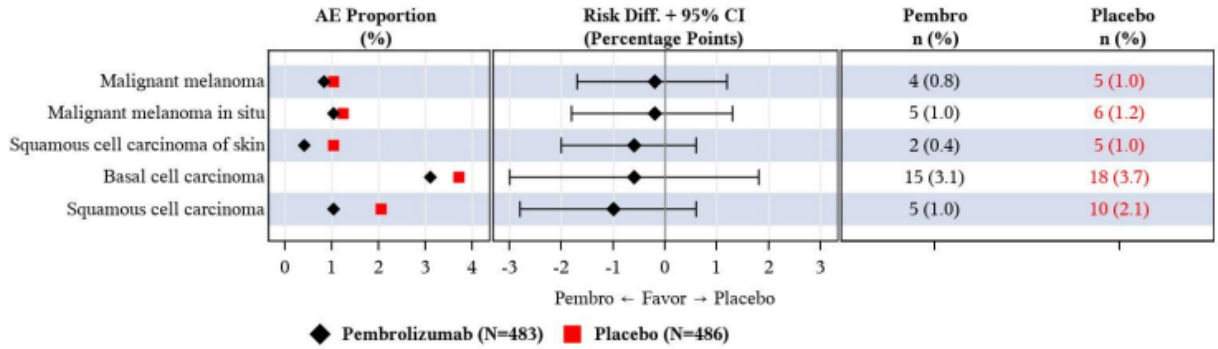


Table 10. Participants with Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	91	(18.8)	85	(17.5)	127	(25.0)	2,371	(38.3)
with no adverse events	392	(81.2)	401	(82.5)	382	(75.0)	3,814	(61.7)
Basal cell carcinoma	15	(3.1)	18	(3.7)	17	(3.3)	40	(0.6)
Malignant melanoma in situ	5	(1.0)	6	(1.2)	1	(0.2)	2	(0.0)
Squamous cell carcinoma	5	(1.0)	10	(2.1)	6	(1.2)	27	(0.4)
Colitis	4	(0.8)	0	(0.0)	7	(1.4)	61	(1.0)
Malignant melanoma	4	(0.8)	5	(1.0)	4	(0.8)	11	(0.2)
Diarrhoea	2	(0.4)	1	(0.2)	5	(1.0)	63	(1.0)
Pneumonia	2	(0.4)	1	(0.2)	2	(0.4)	257	(4.2)
Squamous cell carcinoma of skin	2	(0.4)	5	(1.0)	1	(0.2)	6	(0.1)
Pleural effusion	1	(0.2)	0	(0.0)	1	(0.2)	83	(1.3)
Pneumonitis	1	(0.2)	0	(0.0)	7	(1.4)	126	(2.0)
Pulmonary embolism	1	(0.2)	2	(0.4)	2	(0.4)	72	(1.2)
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	61	(1.0)
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	82	(1.3)
Pyrexia	0	(0.0)	1	(0.2)	4	(0.8)	75	(1.2)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Urinary tract infection	0	(0.0)	1	(0.2)	0	(0.0)	59	(1.0)

Every participant 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.

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

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Drug-related Serious Adverse Events

The overall incidence of treatment-related SAEs was higher in the pembrolizumab group than in the placebo group (9.1% vs. 1.9%). The most frequently reported treatment-related SAEs in the pembrolizumab group were *adrenal insufficiency* and *colitis*, each reported for 4 participants (0.8%) (Table 11). Overall, the incidences and types of drug-related SAEs in the KEYNOTE-716 pembrolizumab group were similar to those in KEYNOTE-054 (12.2%) and generally consistent with the RSD (11.3%) (Table 12)

Table 11. Participants With Serious Drug-Related Adverse Events by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)
Type 2 diabetes mellitus	1	(0.2)	0	(0.0)
Autoimmune myocarditis	0	(0.0)	1	(0.2)
Cardiac failure	0	(0.0)	1	(0.2)
Facial paralysis	0	(0.0)	1	(0.2)
Infusion related reaction	0	(0.0)	1	(0.2)
Infusion site rash	0	(0.0)	1	(0.2)
Neuralgic amyotrophy	0	(0.0)	1	(0.2)
Pyrexia	0	(0.0)	1	(0.2)

Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V23.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adae]

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	483		486	
with one or more adverse events	44	(9.1)	9	(1.9)
with no adverse events	439	(90.9)	477	(98.1)
Adrenal insufficiency	4	(0.8)	0	(0.0)
Colitis	4	(0.8)	0	(0.0)
Acute kidney injury	2	(0.4)	0	(0.0)
Autoimmune colitis	2	(0.4)	0	(0.0)
Autoimmune hepatitis	2	(0.4)	1	(0.2)
Autoimmune nephritis	2	(0.4)	0	(0.0)
Diarrhoea	2	(0.4)	1	(0.2)
Hypophysitis	2	(0.4)	0	(0.0)
Hypopituitarism	2	(0.4)	0	(0.0)
Immune-mediated pneumonitis	2	(0.4)	0	(0.0)
Myasthenia gravis	2	(0.4)	0	(0.0)
Myositis	2	(0.4)	0	(0.0)
Type 1 diabetes mellitus	2	(0.4)	0	(0.0)
Abscess soft tissue	1	(0.2)	0	(0.0)
Acute respiratory failure	1	(0.2)	0	(0.0)
Arthritis	1	(0.2)	0	(0.0)
Blood creatine phosphokinase increased	1	(0.2)	0	(0.0)
Cellulitis	1	(0.2)	0	(0.0)
Cough	1	(0.2)	0	(0.0)
Decreased appetite	1	(0.2)	0	(0.0)
Dermatitis bullous	1	(0.2)	0	(0.0)
Endocrine disorder	1	(0.2)	0	(0.0)
Immune-mediated enterocolitis	1	(0.2)	0	(0.0)
Lipase increased	1	(0.2)	0	(0.0)
Lung disorder	1	(0.2)	0	(0.0)
Macular detachment	1	(0.2)	0	(0.0)
Muscular weakness	1	(0.2)	0	(0.0)
Myelitis transverse	1	(0.2)	0	(0.0)
Myopathy	1	(0.2)	0	(0.0)
Nephritis	1	(0.2)	0	(0.0)
Peripheral sensory neuropathy	1	(0.2)	0	(0.0)
Pneumonia	1	(0.2)	0	(0.0)
Pneumonitis	1	(0.2)	0	(0.0)
Sarcoidosis	1	(0.2)	0	(0.0)

Table 12. Participants with Drug-related Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	44	(9.1)	9	(1.9)	62	(12.2)	701	(11.3)
with no adverse events	439	(90.9)	477	(98.1)	447	(87.8)	5,484	(88.7)
Colitis	4	(0.8)	0	(0.0)	7	(1.4)	53	(0.9)
Pneumonitis	1	(0.2)	0	(0.0)	7	(1.4)	120	(1.9)

Every participant 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.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Adverse Events of Special Interest (AEOSI)

Summary of Adverse Event of Special Interest

In KEYNOTE-716, the overall incidence of AEOSI was higher in the pembrolizumab group (36.2%) compared with the placebo group (8.4%). Fewer than 10% of participants in the pembrolizumab group discontinued study treatment due to an AEOSI (Table 13). In the pembrolizumab group, the median time to onset of participants' first AEOSI episode was 64.0 days and the median duration of AEOSI episodes in the pembrolizumab group was 193.0 days, with an average of 1.5 AEOSI episodes per participant. The most frequently reported AEOSI in the pembrolizumab group were *hypothyroidism* and *hyperthyroidism*, similar to those reported in KEYNOTE-054 and generally consistent with the RSD (Table 14~~2~~). Most AEOSI were Grade 1 or Grade 2 and the use of systemic corticosteroids was reported for management of some or all episodes of AEOSI, with the following exceptions*:* *hyperthyroidism*, *infusion reactions*, *pancreatitis, type 1 diabetes mellitus*, and *uveitis*. In addition, the exposure-adjusted incidences of AEOSI were generally similar between KEYNOTE-716, KEYNOTE-054 and the RSD (Table 15).

Table 13. Adverse Event Summary AEOSI (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	175	(36.2)	41	(8.4)	179	(35.2)	1,580	(25.5)
with no adverse event	308	(63.8)	445	(91.6)	330	(64.8)	4,605	(74.5)
with drug-related[a] adverse events	167	(34.6)	30	(6.2)	165	(32.4)	1,369	(22.1)
with toxicity grade 3-5 adverse events	47	(9.7)	6	(1.2)	39	(7.7)	407	(6.6)
with toxicity grade 3-5 drug-related adverse events	46	(9.5)	4	(0.8)	34	(6.7)	352	(5.7)
with serious adverse events	33	(6.8)	4	(0.8)	40	(7.9)	407	(6.6)
with serious drug-related adverse events	32	(6.6)	3	(0.6)	36	(7.1)	360	(5.8)
who died	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)
discontinued drug due to an adverse event	41	(8.5)	3	(0.6)	34	(6.7)	256	(4.1)
discontinued drug due to a drug-related adverse event	41	(8.5)	3	(0.6)	34	(6.7)	252	(4.1)
discontinued drug due to a serious adverse event	23	(4.8)	2	(0.4)	12	(2.4)	172	(2.8)
discontinued drug due to a serious drug-related adverse event	23	(4.8)	2	(0.4)	12	(2.4)	170	(2.7)

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

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.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Table 14. Participants With Adverse Events of Special Interest (Incidence > 0% in One or More Treatment Groups) By AEOSI Category and Preferred Term (APaT Population)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	175	(36.2)	41	(8.4)	179	(35.2)	1,580	(25.5)
with no adverse events	308	(63.8)	445	(91.6)	330	(64.8)	4,605	(74.5)
Adrenal Insufficiency	**11**	**(2.3)**	**0**	**(0.0)**	**5**	**(1.0)**	**52**	**(0.8)**
Adrenal insufficiency	11	(2.3)	0	(0.0)	4	(0.8)	47	(0.8)
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Colitis	**17**	**(3.5)**	**4**	**(0.8)**	**20**	**(3.9)**	**122**	**(2.0)**
Colitis	13	(2.7)	4	(0.8)	13	(2.6)	104	(1.7)
Autoimmune colitis	2	(0.4)	0	(0.0)	1	(0.2)	4	(0.1)
Immune-mediated enterocolitis	2	(0.4)	0	(0.0)	4	(0.8)	4	(0.1)
Colitis microscopic	0	(0.0)	0	(0.0)	2	(0.4)	4	(0.1)
Enterocolitis	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**
Encephalitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hepatitis	**10**	**(2.1)**	**3**	**(0.6)**	**9**	**(1.8)**	**61**	**(1.0)**
Autoimmune hepatitis	7	(1.4)	2	(0.4)	3	(0.6)	26	(0.4)
Hepatitis	3	(0.6)	1	(0.2)	6	(1.2)	26	(0.4)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Hepatitis	**10**	**(2.1)**	**3**	**(0.6)**	**9**	**(1.8)**	**61**	**(1.0)**
Immune-mediated hepatitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hyperthyroidism	**50**	**(10.4)**	**3**	**(0.6)**	**53**	**(10.4)**	**261**	**(4.2)**
Hyperthyroidism	50	(10.4)	3	(0.6)	53	(10.4)	261	(4.2)
Hypophysitis	**10**	**(2.1)**	**0**	**(0.0)**	**11**	**(2.2)**	**38**	**(0.6)**
Hypophysitis	5	(1.0)	0	(0.0)	7	(1.4)	23	(0.4)
Hypopituitarism	5	(1.0)	0	(0.0)	3	(0.6)	14	(0.2)
Lymphocytic hypophysitis	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.0)
Hypothyroidism	**76**	**(15.7)**	**17**	**(3.5)**	**76**	**(14.9)**	**700**	**(11.3)**
Hypothyroidism	75	(15.5)	16	(3.3)	76	(14.9)	699	(11.3)
Autoimmune hypothyroidism	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated hypothyroidism	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**5**	**(1.0)**	**6**	**(1.2)**	**11**	**(2.2)**	**152**	**(2.5)**
Hypersensitivity	2	(0.4)	0	(0.0)	3	(0.6)	51	(0.8)
Infusion related reaction	2	(0.4)	4	(0.8)	2	(0.4)	63	(1.0)
Drug hypersensitivity	1	(0.2)	2	(0.4)	4	(0.8)	21	(0.3)
Anaphylactic reaction	0	(0.0)	0	(0.0)	2	(0.4)	10	(0.2)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Myasthenic Syndrome	**2**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.2)**	**3**	**(0.0)**
Myasthenia gravis	2	(0.4)	0	(0.0)	1	(0.2)	1	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myelitis	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Myelitis transverse	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Myelitis	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**	**7**	**(0.1)**
Autoimmune myocarditis	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Myocarditis	0	(0.0)	0	(0.0)	1	(0.2)	7	(0.1)
Myositis	**6**	**(1.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**21**	**(0.3)**
Myositis	4	(0.8)	0	(0.0)	1	(0.2)	14	(0.2)
Myopathy	2	(0.4)	0	(0.0)	0	(0.0)	4	(0.1)
Necrotising myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Nephritis	**7**	**(1.4)**	**0**	**(0.0)**	**2**	**(0.4)**	**25**	**(0.4)**
Autoimmune nephritis	3	(0.6)	0	(0.0)	1	(0.2)	3	(0.0)
Nephritis	3	(0.6)	0	(0.0)	0	(0.0)	4	(0.1)
Glomerulonephritis acute	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)	1	(0.2)	11	(0.2)
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Glomerulonephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pancreatitis	**2**	**(0.4)**	**0**	**(0.0)**	**2**	**(0.4)**	**21**	**(0.3)**
Pancreatitis	2	(0.4)	0	(0.0)	2	(0.4)	17	(0.3)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis acute	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.1)
Pneumonitis	**9**	**(1.9)**	**3**	**(0.6)**	**19**	**(3.7)**	**288**	**(4.7)**
Pneumonitis	7	(1.4)	3	(0.6)	18	(3.5)	263	(4.3)
Immune-mediated pneumonitis	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Pneumonitis	**9**	**(1.9)**	**3**	**(0.6)**	**19**	**(3.7)**	**288**	**(4.7)**
Interstitial lung disease	0	(0.0)	0	(0.0)	1	(0.2)	25	(0.4)
Organising pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Sarcoidosis	**5**	**(1.0)**	**0**	**(0.0)**	**7**	**(1.4)**	**10**	**(0.2)**
Sarcoidosis	3	(0.6)	0	(0.0)	7	(1.4)	10	(0.2)
Pulmonary sarcoidosis	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Cutaneous sarcoidosis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Severe Skin Reactions	**14**	**(2.9)**	**3**	**(0.6)**	**5**	**(1.0)**	**102**	**(1.6)**
Rash	7	(1.4)	2	(0.4)	2	(0.4)	31	(0.5)
Pruritus	3	(0.6)	0	(0.0)	0	(0.0)	12	(0.2)
Rash maculo-papular	2	(0.4)	1	(0.2)	1	(0.2)	17	(0.3)
Rash pruritic	2	(0.4)	0	(0.0)	0	(0.0)	2	(0.0)
Dermatitis bullous	1	(0.2)	0	(0.0)	0	(0.0)	8	(0.1)
Erythema multiforme	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Rash pustular	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	1	(0.2)	5	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Pemphigoid	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash erythematous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Toxic skin eruption	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Thyroiditis	**8**	**(1.7)**	**2**	**(0.4)**	**14**	**(2.8)**	**60**	**(1.0)**
Autoimmune thyroiditis	5	(1.0)	1	(0.2)	3	(0.6)	16	(0.3)

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Thyroiditis	**8**	**(1.7)**	**2**	**(0.4)**	**14**	**(2.8)**	**60**	**(1.0)**
Thyroiditis	2	(0.4)	1	(0.2)	11	(2.2)	43	(0.7)
Immune-mediated thyroiditis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroid disorder	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Type 1 Diabetes Mellitus	**2**	**(0.4)**	**0**	**(0.0)**	**5**	**(1.0)**	**21**	**(0.3)**
Type 1 diabetes mellitus	2	(0.4)	0	(0.0)	5	(1.0)	17	(0.3)
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	2	(0.4)	9	(0.1)
Uveitis	**1**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.4)**	**23**	**(0.4)**
Iritis	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.0)
Chorioretinitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.1)
Uveitis	0	(0.0)	0	(0.0)	1	(0.2)	15	(0.2)
Vasculitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Vasculitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Vasculitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

Every participant 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.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Table 15. Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) AEOSI (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN716 Data for Pembrolizumab[k]	KN716 Data for Placebo[l]	KN054 Data for Pembrolizumab[m]	EU Reference Safety Dataset for Pembrolizumab[n]
Number of participants exposed	483	486	509	6185
Total exposure[b] in person-months	4376.85	4776.40	5230.95	52032.15
Total events (rate)				
adverse events	256 (5.85)	43 (0.90)	364 (6.96)	2322 (4.46)
drug-related[c] adverse events	241 (5.51)	31 (0.65)	336 (6.42)	1995 (3.83)
toxicity grade 3-5 adverse events	54 (1.23)	6 (0.13)	66 (1.26)	484 (0.93)
toxicity grade 3-5 drug-related adverse events	52 (1.19)	4 (0.08)	59 (1.13)	419 (0.81)
serious adverse events	35 (0.80)	4 (0.08)	65 (1.24)	482 (0.93)
serious drug-related adverse events	34 (0.78)	3 (0.06)	60 (1.15)	429 (0.82)
adverse events leading to death	0 (0.00)	0 (0.00)	0 (0.00)	11 (0.02)
drug-related adverse events leading to death	0 (0.00)	0 (0.00)	0 (0.00)	11 (0.02)
adverse events resulting in drug discontinuation	41 (0.94)	3 (0.06)	34 (0.65)	262 (0.50)
drug-related adverse events resulting in drug discontinuation	41 (0.94)	3 (0.06)	34 (0.65)	258 (0.50)
serious adverse events resulting in drug discontinuation	23 (0.53)	2 (0.04)	12 (0.23)	177 (0.34)

	Event Count and Rate (Events/100 person-months)[a]			
	KN716 Data for Pembrolizumab[k]	KN716 Data for Placebo[l]	KN054 Data for Pembrolizumab[m]	EU Reference Safety Dataset for Pembrolizumab[n]
serious drug-related adverse events resulting in drug discontinuation	23 (0.53)	2 (0.04)	12 (0.23)	175 (0.34)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[b] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
For participants who received second course treatment, adverse events which occurred in second course phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Laboratory findings

Changes over time from baseline laboratory measurements were generally representative of the pre-existing, underlying disease state. In KEYNOTE-716 most changes in toxicity grade from baseline to the worst post-baseline value were changes to toxicity Grades ⩽2 (Table 16). The proportions of participants in KEYNOTE-716 who had at least 1 postbaseline abnormality in ALT or AST (i.e., toxicity Grade 1, 2, 3, or 4) were 28.9% and 24.2%, respectively in the pembrolizumab group, compared with 14.6% and 12.3%, respectively in the placebo group. Shifts to a highest postbaseline value of Grades 3 and 4 were reported for the following laboratory test results in >1% of participants in the pembrolizumab arm (vs. placebo group): lymphocytes decreased (2.9% vs. 3.3%), GGT increased (2.2% vs. 1.5%), ALT increased (2.5% vs. 0.4%), cholesterol increased (2.7% vs. 0%), and AST increased (1.5% vs. 0.8).

Table 16. Summary of Subjects with Increases from Baseline in Laboratory Test Toxicity Grade Based on Highest Post-baseline Toxicity Grade (Overall Incidence > 0% in One or More Treatment Groups) (APaT Population)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Activated Partial Thromboplastin Time Increased (Activated partial thromboplastin time prolonged)						
Subjects with Baseline and Post-baseline Measurements	125		141		266	
Grade 1	10	(8.0)	11	(7.8)	21	(7.9)
Grade 2	0	(0.0)	2	(1.4)	2	(0.8)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)
All Grades	10	(8.0)	13	(9.2)	23	(8.6)
Alanine Aminotransferase Increased (Alanine aminotransferase increased)						
Subjects with Baseline and Post-baseline Measurements	481		480		961	
Grade 1	116	(24.1)	64	(13.3)	180	(18.7)
Grade 2	11	(2.3)	4	(0.8)	15	(1.6)
Grade 3	12	(2.5)	2	(0.4)	14	(1.5)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	12	(2.5)	2	(0.4)	14	(1.5)
All Grades	139	(28.9)	70	(14.6)	209	(21.7)
Albumin Decreased (Hypoalbuminemia)						
Subjects with Baseline and Post-baseline Measurements	477		478		955	
Grade 1	39	(8.2)	19	(4.0)	58	(6.1)
Grade 2	7	(1.5)	2	(0.4)	9	(0.9)
Grade 3	3	(0.6)	2	(0.4)	5	(0.5)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	3	(0.6)	2	(0.4)	5	(0.5)
All Grades	49	(10.3)	23	(4.8)	72	(7.5)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Alkaline Phosphatase Increased (Alkaline phosphatase increased)						
Subjects with Baseline and Post-baseline Measurements	477		479		956	
Grade 1	41	(8.6)	28	(5.8)	69	(7.2)
Grade 2	2	(0.4)	1	(0.2)	3	(0.3)
Grade 3	1	(0.2)	0	(0.0)	1	(0.1)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	1	(0.2)	0	(0.0)	1	(0.1)
All Grades	44	(9.2)	29	(6.1)	73	(7.6)
Aspartate Aminotransferase Increased (Aspartate aminotransferase increased)						
Subjects with Baseline and Post-baseline Measurements	480		479		959	
Grade 1	97	(20.2)	52	(10.9)	149	(15.5)
Grade 2	12	(2.5)	3	(0.6)	15	(1.6)
Grade 3	7	(1.5)	4	(0.8)	11	(1.1)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	7	(1.5)	4	(0.8)	11	(1.1)
All Grades	116	(24.2)	59	(12.3)	175	(18.2)
Bilirubin Increased (Blood bilirubin increased)						
Subjects with Baseline and Post-baseline Measurements	481		480		961	
Grade 1	42	(8.7)	46	(9.6)	88	(9.2)
Grade 2	8	(1.7)	12	(2.5)	20	(2.1)
Grade 3	1	(0.2)	1	(0.2)	2	(0.2)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	1	(0.2)	1	(0.2)	2	(0.2)
All Grades	51	(10.6)	59	(12.3)	110	(11.4)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Calcium Decreased (Hypocalcemia)						
Subjects with Baseline and Post-baseline Measurements	475		482		957	
Grade 1	42	(8.8)	40	(8.3)	82	(8.6)
Grade 2	4	(0.8)	4	(0.8)	8	(0.8)
Grade 3	1	(0.2)	1	(0.2)	2	(0.2)
Grade 4	3	(0.6)	0	(0.0)	3	(0.3)
Grade 3-4	4	(0.8)	1	(0.2)	5	(0.5)
All Grades	50	(10.5)	45	(9.3)	95	(9.9)
Calcium Increased (Hypercalcemia)						
Subjects with Baseline and Post-baseline Measurements	475		482		957	
Grade 1	32	(6.7)	28	(5.8)	60	(6.3)
Grade 2	1	(0.2)	3	(0.6)	4	(0.4)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)
All Grades	33	(6.9)	31	(6.4)	64	(6.7)
Cholesterol Increased (Cholesterol high)						
Subjects with Baseline and Post-baseline Measurements	75		91		166	
Grade 1	14	(18.7)	13	(14.3)	27	(16.3)
Grade 2	5	(6.7)	2	(2.2)	7	(4.2)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	2	(2.7)	0	(0.0)	2	(1.2)
Grade 3-4	2	(2.7)	0	(0.0)	2	(1.2)
All Grades	21	(28.0)	15	(16.5)	36	(21.7)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Creatinine Increased (Creatinine increased)						
Subjects with Baseline and Post-baseline Measurements	481		483		964	
Grade 1	59	(12.3)	42	(8.7)	101	(10.5)
Grade 2	13	(2.7)	6	(1.2)	19	(2.0)
Grade 3	1	(0.2)	1	(0.2)	2	(0.2)
Grade 4	3	(0.6)	0	(0.0)	3	(0.3)
Grade 3-4	4	(0.8)	1	(0.2)	5	(0.5)
All Grades	76	(15.8)	49	(10.1)	125	(13.0)
Gamma Glutamyl Transferase Increased (GGT increased)						
Subjects with Baseline and Post-baseline Measurements	186		199		385	
Grade 1	25	(13.4)	21	(10.6)	46	(11.9)
Grade 2	9	(4.8)	4	(2.0)	13	(3.4)
Grade 3	3	(1.6)	3	(1.5)	6	(1.6)
Grade 4	1	(0.5)	0	(0.0)	1	(0.3)
Grade 3-4	4	(2.2)	3	(1.5)	7	(1.8)
All Grades	38	(20.4)	28	(14.1)	66	(17.1)
Glucose Decreased (Hypoglycemia)						
Subjects with Baseline and Post-baseline Measurements	478		475		953	
Grade 1	29	(6.1)	29	(6.1)	58	(6.1)
Grade 2	5	(1.0)	3	(0.6)	8	(0.8)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	3	(0.6)	1	(0.2)	4	(0.4)
Grade 3-4	3	(0.6)	1	(0.2)	4	(0.4)
All Grades	37	(7.7)	33	(6.9)	70	(7.3)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Hemoglobin Decreased (Anemia)						
Subjects with Baseline and Post-baseline Measurements	480		485		965	
Grade 1	97	(20.2)	65	(13.4)	162	(16.8)
Grade 2	5	(1.0)	1	(0.2)	6	(0.6)
Grade 3	1	(0.2)	0	(0.0)	1	(0.1)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	1	(0.2)	0	(0.0)	1	(0.1)
All Grades	103	(21.5)	66	(13.6)	169	(17.5)
Hemoglobin Increased (Hemoglobin increased)						
Subjects with Baseline and Post-baseline Measurements	480		485		965	
Grade 1	1	(0.2)	0	(0.0)	1	(0.1)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)
All Grades	1	(0.2)	0	(0.0)	1	(0.1)
Leukocytes Decreased (White blood cell decreased)						
Subjects with Baseline and Post-baseline Measurements	480		485		965	
Grade 1	33	(6.9)	39	(8.0)	72	(7.5)
Grade 2	1	(0.2)	4	(0.8)	5	(0.5)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	4	(0.8)	4	(0.8)	8	(0.8)
Grade 3-4	4	(0.8)	4	(0.8)	8	(0.8)
All Grades	38	(7.9)	47	(9.7)	85	(8.8)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Lymphocytes Decreased (Lymphocyte count decreased)						
Subjects with Baseline and Post-baseline Measurements	478		483		961	
Grade 1	52	(10.9)	57	(11.8)	109	(11.3)
Grade 2	24	(5.0)	10	(2.1)	34	(3.5)
Grade 3	9	(1.9)	6	(1.2)	15	(1.6)
Grade 4	5	(1.0)	10	(2.1)	15	(1.6)
Grade 3-4	14	(2.9)	16	(3.3)	30	(3.1)
All Grades	90	(18.8)	83	(17.2)	173	(18.0)

Laboratory Test	Pembrolizumab (N=483) n	(%)	Placebo (N=486) n	(%)	Total (N=969) n	(%)
Neutrophils Decreased (Neutrophil count decreased)						
Subjects with Baseline and Post-baseline Measurements	479		484		963	
Grade 1	17	(3.5)	31	(6.4)	48	(5.0)
Grade 2	10	(2.1)	8	(1.7)	18	(1.9)
Grade 3	0	(0.0)	2	(0.4)	2	(0.2)
Grade 4	1	(0.2)	1	(0.2)	2	(0.2)
Grade 3-4	1	(0.2)	3	(0.6)	4	(0.4)
All Grades	28	(5.8)	42	(8.7)	70	(7.3)
Platelets Decreased (Platelet count decreased)						
Subjects with Baseline and Post-baseline Measurements	479		485		964	
Grade 1	16	(3.3)	22	(4.5)	38	(3.9)
Grade 2	1	(0.2)	1	(0.2)	2	(0.2)
Grade 3	2	(0.4)	1	(0.2)	3	(0.3)
Grade 4	1	(0.2)	0	(0.0)	1	(0.1)
Grade 3-4	3	(0.6)	1	(0.2)	4	(0.4)
All Grades	20	(4.2)	24	(4.9)	44	(4.6)
Potassium Decreased (Hypokalemia)						
Subjects with Baseline and Post-baseline Measurements	478		480		958	
Grade 1	41	(8.6)	29	(6.0)	70	(7.3)
Grade 2	5	(1.0)	2	(0.4)	7	(0.7)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)
All Grades	46	(9.6)	31	(6.5)	77	(8.0)

VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

There were no clinically meaningful differences in vital signs over time between the pembrolizumab and placebo groups in KEYNOTE-716. No new safety concerns based on vital signs changes or other observations were reported in the KEYNOTE-716 pembrolizumab group.

Safety in special populations

Subgroup analyses in KEYNOTE-716 based on intrinsic (age, sex, ECOG performance status) and extrinsic factors (region) are reported below.

Intrinsic Factors

Higher incidences of some AE categories were reported for participants in the pembrolizumab group compared with those in the placebo group when compared by age, sex, and ECOG performance status.

Age

The AE profile across age groups (<65 years, 65-74 years, and 75-84 years) in the KEYNOTE-716 pembrolizumab group was similar to what was observed across the age groups in KEYNOTE-054 and generally consistent with the RSD (Table 17). A summary of AEs by age and categories of interest analysed (central nervous system-confusion/extrapyramidal, AE related to falling, cardiovascular events, cerebrovascular events, and infections) has been also presented (Table 18).

Table 17. Adverse Event Summary by Age Category (<65, 65-74, 75-84, ≥85 Years) (APaT Population)

	KN716 Data for Pembrolizumab[k]								KN716 Data for Placebo[l]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	299		132		52		0		295		134		55		2	
with one or more adverse events	276	(92.3)	123	(93.2)	50	(96.2)	0	(0.0)	264	(89.5)	120	(89.6)	47	(85.5)	2	(100.0)
with no adverse event	23	(7.7)	9	(6.8)	2	(3.8)	0	(0.0)	31	(10.5)	14	(10.4)	8	(14.5)	0	(0.0)
with drug-related[a] adverse events	241	(80.6)	102	(77.3)	43	(82.7)	0	(0.0)	188	(63.7)	78	(58.2)	28	(50.9)	2	(100.0)
with toxicity grade 3-5 adverse events	62	(20.7)	44	(33.3)	19	(36.5)	0	(0.0)	55	(18.6)	20	(14.9)	7	(12.7)	1	(50.0)
with toxicity grade 3-5 drug-related adverse events	38	(12.7)	28	(21.2)	12	(23.1)	0	(0.0)	14	(4.7)	6	(4.5)	1	(1.8)	0	(0.0)
with serious adverse events	46	(15.4)	25	(18.9)	20	(38.5)	0	(0.0)	48	(16.3)	20	(14.9)	16	(29.1)	1	(50.0)
with serious drug-related adverse events	23	(7.7)	15	(11.4)	6	(11.5)	0	(0.0)	6	(2.0)	1	(0.7)	2	(3.6)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	1	(50.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	42	(14.0)	23	(17.4)	12	(23.1)	0	(0.0)	11	(3.7)	6	(4.5)	4	(7.3)	1	(50.0)
discontinued drug due to a drug-related adverse event	39	(13.0)	23	(17.4)	12	(23.1)	0	(0.0)	6	(2.0)	4	(3.0)	2	(3.6)	0	(0.0)
discontinued drug due to a serious adverse event	18	(6.0)	10	(7.6)	5	(9.6)	0	(0.0)	6	(2.0)	3	(2.2)	2	(3.6)	1	(50.0)
discontinued drug due to a serious drug-related adverse event	15	(5.0)	10	(7.6)	5	(9.6)	0	(0.0)	3	(1.0)	1	(0.7)	0	(0.0)	0	(0.0)

	KN054 Data for Pembrolizumab[m]								EU Reference Safety Dataset for Pembrolizumab[n]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	385		96		26		2		3,587		1,797		694		107	
with one or more adverse events	362	(94.0)	92	(95.8)	24	(92.3)	2	(100.0)	3,469	(96.7)	1,737	(96.7)	677	(97.6)	106	(99.1)
with no adverse event	23	(6.0)	4	(4.2)	2	(7.7)	0	(0.0)	118	(3.3)	60	(3.3)	17	(2.4)	1	(0.9)
with drug-related[a] adverse events	302	(78.4)	75	(78.1)	19	(73.1)	2	(100.0)	2,521	(70.3)	1,272	(70.8)	491	(70.7)	82	(76.6)
with toxicity grade 3-5 adverse events	109	(28.3)	37	(38.5)	15	(57.7)	1	(50.0)	1,596	(44.5)	928	(51.6)	392	(56.5)	68	(63.6)
with toxicity grade 3-5 drug-related adverse events	51	(13.2)	15	(15.6)	7	(26.9)	1	(50.0)	495	(13.8)	321	(17.9)	135	(19.5)	24	(22.4)
with serious adverse events	84	(21.8)	29	(30.2)	12	(46.2)	2	(100.0)	1,236	(34.5)	749	(41.7)	329	(47.4)	57	(53.3)
with serious drug-related adverse events	46	(11.9)	10	(10.4)	4	(15.4)	2	(100.0)	371	(10.3)	223	(12.4)	90	(13.0)	17	(15.9)
who died	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	148	(4.1)	106	(5.9)	55	(7.9)	12	(11.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	21	(0.6)	12	(0.7)	5	(0.7)	1	(0.9)
discontinued drug due to an adverse event	55	(14.3)	9	(9.4)	6	(23.1)	1	(50.0)	423	(11.8)	255	(14.2)	138	(19.9)	16	(15.0)
discontinued drug due to a drug-related adverse event	49	(12.7)	8	(8.3)	4	(15.4)	1	(50.0)	228	(6.4)	142	(7.9)	67	(9.7)	7	(6.5)
discontinued drug due to a serious adverse event	22	(5.7)	3	(3.1)	3	(11.5)	1	(50.0)	301	(8.4)	181	(10.1)	103	(14.8)	13	(12.1)

	KN054 Data for Pembrolizumab[m]								EU Reference Safety Dataset for Pembrolizumab[n]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	18	(4.7)	2	(2.1)	1	(3.8)	1	(50.0)	135	(3.8)	86	(4.8)	40	(5.8)	4	(3.7)

[a] Determined by the investigator to be related to the drug.
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.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Table 18. Adverse Event Summary for Elderly Participants by Age (APaT Population)

	Age (Years) Pembrolizumab							
	< 65		65 - 74		75 - 84		85+	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	299		132		52		0	
with one or more adverse events	276	(92.3)	123	(93.2)	50	(96.2)	0	(NA)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(NA)
with serious adverse events	46	(15.4)	25	(18.9)	20	(38.5)	0	(NA)
discontinued due to an adverse event	42	(14.0)	23	(17.4)	12	(23.1)	0	(NA)
CNS (confusion/extrapyramidal)	0	(0.0)	0	(0.0)	0	(0.0)	0	(NA)
AE related to falling	0	(0.0)	1	(0.8)	0	(0.0)	0	(NA)
CV events	6	(2.0)	9	(6.8)	3	(5.8)	0	(NA)
Cerebrovascular events	0	(0.0)	0	(0.0)	0	(0.0)	0	(NA)
Infections	6	(2.0)	4	(3.0)	2	(3.8)	0	(NA)

	Age (Years) Placebo							
	< 65		65 - 74		75 - 84		85+	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	295		134		55		2	
with one or more adverse events	264	(89.5)	120	(89.6)	47	(85.5)	2	(100.0)
who died	3	(1.0)	0	(0.0)	0	(0.0)	1	(50.0)
with serious adverse events	48	(16.3)	20	(14.9)	16	(29.1)	1	(50.0)
discontinued due to an adverse event	11	(3.7)	6	(4.5)	4	(7.3)	1	(50.0)
CNS (confusion/extrapyramidal)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
AE related to falling	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
CV events	13	(4.4)	6	(4.5)	3	(5.5)	0	(0.0)
Cerebrovascular events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infections	6	(2.0)	2	(1.5)	0	(0.0)	1	(50.0)

AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
MedDRA V23.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 04DEC2020.

Source: [P716V01MK3475: adam-adsl; adae]

Sex

With regard to gender subgroup analyses, the AE profile between male and female participants in the KEYNOTE-716 Dataset, in KEYNOTE-054 and in the RSD is reported in Table 19.

Table 19. Adverse Event Summary by Sex (Male, Female) (APaT Population)

	KN716 Data for Pembrolizumab[k]				KN716 Data for Placebo[l]				KN054 Data for Pembrolizumab[m]				EU Reference Safety Dataset for Pembrolizumab[n]			
	Male		Female		Male		Female		Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	297		186		287		199		320		189		4,039		2,146	
with one or more adverse events	270	(90.9)	179	(96.2)	251	(87.5)	182	(91.5)	303	(94.7)	177	(93.7)	3,908	(96.8)	2,081	(97.0)
with no adverse event	27	(9.1)	7	(3.8)	36	(12.5)	17	(8.5)	17	(5.3)	12	(6.3)	131	(3.2)	65	(3.0)
with drug-related[a] adverse events	227	(76.4)	159	(85.5)	160	(55.7)	136	(68.3)	242	(75.6)	156	(82.5)	2,826	(70.0)	1,540	(71.8)
with toxicity grade 3-5 adverse events	86	(29.0)	39	(21.0)	54	(18.8)	29	(14.6)	103	(32.2)	59	(31.2)	1,965	(48.7)	1,019	(47.5)
with toxicity grade 3-5 drug-related adverse events	55	(18.5)	23	(12.4)	18	(6.3)	3	(1.5)	45	(14.1)	29	(15.3)	662	(16.4)	313	(14.6)
with serious adverse events	64	(21.5)	27	(14.5)	54	(18.8)	31	(15.6)	75	(23.4)	52	(27.5)	1,580	(39.1)	791	(36.9)
with serious drug-related adverse events	29	(9.8)	15	(8.1)	6	(2.1)	3	(1.5)	33	(10.3)	29	(15.3)	473	(11.7)	228	(10.6)
who died	0	(0.0)	0	(0.0)	3	(1.0)	1	(0.5)	1	(0.3)	0	(0.0)	224	(5.5)	97	(4.5)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	24	(0.6)	15	(0.7)
discontinued drug due to an adverse event	53	(17.8)	24	(12.9)	15	(5.2)	7	(3.5)	38	(11.9)	33	(17.5)	544	(13.5)	288	(13.4)
discontinued drug due to a drug-related adverse event	50	(16.8)	24	(12.9)	8	(2.8)	4	(2.0)	32	(10.0)	30	(15.9)	292	(7.2)	152	(7.1)
discontinued drug due to a serious adverse event	22	(7.4)	11	(5.9)	10	(3.5)	2	(1.0)	14	(4.4)	15	(7.9)	397	(9.8)	201	(9.4)
discontinued drug due to a serious drug-related adverse event	19	(6.4)	11	(5.9)	3	(1.0)	1	(0.5)	9	(2.8)	13	(6.9)	177	(4.4)	88	(4.1)

[a] Determined by the investigator to be related to the drug.
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.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

ECOG Performance Status

The AE profile was generally similar between participants with an ECOG status of 0 and 1 in the KEYNOTE 716 pembrolizumab group, which was similar to the pattern observed in KEYNOTE 054 and was generally consistent with the RSD (Table 20~~18~~).

Table 20. Adverse Event Summary by ECOG Status Category (0, 1, Other/Missing) (APaT Population)

	KN716 Data for Pembrolizumab[k]						KN716 Data for Placebo[l]					
	[0] Normal Activity		[1] Symptoms, but ambulatory		Other/Missing		[0] Normal Activity		[1] Symptoms, but ambulatory		Other/Missing	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	450		32		1		449		35		2	
with one or more adverse events	421	(93.6)	27	(84.4)	1	(100.0)	405	(90.2)	27	(77.1)	1	(50.0)
with no adverse event	29	(6.4)	5	(15.6)	0	(0.0)	44	(9.8)	8	(22.9)	1	(50.0)
with drug-related[a] adverse events	363	(80.7)	23	(71.9)	0	(0.0)	277	(61.7)	19	(54.3)	0	(0.0)
with toxicity grade 3-5 adverse events	118	(26.2)	7	(21.9)	0	(0.0)	76	(16.9)	7	(20.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	73	(16.2)	5	(15.6)	0	(0.0)	18	(4.0)	3	(8.6)	0	(0.0)
with serious adverse events	85	(18.9)	6	(18.8)	0	(0.0)	78	(17.4)	6	(17.1)	1	(50.0)
with serious drug-related adverse events	42	(9.3)	2	(6.3)	0	(0.0)	7	(1.6)	2	(5.7)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.7)	1	(2.9)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	75	(16.7)	2	(6.3)	0	(0.0)	18	(4.0)	4	(11.4)	0	(0.0)
discontinued drug due to a drug-related adverse event	72	(16.0)	2	(6.3)	0	(0.0)	10	(2.2)	2	(5.7)	0	(0.0)
discontinued drug due to a serious adverse event	32	(7.1)	1	(3.1)	0	(0.0)	8	(1.8)	4	(11.4)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	29	(6.4)	1	(3.1)	0	(0.0)	2	(0.4)	2	(5.7)	0	(0.0)

	KN054 Data for Pembrolizumab[m]						EU Reference Safety Dataset for Pembrolizumab[n]					
	[0] Normal Activity		[1] Symptoms, but ambulatory		Other/Missing		[0] Normal Activity		[1] Symptoms, but ambulatory		Other/Missing	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	481		28		0		2,942		3,069		174	
with one or more adverse events	453	(94.2)	27	(96.4)	0	(0.0)	2,852	(96.9)	2,970	(96.8)	167	(96.0)
with no adverse event	28	(5.8)	1	(3.6)	0	(0.0)	90	(3.1)	99	(3.2)	7	(4.0)
with drug-related[a] adverse events	375	(78.0)	23	(82.1)	0	(0.0)	2,223	(75.6)	2,048	(66.7)	95	(54.6)
with toxicity grade 3-5 adverse events	155	(32.2)	7	(25.0)	0	(0.0)	1,196	(40.7)	1,680	(54.7)	108	(62.1)
with toxicity grade 3-5 drug-related adverse events	73	(15.2)	1	(3.6)	0	(0.0)	446	(15.2)	499	(16.3)	30	(17.2)
with serious adverse events	120	(24.9)	7	(25.0)	0	(0.0)	930	(31.6)	1,347	(43.9)	94	(54.0)
with serious drug-related adverse events	58	(12.1)	4	(14.3)	0	(0.0)	336	(11.4)	348	(11.3)	17	(9.8)
who died	1	(0.2)	0	(0.0)	0	(0.0)	83	(2.8)	222	(7.2)	16	(9.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	13	(0.4)	26	(0.8)	0	(0.0)
discontinued drug due to an adverse event	68	(14.1)	3	(10.7)	0	(0.0)	333	(11.3)	470	(15.3)	29	(16.7)
discontinued drug due to a drug-related adverse event	59	(12.3)	3	(10.7)	0	(0.0)	217	(7.4)	214	(7.0)	13	(7.5)
discontinued drug due to a serious adverse event	28	(5.8)	1	(3.6)	0	(0.0)	214	(7.3)	363	(11.8)	21	(12.1)
discontinued drug due to a serious drug-related adverse event	21	(4.4)	1	(3.6)	0	(0.0)	118	(4.0)	140	(4.6)	7	(4.0)

[a] Determined by the investigator to be related to the drug.
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.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Extrinsic Factors

Region

The overall incidence of AEs in EU and non-EU participants was similar in the pembrolizumab and placebo groups and the AE profile based on region in the KEYNOTE-716 pembrolizumab group remained generally consistent with the established safety profile of pembrolizumab (Table 21).

Table 21. Adverse Event Summary by Region (EU, Ex-EU) (APaT Population)

	KN716 Data for Pembrolizumab[k]				KN716 Data for Placebo[l]				KN054 Data for Pembrolizumab[m]				EU Reference Safety Dataset for Pembrolizumab[n]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	250		233		302		184		319		190		2,217		3,968	
with one or more adverse events	236	(94.4)	213	(91.4)	258	(85.4)	175	(95.1)	306	(95.9)	174	(91.6)	2,135	(96.3)	3,854	(97.1)
with no adverse event	14	(5.6)	20	(8.6)	44	(14.6)	9	(4.9)	13	(4.1)	16	(8.4)	82	(3.7)	114	(2.9)
with drug-related[a] adverse events	204	(81.6)	182	(78.1)	168	(55.6)	128	(69.6)	257	(80.6)	141	(74.2)	1,526	(68.8)	2,840	(71.6)
with toxicity grade 3-5 adverse events	57	(22.8)	68	(29.2)	45	(14.9)	38	(20.7)	98	(30.7)	64	(33.7)	1,022	(46.1)	1,962	(49.4)
with toxicity grade 3-5 drug-related adverse events	37	(14.8)	41	(17.6)	15	(5.0)	6	(3.3)	48	(15.0)	26	(13.7)	341	(15.4)	634	(16.0)
with serious adverse events	46	(18.4)	45	(19.3)	43	(14.2)	42	(22.8)	66	(20.7)	61	(32.1)	846	(38.2)	1,525	(38.4)
with serious drug-related adverse events	28	(11.2)	16	(6.9)	8	(2.6)	1	(0.5)	36	(11.3)	26	(13.7)	260	(11.7)	441	(11.1)
who died	0	(0.0)	0	(0.0)	2	(0.7)	2	(1.1)	1	(0.3)	0	(0.0)	113	(5.1)	208	(5.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.5)	28	(0.7)
discontinued drug due to an adverse event	46	(18.4)	31	(13.3)	15	(5.0)	7	(3.8)	45	(14.1)	26	(13.7)	287	(12.9)	545	(13.7)
discontinued drug due to a drug-related adverse event	44	(17.6)	30	(12.9)	10	(3.3)	2	(1.1)	41	(12.9)	21	(11.1)	166	(7.5)	278	(7.0)
discontinued drug due to a serious adverse	23	(9.2)	10	(4.3)	7	(2.3)	5	(2.7)	18	(5.6)	11	(5.8)	205	(9.2)	393	(9.9)

	KN716 Data for Pembrolizumab[k]				KN716 Data for Placebo[l]				KN054 Data for Pembrolizumab[m]				EU Reference Safety Dataset for Pembrolizumab[n]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	21	(8.4)	9	(3.9)	3	(1.0)	1	(0.5)	15	(4.7)	7	(3.7)	98	(4.4)	167	(4.2)

[a] Determined by the investigator to be related to the drug.
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.
[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.
[l] Includes all participants who received at least one dose of Placebo in KN716.
[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.
[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction (DDI) studies have been performed. However, as pembrolizumab is an IgG antibody administrated parenterally and cleared by catabolism, food and DDI are not able to influence exposure, and drugs that affect cytochrome P450 enzymes are not expected to interfere with the metabolism of pembrolizumab. Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, the use of systemic corticosteroids or other immunosuppressive drugs should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab, although these drugs can be used to treat immune-related adverse reactions during the pembrolizumab treatment. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy related adverse reactions.

Use in Pregnancy and Lactation

As of the DCO, no pregnancies were reported in the KEYNOTE-716 Safety Dataset. Pembrolizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. It is not known whether pembrolizumab is secreted in human milk. Because many drugs and IgG antibodies are secreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the importance of the drug to the mother.

Withdrawal and Rebound

No withdrawal or rebound effects are expected with an anti-PD-1 mAb, and none has been observed in pembrolizumab clinical studies to date.

Effect on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Impairment of cognitive ability is not expected from an anti-PD-1 mAb. No additional studies have been conducted to determine the effect of pembrolizumab on the impairment of mental function or the ability to drive or operate machinery.

Discontinuation due to adverse events

Adverse Events and Drug-related Adverse Events leading to Treatment Discontinuation

Adverse Events Leading to Treatment Discontinuation

The overall incidence of AEs that led to discontinuation of study treatment in KEYNOTE-716 was higher in the pembrolizumab group (15.9%) compared with the placebo group (4.5%). However, it was similar to KEYNOTE-054 (13.9%) and the RSD (13.5%) (Table 22). Most AEs leading to discontinuation of pembrolizumab in KEYNOTE 716 occurred in <1% of participants, except for *colitis* and *autoimmune hepatitis* (1.0% each). These AEs were similar to the most frequently reported AEs leading to discontinuation of pembrolizumab in KEYNOTE-054.

Table 22. Participants With Adverse Events Resulting in Treatment Discontinuation

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	77	(15.9)	22	(4.5)	71	(13.9)	832	(13.5)
with no adverse events	406	(84.1)	464	(95.5)	438	(86.1)	5,353	(86.5)

Drug-related Adverse Events Leading to Treatment Discontinuation

The overall incidence of treatment-related AEs that led to discontinuation of study treatment in KEYNOTE-716 was higher in the pembrolizumab group (15.3%) than in the placebo group (2.5%), and was similar to KEYNOTE-054 (12.2%) but higher than the RSD (7.2%) (Table 23). Each PT for an AE that led to discontinuation of study treatment was reported for ≤1.0% of participants in each treatment group. The most frequently reported of these AEs were *colitis* and *autoimmune hepatitis* (1%, each) in the pembrolizumab group, *diarrhoea* and *autoimmune hepatitis* (0.4%, each) in the placebo group. Drug-related AEs leading to discontinuation of pembrolizumab in KEYNOTE-716 were similar to the most frequently reported drug-related AEs leading to discontinuation of pembrolizumab in KEYNOTE-054.

Table 23. Participants with Drug-Related Adverse Events Resulting in Treatment Discontinuation

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	74	(15.3)	12	(2.5)	62	(12.2)	444	(7.2)
with no adverse events	409	(84.7)	474	(97.5)	447	(87.8)	5,741	(92.8)

Adverse Events and Drug-related Adverse Events leading to Treatment Interruption

Adverse Events Leading to Treatment Interruption

The overall incidence of AEs that led to interruption of study treatment in KEYNOTE-716 was similar in the pembrolizumab group (20.3%) and KEYNOTE-054 (19.3%) but was slightly lower than the RSD (25.8%) (Table 24~~2~~). The most frequently reported AEs resulting in study treatment interruption in the pembrolizumab group (in >1.0% of participants) were *diarrhoea* (2.3%); *arthralgia* (1.7%); *hyperthyroidism, cough*, and *pyrexia* (each in 1.2% of participants). In the placebo group, the most frequently reported AEs resulting in study treatment interruption were *diarrhoea* and p*yrexia* (each in 1.2% of participants). These AEs were similar to the most frequently reported AEs leading to pembrolizumab interruption in KEYNOTE 054.

Table 24. Participants With Adverse Events Resulting in Treatment Interruption

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	98	(20.3)	71	(14.6)	98	(19.3)	1,596	(25.8)
with no adverse events	385	(79.7)	415	(85.4)	411	(80.7)	4,589	(74.2)

Drug-related Adverse Events Leading to Treatment Interruption

The overall incidence of drug-related AEs that led to interruption of study treatment in KEYNOTE 716 was higher in the pembrolizumab group (14.1%) compared with the placebo group (5.3%), similar to KEYNOTE-054 (14.5%) and the RSD (14.6%) (Table 25~~3~~). The most frequently reported drug-related AEs leading to pembrolizumab interruption (incidence >1%) in KEYNOTE 716 were *arthralgia* (1.7%), *diarrhoea* (1.7%), and *hyperthyroidism* (1.2%); *diarrhoea* (1%) in the placebo group.

Table 25. Participants With Drug-Related Adverse Events Resulting in Treatment Interruption

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	68	(14.1)	26	(5.3)	74	(14.5)	902	(14.6)
with no adverse events	415	(85.9)	460	(94.7)	435	(85.5)	5,283	(85.4)

Post marketing experience

No further data besides those included in the last PSUR have been submitted, covering the period 04-Sep-2019 through 03-Sep-2020.

Assessment of paediatric data on clinical safety

The first patient, was diagnosed with melanoma approximately 3 months and 28 days prior to the first dose of pembrolizumab. The patient was newly diagnosed with Stage IIB cutaneous melanoma confirmed by histology, which was completely resected, and had negative SLN biopsy prior to enrolment. At screening, KPS score was 100 and T4aN0M0. Pembrolizumab 2 mg/kg IV Q3W was started on Day 1 (Cycle 1) for the treatment of resected high-risk Stage II melanoma and the patient received 17 cycles during the study. The participant entered the study with a history of acne, cystic acne, and hidradenitis, treated with oral clindamycin, which was stopped on Day -14. On Day 41 the dose of pembrolizumab was given (Cycle 3), and on Day 58, the patient experienced hidradenitis (Grade 1) in the left axilla. Treatment with topical fusidic acid was started on Day 62 and hidradenitis resolved on Day 69 (while fusidic acid was stopped on Day 70). On Day 104, the dose of pembrolizumab was given (Cycle 6), and on Day 124, the participant had a second episode of worsening of left axilla hidradenitis (Grade 1). No treatment was reported, and no further information was available. On Day 293 increased WBCs was observed (Table 27). On Day 314 the dose of pembrolizumab was given (Cycle 15), and on Day 335, the participant was diagnosed with increased lymphocyte count (Grade 2, Table 27). No treatment was reported, and increased lymphocyte count resolved on Day 356. On Day 356 the participant completed pembrolizumab; as of Day 425, last contact before data cut-off, the participant was alive. The investigator considered the non-serious AEs of hidradenitis (2 episodes) and increased lymphocyte count as not related to pembrolizumab.

Table 27. Complete Blood Count (from Clinical Study report KN-716)

Study Day	RBC 10^{12}/L	HCT %	HGB g/L	WBC 10^9/L	PLT 10^9/L	NEUT 10^9/L	LYM 10^9/L
-15	5.2	43.4	147	7.89	228	4.95	2.45
1	4.99	41	140	6.65	206	3.26	2.91
22	4.76	39.3	134	6.88	200	3.25	3.02
62	4.78	39.6	134	6.65	201	3.08	2.91
104	4.84	40.2	134	6.99	224	2.66	3.41
146	4.72	39	133	7.94	225	3.55	3.45
188	4.78	39.2	134	5.69	199	1.82	3
230	4.97	41	140	8.39	241	3.12	4.09(H)
293	4.95	39.8	139	12.15(H)	275	6.5	4.2(H)
335	4.88	39.3	137	9.47	233	3.86	4.39(H)
384	4.67	38.6	130	5.6	208	2.21	2.41

A = abnormal; H = high; L = low; indicates value is out of normal range.
HCT = hematocrit; HGB = hemoglobin; LYM = lymphocytes; NEUT = neutrophils; PLT = platelets; RBC = red blood cells; WBC = white blood cells.

The second patient, was diagnosed with melanoma approximately 4 months and 5 days prior to the first dose of study medication. The patient was newly diagnosed with Stage IIB cutaneous melanoma confirmed by histology, which was completely resected, and had negative SLN biopsy prior to enrolment. At screening, KPS score was 100 and T3bN0M0. Placebo (saline solution) IV Q3W was started on Day 1 (Cycle 1) after being randomized in the study due to high-risk Stage II melanoma. The patient had received 14 cycles at the time of data cut-off, and at the time of data cut-off, no

adverse events were reported. As of Day 293, last contact before data cut-off, the participant was alive.

Comparative analysis of paediatric/adult safety data post RSI

The safety of pembrolizumab has been assessed in the paediatric participants in the ongoing study KEYNOTE-051, with 161 participants, aged 9 months to 17 years old, in the ASaT population. Safety results from the analysis of KEYNOTE-051 in a paediatric population with advanced cancers support that the safety profile of pembrolizumab monotherapy is consistent with the known safety profile of pembrolizumab monotherapy in adults from the different indications approved so far for adults in the EU. Pembrolizumab monotherapy was generally well tolerated in paediatric participants who have solid tumours and lymphoma. No new safety signals were observed. Additionally, in KEYNOTE-051 there were no treatment-emergent positive ADA found in 125 paediatric participants with evaluable immunogenicity samples and these results were comparable to the ADA data in adults reported in the pembrolizumab development program.

As requested, a comparative analysis of the safety data from paediatric participants in KEYNOTE-051 and adult melanoma participants in the adjuvant setting (KEYNOTE-716 and KEYNOTE-054) and adults with advanced melanoma was conducted using 4 safety datasets as presented:

1. Safety data from the paediatric melanoma patients in KEYNOTE-051 (N=9).
2. The cumulative safety data from KEYNOTE-051 (N=161).
3. Pooled safety data from the 2 adjuvant melanoma studies (KEYNOTE-716 and KEYNOTE-054) (N=992).
4. Pooled safety dataset for adults with advanced melanoma (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006) (N=1567).

Overall Extent of Exposure. The median duration of exposure to pembrolizumab for the paediatric melanoma participants in KEYNOTE-051 is 1.4 months. Overall, the median duration of exposure in KEYNOTE-051 is 2.1 months. The median duration of exposure in the pooled adjuvant population (KEYNOTE-716 and KEYNOTE-054) dataset is 11.1 months, which is twice the duration of exposure of that in the advanced adult melanoma safety dataset (5.1 months) (Table 28).

Table 28. Summary of Drug Exposure (APaT Population)

	Pediatric Melanoma KN051 (Pembro Monotherapy)[k] (N=9)	All Pediatrics Population KN051 (Pembro Monotherapy)[l] (N=161)	Adjuvant Melanoma population (Pembro Monotherapy) (KN054+ KN716)[m] (N=992)	Advanced Melanoma Safety Dataset (Pembro Monotherapy)[n] (N=1567)
Study Days On-Therapy (Months)				
Mean	3.90	5.32	8.79	7.49
Median	1.4	2.1	11.1	5.1
SD	6.09	7.17	3.91	6.30
Range	0.0 to 19.6	0.0 to 24.2	0.0 to 15.7	0.0 to 28.3
Number of Administrations				
Mean	6.56	8.49	13.21	12.86
Median	3.0	4.0	17.0	9.0
SD	8.72	10.19	5.48	10.35
Range	1.0 to 29.0	1.0 to 35.0	1.0 to 18.0	1.0 to 59.0

Each participant is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[k] Includes all participants who diagnosed with Melanoma and received at least one dose of Pembro Monotherapy in KN051.

[l] Includes all participants who received at least one dose of Pembro Monotherapy in KN051.

[m] Includes all participants who received at least one dose of Pembro Monotherapy in KN054 and KN716.

[n] Includes all participants who received at least one dose of Pembro Monotherapy in KN001 Part B1, B2, B3, D, KN002 (original phase), and KN006.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN051: 10JAN2020, KN054: 03APR2020, KN716: 04DEC2020)

Source: [ISS: adam-adsl; adexsum]

Analysis of Adverse Events. The incidences of drug-related AEs, drug-related SAEs and drug-related Grade 3 to 5 AEs were generally consistent across all the datasets (Table 29).

Table 29. Adverse Event Summary (APaT Population)

	Pediatric Melanoma KN051 (Pembro Monotherapy)[k]		All Pediatrics Population KN051 (Pembro Monotherapy)[l]		Adjuvant Melanoma population (Pembro Monotherapy) (KN054+ KN716)[m]		Advanced Melanoma Safety Dataset (Pembro Monotherapy)[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	9		161		992		1,567	
with one or more adverse events	9	(100.0)	155	(96.3)	929	(93.6)	1,535	(98.0)
with no adverse event	0	(0.0)	6	(3.7)	63	(6.4)	32	(2.0)
with drug-related[a] adverse events	6	(66.7)	93	(57.8)	784	(79.0)	1,241	(79.2)
with toxicity grade 3-5 adverse events	5	(55.6)	76	(47.2)	287	(28.9)	705	(45.0)
with toxicity grade 3-5 drug-related adverse events	1	(11.1)	14	(8.7)	152	(15.3)	228	(14.6)
with serious adverse events	3	(33.3)	62	(38.5)	218	(22.0)	568	(36.2)
with serious drug-related adverse events	0	(0.0)	16	(9.9)	106	(10.7)	165	(10.5)
who died	0	(0.0)	5	(3.1)	1	(0.1)	48	(3.1)
who died due to a drug-related adverse event	0	(0.0)	2	(1.2)	0	(0.0)	1	(0.1)
discontinued drug due to an adverse event	0	(0.0)	10	(6.2)	148	(14.9)	195	(12.4)
discontinued drug due to a drug-related adverse event	0	(0.0)	6	(3.7)	136	(13.7)	89	(5.7)
discontinued drug due to a serious adverse event	0	(0.0)	8	(5.0)	62	(6.3)	142	(9.1)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	4	(2.5)	52	(5.2)	57	(3.6)

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

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.

[k] Includes all participants who were diagnosed with Melanoma and received at least one dose of Pembro Monotherapy in KN051.

[l] Includes all participants who received at least one dose of Pembro Monotherapy in KN051.

[m] Includes all participants who received at least one dose of Pembro Monotherapy in KN054 and KN716.

[n] Includes all participants who received at least one dose of Pembro Monotherapy in KN001 Part B1, B2, B3, D, KN002 (original phase), and KN006.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN051: 10JAN2020, KN054: 03APR2020, KN716: 04DEC2020)

Source: [ISS: adam-adsl; adae]

The overall incidence of AEOSI (immune-related AEs and infusion reactions) in KEYNOTE-051, (18.6%), is comparable with the adult advanced melanoma dataset (22.9%) as well as for Grade ≥ 3 AEOSI, serious AEOSI, and discontinuations due to an AEOSI (Table 30). The nature and severity of AEOSI in the paediatric melanoma participants and in KEYNOTE-051 paediatric participants were comparable to that of the adult adjuvant and advanced melanoma participants. The majority of participants across the datasets reported AEOSI severity of Grade 1 or Grade 2. One participant in KEYNOTE-051 reported Grade 5 pneumonitis. The fatal AEOSI of pneumonitis was in a participant with extensive right chest involvement of the underlying epithelioid sarcoma.

Table 30. Adverse Event Summary AEOSI (APaT Population)

	Pediatric Melanoma KN051 (Pembro Monotherapy)[k]		All Pediatrics Population KN051 (Pembro Monotherapy)[l]		Adjuvant Melanoma population (Pembro Monotherapy) (KN054+ KN716)[m]		Advanced Melanoma Safety Dataset (Pembro Monotherapy)[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	9		161		992		1,567	
with one or more adverse events	1	(11.1)	30	(18.6)	354	(35.7)	359	(22.9)
with no adverse event	8	(88.9)	131	(81.4)	638	(64.3)	1,208	(77.1)
with drug-related[a] adverse events	1	(11.1)	21	(13.0)	332	(33.5)	306	(19.5)
with toxicity grade 3-5 adverse events	0	(0.0)	4	(2.5)	86	(8.7)	99	(6.3)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	4	(2.5)	80	(8.1)	82	(5.2)
with serious adverse events	0	(0.0)	4	(2.5)	73	(7.4)	99	(6.3)
with serious drug-related adverse events	0	(0.0)	3	(1.9)	68	(6.9)	83	(5.3)
who died	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	2	(1.2)	75	(7.6)	54	(3.4)
discontinued drug due to a drug-related adverse event	0	(0.0)	2	(1.2)	75	(7.6)	53	(3.4)
discontinued drug due to a serious adverse event	0	(0.0)	2	(1.2)	35	(3.5)	45	(2.9)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	2	(1.2)	35	(3.5)	44	(2.8)

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

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.

[k] Includes all participants who were diagnosed with Melanoma and received at least one dose of Pembro Monotherapy in KN051.

[l] Includes all participants who received at least one dose of Pembro Monotherapy in KN051.

[m] Includes all participants who received at least one dose of Pembro Monotherapy in KN054 and KN716.

[n] Includes all participants who received at least one dose of Pembro Monotherapy in KN001 Part B1, B2, B3, D, KN002 (original phase), and KN006.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN051: 10JAN2020, KN054: 03APR2020, KN716: 04DEC2020)

Source: [ISS: adam-adsl; adae]

The sample size of participants in the paediatric melanoma safety datasets (n=9) and KEYNOTE-051 (n=161) are relatively small, when compared to the pooled adjuvant melanoma safety dataset (n=992) and the adult advanced melanoma safety dataset (n=1567). There are differences in the duration of exposure across the datasets. After adjusting for duration of exposure in the datasets, the incidence of AEs or AEOSI in the paediatric melanoma dataset and KEYNOTE-051 remains generally consistent with the adult advanced melanoma safety dataset. The exposure-adjusted incidence of AEOSI in the paediatric melanoma and KEYNOTE-051 safety datasets were generally similar to the exposure-adjusted incidence in the adult advanced melanoma safety dataset and lower than in the pooled adjuvant melanoma safety dataset (Table 31).

Table 31. Exposure-adjusted Adverse Event Summary (Including Multiple Occurrences of Events) AEOSI (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	Pediatric Melanoma KN051 (Pembro Monotherapy)[k]	All Pediatrics Population KN051 (Pembro Monotherapy)[l]	Adjuvant Melanoma population (Pembro Monotherapy) (KN054+ KN716)[m]	Advanced Melanoma Safety Dataset (Pembro Monotherapy)[n]
Number of participants exposed	9	161	992	1567
Total exposure[b] in person-months	43.99	1011.67	9607.81	12961.52
Total events (rate)				
adverse events	1 (2.27)	38 (3.76)	620 (6.45)	496 (3.83)
drug-related[c] adverse events	1 (2.27)	27 (2.67)	577 (6.01)	421 (3.25)
toxicity grade 3-5 adverse events	0 (0.00)	4 (0.40)	120 (1.25)	112 (0.86)
toxicity grade 3-5 drug-related adverse events	0 (0.00)	4 (0.40)	111 (1.16)	94 (0.73)
serious adverse events	0 (0.00)	5 (0.49)	100 (1.04)	114 (0.88)
serious drug-related adverse events	0 (0.00)	4 (0.40)	94 (0.98)	98 (0.76)
adverse events leading to death	0 (0.00)	1 (0.10)	0 (0.00)	0 (0.00)
drug-related adverse events leading to death	0 (0.00)	1 (0.10)	0 (0.00)	0 (0.00)
adverse events resulting in drug discontinuation	0 (0.00)	2 (0.20)	75 (0.78)	56 (0.43)
drug-related adverse events resulting in drug discontinuation	0 (0.00)	2 (0.20)	75 (0.78)	55 (0.42)
serious adverse events resulting in drug discontinuation	0 (0.00)	2 (0.20)	35 (0.36)	47 (0.36)
serious drug-related adverse events resulting in drug discontinuation	0 (0.00)	2 (0.20)	35 (0.36)	46 (0.35)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.

[b] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

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

For participants who received second course treatment, adverse events which occurred in second course phase are excluded.

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

[k] Includes all participants who diagnosed with Melanoma and received at least one dose of Pembro Monotherapy in KN051.

[l] Includes all participants who received at least one dose of Pembro Monotherapy in KN051.

[m] Includes all participants who received at least one dose of Pembro Monotherapy in KN054 and KN716.

[n] Includes all participants who received at least one dose of Pembro Monotherapy in KN001 Part B1, B2, B3, D, KN002 (original phase), and KN006.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN051: 10JAN2020, KN054: 03APR2020, KN716: 04DEC2020)

Source: [ISS: adam-adsl; adae]

2.5.1. Discussion on clinical safety

To support the proposed use of pembrolizumab for the adjuvant treatment of adult and paediatric (12 years and older) patients with Stage IIB and IIC melanoma following complete resection, safety results have been presented from study KEYNOTE-716, a randomized, placebo controlled, multicentre study with a total population of 483 Stage IIB and IIC melanoma treated with pembrolizumab 200 mg Q3W

as adjuvant therapy (or 2 mg/kg up to a maximum of 200 mg for participants ≥12 years of age and <18 years of age) (APaT population), in comparison with a control arm (placebo) of 486 patients (1:1 randomisation scheme) (Part 1 of the study; DCO date 04-DEC-2020). Additional safety comparative data are provided based on the prior clinical experience of pembrolizumab monotherapy in the adjuvant treatment setting (KEYNOTE-054) in 509 patients with resected, lymph node-positive, Stage III melanoma (DCO date 03-APR-2020) as well as the totality of clinical trials conducted so far (Reference Safety Dataset; N=6185).

In KEYNOTE-716, the demographic and baseline characteristics were balanced across the pembrolizumab and placebo groups. Most participants were male, white, not Hispanic or Latino, and were from EU regions (in the RSD, more participants were enrolled at sites outside the EU). Participants in the KEYNOTE-716 Safety Dataset were generally younger, had better ECOG performance status at study entry, and did not have evidence of metastatic disease compared with those in the RSD (most [93.2%] participants in the KEYNOTE-716 pembrolizumab group had an ECOG performance status of 0). The age of participants ranged from 16 to 87 years, with a median age of 61 years. Of note, only one adolescent patient in the pembrolizumab arm, and one adolescent patient in the placebo group were enrolled in KEYNOTE-716. The median duration of **exposure** to pembrolizumab was similar to that in KEYNOTE-054 (9.9 months and 11.8 months, respectively), but twice as long as the median duration of exposure in the RSD (4.9 months). In the pembrolizumab and placebo groups, 69.8% and 78.6% of participants had at least 6 months of exposure respectively, similar to KEYNOTE-054 (76%) but higher than the RSD (45.4%).

As expected, the comparison with the placebo showed an unfavourable safety profile of pembrolizumab in the adjuvant setting of resectable melanoma: the drug-related AEs (79.9% vs. 60.9% in the placebo group), the incidence of drug-related Grade 3-5 AEs (16.1 % vs. 4.3%), drug-related SAEs (9.1% vs. 1.9%), drug discontinuations due to either drug-related AEs (15.3% vs. 2.5%) or drug-related SAEs (6.8% vs. 2.5%) were all more frequent in the experimental group compared to control.

The safety profile of pembrolizumab was consistent with prior experience, although it must be acknowledged that a lower incidence of Grade 3-5 AEs, SAEs and drug-related AEs leading to death were reported in KEYNOTE-716 compared to KEYNOTE-054 and the reference datasets (SAEs: 18.8% vs. 25% in KN-054 vs. 38.3% in RSD; Grade 3-5 AEs 25.9% vs. 31.8% in KN-054 vs. 48.8% in RSD). 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-716 study population, without evidence of metastatic disease and with better ECOG performance status at study entry. The incidences of drug-related SAEs and drug-related grade 3 to 5 AEs were generally consistent with the RSD, whereas the incidence of drug-related AEs leading to discontinuation and of AEOSIs were higher in KEYNOTE-716 than the RSD, similarly to the KN-054 (discontinuation due to drug-related AEs: 15.3% in KN-716; 12.2% in KN-054; 7.2% in RSD; AEOSI: 36.2% vs. 35.2% vs. 25.5%, respectively). The longer duration of exposure to pembrolizumab in KEYNOTE-716 may have contributed to the higher incidence of drug-related AEs leading to treatment discontinuation compared with the RSD. After adjusting for exposure, the incidence of AEOSI and AEOSI leading to treatment discontinuation were partially corrected for KEYNOTE-716 and KEYNOTE-054. As requested, the summary of adverse events after adjusting for duration of exposure in the different safety datasets has been provided. The incidences by AE category were consistent or lower in the pembrolizumab group of KEYNOTE-716 compared with the RSD and no new safety concerns have been identified.

In KEYNOTE-716, **the most frequently reported AEs** were generally similar between the pembrolizumab and the placebo groups, despite the higher incidences for *diarrhoea*, *pruritus*, *rash*, *hypothyroidism*, and *hyperthyroidism*, which are known ADRs for pembrolizumab. Overall, the incidences, types, and severity of AEs in KEYNOTE-716 were similar to those in KEYNOTE-054 and

generally consistent with the RSD, despite some differences (≥5 percentage points difference) compared with the RSD, including *diarrhoea* (26.7% vs. 20.9%), *hyperthyroidism* (10.4% vs. 4.2%), and *pruritus* (25.9 vs. 18%).

The overall incidence of **drug-related AEs** in KEYNOTE-716 was higher in the pembrolizumab group compared with the placebo group. *Pruritus*, *rash*, *hypothyroidism*, and *hyperthyroidism* were reported at higher incidences in the pembrolizumab group compared with the placebo group (most of these of toxicity Grade 1 or 2). The most frequently reported drug-related AEs (incidence >10%) in KEYNOTE 716, *pruritus*, *fatigue*, *diarrhoea*, *rash*, *hypothyroidism*, and *arthralgia*, were consistent with the most frequently reported drug-related AEs in KEYNOTE-054, but higher than the RSD. In particular, a prevalence of endocrine disturbances has been observed in the experimental group, being higher than previously reported (*hypothyroidism* 14.5% vs. 9.8% in the RSD; *hyperthyroidism* 9.9% vs. 3.7%, respectively). More details have been provided on thyroid abnormalities observed in the adjuvant setting. In the KEYNOTE-716 pembrolizumab group, 70 (14.5%) patients reported drug-related *hypothyroidism* and 48 (9.9%) patients reported drug-related *hyperthyroidism*. Of the 70 patients with *hypothyroidism* and of 48 patients with *hyperthyroidism*, 4 patients each had preexisting thyroid disorders. Based on this evaluation, the number of participants with preexisting thyroid disorders was low and may not have affected the incidence of drug-related *hypothyroidism* and *hyperthyroidism* in KEYNOTE-716. *Hypothyroidism* and *hyperthyroidism* (listed, respectively, as a very common and a common ADR for pembrolizumab monotherapy) are known ADRs for pembrolizumab and are listed under section 4.4 (Special Warnings and Precautions), and in section 4.8 (Undesirable Effect) of the SmPC.

Recently, the incidence of immune-related adverse events in the adjuvant setting has been a topic for review in the procedure EMEA/H/C/3820/II/0108 for adjuvant treatment of RCC. The wording in section 4.8 of the SmPC has been updated to reflect the incidences of AEOSI in the adjuvant vs. the metastatic setting. Therefore, the proposed wording under "*Pembrolizumab in monotherapy"* and "*Immune-related endocrinopathies"* reflects the safety data of patients with RCC and melanoma treated with pembrolizumab monotherapy in the adjuvant setting (n=1,480), confirming the higher incidences of AEOSI in this setting. The overall incidence of **Grade 3 to 5 AEs** in KEYNOTE-716 was higher in the pembrolizumab group compared with the placebo group (25.9% vs. 17.1%) and lower than KEYNOTE-054 and the RSD (31.8% and 48.2%, respectively). The only grade 3 to 5 AEs reported more frequently in the KEYNOTE-716 pembrolizumab arm than KEYNOTE-054 and the RSD were *rash* (1.4% vs. 0.4% vs. 0.5%) and *autoimmune hepatitis* (1.2% vs. 0.6% vs. 0.3%, respectively), for which the contribution of the immune dysregulation induced by pembrolizumab cannot be excluded. No **Grade 5 AEs** occurred in the pembrolizumab arm. The overall incidence of **Grade 3 to 5 drug-related AEs** in KEYNOTE-716 was higher in the pembrolizumab group compared with the placebo group (16.1% vs. 4.3%, respectively). The incidences and types of Grade 3 to 5 drug-related AEs in the KEYNOTE-716 pembrolizumab group were similar to those in KEYNOTE-054 and generally consistent with the RSD (16.1% vs. 14.5% vs. 15.8%). The most frequently reported Grade 3 to 5 drug-related AEs (incidence ≥1%) in the pembrolizumab group were *rash (1.4%)*, *autoimmune hepatitis (1.2%)*, *colitis* (1%) and *diarrhoea (1%)*, slightly higher than those reported in KEYNOTE-054 and the RSD (except for *colitis* 1.4% in KN-054). As requested, details on the treatment and on the clinical outcomes on *autoimmune hepatitis* have been provided. In particular, the majority (80%) of participants in the pembrolizumab group of KEYNOTE-716 (and the RSD) that reported drug-related *autoimmune hepatitis* and *hepatitis* had outcomes reported as resolved or resolving at the time of the DCO. Regarding the gastrointestinal toxicities that may lead to dehydration, the incidence of *diarrhoea* and *vomiting* was comparable between KEYNOTE-716 and the RSD and was as expected also in the paediatric setting.

The incidence of **SAEs** in the KEYNOTE-716 pembrolizumab group was lower than in the KEYNOTE 054 and the RSD (18.8% vs. 25% vs. 38.3%). However, the types of SAEs in the KEYNOTE 716 pembrolizumab group were similar to those in KEYNOTE-054 and generally consistent with the RSD. SAEs reported more frequently in KEYNOTE-716 than in the RSD included *basal cell carcinoma, malignant melanoma in situ* and *squamous cell carcinoma.* The similar incidences of *basal cell carcinoma* and *squamous cell carcinoma* in KEYNOTE-716 and KEYNOTE-054 are consistent with the incidences observed in patients with melanoma (similar incidences were also observed in placebo arm in KEYNOTE-716).

The overall incidence of **treatment-related SAEs** was higher in the pembrolizumab group than in the placebo group (9.1% vs. 1.9%). Overall, the incidences and types of drug-related SAEs in the KEYNOTE-716 pembrolizumab group were similar to those in KEYNOTE-054 (12.2%) and generally consistent with the RSD (11.3%). In KEYNOTE-716, the most frequently reported treatment-related SAEs in the pembrolizumab group were *adrenal insufficiency* and c*olitis* (each reported for 4 participants). *Adrenal insufficiency* and *colitis* are known ADRs for pembrolizumab. Immune checkpoint inhibitor (ICI)-associated *primary adrenal insufficiency* is a rare adverse event that is important to recognize because it may be severe and life-threatening, requiring emergent and often lifelong hormonal replacement therapy. The risk of injury of other organ systems and endocrine disease has been noted (i.e., with *severe acute kidney injury*, occasional cases of cardiotoxicity, including *myocarditis*). Awareness regarding this ICI-related endocrinopathy is strongly encouraged among clinicians in addition to patient education about common primary *adrenal insufficiency* symptoms that should prompt urgent medical evaluation. In clinical practice, close monitoring and investigation for adrenal insufficiency is crucial to allow for early management and to further define the pathophysiology and prognosis of *ICI-adrenal insufficiency* (*Grouthier V et al. Oncologist 2020*) Corticotrophin (adrenocorticotrophic hormone) circulating level evaluation may be often lacking but should be considered as part of the diagnostic workup to differentiate *primary adrenal insufficiency* from *secondary (central) adrenal insufficiency.* The MAH has summarized the data and the outcomes of the cases with *adrenal insufficiency* related to pembrolizumab. In KEYNOTE-716, drug-related *adrenal insufficiency* was reported in 11 (2.3%) participants that received pembrolizumab, in 7 participants with maximum toxicity of ≤ Grade 2, and in 4 participants as Grade 3 *adrenal insufficiency*. All patients, with one exception, required systemic corticosteroid therapy and events were reported as resolved or resolving in 6 out of 11 patients. *Adrenal insufficiency* is reported in the SmPC, described in section 4.4 (Warnings and Precautions) and listed as uncommon ADR in section 4.8 (Undesirable effects) of the SmPC. Based on this evaluation, no additional warning is necessary in the SmPC.

The nature and severity of **AEOSIs** in the KEYNOTE-716 pembrolizumab group were consistent with the established safety profile of pembrolizumab. No new immune-related AEs for pembrolizumab were identified. Overall, incidences, types and severity of AEOSIs in the KEYNOTE-716 pembrolizumab arm were similar to those in KEYNOTE-054, but higher than those reported in the RSD (36.2% vs. 35.2% vs. 25.5%, respectively), probably mainly driven by increased incidences of *hypothyroidism* and *hyperthyroidism* (15.7% and 10.4% in KEYNOTE-716 vs. 11.3% and 4.2% in RSD, respectively). AEOSIs were manageable with treatment interruption, discontinuation and/or corticosteroid therapy and none were fatal. Among participants in the pembrolizumab group, most (54.9%) had AEOSIs that were resolved or resolving at the time of the DCO. AEOSIs that were unresolved included endocrinopathies (i.e., *hypothyroidism*, *adrenal insufficiency*, *hypophysitis*, *thyroiditis*, and *type 1 diabetes mellitus)* requiring long-term hormone replacement therapy. In particular, the incidence of *adrenal insufficiency* in KEYNOTE-716 (2.3%) was higher than in the RSD (0.8%), likewise, the incidence of *hypophysitis* in KEYNOTE-716 (2.1%) was higher than in the RSD (0.6%). However, the incidence of immune-related *hypothyroidism*, *thyroiditis* and *type 1 diabetes mellitus* were comparable across the datasets. Overall, the proportion of participants in KEYNOTE-716 with immune-related

endocrinopathies that were unresolved and required hormone replacement therapy (HRT) was consistent with that previously observed in the adjuvant treatment of resected Stage III melanoma with pembrolizumab in KEYNOTE-054. In detail, a total of 18.6% of patients in the pembrolizumab arm of KEYNOTE-716 received HRT for endocrinopathies (compared with 12.6% of patients in pembrolizumab arm of KEYNOTE-054), and *hypothyroidism* was the most frequently occurring endocrinopathy requiring HRT. In conclusion, the findings from KEYNOTE-716 for endocrinopathies were consistent with the known safety profile of pembrolizumab and no additional warning is necessary in the SmPC.

No new safety concerns based on **laboratory abnormalities** were reported in the KEYNOTE-716 pembrolizumab group. The most frequently reported post baseline laboratory abnormalities in the KEYNOTE-716 pembrolizumab group were generally consistent with KEYNOTE-054 and the RSD.

No participants in the pembrolizumab group died due to an AE; 4 participants in the placebo group had an AE that resulted in death during the study or follow-up period and none of the deaths were reported as related to study treatment.

The incidences and types of **AEs leading to discontinuation** of pembrolizumab in the KEYNOTE-716 Safety Dataset were similar to those in KEYNOTE-054 and were generally consistent with the RSD (15.9% vs. 13.9% vs. 13.5%, respectively). Conversely, incidences of **drug-related AEs leading to discontinuation** of pembrolizumab in KEYNOTE-716 and KEYNOTE-054 were higher than in the RSD (15.3% vs. 12.2% vs. 7.2%, respectively) (of note, participants in KEYNOTE-716 had 2 times longer median duration of exposure to pembrolizumab than participants in the RSD). Most drug-related AEs leading to treatment discontinuation of pembrolizumab in KEYNOTE-716 occurred in <1% of the participants, except for *colitis* and *autoimmune hepatitis* (1.0% each), with a similar frequency reported in KEYNOTE-054 but higher than those reported in the RSD (*colitis*: 1.2% and 0.5%, respectively; *autoimmune hepatitis:* 0.4% and 0.2%). *Colitis* and *autoimmune hepatitis* are AEOSIs for which treatment interruption or discontinuation is recommended, depending on the severity of the AE.

The types of **drug-related AEs leading to pembrolizumab interruption** in the KEYNOTE-716 Safety Dataset were similar to those in KEYNOTE-054 and the RSD, but with a slightly higher frequency in KEYNOTE-716 for some drug-related AEs *(arthralgia*: 1.7% vs. 1.4% vs. 0.6%; *hyperthyroidism*: 1.2% vs. 0.4% vs. 0.2%, respectively). These findings suggest that the overall tolerability of pembrolizumab among participants in KEYNOTE-716 was generally consistent with what was previously observed in the adjuvant melanoma KEYNOTE-054 Safety Dataset, but the higher incidences of endocrinopathies in this population could represent a concern.

Subgroup analyses in KEYNOTE-716 based on **intrinsic (age, sex, ECOG performance status) and extrinsic factors (region)** were also performed.

There was an **age**-dependent increase in Grade 3-5 AEs, Grade 3-5 drug-related AEs and SAEs in the pembrolizumab arm. Tolerability to pembrolizumab was particularly reduced in patients aged ≥75 years compared to younger subgroups (23.1% vs. 12.7% in patients <65 years old for drug-related grade 3-5 AEs; 38.5% vs. 15.8% in patients <65 years old for SAEs), in parallel to higher incidence of discontinuation due to an adverse event (23.1% vs. 14% in patients <65 years old for discontinuation due to an AE; 23.1% vs. 13% in patients <65 years old for discontinuation due to a drug-related AE). Additionally, a summary of AEs by age and categories of interest analysed (central nervous system-confusion/extrapyramidal, AE related to falling, cardiovascular events-CV, cerebrovascular events, and infections) showed higher incidence of CV events in subgroups aged 65-74 and 75-84, in both the pembrolizumab and placebo groups. Overall, the safety data of pembrolizumab in the adjuvant melanoma setting in patients ≥ 75 years are limited and no definitive conclusion can be drawn.

With regard to **gender subgroup analyses**, the safety profile of male and female participants in KEYNOTE-716 and KEYNOTE-054 was consistent with the established safety profile of pembrolizumab

monotherapy in the RSD. Based on evaluable data, there were no significant differences in the various AE categories by gender for pembrolizumab. In particular, the 95% CI of the risk difference between male and female participants in KEYNOTE-716 and KEYNOTE-054 (including AE categories Grade 3 - 5 AEs, SAEs, Grade 3 - 5 drug -related AEs, and discontinuation due to an AE or drug-related AE) showed no clinically significant differences in the AE profile by gender for the two studies. In conclusion, there are no clinically significant differences in the observed AE profile by gender for pembrolizumab.

For ECOG performance status and region, the AE profile in the KEYNOTE-716 pembrolizumab group remained generally consistent with the established safety profile of pembrolizumab.

Assessment of paediatric data on clinical safety

For the proposed indication of pembrolizumab as adjuvant treatment of paediatric (12 years and older) patients with Stage IIB and IIC melanoma following complete resection, safety results have been presented from study KEYNOTE-716, including only two adolescent patients (one enrolled in the pembrolizumab arm, one in the placebo group). The first patient, was diagnosed with melanoma approximately 3 months and 28 days prior to the first dose of pembrolizumab. At screening, a KPS score was 100 and T4aN0M0. Pembrolizumab 2 mg/kg IV Q3W was started on Day 1 (Cycle 1) for the treatment of resected high-risk Stage II melanoma and the patient received 17 cycles during the study. The participant entered the study with a history of *acne*, *cystic acne*, and *hidradenitis*, treated with oral clindamycin, which was stopped on Day -14. The patients experienced two episodes of *hidradenitis* (Grade 1) in the left axilla (on Day 58 and Day 124), for which no treatment was reported, and no further information was available. Additionally, on day 293 increased WBCs were observed, followed by *increased lymphocyte count* on day 335 (resolved on day 356). On day 356 the participant completed pembrolizumab; as of day 425, last contact before data cut-off, the participant was alive. The investigator considered the non-serious AEs of *hidradenitis* (2 episodes) and *increased lymphocyte count* as not related to pembrolizumab. The second patient, was diagnosed with melanoma approximately 4 months and 5 days prior to first dose of study medication. The patient was newly diagnosed with Stage IIB cutaneous melanoma confirmed by histology, which was completely resected, and had negative SLN biopsy prior to enrolment. At screening, a KPS score was 100 and T3bN0M0. No adverse events were reported. As of day 293, last contact before data cut-off, the participant was alive.

The MAH provided a comparative analysis of the safety data of paediatric melanoma patients in KEYNOTE-051 (n=9), the cumulative safety data of KEYNOTE-051 (n=161), the pooled safety data from the 2 adjuvant melanoma studies (KEYNOTE-716 and KEYNOTE-054) (n=992) and the pooled safety dataset for adults with advanced melanoma (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006) (n=1567). The safety profile of pembrolizumab for paediatric participants in KEYNOTE-051 was generally consistent with the established safety profile of pembrolizumab monotherapy in adults with advanced melanoma. The incidence of AEOSI was higher in the pooled adjuvant melanoma dataset (35.7%) compared to the adult advanced melanoma dataset (22.9%) and KEYNOTE-051 (18.6%), but the nature and severity of AEOSI were similar when compared across all the datasets, mostly mild to moderate in severity. They were manageable with treatment interruption, discontinuation, corticosteroid therapy and/or hormone replacement therapy. Overall, the AEOSIs in the paediatric melanoma participants and in KEYNOTE-051 patients were comparable to that of the adult adjuvant and advanced melanoma participants. The most frequently reported endocrinopathy in KEYNOTE-051 was *hypothyroidism* and there were no reported cases of *immune-related hepatitis*, *nephritis*, *type 1 diabetes mellitus* or *hypophysitis*. After adjusting for duration of exposure in the datasets, the incidence of AEs or AEOSI in the paediatric melanoma dataset and KEYNOTE-051 remained generally

consistent with the adult advanced melanoma safety dataset and lower than in the pooled adjuvant melanoma safety dataset. No new safety signals were observed when the paediatric safety datasets were compared with the adult safety datasets. In conclusion, the safety results presented are limited due to the low number of included adolescent patients precluding any firm conclusions and unknown are the long-term toxicities associated to treatment with check point inhibitors (like autoimmune endocrine, hepatic and renal toxicity) in the adolescent population. However, the overall safety profile appears to be as expected from the known safety profile of pembrolizumab and the safety data from the KEYNOTE-716 and KEYNOTE-054 studies does not give raise to new safety concerns. There are, however, uncertainties related to the long-term safety of pembrolizumab, especially in the adjuvant adolescent setting, with endocrine related ADRs that may affect hormonal development in these patients. In order to address this issue, the MAH plans to open a new cohort in KEYNOTE-051 to collect long-term safety data for the treatment of adolescent melanoma in the adjuvant setting (resected Stage IIB, IIC and Stage III) for a total duration of 4 years including follow-up. The expected number of patients to be enrolled in the new cohort is difficult to predict at this point, but it is anticipated to be in the order of 1 patient/year for a total duration of 4 years. Considering the limited number of additional cases deriving from study KEYNOTE-051, a suggestion was made to explore additional options able to gather as more data as possible in this age category (e.g., with the collection of post-marketing adolescent safety data facilitated through joining the existing Dutch Melanoma Treatment Registry (DMTR). Taking into account that DMTR has only registered 3 patients between years 2013-2018, the MAH was recommended to continue to explore other means to gather more adolescent melanoma patients safety data in the post-marketing setting, but the plan to further expand the numerosity of clinical cases was not specifically mentioned. Relying on routine pharmacovigilance activities as well as exploring other means to gather more data is supported. However, in the absence of a clear program to collect long term safety data in the post-marketing that go beyond the limited timeline of the Study KN-051, the MAH was recommended to prolong the follow-up for each participant for as long as the KEYNOTE-051 study is open (until 2028). This request is based on the observed time to onset of AEOSI (median 64 days; range 1 to 371) and episode duration (median 193 days; range 1 to 684+) from KN-716. The lack of data on the safety of pembrolizumab on the very long term in adolescents with Stage IIB, IIC and III melanoma treated in the adjuvant setting was reflected in section *4.8 Paediatric population* of the SmPC.

2.5.2. Conclusions on clinical safety

There were no new safety signals observed in study KEYNOTE-716 in the pembrolizumab treatment arm in the adjuvant setting of completely resected Stage IIB and IIC 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 discontinuations occurred more often in the experimental arm than placebo, which is expected, and frequencies were generally comparable to what has been observed in KEYNOTE-054 with pembrolizumab monotherapy in the adjuvant setting and generally consistent with the RSD. However, an increased rate of AEOSIs mainly related to endocrine disturbances (i.e., *hypothyroidism* and *hyperthyroidism*) and of discontinuations due to drug-related AEs were observed in the pembrolizumab group compared with the placebo group and the RSD, to which the longer exposure of patients in KEYNOTE-716 than in prior trials contributed. No new safety signals were observed when the paediatric safety datasets were compared with the adult safety datasets. However, the safety results presented are limited due to the low number of included adolescent patients precluding any firm conclusions and unknown are the long-term toxicities associated to treatment with check point inhibitors (like autoimmune endocrine, hepatic and renal toxicity) in the adolescent population. The MAH is recommended to add a new cohort to KEYNOTE-051 to collect long-term safety data for the treatment of adolescent melanoma in the adjuvant setting for as long as the KEYNOTE-

051 study is open (until 2028). The safety of adolescent melanoma patients will be also monitored through routine pharmacovigilance activities. Taking into account that DMTR has only registered 3 patients between years 2013-2018, the MAH will continue to explore other means to gather more adolescent melanoma patients safety data in the post-marketing setting, but the plan to further expand the numerosity of clinical cases was not specifically mentioned. Relying on routine pharmacovigilance activities as well as exploring other means to gather more data is supported.

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 MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 37 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 37 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	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)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table V.3.1: 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 adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) 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
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types
Important Potential Risks		
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. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trial (KN204).

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
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. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 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 package leaflet are limited; in particular, the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, these proposed revisions do not constitute significant changes that would require the need to conduct a new user consultation or a bridged focus testing.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Extension of indication to include the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or Stage IIC melanoma and to include adolescents aged 12 years and older in the adjuvant treatment of Stage III melanoma and treatment of advanced melanoma.

3.1.2. Available therapies and unmet medical need

With particular reference to the treatment of primary melanoma Stage IIB and IIC, surgical resection with a sentinel lymph node biopsy (SNB) represents the first-line approach. In the event of a negative

SNB, follow-up with active surveillance for recurrence is the solely recommended action to be undertaken accordingly with the most recent guidelines. It is estimated that 90% of relapse occurs during the first 5 years post-surgery, which is therefore considered the most critical period for monitoring. Adjuvant systemic therapy is contemplated at relapse. It is acknowledged that the prognosis in terms of probability of survival in Stage IIC is similar to Stage IIIB, for which adjuvant therapies are currently available.

There is therefore the need to improve the clinical management within the setting of Stage II to ameliorate clinical outcomes. Treatment in adolescents relies upon surgical strategies. Adjuvant systemic therapies are currently not licensed in Europe. There is, therefore, an unmet medical need to be satisfied within the paediatric setting.

3.1.3. Main clinical studies

The proposed adult and paediatric indication in Stage II melanoma relies upon data from Study KEYNOTE-716, a Phase 3 randomized, placebo-controlled, parallel-group, crossover/rechallenge, multicenter study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma. The study consists of Part 1 where patients were assigned to either pembrolizumab or placebo for a 17 cycles length of treatment, followed by Part 2 in which participants who completed Part 1 and experienced a recurrence were started on pembrolizumab regardless of the treatment received in Part 1. In the current application, only data from Part 1 are presented.

In support of the paediatric indication (also including Stage III and advanced) the MAH claims similarity between the adult and paediatric disease in terms of biology and pharmacology of drug effect.

3.2. Favourable effects

A statistically significant advantage of pembrolizumab relative to placebo on RFS (HR=0.65; 95% CI: 0.46,0.92; p=0.00658 at IA1; HR=0.6195% CI: 0.45, 0.82; p=0.00046 at IA2; IA2 represents the final RFS analysis prespecified according to SAP). Further support derives from the statistically significant effect of pembrolizumab relative to placebo on DMFS at the first interim analysis.

3.3. Uncertainties and limitations about favourable effects

Confirmation is required for longer follow-up and additional clinical endpoints. The MAH will submit results from the planned future analyses of clinical endpoints; DMFS and OS (Annex II condition).

Limited paediatric data are available, however the extrapolation based on the similarity between the adult and paediatric disease in terms of biology and pharmacology of drug effect is supported.

3.4. Unfavourable effects

The incidence of drug-related AEs (79.9% vs. 60.9%), drug-related Grade 3-5 AEs (16.1 % vs. 4.3%), drug-related SAEs (9.1% vs. 1.9%), drug discontinuations due to either drug-related AEs (15.3% vs. 2.5%) or drug-related SAEs (6.8% vs. 2.5%) were all more frequent in the pembrolizumab group compared to control.

The most frequently reported drug-related AEs (incidence >10%) in KEYNOTE-716, pruritus, fatigue, diarrhoea, rash, hypothyroidism, and arthralgia, were consistent with the most frequently reported drug-related AEs in KEYNOTE-054, but higher than the RSD. In particular, the frequencies of hypothyroidism and hyperthyroidism in KEYNOTE-716 (14.5% and 9.9%, respectively), similar to those observed in KEYNOTE-054 (14.5% and 9.6%, respectively), were higher than in the RSD (9.8% and 3.7%, respectively).

The most frequently reported Grade 3 to 5 AEs (in ≥1.0% of participants in either treatment group) were hypertension, diarrhoea, rash, autoimmune hepatitis, ALT increased, colitis, and lipase increased but no clinically meaningful difference was observed between the pembrolizumab and placebo groups in the incidences of these Grade 3 to 5 AEs.

The incidences and types of Grade 3 to 5 drug-related AEs in the KEYNOTE-716 pembrolizumab group were similar to those in KEYNOTE-054 and generally consistent with the RSD (16.1% vs. 14.5% vs. 15.8%). The most frequently reported Grade 3 to 5 drug-related AEs (incidence ≥1%) in the pembrolizumab group were rash (1.4%), autoimmune hepatitis (1.2%), colitis (1%) and diarrhoea (1%), slightly higher than those reported in KEYNOTE-054 and the RSD (except for colitis 1.4% in KEYNOTE-054).

Colitis and adrenal insufficiency were also the main pembrolizumab-related SAEs in KEYNOTE-716 (each reported for 4 participants 0,8%). Neither colitis nor adrenal insufficiency were observed in the placebo group.

3.5. Uncertainties and limitations about unfavourable effects

No data on the safety in the paediatric/adolescent adjuvant melanoma setting were available, since the majority of patients has already been cured by surgery. Unknown are the long-term toxicities associated to treatment with check point inhibitors (like autoimmune endocrine, hepatic and renal toxicity) in the adolescent population. The MAH was recommended to collect long-term data for each participant as long as the KEYNOTE-051 study is open (until 2028).

3.6. Effects Table

Table 10. Effects Table for Keytruda for the adjuvant treatment of melanoma in adult and paediatric (12 years and older) patients with Stage IIB and IIC melanoma following complete resection (KEYNOTE-716, data cut-off: 04-DEC-2020, RFS Interim Analysis)

Effect	Short description	Unit	Pembro 200 mq Q3W	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
RFS	time from randomization to (1) any recurrence (local or regional [including invasive ipsilateral tumour and invasive locoregional tumour], or distant) as assessed by the	N events (%)	54/487 (11.1%)	82/489 (16.8%)	Immaturity of IA1, insufficient length of observation, inconsistency across relevant subgroups, lack of additional clinical endpoints	CSR

Effect	Short description	Unit	Pembro 200 mq Q3W	Placebo	Uncertainties / Strength of evidence	References
	investigator, or (2) death due to any cause (both cancer and noncancer causes of death)					
Unfavourable Effects						
	drug related Grade≥3 AE	%	16.1	4.3	Higher rate of AEOSIs were reported in KN-716 compared to the reference safety datasets, including *colitis* and *autoimmune hepatitis* (<2%), and *endocrine disturbances* (*thyroid dysfunction*) [<10%]	CSR
	drug related SAEs	%	9.1	1.9		
	drug related deaths	%	0	0		
	discontinuation drug related AEs	%	15.3	2.5		
	discontinuation drug related SAEs	%	6.8	2.5		

Abbreviations: CSR: Clinical Study report; RFS: recurrence free survival

Notes: based on date cut-off 04DEC2020 of IA1

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Within the setting of an adjuvant therapy, RFS can be considered a valid surrogate endpoint to infer treatment effects. Study KEYNOTE-716 provides evidence for a statistically significant advantage of pembrolizumab over placebo as adjuvant therapy in Stage II melanoma over a median follow-up of 26.9 months. However, the submitted analysis is limited by the high degree of immaturity and censoring rate and insufficient length of follow-up considering that only 23.5% of events was registered in the control arm and the estimate of treatment mainly relies upon a comparison of cases occurred during the first 12 months of observation, which correspond to the on-treatment phase. Although immature, the initial DMFS evaluation at IA3 provided evidence of a statistically significant reduction of events in the pembrolizumab arm relative to placebo. In any case, the benefit of treatment based on RFS results in study KEYNOTE-716 requires confirmation by longer duration of follow-up and support by additional clinically relevant endpoints to positively conclude on the benefit of such an early intervention vs delayed therapies (at recurrence). The MAH has committed to submit final DMFS and interim OS results as part of an Annex II condition.

Lack of characterisation of effect of treatment by PD-L1 expression and BRAF mutation status is an important limiting factor to verify consistency across relevant patient subgroups especially in the context of a rapidly evolving therapeutic landscape, where the potential availability of targeted therapies might question the place in therapy of immunomodulation. It should be considered, however, that study KEYNOTE-054 showed independence of response to treatment from PD-L1 and BRAF hallmarks in the adjuvant setting of Stage III melanoma, and this information can be regarded as pertinent to the current pursued indication.

As regards the paediatric indication, efficacy data in adolescents aged >12 years are numerically limited to 5 of the total 9 paediatric cases of advanced melanoma recruited in study KEYNOTE-051, (none of them showing response to therapy), and only 1 patient in each arm in study KEYNOTE-716. Due to the small sample size, results are inconclusive. The MAH proposed a bridging strategy on the basis of biological similarity between adult and adolescent melanoma and similar pharmacology of pembrolizumab in the two age categories. Although disease similarity can be recognised based upon biological considerations and evidence of response to treatments, including immunotherapy, thus overcoming the unavailability of clinical data, evidence of exposure-response relationships are indirect and derived from the cHL disease setting. Based on the assumption that the flat exposure-response relationship seen in adults across multiple tumour types is preserved in paediatric patients across indications, the MAH concludes for a similar exposure-response profile in adult and adolescent melanoma. Despite the limitations of an indirect exposure-response determination, the bridging strategy adopted by the MAH could be deemed acceptable within the specific tumour-type, considering the historically recognised immunoresponsive nature of melanoma, and taking into account that extrapolation of pembrolizumab pharmacology from adults is limited to adolescents. However, since currently available clinical observations trend toward lack of response, commitment is requested to the MAH for prospectively collecting meaningful data in the post-marketing as regards efficacy and safety aspects in both the adjuvant and advanced disease treatment settings of adolescent melanoma (see also below).

In terms of safety, no new signals have emerged from study KEYNOTE-716. However, it has been observed a higher incidence of AEOSIs than previously reported in the RSD, similarly to KEYNOTE-054. No new safety signals were observed when the paediatric safety datasets were compared with the adult safety datasets. However, the safety results presented are limited due to the low number of included adolescent patients precluding any firm conclusions and unknown are the long-term toxicities associated to treatment with check point inhibitors (like autoimmune endocrine, hepatic and renal toxicity) in the adolescent population. Therefore, it is considered important to collect as much post-authorisation data as possible (on efficacy and safety outcomes) on paediatric/adolescent treated patients in the approved indication(s). The MAH was recommended to open a new cohort in Study KEYNOTE-051 to recruit paediatric patients in the adjuvant melanoma setting.

3.7.2. Balance of benefits and risks

Based upon a statistically significant effect on RFS and considering the supportive data derived from study KEYNOTE-054, benefit of treatment can be considered sufficiently demonstrated. Further support derives from the statistically significant effect of pembrolizumab relative to placebo on DMFS at the first interim analysis. Taking in to account the acceptable safety profile, it can be concluded that the benefit/risk is positive.

3.7.3. Additional considerations on the benefit-risk balance

The paediatric indication can be considered adequately supported by the proposed bridging strategy. For the adjuvant setting, only 2 paediatric patients were included in the pivotal study KEYNOTE-716, while data available in the paediatric advanced disease stage as derived from study KEYNOTE-051 were scarce. Conclusions are supported by the extrapolation of the benefit/risk profile from adults. However, uncertainties remain on the long-term safety of pembrolizumab in adolescents, especially in the adjuvant adolescent setting, with endocrine related ADRs that may affect hormonal development in these patients. A recommendation has been made to address this issue in the post-marketing (PAM-REC). A new cohort to KEYNOTE-051 to collect long-term safety data for the treatment of adolescent

melanoma in the adjuvant setting as long as the KEYNOTE-051 study is open (until 2028) will be added and the safety of adolescent melanoma patients will be also monitored through routine pharmacovigilance activities. Taking into account that DMTR has only registered 3 patients between years 2013-2018, the MAH will continue to explore other means to gather more adolescent melanoma patient safety data in the post-marketing setting, but the plan to further expand the numerosity of clinical cases has not been specifically mentioned. Relying on routine pharmacovigilance activities as well as exploring other means to gather more data is supported.

3.8. Conclusions

The overall B/R of Keytruda as adjuvant therapy in adult and paediatric Stage II melanoma is positive. The paediatric indication of Keytruda as adjuvant in Stage III and treatment in advanced disease in the paediatric setting can be considered approvable.

The following measures are considered necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of pembrolizumab as adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma, the MAH should submit the per-protocol specified final analysis of DMFS and interim analysis of OS for study KN716: A Phase III Clinical Trial of Pembrolizumab (MK-3475) in Subjects with complete resection of high-risk Stage II melanoma

4. Recommendations

Outcome

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

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

Extension of indication to include the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, Stage IIC or stage III melanoma and to inlcude the treatment of adolescents aged 12 years and older with advanced melanoma for Keytruda; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 37 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial improvements in the wording of the indication for MSI-H or dMMR cancers in section 4.1 of the SmPC and update the list of local representatives in the Package Leaflet.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0043/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0111'