27 February 2025
EMA/CHMP/507869/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMEA/H/C/003820/II/0154

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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List of abbreviations

Abbreviation/Term	Definition
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate aminotransferase
BAP1	BRCA1 associated protein 1
BICR	blinded independent central review
CCTG	Canadian Cancer Trials Group
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPS	combined positive score
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DOR	duration of response
EC_{50}	half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
E-R	exposure-response
EU	European Union
FA	final analysis
FAS	Full Analysis Set
FDA	Food and Drug Administration
GHS	global health score
HIPEC	hyperthermic intraperitoneal chemotherapy
HR	hazard ratio
IA	interim analysis
IFNγ	interferon-gamma
IgG4	immunoglobulin G4
IL	interleukin
ITT	Intent-to-Treat
IV	intravenous
KM	Kaplan-Meier
LS	least squares
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Merck Sharp & Dohme, LLC	Merck Sharp & Dohme, LLC (Rahway, NJ, USA); also, the Company
MPM	malignant pleural mesothelioma
mRECIST	modified Response Evaluation Criteria in Solid Tumors
NCCN	National Comprehensive Cancer Network
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PSUR	Periodic Safety Update Report
Q3W	every 3 weeks
Q6W	every 6 weeks
QLQ	Quality of Life Questionnaire

Abbreviation/Term	Definition
QoL	quality of life
RSD	Reference Safety Dataset
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SEER	Surveillance, Epidemiology, and End Results
SOC	standard of care
sSAP	supplemental statistical analysis plan
TIL	tumor-infiltrating lymphocyte
TNFα	tumor necrosis factor alpha
TRAE	treatment-related adverse event
TTD	time to deterioration
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Product Insert

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 8 April 2024 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 in combination with pemetrexed and platinum chemotherapy the first-line treatment of adults and adolescents aged 12 years and older with unresectable advanced or metastatic malignant pleural mesothelioma for Keytruda, based on final results from study KEYNOTE-483; this is a multicenter, open-label, Phase 2/3 randomized study to evaluate the efficacy and safety of pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with unresectable advanced or metastatic malignant pleural mesothelioma (MPM). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 47.1 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 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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	8 April 2024
Start of procedure:	27 April 2024
CHMP Rapporteur Assessment Report	1 July 2024
PRAC Rapporteur Assessment Report	27 June 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	24 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	7 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	4 November 2024
CHMP members comments	7 November 2024
Updated CHMP Rapporteur Assessment Report	10 November 2024
An Oral explanation took place on:	13 November 2024
Opinion	14 November 2024

1.3. Steps taken for the re-examination procedure

The Rapporteur appointed by the CHMP and the evaluation teams was:

Rapporteur: Filip Josephson

Timetable	Actual dates
Written notice to the EMA to request a re-examination of Keytruda CHMP opinion of 14 November 2025	18 November 2024
Rapporteur's appointment	13 December 2024
Detailed grounds for the Re-examination (Appendix 2 of Final Opinion) submitted on	20 December 2024
Start of procedure:	6 January 2025
Rapporteur assessment report	27 January 2025
Rapporteur's updated assessment report circulated on:	14 February 2025
An Oral explanation on the detailed grounds for re-examination took place on:	26 February 2025
CHMP opinion:	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The initially proposed indication was:

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults and adolescents aged 12 years and older with unresectable advanced or metastatic malignant pleural mesothelioma.

The indication as adopted by the CHMP is:

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

Epidemiology and risk factors

Malignant pleural mesothelioma (MPM) remains a rare thoracic malignancy with an incidence in Europe of 1.83 cases per 100 000 individuals annually[1]. The tumour develops in the mesothelial lining of the pleura, and is mostly and directly attributable to all types of asbestos exposure. Pleural is the most common type of malignant mesothelioma, accounting for more than 80% of mesothelioma cases[2].

Malignant pleural mesothelioma (MPM) is a disease of the elderly population, with a median age at diagnosis of 76 years, while is even more rare below the age of 50 years. Incidence is higher in male than female, and better survival in female has been reported[3].
Exposure to asbestos is the most common aetiology and primary risk factor for developing mesothelioma, with a lag time of ~40 years between exposure and presentation. Asbestos use is currently banned in 67 countries but continues to be high in Central Asia compared with Europe, and the United States have no ban but only usage restrictions. Therefore, incidence of disease continues to rise in many countries[4]. Other potential risk factors include prior exposure to radiation and inherited susceptibility (such as the germline BAP1 mutation)[5].

Biologic features

Nearly all pleural mesotheliomas are diffuse, although very rarely tumours are localised, defined by a single circumscribed mass with no clinical or histological evidence of spread. There are three

[1] Gatta G, et al; Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet – a population-based study. Lancet Oncol. 2017; 18:1022-1039.
[2] Popat S, Baas P, Faivre-Finn C, et al; ESMO Guidelines Committee. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022 Feb;33(2):129-142.
[3] Sirri E, Kieschke J, Vohmann C, et al. Survival of malignant mesothelioma and other rare thoracic cancers in Germany and the United States: a population-based study. Int J Cancer. 2020;147(6):1548-1558.
[4] Alpert N, van Gerwen M, Taioli E. Epidemiology of mesothelioma in the 21st century in Europe and the United States, 40 years after restricted/banned asbestos use. Transl Lung Cancer Res. 2020;9(suppl 1):S28-S38.
[5] Carbone M, Adusumilli PS, Alexander HR Jr, et al. Mesothelioma: scientific clues for prevention, diagnosis, and therapy. CA Cancer J Clin. 2019 Sep-Oct;69(5):402-29. Erratum in: CA Cancer J Clin. 2020 Jul-Aug;70(4):313-4.

histological subtypes: epithelioid, sarcomatoid and biphasic. The epithelioid subtype is the prevailing tumour; prognosis is worse in non-epithelioid disease[3,6].

Clinical presentation, diagnosis and stage/prognosis

MPM usually manifests at a late stage of disease when therapeutic options are generally palliative in nature, and this makes the prognosis generally poor. Diagnosis is based on imaging, occupational history and, importantly, on histological confirmation. Thoracoscopy is the preferred method to obtain tumor samples, and when contraindicated, CT-/US-guided histological biopsy represent a valid alternative. Surgical resection is indicated in a minority of the population (10% to 15% of patients). The median OS for patients with untreated MPM is generally less than a year, and less than 10% of patients survive beyond 5 years[7].

Management

Factors such as stage, histology, age, PS, comorbidities and the patient's preferences, should be taken into account into treatment's decisions, ideally be discussed within experienced multidisciplinary tumour board. A multimodality approach including surgery, or palliative care, or systemic therapy only are the available options for MPM management[3].

In subjects not suitable for cytoreductive surgery with radical intent candidate for a non-surgical approach, pemetrexed-platinum chemotherapy has long been the standard-of-care as a first line treatment[3]. A Phase 3 study of cisplatin in combination with pemetrexed in MPM demonstrated that, compared with cisplatin alone, the combination significantly improved median OS (12.1 vs 9.3 months)[8]. The Phase 3 MAPS study showed improved median OS for patients with unresectable MPM when bevacizumab was added to a cisplatin/pemetrexed regimen and followed by maintenance bevacizumab compared with cisplatin/pemetrexed alone (18.8 months vs 16.1 months, HR=0.77; p=0.0167)[9]. However, bevacizumab is not currently licensed for MPM treatment, and its use varies across centers. Nivolumab–ipilimumab is a new first-line option for unresectable MPM, that was licensed (in June 2021 in the EU[10]) based on the supportive data from the CheckMate 743 study, demonstrating improvement in OS with nivolumab–ipilimumab over cisplatin/carboplatin and pemetrexed chemotherapy (median OS of 18.1 vs 14.1 months, HR=0.74; p=0.0020). Updated analyses reported 3-years OS rate 23% vs 15%. However, a difference in treatment effect was observed between the epithelioid (HR=0.85 [95% CI: 0.68, 1.06]) and non-epithelioid histology (HR=0.46 [95% CI: 0.31,0.70]), mostly attributable to the known reduced response to chemotherapy in non-epitheliod tumours that translated in a larger immunotherapy OS benefit considering that the performance of nivolumab–ipilimumab was similar regardless of histology[3 11 12]. PD-L1 is expressed in 40%-60% of MPM tumour cells, strongly in sarcomatoid cases[13]. PD-L1 expression has been variably

[6] Nicholson AG, Sauter JL, Nowak AK, et al. EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach. J Thorac Oncol. 2020;15(1):29-49
[7] Milano MT, Zhang H. Malignant pleural mesothelioma: a population-based study of survival. J Thorac Oncol. 2010 Nov;5(11):1841-8.
[8] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21(14):2636-2644.
[9] Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387(10026):1405-1414
[10] EPAR Opdivo/Yervoy WS-1881
[11] Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021;397(10272):375-386.
[12] Peters S, Scherpereel A, Cornelissen R, et al. LBA65 First-line nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) in patients (pts) with unresectable malignant pleural mesothelioma (MPM): 3-year update from CheckMate 743. Ann Oncol. 2021;32:S1341-S1342
[13] Ghanim B, Rosenmayr A, Stockhammer P, et al. Tumour cell PD-L1 expression is prognostic in patients with malignant pleural effusion: the impact of C-reactive protein and immune-checkpoint inhibition. Sci Rep. 2020;10(1):5784

correlated with response to ICI[3], although the optimal testing method and cut-off remain unknown. Tumour mutational burden is low and micro-satellite instability is rare in MPM[14].

There are no strong literature data suggesting a benefit for maintenance treatment after standard first-line platinum-pemetrexed, and there is also limited evidence base for active second-line cytotoxic chemotherapies[3]. Thus, prognosis, remains poor in advanced MPM, and new effective treatments are needed in this clinical condition.

2.1.2. About the product

Pembrolizumab is a humanized monoclonal antibody (mAb) designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumour regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using an mAb can result in activation of antitumor T-cells and subsequent tumor regression. Pembrolizumab was approved in Europe in July 2015, and it is currently authorised for the treatment of multiple cancers, both as monotherapy and in combination with chemotherapy or other agents. There is no previous indication for mesothelioma.

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

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

An overview of the development programme of pembrolizumab in MPM is shown in the tables below.

Table 1. Overview of the Pembrolizumab Clinical Development Program for Unresectable Advanced and/or Metastatic MPM

Study Number / Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-A17 Completed	Phase 1b, multisite, single arm, open-label clinical study of Japanese participants with advanced MPM	Japanese participants with histologically confirmed advanced/unresectable MPM who were naïve to previous systemic therapy	Pembrolizumab: 200 mg IV Q3W Pemetrexed: 500 mg/m2 IV Q3W Cisplatin: 75 mg/m2 IV Q3W	DLT rate, AEs, discontinuing study treatment due to AEs

[14] . Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov. 2018;8(12):1548-1565

Study Number / Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-028 Completed	Phase 1b, multisite, open-label, nonrandomized, multicohort interventional study of participants with various advanced (unresectable and/or metastatic) solid tumor indications	Participants in Cohort C2 had histologically or cytologically-documented, locally advanced, or metastatic mesothelioma (MPM) that was incurable and either (a) failed prior standard therapy, (b) no standard therapy existed, or (c) standard therapy was not considered appropriate.	Pembrolizumab: 10 mg/kg IV Q2W	Best overall response rate
KEYNOTE-139 (NCI-2015-00348) Ongoing (Study sponsored by the University of Chicago)	Non-randomized, open-label, Phase 2 study	~65 patients with MPM or malignant peritoneal mesothelioma and ECOG performance status 0 or 1, who had previously failed standard therapy	Pembrolizumab 200 mg IV Q3W for up to 2 years, or until disease progression or unacceptable toxicity	ORR in unselected and PD-L1 positive patients
KEYNOTE-158 Ongoing	Phase 2, multisite, nonrandomized, multicohort, efficacy and safety intervention study of participants with various advanced (unresectable and/or metastatic) solid tumor types	Participants in Cohort H had histologically or cytologically documented advanced (unresectable or metastatic) MPM for which prior standard first-line therapy had failed.	Participants in Cohort H with MPM received pembrolizumab 200 mg IV Q3W.	ORR
KEYNOTE-483 Ongoing (Study sponsored by CCTG)	Phase 2/3, randomized, multisite, open-label clinical study of participants with unresectable advanced and/or metastatic MPM	Participants with histologically-confirmed unresectable advanced and/or metastatic MPM who had not received prior therapy for any stage of advanced/metastatic disease	Chemo Only (Arm A) Pemetrexed: 500 mg/m2 IV Q3W Cisplatin[a]: 75 mg/m2 IV Q3W Pembro + Chemo (Arm B) Pembrolizumab: 200 mg IV Q3W Pemetrexed: 500 mg/m2 IV Q3W Cisplatin[a]: 75 mg/m2 IV Q3W Pembro Only[b] (Arm C) Pembrolizumab: 200 mg IV Q3W	Phase 2: PFS Phase 3: OS

Study Number / Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-594 (ETOP 9-15, "PROMISE-meso") *Completed* (Study sponsored by ETOP IBCSG Partners Foundation)	Multicenter, randomized, open-label Phase 3 study	144 patients with MPM and ECOG performance status 0 or 1, who had previously failed standard therapy	Pembrolizumab 200 mg IV Q3W for up to 2 years, or until disease progression or unacceptable toxicity **or** Gemcitabine 1000 mg/m^2 IV, or vinorelbine 30 mg/m^2 IV or 60/80 mg/m^2 PO, Q3W until disease progression of unacceptable toxicity	PFS

AE=adverse event; AUC=area under the curve; CCTG= Canadian Cancer Trials Group; DLT=dose-limiting toxicity; ECOG=Eastern Cooperative Oncology Group; ETOP IBCSG=European Thoracic Oncology Platform and International Breast Cancer Study Group; IV=intravenous; MPM=malignant pleural mesothelioma; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; PO=orally; Q2W=every 2 weeks; Q3W=every 3 weeks.

a. The substitution of carboplatin (AUC 5-6) for cisplatin was permitted on a case-by-case basis after review and approval by CCTG.

b. The pembrolizumab monotherapy arm was only evaluated in Phase 2, as described in [Ref. 5.3.5.1: P483V01MK3475: 9.1].

Table: Summary of Treatment Outcomes for Pembrolizumab Monotherapy in Advanced MPM (pre-treated)

Study	Population	Treatment	N	ORR	Median DOR	Median PFS	Median OS	Reference
KEYNOTE-028	Previously treated, PD-L1-positive MPM	Pembrolizumab	25	20%	12.0 m	5.4 m	18 m	[15]
KEYNOTE-158	Advanced (metastatic and/or unresectable) MPM	Pembrolizumab	118	8%	14.3 m	2.1 m	10.0 m	[16]
		Pembrolizumab	73	22%	4.6 m	2.5 m[a]	10.7 m[b]	[17]

[15] Alley EW, Lopez J, Santoro A, Morosky A, Saraf S, Piperdi B. et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol. 2017 May;18(5):623-630.
[16] Yap TA, Nakagawa K, Fujimoto N, Kuribayashi K, Guren TK, Calabrò L, Shapira-Frommer R, Gao B, Kao S, Matos I, Planchard D, Chatterjee A, Jin F, Norwood K, Kindler HL. Efficacy and safety of pembrolizumab in patients with advanced mesothelioma in the open-label, single-arm, phase 2 KEYNOTE-158 study. Lancet Respir Med. 2021 Jun;9(6):613-621.
[17] Popat S, Curioni-Fontecedro A, Dafni U, Shah R, O'Brien M, Pope A, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol. 2020;31(12):1734-45.

Study	Population	Treatment	N	ORR	Median DOR	Median PFS	Median OS	Reference
PROMISE-meso	Relapsed MPM that progressed on or after prior platinum-based chemotherapy	SOC chemotherapy[c]	71	6%	7.2 m	3.4 m	12.4 m	
NCT02399371	Pretreated malignant mesothelioma	Pembrolizumab	65	19%	-	4.5 m	11.5 m	[18]

CI=confidence interval; DOR=duration of response; HR=hazard ratio; m=months; MPM= malignant pleural mesothelioma; NS=not significant; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; SOC=standard of care.

The PFS HR (95% CI) compared with SOC chemotherapy was 1.06 (0.73, 1.53); *p*=NS

The OS HR (95% CI) compared with SOC chemotherapy was 1.12 (0.74,1.69); *p*=NS

Gemcitabine or vinorelbine

During the development of pembrolizumab for the MPM indication, no scientific advice was sought to CHMP.

2.1.4. General comments on compliance with GCP

The Applicant claimed that all clinical trials were conducted according to Good Clinical Practice as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

During the assessment of the dossier, no concern has been raised leading to trigger a GPC inspection.

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).

[18] Desai A, Karrison T, Rose B, Tan Y, Hill B, Pemberton E, et al. Phase II trial of pembrolizumab (NCT02399371) in previously-treated malignant mesothelioma (MM): final analysis [abstract]. Presented at: International Association for the Study of Lung Cancer (IASLC) 19th World Conference on Lung Cancer (WCLC); 2018 Sep 23-26; Toronto (Canada). J Thorac Oncol. 2018 Oct;13(10 suppl):S339. Abstract No. OA08.03.

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.

Table 2. Tabular overview of clinical studies

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
3475-483 [Ref. 5.3.5.1: P483V01MK3475]	2/3	Canada, France, Italy	A Phase 2/3 randomized study of pembrolizumab in patients with advanced malignant pleural mesothelioma	Randomized, open-label, multicenter parallel-assignment, active-comparator study to evaluate efficacy and safety of pembrolizumab in combination with chemotherapy compared with chemotherapy alone. A pembrolizumab monotherapy group was included to support the safety analysis.	Pembrolizumab: 200 mg IV Day 1 every 21 days for up to 2 years (35 cycles). Pemetrexed 500 mg/m² IV Day 1 every 21 days for up to 6 cycles. Cisplatin 75 mg/m² IV Day 1 every 21 days for up to 6 cycles.	Male and female participants ≥18 years of age with MPM receiving first-line treatment for unresectable advanced and/or metastatic disease.	Pembrolizumab in combination with chemotherapy: 222 participants Chemotherapy: 211 participants Pembrolizumab monotherapy: 40 participants

Study ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
3475-A17 [Ref. 5.3.5.2: PA17MK3475]	1	Japan	A Phase Ib Clinical Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Cisplatin and Pemetrexed in Treatment-naive Participants with Advanced Malignant Pleural Mesothelioma (KEYNOTE-A17)	Multicenter, non-randomized, open-label	Pembrolizumab: 200 mg IV Q3W for 35 cycles Pemetrexed: 500 mg/m² IV Q3W for 4-6 cycles Cisplatin: 75 mg/m² IV Q3W for 4-6 cycles	Males/females Age: ≥20 Participants with advanced malignant pleural mesothelioma	Received at least 1 dose: 19

2.3.2. Pharmacokinetics

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

PK data form study KEYNOTE-158 were used in support of 200 mg Q3W as the recommended dose of pembrolizumab in combination with chemotherapy in participants with advanced MPM.

Substantial characterization of the PK and immunogenicity of pembrolizumab 200 mg Q3W have been provided in previous submissions. In particular, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and EU SmPC.

In addition to initially licensed dosing regimens of 200 mg Q3W or 2 mg/kg Q3W, an additional dosing regimen of the 400 mg Q6W was subsequently approved in the EU for all adult monotherapy indications

(procedure number EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure number EMEA/H/C/003820/II/0102).

The dosing regimen of 400 mg Q6W is applicable across all adult indications regardless of the combination treatment type. Based on the robust understanding of pembrolizumab clinical pharmacology and its

well-established flat E-R profiles over a 5-fold dose range, thus, the 400 mg Q6W dosing regimen would have a similar benefit-risk profile as the 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in the clinical use of pembrolizumab in adults with unresectable advanced and/or metastatic MPM.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in target population

The efficacy and safety data in support of the current submission were obtained from study KEYNOTE-483 where patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM) were treated with the combination of pembrolizumab plus pemetrexed/platinum chemotherapy. Efficacy results are also supported by data from KEYNOTE-A17.

In support of 200 mg Q3W as the recommended dose of pembrolizumab in this patient population, the characterization of the pharmacology of pembrolizumab is provided using data from participants with advanced (metastatic and/or unresectable) MPM in KEYNOTE-158, Cohort H treated with pembrolizumab as monotherapy.

Briefly, regarding PK aspects, in this submission the focus is on the data related to the characterization of the pharmacology in patients with advanced MPM.

This approach takes in consideration that an extensive characterization of the PK and immunogenicity profile of pembrolizumab have been provided in previous submissions and also that the combination of pembrolizumab with chemotherapy has been extensively evaluated in a number of cancer indications and demonstrates that the PK of pembrolizumab is not impacted by concomitant chemotherapy. The Applicant is requesting this extension of indication to include also adolescents from 12 years and older.

Efficacy in paediatric patients with MPM is supported by extrapolation of efficacy data in adults (advanced MPM in KEYNOTE-483 and KEYNOTE-A17) and the E-R relationship. The proposed dose of 2 mg/kg Q3W dosing regimen in paediatric patients with MPM is supported by a model-based PK bridging analysis performed to demonstrate that a dose of 2 mg/kg (up to 200 mg) Q3W in paediatric participants provided PK exposures similar to those achieved at 2 mg/kg (or 200 mg) Q3W in adults.

PK Data Keynote-158

KEYNOTE-158 is *an ongoing*, non-randomized, single arm, multi-site, open-label study of pembrolizumab in previously treated participants who have locally advanced unresectable or metastatic rare cancers for whom prior standard first-line treatment had failed. Eligible participants received pembrolizumab 200 mg IV Q3W. This study is composed of different cohort (13, named from A to M), patients with MPM were enrolled in cohort H.

PK ANALYSIS KEYNOTE-158 MALIGNANT PLEURAL MESOTHELIOMA (COHORT H)

Table 3. Overview of Cohorts Included in KEYNOTE-158 Pembrolizumab PK Analysis

Study	Cohort/Part	Treatment	Cancer Type	Number of subjects providing PK [a]	Data cutoff
KEYNOTE-158	Cohort H	200 mg Q3W	Malignant Pleural Mesothelioma	118	28-October-2016

[a] Number of unique subjects providing PK samples.
Q3W = Every 3 weeks.

PK schedule in KEYNOTE-158 200 mg Q3W: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1 and 4. Postdose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1.

Summary descriptive statistics of the predose concentrations by cycle are presented in the following table:

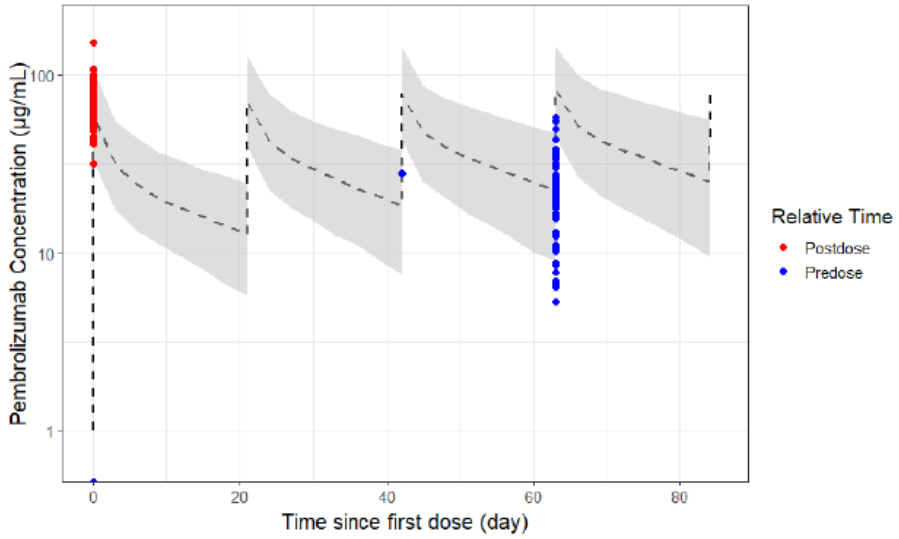
Table 4. Summary Statistics of Pembrolizumab Cycle 1 Postdose and Cycle 4 Predose, Serum Concentration Values Following Administration of Multiple Pembrolizumab 200 mg Q3W I.V. Doses in KEYNOTE-158 Cohort H Malignant Pleural Mesothelioma Subjects

Cycle	NOMTAFD (day)	ATPTN (minutes)	N	GM (%CV)	GM (GeoSD)	AM (SD) (µg/mL)	Min	Median	Max
Cycle 1 (Week 0)	0.021	30	112	66.9 (24.8)	66.9 (1.3)	69 (17.6)	31.7	67.2	153
Cycle 4 (Week 9)	63	0	81	20.5 (56.9)	20.5 (1.7)	23.2 (11.1)	5.32	21.8	58.3

NOMTAFD = Nominal time after first pembrolizumab administration; ATPTN = Analysis time point;
GM = Geometric Mean; %CV = Geometric Coefficient of Variation;
GeoSD = Geometric Standard Deviation; SD = Standard Deviation; AM = Arithmetic Mean;
Results reported for time points with N ≥ 3.

Observed pembrolizumab concentration data in KEYNOTE-158 group H for pembrolizumab are overlaid on the simulated profile using the reference PK model as shown in the following figure:

Figure 1. Observed Concentration Data in KEYNOTE-158 Cohort H Malignant Pleural Mesothelioma Subjects Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W IV Dose Regimen



Note: Pembrolizumab model predictions and observed concentration data for KEYNOTE-158 Cohort H subjects After 1st dose; and at cycle 4, with a 28-day time since last dose sample cut off. Symbols are individual observed data (nominal time); black dashed line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval; plots are displayed on log scale.

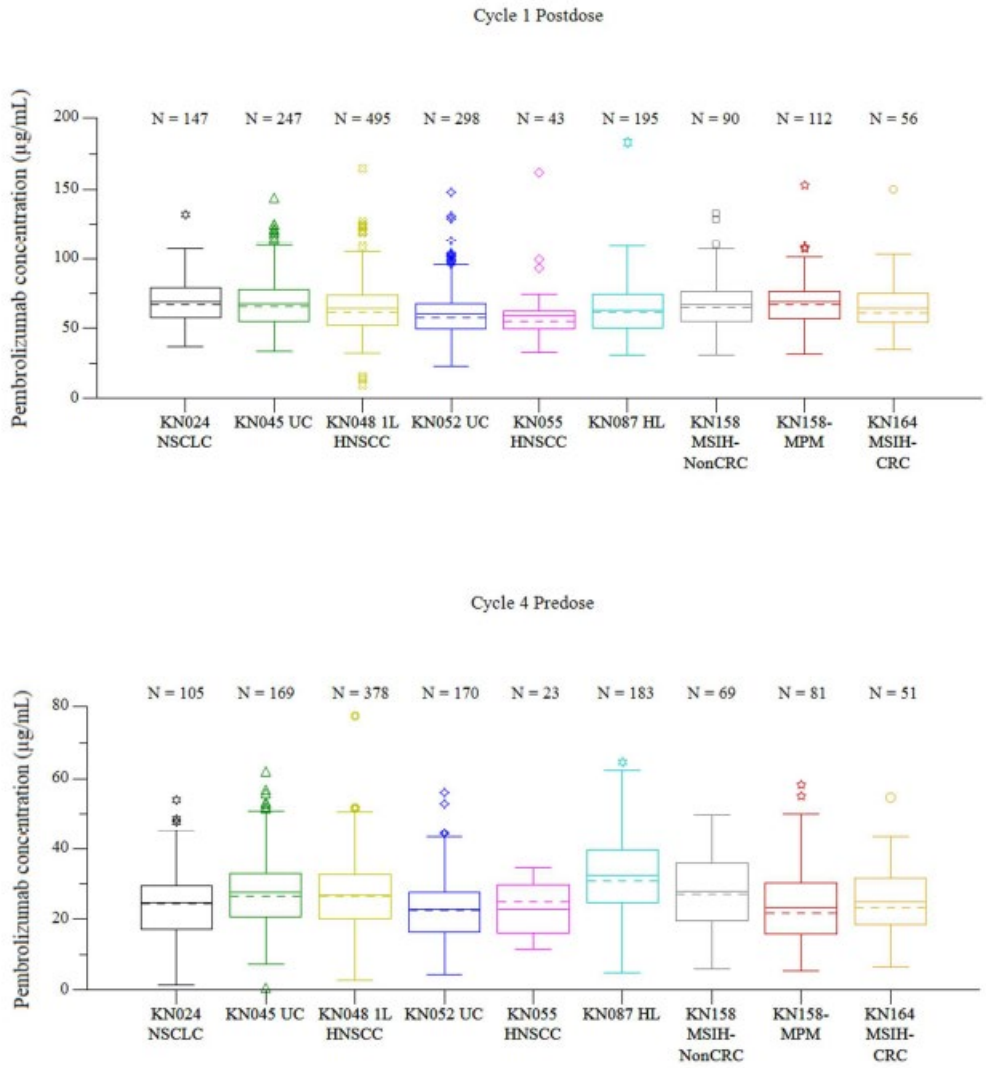
Tabular summaries of descriptive statistics and boxplots from early drug treatment at Cycle 1 end of infusion (postdose) and at predose Cycle 4, comparing observed pembrolizumab concentrations in KEYNOTE-158 Cohort H MPM subjects with pembrolizumab concentrations observed in monotherapy trials in other solid tumor type are presented in the following table and figure:

Table 5. Summary Statistics of Observed Pembrolizumab Concentrations at Cycle 1 Postdose and Cycle 4 Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, 158 MSI-H non-CRC, -164) and KEYNOTE-158 Cohort H Malignant Pleural Mesothelioma

Time point	Dose	Study/ Indication	N	GM (CV%) (µg/mL)	AM (SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	200 mg	KN024 NSCLC	147	67.5 (23.1)	69.3 (16.2)	36.6	66.8	132
	200 mg	KN045 UC	247	65.7 (26.2)	67.9 (18.2)	33.9	65.9	144
	200 mg	KN048 1L HNSCC	495	61.8 (28.7)	64.2 (17.6)	9.48	61.7	165
	200 mg	KN052 UC	298	58.0 (27.9)	60.2 (17.3)	22.8	57.4	148
	200 mg	KN055 HNSCC	43	56.5 (27.8)	58.9 (20.7)	33.1	54.9	162
	200 mg	KN087 HL	195	60.7 (28)	63.1 (18.3)	31.2	61.3	183
	200 mg	KN158 MSI-H NonCRC	90	64.4 (27)	66.7 (18.3)	31.2	65.2	133
	200 mg	KN158-MPM	112	66.9 (24.8)	69.0 (17.6)	31.7	67.2	153
	200 mg	KN164 MSI-H CRC	56	62.2 (27.8)	64.6 (19.1)	34.9	61.2	150
Cycle 4 Predose	200 mg	KN024 NSCLC	105	22.5 (51.6)	24.7 (9.6)	1.35	24.5	54.0
	200 mg	KN045 UC	169	25.3 (51.5)	27.7 (10.6)	0.677	26.6	62.1
	200 mg	KN048 1L HNSCC	378	24.8 (44.1)	26.8 (9.8)	2.67	26.4	77.3
	200 mg	KN052 UC	170	20.6 (51)	22.8 (9.4)	4.41	22.4	56.1
	200 mg	KN055 HNSCC	23	21.5 (35.6)	22.7 (7.3)	11.5	24.9	34.4
	200 mg	KN087 HL	183	30.3 (40)	32.3 (11.1)	4.93	30.7	64.7
	200 mg	KN158 MSI-H NonCRC	69	25.4 (49.8)	27.9 (11.1)	6.01	27.0	49.7
	200 mg	KN158-MPM	81	20.5 (56.9)	23.2 (11.1)	5.32	21.8	58.3
	200 mg	KN164 MSI-H CRC	51	23.1 (42.2)	24.9 (9.4)	6.52	23.4	54.7

GM = Geometric Mean; %CV = Geometric Coefficient of Variation; AM = Arithmetic Mean; SD = Standard Deviation; NSCLC = non-small cell lung cancer; UC = urothelial cancer; HNSCC = head and neck squamous cell carcinoma; HL = Hodgkin lymphoma; MSI-H CRC= micro satellite instability high cancer colorectal cancer; MPM = Malignant Pleural Mesothelioma.

Figure 2. Observed Pembrolizumab Concentrations at Cycle 1 Postdose and Cycle 4 Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, - 052, -055, -087, 158 MSI-H non-CRC, -164) and KEYNOTE-158 Cohort H Malignant Pleural Mesothelioma



2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Primary and secondary pharmacology

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently summarized in the EU SmPC and USPI. This low rate of immunogenicity has been shown to be consistent across tumor type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading. Additionally, incidence of ADA has not been impacted by the presence of another small molecule or chemotherapy in combination with pembrolizumab.

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

2.3.5. Discussion on clinical pharmacology

The MAH is applying for an Extension of indication to include a new indication for Keytruda, in combination with chemotherapy (pemetrexed and platinum), for the treatment of unresectable advanced or metastatic malignant pleural mesothelioma (MPM) cancer in adults and adolescents.

The efficacy and safety data in support of the current submission in adults were obtained from study KEYNOTE-483 where patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM) were treated with the combination of pembrolizumab plus pemetrexed/platinum chemotherapy. Efficacy results are also supported by data from KEYNOTE-A17.

In support of 200 mg Q3W as the recommended dose of pembrolizumab in this patient population, the characterization of the pharmacology of pembrolizumab is provided using data from participants with advanced (metastatic and/or unresectable) MPM in KEYNOTE-158, Cohort H, treated with pembrolizumab as monotherapy.

The observed serum concentration values in subjects with mesothelioma from KEYNOTE-158 study are contained within the 90% CI of the reference PK model, which indicate that pembrolizumab data from KEYNOTE-158 group H is consistent with the historical data in both cycle 1 postdose and cycle 4 predose and are consistent with other globally approved studies in different cancer indications (KEYNOTE-024 in NSCLC, KEYNOTE-045 and KEYNOTE-052 in UC, KEYNOTE-055 in HNSCC, KEYNOTE-087 in cHL, KEYNOTE-158 in MSI-H-non CRC and KEYNOTE-164 in MSI-H-CRC) following administration of 200 mg Q3W.

However, it is of note that in KEYNOTE-158 study, concentrations at cycle 4 are not likely to have reached the steady state (half-life 22 days) and for this reason a full characterization of exposure at Steady state is lacking in patients with MPM, although it is not expected to be different than that observed in other tumour types/indications. In addition, PK data in the proposed setting (patients with advanced metastatic and/or unresectable MPM) have been collected in patients treated with monotherapy, however, this is not an issue, considering that the combination of pembrolizumab with pemetrexed and platinum chemotherapy is already authorized for the first-line treatment of metastatic non squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.

No new data on PD or Immunogenicity have been submitted within this application and this is acceptable considering that the incidence of ADA has been already evaluated in the presence of chemotherapy in combination with pembrolizumab.

The Applicant is requesting this extension of indication to include also **adolescents** from 12 years and older. Efficacy in paediatric patients with MPM is supported by extrapolation of efficacy data in adults (advanced MPM in KEYNOTE-483 and KEYNOTE-A17) and the E-R relationship. The proposed dose of 2 mg/kg Q3W dosing regimen in paediatric patients with MPM is supported by a model-based PK bridging analysis performed to demonstrate that a dose of 2 mg/kg (up to 200 mg) Q3W in paediatric participants provided PK exposures like those achieved at 2 mg/kg (or 200 mg) Q3W in adults. See section 2.4 "Clinical studies in special populations" and relevant part in the efficacy discussion for a comprehensive assessment regarding the extrapolation inclusion of adolescents.

2.3.6. Conclusions on clinical pharmacology

Although the sought indication is for treatment of patients with MPM in combination with chemotherapy (pemetrexed and platinum), PK data in support arises from patients with MPM treated in monotherapy. This is considered acceptable considering that the PK of pembrolizumab when used in combination with chemotherapy has been extensively evaluated in a number of cancer indications and demonstrates that the PK profile of pembrolizumab is consistent across tumour types and it is not impacted by concomitant chemotherapy.

2.4. Clinical efficacy

2.4.1. Main study

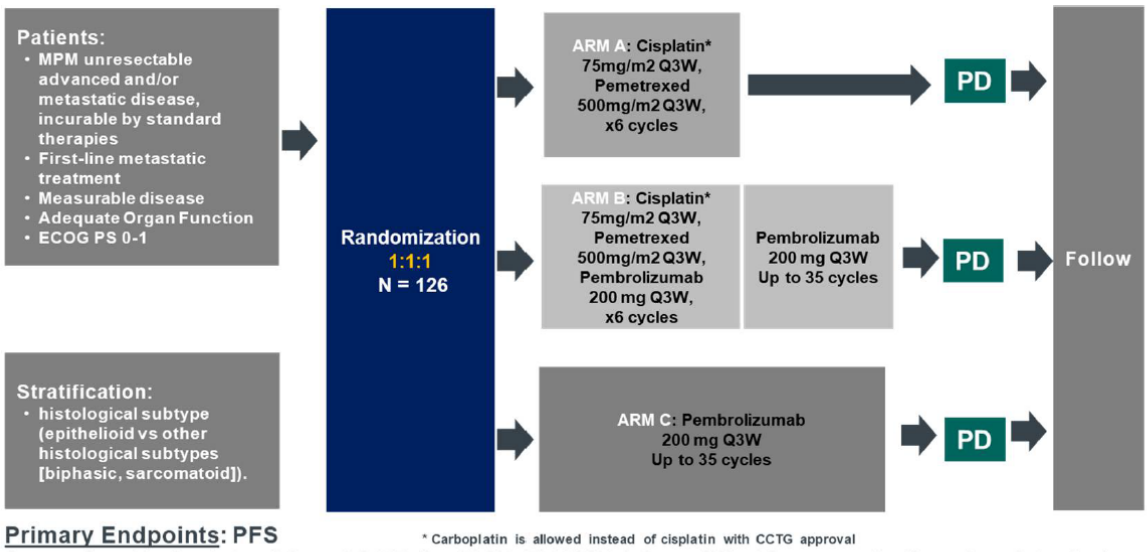
A Phase 2/3 Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma (KEYNOTE-483).

Methods

KEYNOTE-483 is an open-label, multicenter, Phase 2/3 randomized study in participants with MPM receiving first-line treatment for unresectable advanced and/or metastatic disease. The study was sponsored and conducted by the Canadian Cancer Trial Group (CCTG).

This study was initially designed as Phase 2 study in which participants were randomized in a 1:1:1 ratio to Arm A (chemo), Arm B (pembro combo), or Arm C (pembro mono). The study was then adjusted to be a Phase 3 study in which participants were randomized into 1 of 2 arms in a 1:1 ratio to Arm A (chemo) or Arm B (pembro combo) (see figures below).

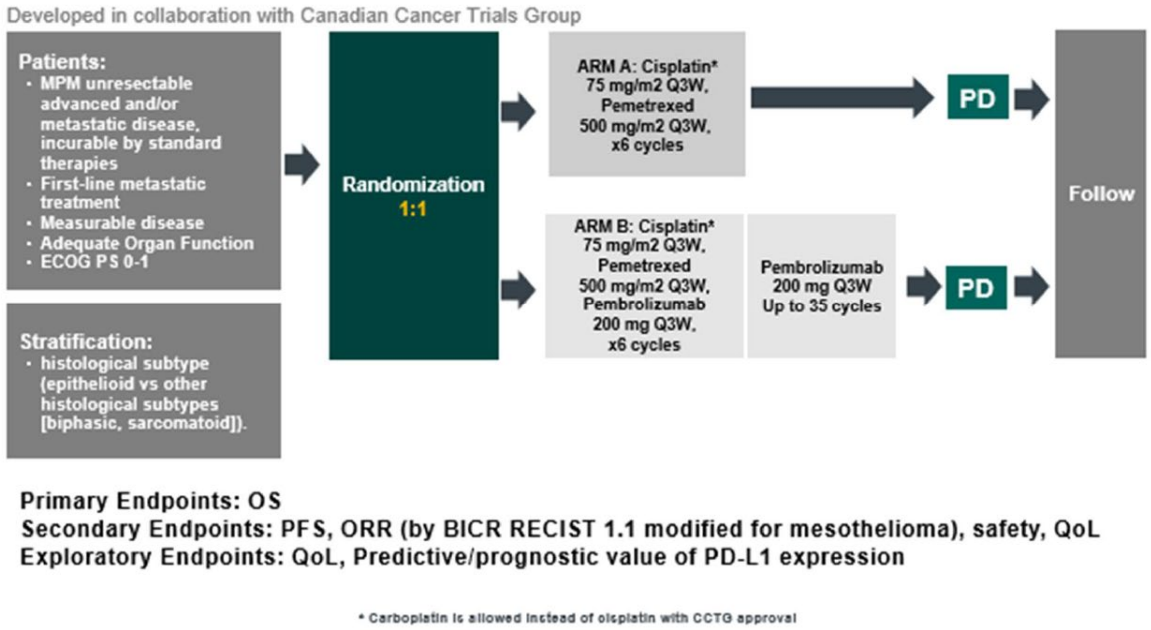
Figure 3. Phase 2 Schema



Primary Endpoints: PFS
Secondary Endpoints: OS and ORR (by BICR RECIST 1.1 modified for mesothelioma), safety, QoL, Predictive/prognostic value of PD-L1 expression
Exploratory Endpoints: QoL

BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MPM=malignant pleural mesothelioma; PD=progressive disease; PD-L1=programmed death-ligand 1; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; QoL=quality of life; Q3W=every 3 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors v1.1

Figure 4. Phase 3 schema



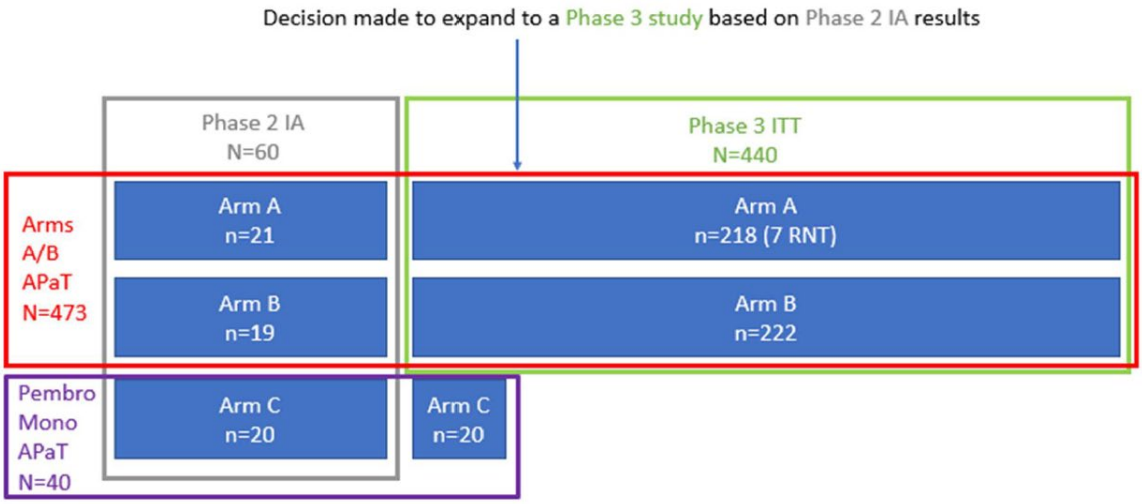
Primary Endpoints: OS
Secondary Endpoints: PFS, ORR (by BICR RECIST 1.1 modified for mesothelioma), safety, QoL
Exploratory Endpoints: QoL, Predictive/prognostic value of PD-L1 expression

BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MPM=malignant pleural mesothelioma; PD=progressive disease; PD-L1=Programmed death-ligand 1; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; QoL=quality of life; Q3W=every 3 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors v1.1

The Phase 2 IA, based on 16-week disease control rate, was performed in November 2017 to determine whether any or all of the treatment arms should be stopped. A total of 60 randomized participants (21 in Arm A, 19 in Arm B, and 20 in Arm C) were included in the Phase 2 IA. Arm C was

discontinued as recommended by CCTG Data and Safety Monitoring Committee due to lower disease control rate compared with Arms A and B, after review of Phase 2 IA results. The study continued as a 2-arm trial comparing the pembro combo (Arm B) and chemo (Arm A) groups (see figure below).

Figure 5. Analysis population



APaT=all participants as treated; ITT=intention to treat; RNT=randomized, not treated

Study participants

Inclusion Criteria

To be eligible for participation, the participant must have:

• Had histologically confirmed MPM. Participants were eligible to receive standard chemotherapy with pemetrexed and cisplatin (or carboplatin upon CCTG approval) and had no contraindications to standard chemotherapy.

• Had unresectable advanced and/or metastatic disease, unresectable by standard therapies.

• Had a cellular tumor block from their primary or metastatic tumor available and consent to release the block/recently cut slides for correlative analyses and the center/pathologist must have agreed to the submission of the specimen(s).

• Had presence of radiologically documented disease. At least one site of disease must have been unidimensionally measurable by mRECIST or RECIST 1.1.

• Had ECOG performance status 0 or 1.

• Been ≥18 years of age.

• Not received prior chemotherapy for any stage of advanced/metastatic disease. Participants who received previous (neo)adjuvant cisplatin-based systemic chemotherapy must have received the last dose of chemotherapy at least 12 months before registration.

• Not received targeted small molecule therapy, immunotherapies and viral therapies, biologic therapies and angiogenesis inhibitors for advanced/metastatic disease, or any prior immunotherapy for any stage of disease.

• Not received prior radiation therapy to the thorax unless clear disease progression was demonstrated and confirmed with CCTG.

Exclusion Criteria

The participant must have been excluded from the study if the participant:

• Had a diagnosis of immunodeficiency or was receiving systemic steroid therapy (at doses more than 10 mg prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first and any dose of trial treatment.

• Had active autoimmune disease that has required systemic treatment in the past 3 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs) or history of allogeneic transplantation.

• Had known active CNS metastases and/or carcinomatous meningitis.

• Had experienced untreated and/or uncontrolled cardiovascular conditions and/or had symptomatic cardiac dysfunction (including cardiac ventricular arrhythmias requiring medication, history of second- or third-degree atrioventricular conduction defects) or had unstable angina congestive heart failure or myocardial infarction within the previous year. Participants with a significant cardiac history, including hypertension, even if controlled, should have had a LVEF ≥50%.

• Received a live vaccine within 30 days of planned start of study therapy.

• History of other malignancies unless having undergone curative therapy (ie, resection, radiation, etc.) and did not require concurrent anticancer therapy.

• Severe/uncontrollable tumor pain that required radiation prior to starting on systemic therapy.

• Had evidence of interstitial lung disease or known history or any evidence of active non-infectious pneumonitis.

• Concurrent treatment with other investigational drugs or anticancer therapy.

Treatments

Table 6. study treatment groups and conventions

Intervention group	Study Arm	In-text Reference
Chemotherapy (pemetrexed + cisplatin or carboplatin)	Arm A	Chemo
Pembrolizumab in combination with chemotherapy (pemetrexed + cisplatin or carboplatin)	Arm B	Pembro combo
Pembrolizumab	Arm C	Pembro mono

Pembrolizumab was administered at 200 mg Q3W up to 35 cycles (2 years).

Cisplatin was given at 75 mg/m2 Q3W plus pemetrexed 500 mg m2 Q3W up to 6 cycles.

Objectives and endpoints

The objective and endpoints of the Phase 3 study are summarised in the table below.

Table 7. objectives and endpoints, phase 3

Primary Objective	Primary Endpoint
• To evaluate whether pembrolizumab improves overall survival when added to standard chemotherapy in MPM. H1: pembrolizumab added to standard chemotherapy is superior to standard chemotherapy with respect to OS.	• OS: the time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
• To evaluate whether pembrolizumab improves PFS per mRECIST when added to standard chemotherapy in MPM. H2: pembrolizumab added to standard chemotherapy is superior to standard chemotherapy with respect to PFS per mRECIST by BICR.	• PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• To assess antitumor activity of pembrolizumab given to participants receiving standard chemotherapy, including objective response rate (complete and partial response), using mRECIST. H3: pembrolizumab combined with standard chemotherapy is superior to standard chemotherapy with respect to ORR per mRECIST by BICR.	• Objective response: complete response or partial response • For testing of H3 hypothesis, confirmed complete response or partial response will be used.
• To evaluate the TTD in the GHS/QoL score, physical functioning, and 3 common MPM symptoms for pembrolizumab in combination with chemotherapy compared to chemotherapy.	• TTD: the time from baseline to first onset of 10 points or more deterioration with confirmation by the subsequent visit in cough (EORTC QLQ-LC13 item 31), chest pain (EORTC QLQ-LC13 item 40), or dyspnea [EORTC QLQ-C30 item 8], and GHS/QoL score (EORTC QLQ-C30 items 29 and 30), physical functioning score (EORTC QLQ-C30 items 1-5).

Sample size

The original phase II sample size calculation of Phase II assumed a median PFS for Arm A of 7.5 months. To detect an increase of median PFS to 11.5 months (HR=0.65) by one of the experimental treatment arms with 80% power at a 1-sided 0.2 level, a minimum of 63 events were required to observe from the three treatment arms. An accrual of 126 patients (42 per arm) was planned.

The sample size calculation was amended twice. In Amendment 2 (11-APR-2018) the phase III sample size calculation estimated a median OS for Arm A of 13.5 months. To detect an increase of median OS to 20.8 months (HR=0.65) by Arm B with 90% power at a 2-sided 0.05 level, a minimum of 226

events would be required to observe from two treatment arms. The required number of events would be observed by accruing up to 390 patients (195 per arm) during 26 months of accrual with 8 months follow-up. Since the primary analysis population for the phase III analysis excluded the 40 participants from the phase II Arms A and B that were included as part of the phase II interim analysis, a total of 430 patients were required to be accrued into the trial.

In amendment 4 (14-APR-2020), the median OS for Arm A was re-estimated as 16 months. So, to detect an increase up to 22.9 months (HR=0.70) by Arm B with approximately 90% power at a 2-sided 0.05 level, a minimum of 334 events were required to observe from two treatment arms. A total accrual of 430 patients during 34 months of enrolment with 31 months follow-up were planned. Assuming 10 patients would drop out earlier, the final sample size of randomized patients was 440 (220 per arm). Considering the 40 patients enrolled to Arm A and B and included in the IA of phase II portion of the study and 40 patients enrolled to Arm C before its closure, a total of 520 patients were planned to be enrolled.

Randomisation

Randomization was provided electronically through the CCTG web-based, password operated Electronic Data Capture (EDC) system, both in phase 2 and phase 3 portion of the study, with a 1:1:1 and a 1:1 ratio, respectively.

Subjects were stratified at the time of randomization by histological subtype (epithelioid vs other histological subtypes).

In addition, participating center was also used in the minimization randomization algorithm.

Blinding (masking)

This was an open label study.

Statistical methods

Protocol Amendments involving statistical methods

The protocol was subject to six general amendments, none of these was implemented due to the COVID-19 pandemic. Amendments modified the SAP language as follows.

- Amendment 2 (11-APR-2018): study design changed from Phase 2 to Phase 3 trial with OS as primary objective, to support registrational intent. PFS, which was primary objective on Phase 2 became secondary objective on Phase 3 part. Statistical analysis including sample size, power, required number of events, accrual period, OS interim analyses were changed and/or added accordingly.
- Amendment 3 (03-JAN-2019): some clarifications were added regarding the study design, the use of RECIST 1.1 for primary and secondary objectives, sample size, the addition of a standard interim analysis as now a Phase 3.
- Amendment 4 (14-APR-2020): the power and sample size for OS was updated.
- Amendment 5 (27-OCT-2020): following FDA feedback, hypothesis testing of secondary endpoints of PFS and ORR was added once primary endpoint of OS is positive, and BICR will be used for the primary response-based analyses. The statistics section was updated accordingly (eg, updating methodology to reflect alpha spending for multiple endpoints, clarifying endpoints for the interim analysis).

- Amendment 6 (21-JUN-2021): the PD-L1 stratified analyses of OS, PFS, and, ORR were removed. Objectives regarding the predictive and prognostic value of PD-L1 were moved from secondary to exploratory, since PD-L1 was not initially applied to the stratified randomization and was missing on some participants.

Interim analysis

Two interim analyses (IAs) were planned in addition to the final analysis (FA) for this study. The Phase 2 IA was planned when 22 patients on each treatment arm had been evaluated for 16 weeks disease control (DC) status (percentage of patients with CR, PR and SD at 16 weeks). If the DC rate in Arm B or C was no worse than the control arm (Arm A), the study accrual would have been continued, otherwise, the accrual to the arm with DC rate worse than Arm A was stopped. Assuming a 70% DC rate on control arm (Arm A) at 16 weeks, if the DC rate in one of the experimental arms was 16% or better it would have been an 80% chance of proceeding to trial with at least one experimental arm.

The interim efficacy analysis was planned on OS, PFS and ORR during the Phase 3 portion (Phase 3 IA) approximately 11 months after the last patient is randomized. The analyses planned, endpoints evaluated, and drivers of timing are summarized in the table below:

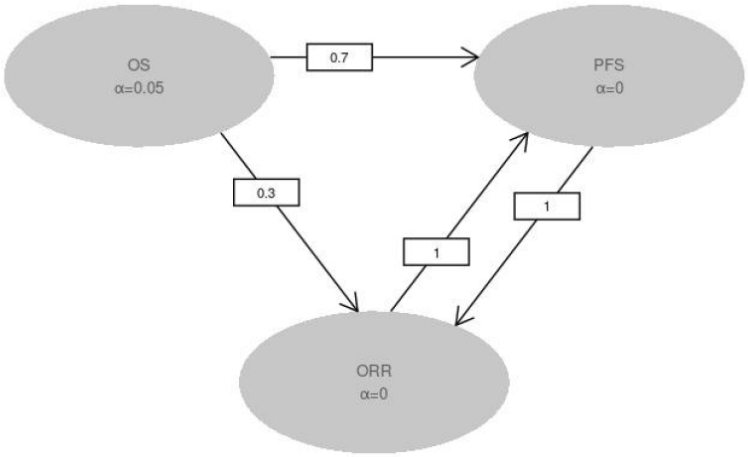
Table 8. Summary of interim and final analyses strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA	OS ORR PFS	~ 11 months after the last participant randomized	~ 45 months	• Interim OS analysis • Final ORR analysis • Interim PFS analysis
FA	OS PFS	~ 334 deaths have occurred	~ 65 months	• Final PFS analysis • Final OS analysis
Abbreviations: FA = final analysis; IA= interim analysis; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.				

Type I error and multiplicity control

The trial used the graphical method of Maurer and Bretz to control for multiple hypotheses as well as interim analyses. Figure below shows the multiplicity diagram for type I error control. The figure below shows the initial two-sided α allocation for each hypothesis in the ellipse representing the hypothesis.

Figure 6. Multiplicity diagram for type I error control



The initial α assigned to OS was 0.05. If OS hypothesis was rejected, the corresponding alpha was reallocated to PFS and ORR. PFS by BICR was tested only when the hypothesis test for OS was significant, either at the time of the OS IA or FA. The stratified log-rank test for the comparison of PFS between the two treatment arms was used to indicate the statistical significance using the methodology of Lan-Demets with O'Brien-Fleming type boundaries. ORR by BICR was tested at the IA at a 0.015 alpha level (2-sided) if OS hypothesis was rejected at the IA. If the OS hypothesis was not rejected at the IA but at the FA, then the 0.015 alpha (2-sided) was rolled over to ORR at the FA, but the test statistics previously computed at the time of the IA for the ORR hypothesis was used for inferential testing to ensure that the type I error of testing ORR upon success of the OS hypothesis testing was controlled at a two-sided 0.015 level.

OS

The OS hypothesis was tested at the IA and FA in the phase III ITT population. Table below shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds under a one-sided test with α=0.025 which is equivalent of two-sided test with α=0.05 and test statistics crossing the upper bound only.

Table 9. Efficacy boundaries and properties for overall survival analyses

Analysis	Value	α =0.05 (2-sided)
IA: 70%* N = 430[e] Events: 234 Month: 45	Z	2.4380
	p (1-sided)[a]	0.0074
	HR at bound[b]	0.7269
	P(Cross) if HR=1[c]	0.0074
	P(Cross) if HR=0.7[d]	0.6152
FA N: 430[e] Events: 334 Month: 65	Z	1.9999
	p (1-sided)[a]	0.0228
	HR at bound[b]	0.8034
	P(Cross) if HR=1[c]	0.0250
	P(Cross) if HR=0.7[d]	0.9000

Abbreviations: HR = hazard ratio; IA = interim analysis, FA = final analysis.
The number of events and timings are estimated.
*Percentage of total planned events at the interim analysis.
[a]*p* (1-sided) is the nominal α for group sequential testing.
[b]HR at bound is the approximate HR required to reach an efficacy bound.
[c]P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d]P(Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.
[e]Assuming 10 patients would drop out earlier, the final sample size of randomized patients would be 440 (220 per arm).

At the time of an analysis, the observed number of events may differ substantially from the expected. In this case, the bounds were updated using the Lan-DeMets spending function approximating O'Brien-Fleming bounds evaluated at the observed information fraction (fraction of observed over expected final events) at each analysis.

PFS

The PFS hypothesis was tested at the IA and FA in the phase III ITT population.

Table 10. Efficacy boundaries and properties for progression free survival analyses

Analysis	Value	α =0.035 (2-sided)	α =0.05 (2-sided)
IA: 89%* N = 440 Events: 317 Month: 45	Z	2.3361	2.1766
	p (1-sided)[a]	0.0097	0.0148
	HR at bound[b]	0.7692	0.7831
	P(Cross) if HR=1[c]	0.0097	0.0148
	P(Cross) if HR=0.7[d]	0.8009	0.8423
FA N = 440 Events: 376 Month: 65.5	Z	2.1783	2.0376
	p (1-sided)[a]	0.0147	0.0208
	HR at bound[b]	0.7985	0.8102
	P(Cross) if HR=1[c]	0.0175	0.0250
	P(Cross) if HR=0.7[d]	0.9065	0.9284

ORR

The ORR hypothesis was tested once at IA and no initial alpha allocation was planned, but ORR might only be tested when the OS was successful either at the IA or FA.

Table 11. Possible alpha levels and approximate ORR difference required to demonstrate efficacy for objective response at IA1

Two-sided α	~Δ Objective Response Rate (ORR)	Power (ΔORR=0.2)
0.015	0.1152	0.875
0.05	0.0929	0.949

Efficacy analyses

The Intention-to-Treat (ITT) population, consisting in all randomized participants in Arm A and Arm B from phase III and phase II but excluding the 40 participants from the phase II that were part of the phase II IA, served as the population for primary efficacy analyses. Participants were included in the treatment group to which they are randomized, regardless of whether they received study treatment.

The non-parametric Kaplan-Meier method was used to estimate the PFS and OS curve in each treatment group.

A summary of the analysis strategy for key efficacy endpoints as well as censoring rules for primary and sensitivity analyses of PFS and DOR are presented in the following tables:

Table 12. Analysis strategy for key efficacy variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participant last known to be alive
Key Secondary Analyses			
PFS per mRECIST by BICR	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 1
ORR per mRECIST by BICR	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered non-responders
Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; mRECIST = the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee.			

Table 13. Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression immediately after ≥ 2 consecutive missed disease assessments, or after new anti-cancer therapy	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 PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

Table 14. Censoring rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥ 2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤ 1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

Subgroup analyses

Subgroup Analyses and Effect of Baseline Factors were planned for the following classification variables: Geographic region (EU vs non-EU); ECOG PS at randomization (0 vs. 1); Initial choice of platinum chemotherapy (cisplatin, carboplatin); PD-L1 CPS (positive vs negative); Age category (<65 years, ≥65 years) (<65 years, 65-74, 75-84, ≥85 years); Sex (female, male); Race (white, all others); Smoking history (never, current/former); Histological subtype (epithelioid vs other subtypes).

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 was less than 10% of the phase III ITT population, the subgroup analysis could not be performed for that category of the subgroup variable. The subgroup analyses for PFS and OS were conducted using an unstratified Cox model, and the subgroup analyses for ORR were conducted using the unstratified Miettinen and Nurminen method.

Safety analyses

Safety analyses were based on the APaT population, which included all randomized participants who received at least 1 dose of study intervention; participants were analyzed according to the study intervention they received.

ePRO analysis

The PRO analyses were based on the PRO Full Analysis Set (FAS) population, defined as all participants in Phase III ITT population and who had received at least 1 dose of study intervention and had completed at least 1 PRO assessment. Participants were analyzed in the intervention group to which they were randomized. The PRO instruments are EORTC QLQ-C30/LC13, and EQ-5D.

Table 15. Censoring rules for time to deterioration

Scenario	Outcome
Deterioration confirmed	Event observed at time of assessment (first deterioration)
Ongoing or discontinued from study without confirmed deterioration	Right censored at time of last assessment
No baseline assessments	Right censored at treatment start date

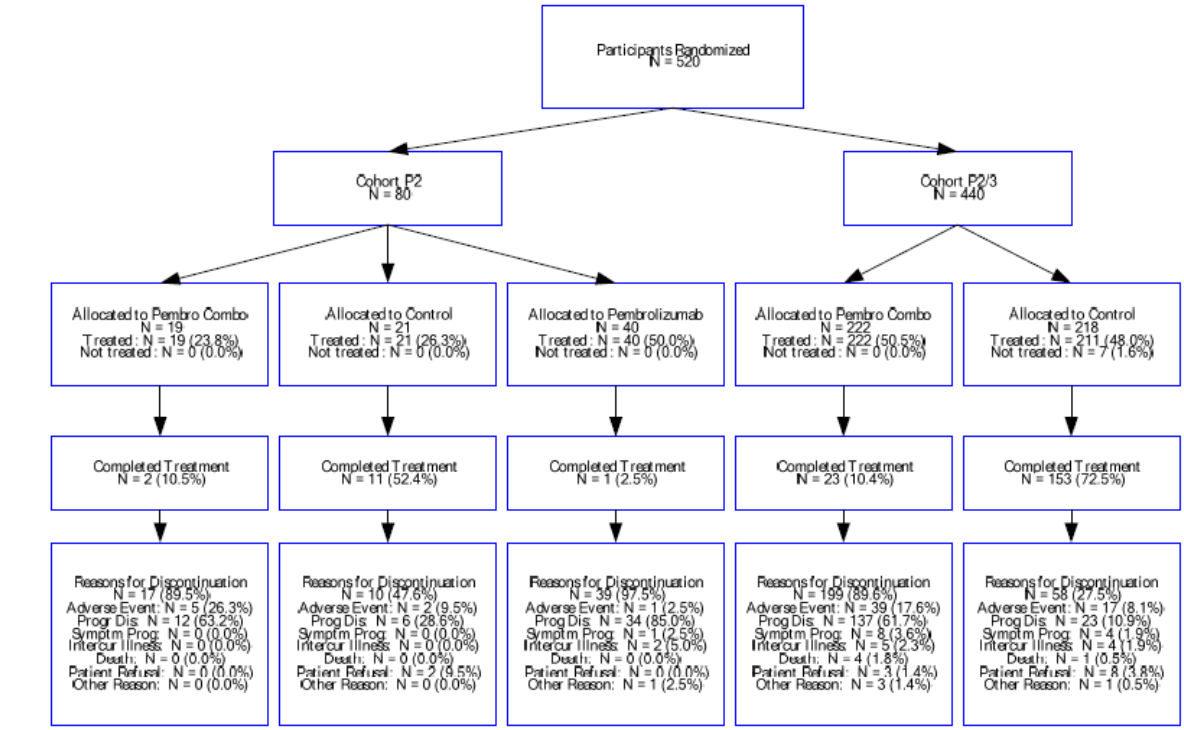
Table 16. Analysis strategy for Key PRO endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Mean change from baseline in • Global health status/QoL EORTC QLQ-C30 (items 29-30) • Physical functioning (EORTC QLQ-C30items 1-5) • Cough (Question 1 in QLQ-LC13) • Dyspnea (Question 8 in QLQ-C30) • Chest pain (QLQ-LC-13, item 10) And EQ-5D VAS	cLDA model	FAS	Model-based.
TTD in • Global health status/QoL (EORTC QLQ-C30 (items 29-30) • Physical functioning (EORTC QLQ-C30items 1-5 • Cough (Question 1 in QLQ-LC13) • Dyspnea (Question 8 in QLQ-C30) • Chest pain (QLQ-LC-13, item 10)	Stratified log-rank test and HR estimation using stratified Cox model with Efron's tie handling method	FAS	Censored according to rules in Table 6.
Overall improvement and overall improvement/stability in • Global health status/QoL (EORTC QLQ-C30 (items 29-30) • Physical functioning EORTC QLQ-C30 (items 29-30) • Cough (Question 1 in QLQ-LC13) • Dyspnea (Question 8 in QLQ-C30) • Chest pain (QLQ-LC-13, item 10)	Stratified Miettinen and Nurminen method	FAS	Participants with missing data are considered not achieving improvement/stability.
Abbreviations: cLDA = constrained longitudinal data analysis, FAS = full analysis set, QoL = quality of life.			

Results

Participant flow

Figure 7. Diagram KEYNOTE-483



Database Cutoff Date: 16SEP2022
[P483V01MK3475: adam-adsl]

Table 17. Disposition of participants (phase 3 ITT population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Participants in population	222		218	
Status for Study Treatment in Trial				
Started	222		211	
Completed	23	(10.4)	153	(72.5)
Discontinued	199	(89.6)	58	(27.5)
Adverse Events Related To Protocol Therapy	39	(17.6)	17	(8.1)
Death	4	(1.8)	1	(0.5)
Intercurrent Illness - Adverse Events Unrelated To Protocol Treatment	5	(2.3)	4	(1.9)
Other Reason	3	(1.4)	1	(0.5)
Patient Refusal (Not Related To Adverse Event)	3	(1.4)	8	(3.8)
Progressive Disease (Objective)	137	(61.7)	23	(10.9)
Symptomatic Progression	8	(3.6)	4	(1.9)
Status for Trial				
Discontinued	168	(75.7)	185	(84.9)
Death	167	(75.2)	175	(80.3)
Lost To Follow-Up	0	(0.0)	1	(0.5)
Withdrawal By Subject	1	(0.5)	9	(4.1)
Participants Ongoing	54	(24.3)	33	(15.1)

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: 16SEP2022

Recruitment

Phase 2/3 study:

First participant first visit: 15-NOV-2016

Last participant last visit and database cut-off for the final analysis: 16-SEP-2022

Database lock: 16-DEC-2022

The study is complete.

KEYNOTE-483 was conducted at 54 centres in 3 countries (Canada, Italy, France).

Conduct of the study

Table 18. Summary of important protocol deviations (Phase 3 ITT population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	222		218		440	
with one or more important protocol deviations	14	(6.3)	10	(4.6)	24	(5.5)
with no important protocol deviations	208	(93.7)	208	(95.4)	416	(94.5)
Discontinuation Criteria	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	1	(0.5)	0	(0.0)	1	(0.2)
Safety Reporting	**13**	**(5.9)**	**10**	**(4.6)**	**23**	**(5.2)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	13	(5.9)	10	(4.6)	23	(5.2)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 16SEP2022

Table 19. Protocol Amendments for KEYNOTE-483

Document	Date of Issue	Change	Rationale
Amendment 6	21-JUN-2021	In order to avoid constraints in the timing of the planned analysis, use of PD-L1 in stratified analyses has been removed from the protocol and study objective moved from secondary to exploratory, as not all PD-L1 results may be in-house in time for primary analysis. Dose modification guidelines updated per pembrolizumab product monograph.	Given that PD-L1 was not initially applied to the stratified randomization, and was missing on some participants, along with the lack of consistent predictive and prognostic value for PD-L1 in MPM, PD-L1 was removed from the stratified analysis of OS, PFS, and, ORR. Predictive and prognostic value of PD-L1 will be evaluated in an exploratory fashion.
Amendment 5	27-OCT-2020	Clarification that BICR will be used for the primary response-based analyses. Updates to statistics sections (eg, updating methodology to reflect alpha spending for multiple endpoints, clarifying endpoints for the interim analysis). Clarifications provided for dose interruptions and continuation of pembrolizumab alone (eg, regarding renal function).	Following FDA feedback, protocol was amended to add hypothesis testing of secondary endpoints of PFS and ORR once primary endpoint of OS is positive, and BICR will be used for the primary response-based analyses.
Amendment 4	14-APR-2020	The power and sample size for OS was updated. Antitumor activity assessed using RECIST modified for mesothelioma (previously assessed by RECIST 1.1).	Following assessment of KEYNOTE-604, the protocol was amended to modify the SAP to target a more conservative treatment effect.

		Clarifications made to eligibility criteria, pleural tumor measurement. SAE criteria updated to specify a threshold of abnormal hepatic tests that may require additional evaluation for underlying etiology. Added possibility of discussing options for follow-up if participant was unable to return to the site.	mRECIST addresses the limitation of RECIST 1.1 when applied to the unique morphology and growth pattern of this disease
Amendment 3	03-JAN-2019	Clarifications added regarding change from Phase 2 to Phase 3 study design, including use of RECIST 1.1 for primary and secondary objectives, interim analysis, sample size. Changes made to the Dose Modification Guidelines updated per updated IB. Wording updated to reflect CCTG standard of practice (ie, ensure participants receive palliative radiation therapy prior to enrollment). Safety reporting was updated (eg, ECI reporting no longer required, pembrolizumab overdose added to SAE definition).	Clarification added to protocol that RECIST 1.1 being used for primary and secondary objective, while iRECIST will be used for exploratory analyses. Standard interim analysis added as now a Phase 3 design. Sample size (n value for Phase 2 vs Phase 3) clarification added in Section 12.3.
Amendment 2	11-APR-2018	Study design changed from Phase 2 to Phase 3 trial with OS as primary objective. PFS, which was primary objective on Phase 2 became secondary objective on Phase 3 part. Statistical analysis including sample size, power, required number of events, accrual period, OS interim analysis were changed and/or added accordingly.	Conversion to a Phase 2/3 to support registrational intent.
Amendment 1	13-DEC-2016	Clarification about continuation of treatment beyond disease progression to account for pseudo-progression. Clarification that skin lesions will be considered non-target lesions. Clarification that immune-related response assessment will be based on iRECIST rather than modified irRC. Clarification that both amylase and lipase are preferred (but either is acceptable for sites where only one of these is routinely measured).	Administrative update.

Baseline data

Table 20. Participants characteristics (phase 3 ITT population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	222		218		440	
Sex						
Male	165	(74.3)	168	(77.1)	333	(75.7)
Female	57	(25.7)	50	(22.9)	107	(24.3)
Age (Years)						
< 65	42	(18.9)	61	(28.0)	103	(23.4)
>= 65	180	(81.1)	157	(72.0)	337	(76.6)
Mean	69.3		68.5		68.9	
Median	70.0		70.0		70.0	
Range	33 to 86		28 to 87		28 to 87	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.5)	1	(0.2)
Asian	1	(0.5)	0	(0.0)	1	(0.2)
Not Reported	37	(16.7)	38	(17.4)	75	(17.0)
Unknown	9	(4.1)	7	(3.2)	16	(3.6)
White	175	(78.8)	172	(78.9)	347	(78.9)
Ethnicity						
Hispanic Or Latino	3	(1.4)	6	(2.8)	9	(2.0)
Not Hispanic Or Latino	172	(77.5)	165	(75.7)	337	(76.6)
Not Reported	37	(16.7)	40	(18.3)	77	(17.5)
Unknown	10	(4.5)	7	(3.2)	17	(3.9)
Age (Years)						
< 65	42	(18.9)	61	(28.0)	103	(23.4)
65 - 74	116	(52.3)	95	(43.6)	211	(48.0)
75 - 84	62	(27.9)	59	(27.1)	121	(27.5)
85+	2	(0.9)	3	(1.4)	5	(1.1)
Region						
North America	70	(31.5)	67	(30.7)	137	(31.1)
European Union	152	(68.5)	151	(69.3)	303	(68.9)
PD-L1 CPS Status						
CPS >= 1	131	(59.0)	132	(60.6)	263	(59.8)
CPS < 1	70	(31.5)	63	(28.9)	133	(30.2)
Unknown	7	(3.2)	6	(2.8)	13	(3.0)

Not Done	14	(6.3)	17	(7.8)	31	(7.0)
Baseline ECOG PS						
0	101	(45.5)	105	(48.2)	206	(46.8)
1	121	(54.5)	113	(51.8)	234	(53.2)
Smoking status						
Current/Former Smoker	129	(58.1)	116	(53.2)	245	(55.7)
Never Smoker	91	(41.0)	102	(46.8)	193	(43.9)
Unknown	2	(0.9)	0	(0.0)	2	(0.5)
Histology Subtype						
Epithelioid	176	(79.3)	169	(77.5)	345	(78.4)
Sarcomatoid	12	(5.4)	18	(8.3)	30	(6.8)
Mixed/Biphasic	31	(14.0)	30	(13.8)	61	(13.9)
Other	3	(1.4)	1	(0.5)	4	(0.9)
Asbestos exposure						
No	98	(44.1)	87	(39.9)	185	(42.0)
Yes, Asbestos only	54	(24.3)	50	(22.9)	104	(23.6)
Yes, Occupational only	42	(18.9)	54	(24.8)	96	(21.8)
Yes, both Occupational and Asbestos	28	(12.6)	26	(11.9)	54	(12.3)
Unknown	0	(0.0)	1	(0.5)	1	(0.2)
Prior Radiation						
Yes	9	(4.1)	16	(7.3)	25	(5.7)
No	213	(95.9)	202	(92.7)	415	(94.3)
Prior Major Surgery						
Yes	17	(7.7)	24	(11.0)	41	(9.3)
No	205	(92.3)	194	(89.0)	399	(90.7)
Prior (Neo)Adjuvant Therapy						
Yes	3	(1.4)	9	(4.1)	12	(2.7)
No	219	(98.6)	209	(95.9)	428	(97.3)
Platinum Used						
Cisplatin Only	94	(42.3)	100	(45.9)	194	(44.1)
Carboplatin Only	96	(43.2)	84	(38.5)	180	(40.9)
Switching from Cisplatin to Carboplatin	32	(14.4)	27	(12.4)	59	(13.4)
Not treated	0	(0.0)	7	(3.2)	7	(1.6)
Database Cutoff Date: 16SEP2022						

Table 21. Participant Characteristics (Non-epithelioid) (Phase 3 ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	46		49		95	
Sex						
Male	38	(82.6)	41	(83.7)	79	(83.2)
Female	8	(17.4)	8	(16.3)	16	(16.8)
Age (Years)						
< 65	6	(13.0)	17	(34.7)	23	(24.2)
>= 65	40	(87.0)	32	(65.3)	72	(75.8)
Mean	72.6		67.7		70.1	
Median	72.5		68.0		71.0	
Range	57 to 85		48 to 83		48 to 85	
Race						
Not Reported	7	(15.2)	4	(8.2)	11	(11.6)

Unknown	0	(0.0)	3	(6.1)	3	(3.2)
White	39	(84.8)	42	(85.7)	81	(85.3)
Ethnicity						
Hispanic Or Latino	0	(0.0)	1	(2.0)	1	(1.1)
Not Hispanic Or Latino	39	(84.8)	40	(81.6)	79	(83.2)
Not Reported	7	(15.2)	5	(10.2)	12	(12.6)
Unknown	0	(0.0)	3	(6.1)	3	(3.2)
Region						
North America	13	(28.3)	17	(34.7)	30	(31.6)
European Union	33	(71.7)	32	(65.3)	65	(68.4)
PD-L1 Expression Level						
Positive	28	(60.9)	33	(67.3)	61	(64.2)
Negative	8	(17.4)	10	(20.4)	18	(18.9)
Unknown	4	(8.7)	3	(6.1)	7	(7.4)
Not Done	6	(13.0)	3	(6.1)	9	(9.5)
Baseline ECOG PS						
0	17	(37.0)	25	(51.0)	42	(44.2)
1	29	(63.0)	24	(49.0)	53	(55.8)
Smoking status						
Current/Former Smoker	24	(52.2)	31	(63.3)	55	(57.9)
Never Smoker	20	(43.5)	18	(36.7)	38	(40.0)
Unknown	2	(4.3)	0	(0.0)	2	(2.1)
Histology Subtype						
Sarcomatoid	12	(26.1)	18	(36.7)	30	(31.6)
Mixed/Biphasic	31	(67.4)	30	(61.2)	61	(64.2)
Other	3	(6.5)	1	(2.0)	4	(4.2)
Asbestos exposure						
No	21	(45.7)	19	(38.8)	40	(42.1)
Yes, Asbestos only	12	(26.1)	8	(16.3)	20	(21.1)
Yes, Occupational only	7	(15.2)	16	(32.7)	23	(24.2)
Yes, both Occupational and Asbestos	6	(13.0)	6	(12.2)	12	(12.6)
Prior Radiation						
Yes	2	(4.3)	4	(8.2)	6	(6.3)
No	44	(95.7)	45	(91.8)	89	(93.7)
Prior Major Surgery						
Yes	2	(4.3)	8	(16.3)	10	(10.5)
No	44	(95.7)	41	(83.7)	85	(89.5)
Prior (Neo)Adjuvant Therapy						
No	46	(100.0)	49	(100.0)	95	(100.0)
Platinum Used						
Cisplatin Only	18	(39.1)	26	(53.1)	44	(46.3)
Carboplatin Only	23	(50.0)	16	(32.7)	39	(41.1)
Switching from Cisplatin to Carboplatin	5	(10.9)	6	(12.2)	11	(11.6)
Not treated	0	(0.0)	1	(2.0)	1	(1.1)
Database Cutoff Date: 16SEP2022						

Numbers analysed

The efficacy analyses were based on the Phase 3 ITT population, defined as all randomized participants in the pembro combo and chemo groups from Phase 3 and Phase 2, excluding the 40 participants from Phase 2 that were part of the Phase 2 IA.

Table 22. Phase 3 ITT population

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Number of Participants Randomized (Planned Treatment)(ITT)	222		218		440	
Number of Participants Received Treatment (Actual Treatment)(APaT)	222	(100.0)	211	(96.8)	433	(98.4)
Number of Participants Randomized and Did not Receive Treatment	0	0.0	7	(3.2)	7	(1.6)
Number of Participants Discontinued Study Medication (Actual Treatment	199	(89.6)	58	(26.6)	257	(58.4)
Database Cutoff Date: 16SEP2022						

Table 23. Analysis population

	Phase 3 ITT	**APaT Arms A/B**	**Pembro Mono (APaT Population in Arm C)**
Population Description	Phase 3 Arms A and Arm B	Treated participants in Phase 3 and Phase 2 IA Arms A and B	All randomized to Arm C (those included in Phase 2 IA + those not included in Phase 2 IA, but randomized before the decision was made to drop the arm)
N	440	473 (433 + 40)	40
Related analysis			
Efficacy	X		
Demographic	X	X	
Safety		X	X

Arm A = Chemo; Arm B = Pembro combo; Arm C = Pembro mono; IA = interim analysis

Outcomes and estimation

The results are based on the final analysis with data cut-off date 16 September 2022, at median survival follow-up of 17 months.

Table 24. Summary of Follow-up Duration (Phase 3 ITT Population)

Follow-up duration (months)[a]	Pembro Combo (N=222)	Control (N=218)	Total (N=440)
Median (Range) Mean (SD)	17.4 (0.8, 60.3) 20.2 (13.1)	16.8 (0.8, 59.3) 19.1 (12.6)	17.0 (0.8, 60.3) 19.7 (12.9)
[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the Participants is still alive. Database Cutoff Date: 16SEP2022			

At the final analysis, statistical significance was reached for the primary endpoint OS and for the secondary endpoint PFS in the ITT population of the Phase 3 study. Statistically significant improvement was reached in ORR at Phase 3 IA.

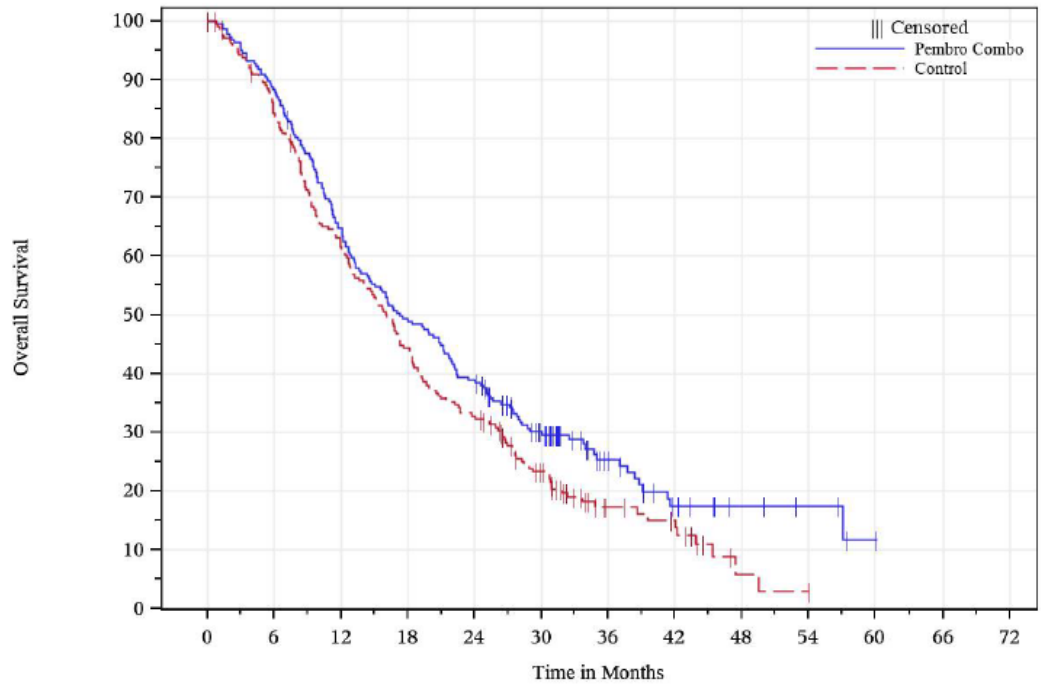
Overall Survival (OS)

Table 25. Analysis of Overall Survival (Phase 3 ITT population)

	Pembro Combo (N=222)	Control (N=218)
Number of Events (%)	167 (75.2)	175 (80.3)
Death	167 (75.2)	175 (80.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
[Q1, Q3]	[9.6, 37.0]	[8.3, 28.3]
Person-months	4457.8	3809.9
Event Rate / 100 Person-months	3.7	4.6
vs Control		
Hazard Ratio (95% CI)[b]	0.79 (0.64, 0.98)	
p-value[c]	0.0162	
Rate at month 6 (%) (95% CI)	88.3 (83.3, 91.9)	84.3 (78.6, 88.5)
Rate at month 12 (%) (95% CI)	64.8 (58.1, 70.7)	61.6 (54.7, 67.9)
Rate at month 18 (%) (95% CI)	49.4 (42.6, 55.8)	44.3 (37.5, 50.9)
Rate at month 24 (%) (95% CI)	38.9 (32.5, 45.3)	32.8 (26.5, 39.2)
Rate at month 30 (%) (95% CI)	30.1 (24.1, 36.3)	23.3 (17.7, 29.3)
Rate at month 36 (%) (95% CI)	25.3 (19.3, 31.8)	17.3 (12.1, 23.2)

[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 Histological Subtype at Randomization (Epithelioid vs Other subtypes).
[c] One-sided p-value based on log-rank test stratified by Histological Subtype at Randomization (Epithelioid vs Other subtypes).
Database Cutoff Date: 16SEP2022

Figure 8. Kaplan Meier plot of overall survival (Phase 3 ITT population)



Database Cutoff Date: 16SEP2022

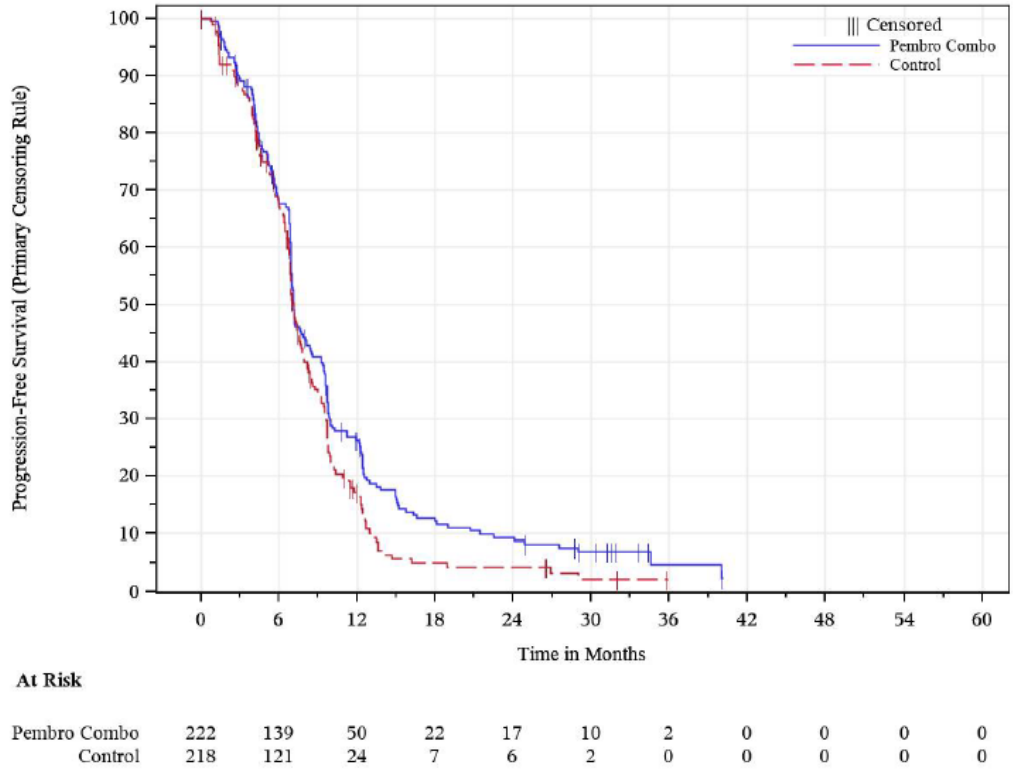
Progression Free Survival (PFS) based on BICR per mRECIST

Table 26. Analysis of PFS (primary censoring rule) based on BICR per mRECIST (Phase 3 ITT population)

	Pembro Combo (N=222)	Control (N=218)
Number of Events (%)	190 (85.6)	166 (76.1)
Death	19 (8.6)	20 (9.2)
Documented progression	171 (77.0)	146 (67.0)
Number of Censored (%)	32 (14.4)	52 (23.9)
Last assessment prior to 2 or more consecutive missed assessments	4 (1.8)	4 (1.8)
Last assessment showing no progression	12 (5.4)	6 (2.8)
Last radiologic assessment prior to new anti-cancer therapy showing no progression	14 (6.3)	26 (11.9)
Randomization	2 (0.9)	16 (7.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
[Q1, Q3]	[5.1, 12.3]	[4.7, 9.8]
Person-months	2052.4	1484.8
Event Rate / 100 Person-months	9.3	11.2
vs Control		
Hazard Ratio (95% CI)[b]	0.80 (0.65, 0.99)	
p-value[c]	0.0194	
Rate at month 6 (%) (95% CI)	67.6 (60.8, 73.4)	67.7 (60.5, 73.9)
Rate at month 9 (%) (95% CI)	40.8 (34.1, 47.4)	34.5 (27.6, 41.6)
Rate at month 12 (%) (95% CI)	26.3 (20.4, 32.4)	17.1 (11.8, 23.3)

[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 Histological Subtype at Randomization (Epithelioid vs Other subtypes).
[c] One-sided p-value based on log-rank test stratified by Histological Subtype at Randomization (Epithelioid vs Other subtypes).
Database Cutoff Date: 16SEP2022

Figure 9. Kaplan-Meier plot of PFS (Primary censoring rule) based on BICR per mRECIST (phase 3 ITT population)



Database Cutoff Date: 16SEP2022

Overall Response Rate (ORR)

Table 27. Analysis of objective response (confirmed) based on BICR per mRECIST (Phase 3 ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)[a]	p-Value[b]
Pembro Combo	222	116	52.3 (45.5,59.0)	23.5 (14.6,32.0)	<0.00001
Control	218	63	28.9 (23.0,35.4)		

Responses are based on BICR assessment per mRECIST.
[a] Based on Miettinen & Nurminen method stratified by Histological Subtype (Epithelioid vs Other subtypes).
[b] One-sided p-value for testing H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 30JUL2021

Table 28. Summary of best overall response based on BICR per mRECIST (Phase 3 ITT population)

Response Evaluation	Pembro Combo			Control		
	n	%	95% CI[a]	n	%	95% CI[a]
Participants in population	222			218		
Complete Response (CR)	1	0.5	(0.0, 2.5)	0	0.0	(0.0, 1.7)
Partial Response (PR)	115	51.8	(45.0, 58.5)	63	28.9	(23.0, 35.4)
Objective Response (CR+PR)	**116**	**52.3**	**(45.5, 59.0)**	**63**	**28.9**	**(23.0, 35.4)**
Stable Disease (SD)	92	41.4	(34.9, 48.2)	122	56.0	(49.1, 62.7)
Disease Control (SD+CR+PR)	**208**	**93.7**	**(89.6, 96.5)**	**185**	**84.9**	**(79.4, 89.3)**
Progressive Disease (PD)	9	4.1	(1.9, 7.6)	11	5.0	(2.5, 8.8)
Not Evaluable (NE)	1	0.5	(0.0, 2.5)	2	0.9	(0.1, 3.3)
No Assessment	4	1.8	(0.5, 4.5)	20	9.2	(5.7, 13.8)

[a] Based on the exact method for binomial data.
Responses are based on BICR assessment per mRECIST
Database Cutoff Date: 30JUL2021

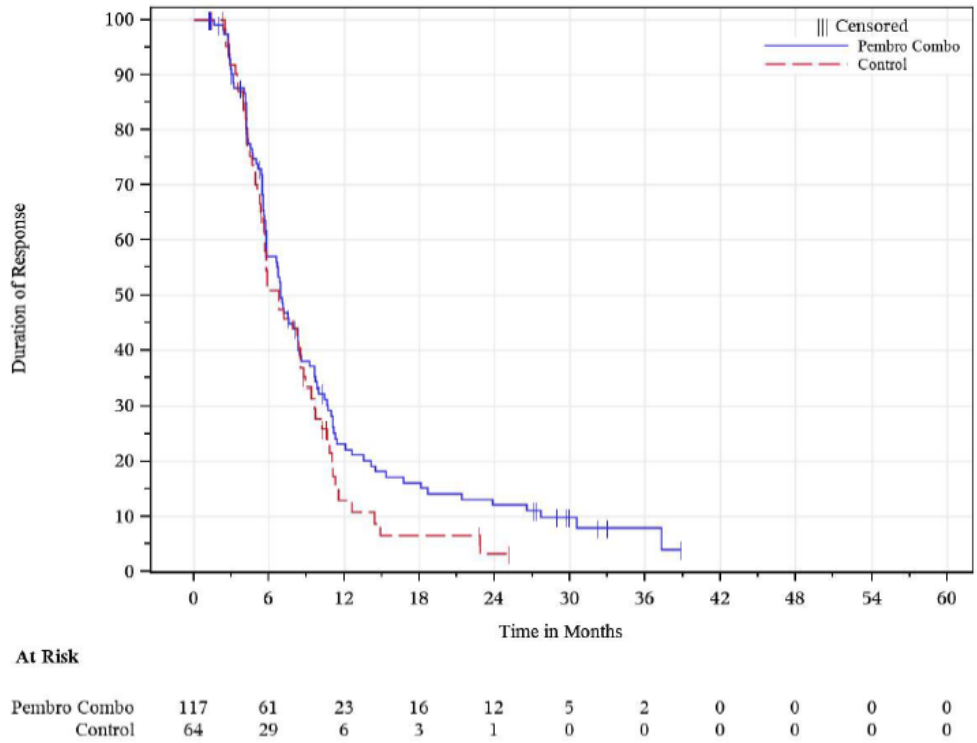
Duration of Response (DoR)

Table 29. Summary of time of response and duration of response based on BICR per mRECIST in participants with a confirmed response (phase 3 ITT population)

	Pembro Combo (N=222)	Control (N=218)
Number of participants with response[a]	117	64
Time to Response (months)		
Mean (SD)	2.5 (1.8)	2.3 (1.6)
Median (Range)	2.1 (0.4 to 12.2)	1.5 (1.2 to 13.1)
Response Duration[b] (months)		
Median (95% CI)	6.9 (5.8, 8.3)	6.8 (5.5, 8.5)
Range	1.2+ to 38.9+	1.4+ to 25.1+
Number (%[b]) of Participants with Extended Response Duration		
≥6 months	61 (57.0)	29 (50.9)
≥9 months	39 (38.0)	18 (33.2)
≥12 months	23 (23.1)	6 (12.9)
≥15 months	18 (18.1)	3 (6.5)

[a] Includes participants with confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 16SEP2022

Figure 10. Kaplan-Meier Plot of duration of response based on BICR per mRECIST (in participants with a confirmed response) (Phase 3 ITT population)



Database Cutoff Date: 16SEP2022

Patient-reported Outcomes

Prespecified key PRO endpoints based on the GHS/QoL, physical functioning, dyspnea, chest pain and cough symptom scores, and supportive PRO endpoints according to the predefined Company's sSAP were provided.

EORTC QLQ-C30/LC13 Scores

• At baseline, completion rates and compliance rates for the EORTC QLQ-C30/LC13 scores were similar in both treatment groups (>99%). At Week 15, the completion rate was slightly higher in the pembro combo group compared with the chemo group (70% vs 66.5%) while compliance rates (95.7% vs 94.6%) remained similar in both treatment groups.

• Baseline GHS/QoL, physical functioning and disease-related symptom (dyspnea, chest pain, cough) scores from the EORTC QLQ-C30 and EORTC QLQ- LC13 were similar in both treatment groups.

• The GHS/QoL, physical functioning and disease-related symptom (dyspnea, chest pain, cough) scores at Week 15 were generally stable relative to baseline in both treatment groups. As exceptions, a slight improvement relative to baseline was observed for the chest pain score in the pembro combo group and for the cough score in both treatment groups; and a slight deterioration was observed for the GHS/QoL score and physical functioning score in both treatment groups at Week 15.

• There were no substantive differences in the LS mean change in GHS/QoL, physical functioning, and disease-related symptom scores between the treatment groups at Week 15.

• The proportion of participants who "improved" was higher in the pembro combo group compared with the chemo group for the GHS/QoL, physical functioning, dyspnea, chest pain and cough scores relative to baseline.

• Median TTD in the GHS/QoL and physical functioning were not achieved in both treatment groups.

• Median TTD in composite endpoint of cough, chest pain, or dyspnea was reached in the pembro group, but not in the chemo group.

• Pembro combo did not delay the TTD in GHS/QoL, physical functioning, and composite endpoint of cough, chest pain, or dyspnea, compared with chemo alone.

• Change from baseline to Week 15 in other scales of the EORTC QLQ-C30 and EORTC QLQ-LC13 were also generally stable in both treatment groups, with few exceptions; no clinically meaningful differences were observed across the treatment groups (ie, 95% CIs surrounding the LS mean change from baseline scores all overlapped across the intervention groups).

Supportive EQ-5D-5L VAS Analysis

• At baseline, completion rates (96.3% vs 97.3%) and compliance rates (98.4% vs 99.4%) for the EQ-5D-5L VAS scores were similar in both treatment groups. At Week 15, the completion rate was slightly higher in the pembro combo group compared with the chemo group (67.9% vs 64.5%), and compliance rates remained similar in both treatment groups (92%).

• Baseline EQ-5D-5L VAS scores were similar in both treatment groups. At Week 15, the LS mean change from baseline was also similar in both treatment groups.

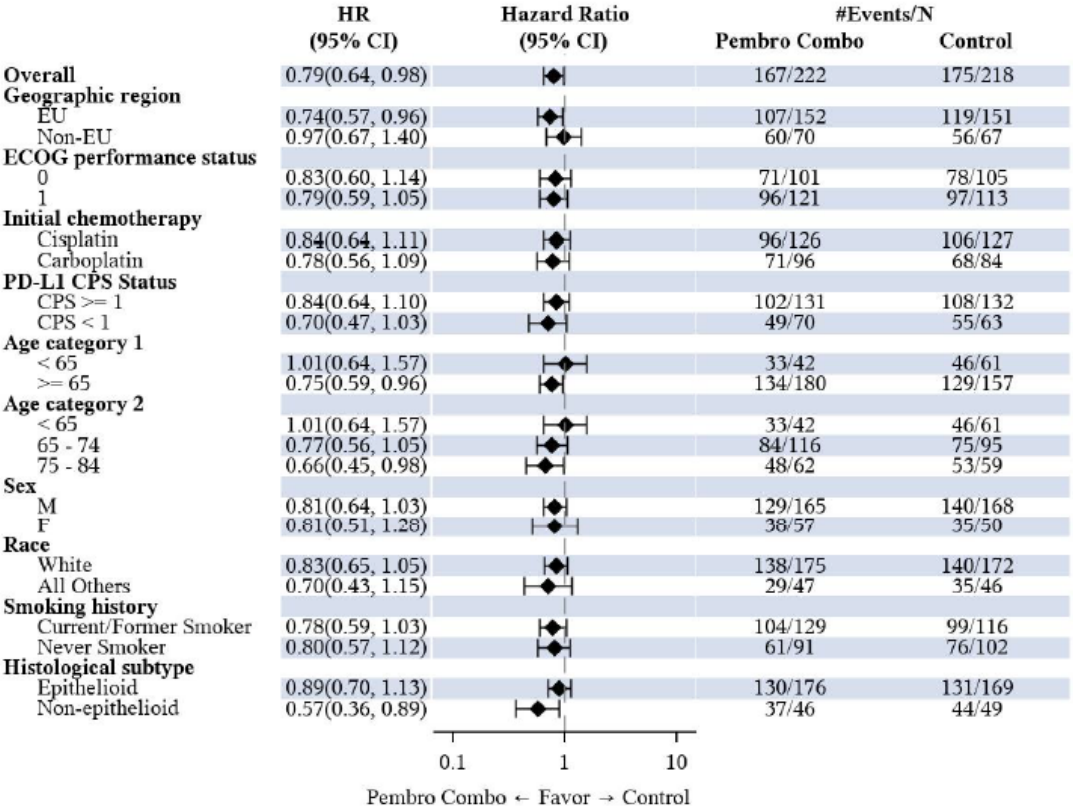
• A higher proportion of participants achieved "improved" EQ-5D-5L VAS scores in the pembro combo vs chemo group.

Ancillary analyses

Subgroup analysis

Overall survival

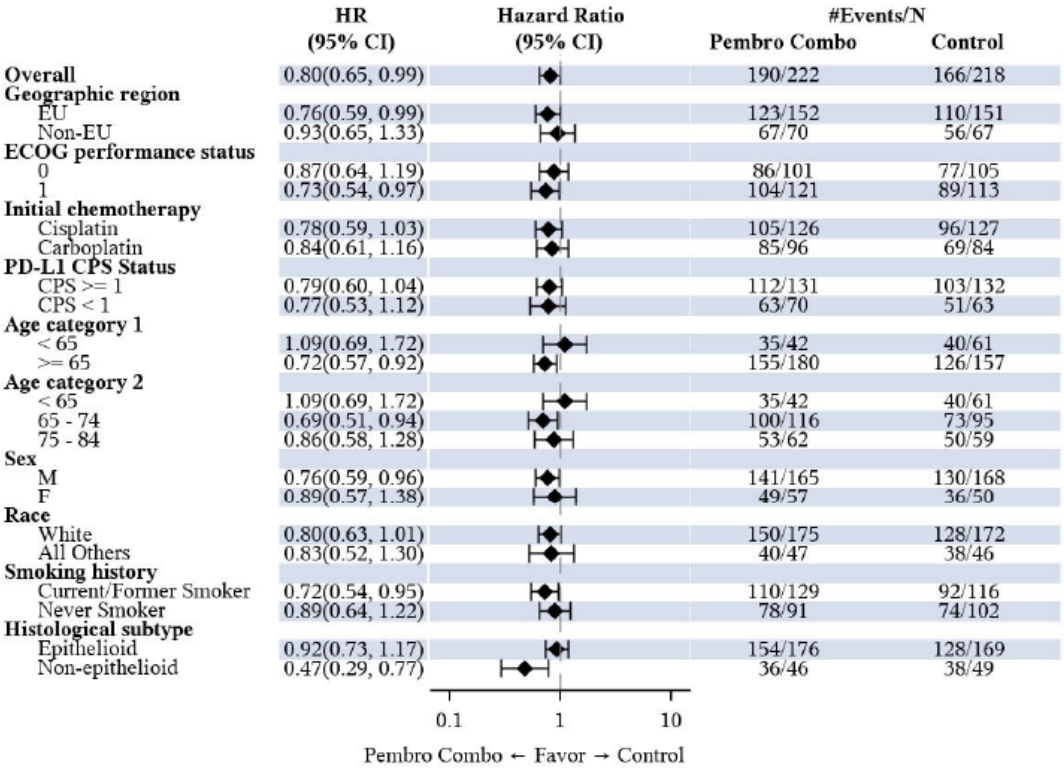
Figure 11. Forest plot for OS Hazard Ratio by subgroup factors (phase 3 ITT population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by Histological Subtype at Randomization (Epithelioid vs Other subtypes).
For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
A subject is assigned to the platinum chemotherapy subgroup based on the platinum which was administered to them at the first dose.
Database Cutoff Date: 16SEP2022

Progression free survival

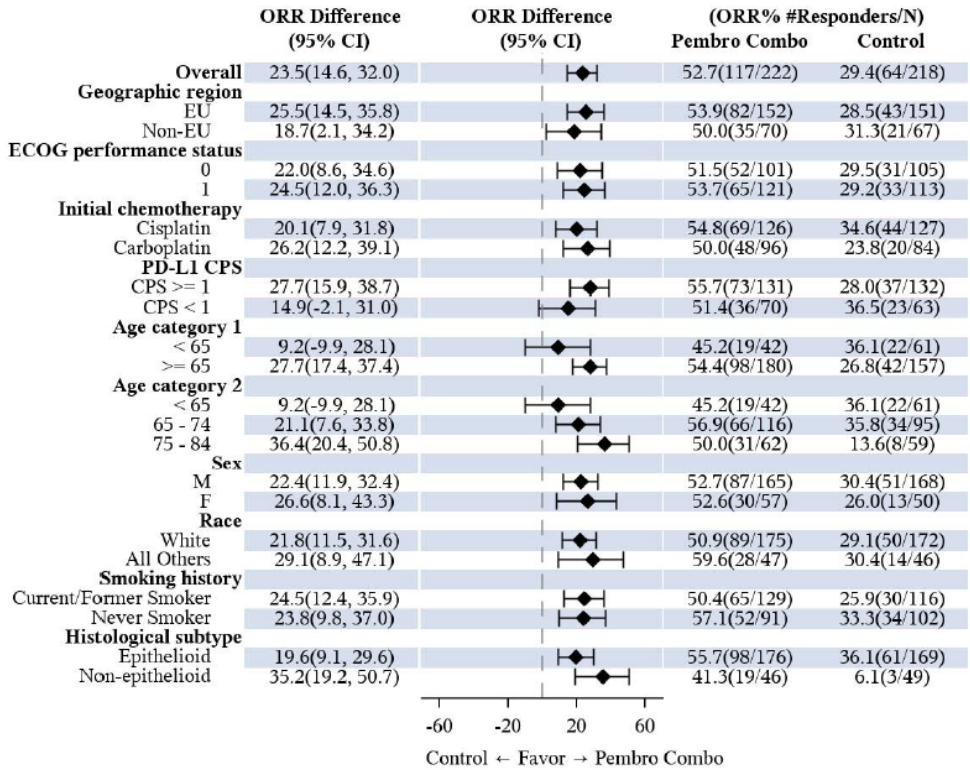
Figure 12. Forest plot for PFS Hazard Ratio by subgroup factors based on BICR per mRECIST (primary censoring rule) (phase 3 ITT population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by stratified by Histological Subtype at Randomization (Epithelioid vs Other subtypes).
For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
A subject is assigned to the platinum chemotherapy subgroup based on the platinum which was administered to them at the first dose.
Database Cutoff Date: 16SEP2022

Objective response

Figure 13. Forest Plot for Objective Response Rate by Subgroup Factors Based on BICR per mRECIST (Phase 3 ITT Population)



Analysis (ORR difference and 95% CI) is based on the Miettinen & Nurminen method stratified by Histological Subtype at Randomization (Epithelioid vs Other subtypes).
For subgroups, analysis is based on unstratified Miettinen & Nurminen method.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Database Cutoff Date: 16SEP2022

Subgroup analysis by histology

Table 30. Efficacy results by Histology

	Epithelioid		Non-epithelioid	
	Pembro Combo	Control	Pembro Combo	Control
	(N=176)	(N=169)	(N=46)	(N=49)
Overall Survival				
Number of Events (%)	130 (73.9)	131 (77.5)	37 (80.4)	44 (89.8)
Hazard Ratio (95% CI)[a]	0.89 (0.70, 1.13)		0.57 (0.36, 0.89)	
Median (months)[b] (95% CI)	19.8 (16.0, 22.2)	18.2 (16.0, 20.4)	12.3 (8.7, 21.2)	8.2 (5.8, 9.8)
Rate at month 24 (%) (95% CI)	40.0 (32.8, 47.2)	36.7 (29.3, 44.1)	34.8 (21.5, 48.4)	19.3 (9.5, 31.5)
Rate at month 36 (%) (95% CI)	25.6 (18.7, 33.1)	20.0 (13.8, 27.1)	23.1 (12.0, 36.2)	7.2 (1.9, 17.4)
Progression-Free Survival by BICR				
Number of Events (%)	154 (87.5)	128 (75.7)	36 (78.3)	38 (77.6)
Hazard Ratio (95% CI) [a]	0.92 (0.73, 1.17)		0.47 (0.29, 0.77)	
Median (months)[b] (95% CI)	7.1 (6.9, 8.1)	7.4 (6.9, 8.3)	7.1 (4.5, 9.8)	4.5 (4.0, 6.4)
Rate at month 12 (%) (95% CI)	25.8 (19.4, 32.7)	20.0 (13.7, 27.2)	28.2 (15.4, 42.3)	6.4 (1.2, 18.3)
Objective Response Rate (%) by BICR	55.7	36.1	41.3	6.1
95% CI[c]	(48.0, 63.2)	(28.9, 43.8)	(27.0, 56.8)	(1.3, 16.9)
Duration of Response[b]				
Median (95% CI)	6.7 (5.7, 7.9)	6.8 (5.6, 8.8)	11.1 (5.6, 30.6)	4.0 (2.8, NR)
Range	1.2+ to 30.0+	1.4+ to 25.1+	1.3+ to 38.9+	2.4+ to 5.2

BICR = blinded independent central review; CI = confidence interval; N = number.

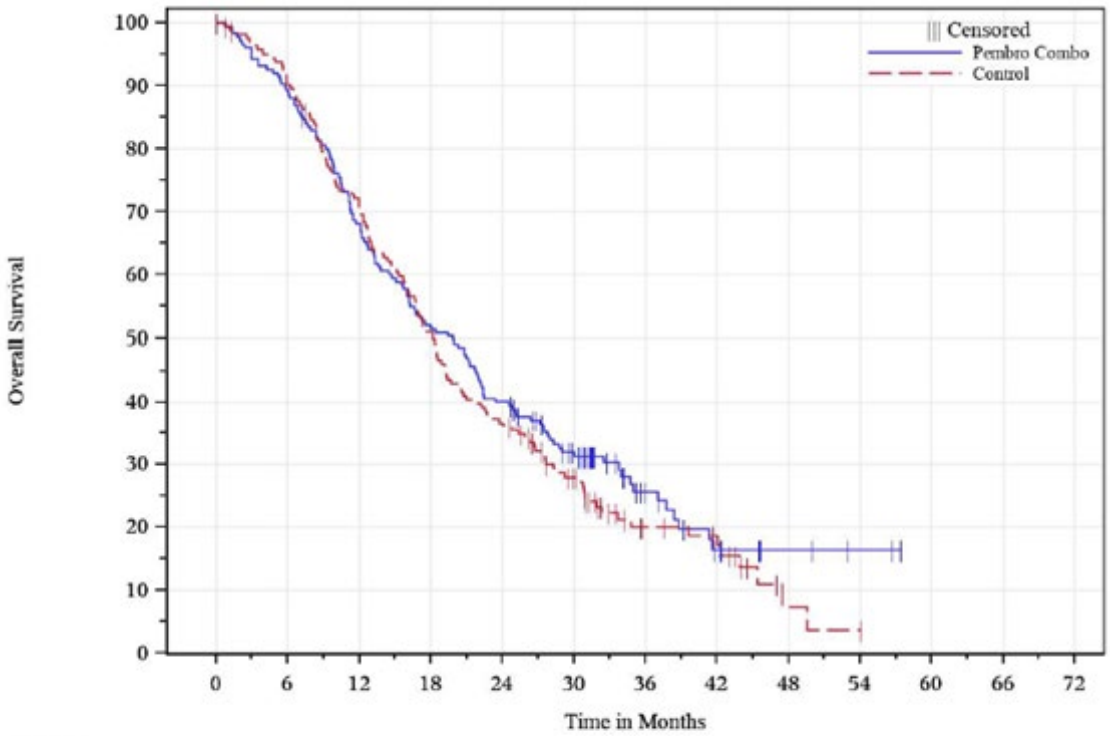
a Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

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

c Based on the exact method for binomial data.

Database Cutoff Date: 16SEP2022

Figure 14. Kaplan-Meier plot of Overall survival (Phase 3 ITT population – Epithelioid)

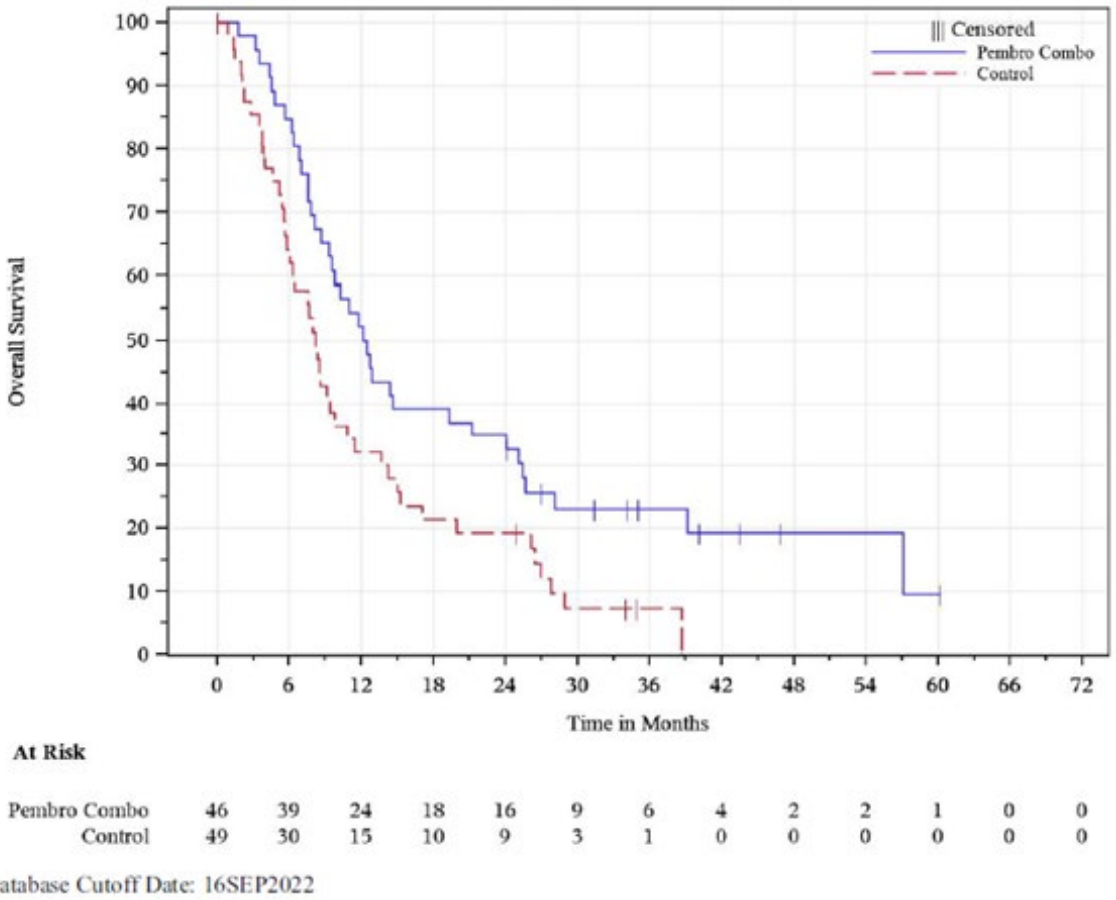


At Risk

Pembro Combo	176	157	119	91	70	45	19	9	4	2	0	0	0
Control	169	146	113	82	59	37	15	12	2	1	0	0	0

Database Cutoff Date: 16SEP2022

Figure 15. Kaplan-Meier plot of Overall survival (Phase 3 ITT population – Non-epithelioid)



Summary of main study(ies)

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

Table 31. Summary of Efficacy for trial Keynote-483

Title: A Phase 2/3 Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma			
Study identifier	EudraCT: 2016- 002286-60		
Design	Multicenter, efficacy, safety, parallel assignment, open-label, active-comparator intervention		
	Duration of main phase:		15-NOV-2016 / 16-SEP-2022
Hypothesis	Superiority		
Treatments groups	Pembro Combo		Pembrolizumab 200 mg Q3W up to 35 cycles, cisplatin+pemetrexted Q3W up to 6 cycles, n=222
	Control		cisplatin+pemetrexted Q3W up to 6 cycles, n=218
Endpoints and definitions	Primary endpoint	OS	Time from randomization to death due to any cause

	Secondary endpoints	PFS ORR DoR	Time from randomization to PD, based upon MRECIST by BICR, or death, whichever occurred earlier proportion of subjects who have a CR or a PR by BICR time from first documented evidence of CR or PR until disease progression or death
Data cut-off Database lock	16-SEP-2022 (final analysis) 16-DEC-2022		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembro Combo	Control
	Number of subject	222	218
	OS (median months)	17.3	16.1
	95% CI	(14.4, 21.3)	(13.1, 18.2)
	PFS (median months)	7.1	7.1
	95% CI	(6.9, 8.1)	(6.8, 7.7)
	ORR (%)	52.3	28.9
	95% CI	(45.5, 59.0)	(23.0, 35.4)
Effect estimate per comparison	Primary endpoint	**Pembro Combo vs Control**	**OS**
		HR	0.79
		95% CI	0.64,0.98
		P-value	<0.0162
	Secondary endpoint	**Pembro Combo vs Control**	**PFS**
		HR	0.80
		95% CI	0.65, 0.99
		P-value	0.0194
	Secondary endpoint	**Pembro Combo vs Control**	**ORR**
		Difference in % vs. Control	23.5
		95% CI	14.6,32.0
		P-value	<0.00001

Clinical studies in special populations (paediatrics)

The MAH had initially requested a paediatric indication in adolescents from 12 years and older for the same indication as in adults.

In the paediatric population, malignant mesothelioma is extremely rare. The age-adjusted incidence rate of mesothelioma is 0.00 per 100,000 in, the EU-27 (ECIS 2022, 4 cases in the age range 0-19 years). Due to the rarity of the disease, unmet medical need, and lack of relevant efficacy data

currently available for MPM in the adolescent population, an inference from adult to adolescent MPM is made and an extrapolation approach has been applied by the MAH and presented below.

In line with E11 (R1) addendum for paediatric research and with the framework proposed in the EU 'Reflection paper on the use of extrapolation in the development of medicines for paediatrics' (2018), the MAH has applied the extrapolation approach based on the following three comparisons between adults and adolescents:

(1) similarity of mesothelioma disease in adult and pediatric populations

In the case of extrapolating the clinical benefit observed for pembrolizumab in combination with pemetrexed and platinum chemotherapy in adult patients with MPM to paediatric patients with MPM, the MAH proposed to only consider adolescent patients (12 years and older) with MPM. This is supported by the median age of 13.4 years in the 33 cases of paediatric mesothelioma retrospectively described by the European Cooperative Study Group on Pediatric Rare Tumors[19] and also by the 2 teenage patients with mesothelioma (1 pleural of unknown histology and 1 peritoneal), both of whom were PD-L1 positive, and also MSI-H positive, who were treated with pembrolizumab monotherapy in KEYNOTE-051 (A Phase I/II Study of Pembrolizumab in Children With Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumor or Lymphoma). Both had a best overall response of PR.

In addition to demonstrating a similar biology, extrapolation requires paediatric data showing a similar pharmacology of drug effect, and PK drug exposures, as well as similar exposure-response for efficacy and safety.

(2) similar pharmacology of drug effect and PK drug exposures

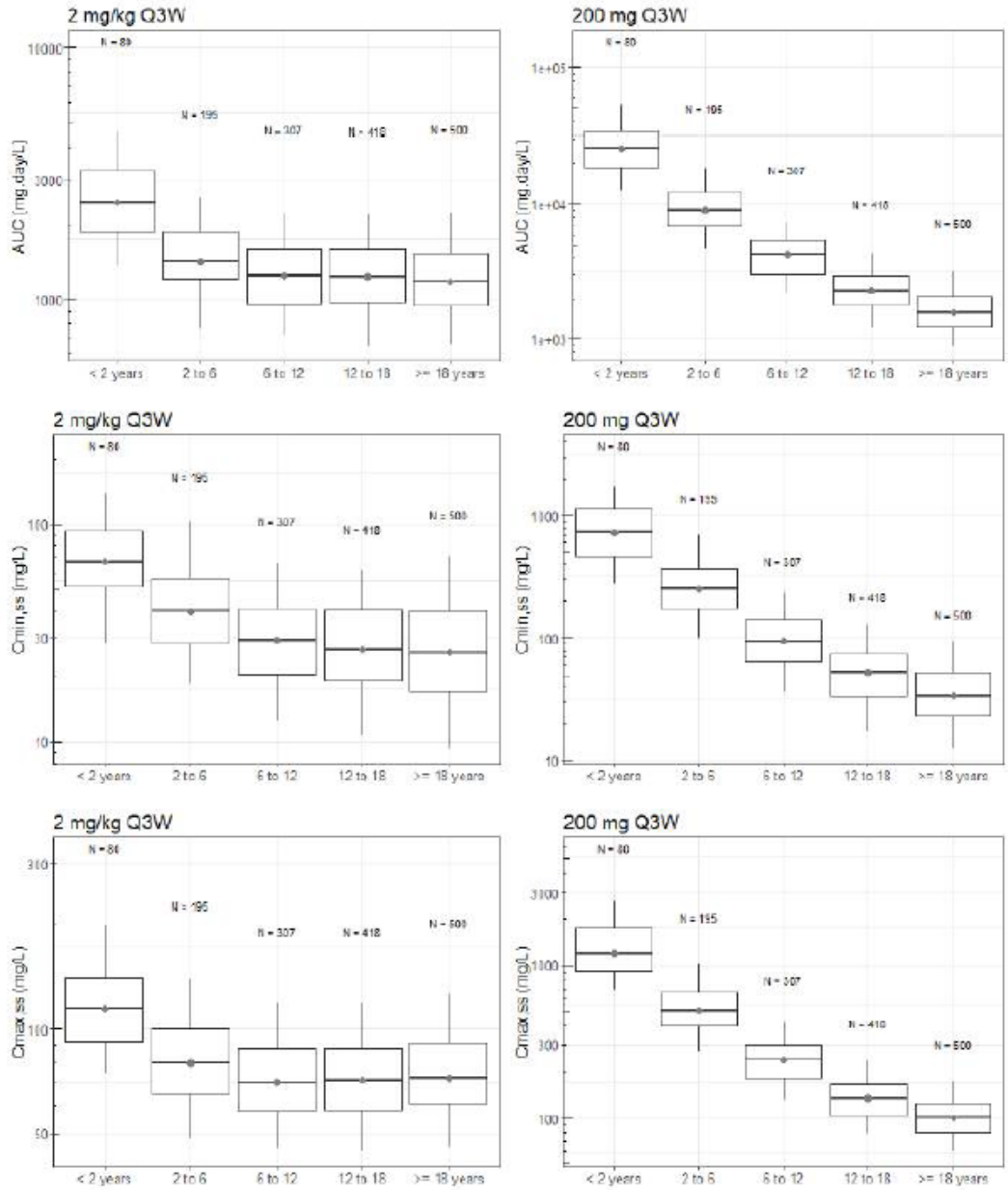
The IL-2 release biomarker reflects the functional blockade of the PD-1 pathway by pembrolizumab and is utilized as a measure of target engagement or a pharmacodynamic endpoint for pembrolizumab. The relationship between IL-2 stimulation and pembrolizumab concentration was assessed based on the first 12 participants enrolled in KEYNOTE-051.

The IL-2 simulation ratio curves in pediatric participants were found to be consistent with those in adults, indicating the exposure simulation ratio relationships are consistent between pediatric and adult participants and supporting the dosage of 2 mg/kg Q3W in pediatric patients. Pembrolizumab exposures from the 2 participants with mesothelioma enrolled in KEYNOTE-051 are within the range observed in other pediatric participants. The PK and target exposures in the pediatric population with MPM are expected to be similar to those in adults with MPM. A model-based PK bridging analysis, which included available pediatric PK data from the pembrolizumab pediatric study KEYNOTE-051 and adult PK data from monotherapy pembrolizumab studies KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, in solid tumors, as well as KEYNOTE-013, KEYNOTE-087, and KEYNOTE-204 in Hodgkin lymphoma, was conducted to determine the pediatric dose based on the approach of exposure matching with adults. Consistent with the effect of body weight on pembrolizumab clearance and volume of distribution, this analysis indicated lower clearance and volume of distribution with decreasing age in the pediatric population. Nevertheless, predictions of exposures following a 2 mg/kg Q3W (ie, weight-based) dosing regimen showed similar PK exposures compared to adults in pediatric subjects as young as 6 years of age, indicating that the weight-based regimen of 2 mg/kg Q3W adequately addresses much of the effects of body weight and age observed on the pembrolizumab PK parameters in the pediatric population (Figure below). Therefore, this model-based PK bridging analysis showed that a dose of 2 mg/kg (up to 200 mg) Q3W in pediatric participants provided PK

[19] Orbach D, Andre N, Brecht IB, Lopez Almaraz R, Ben-Ami T, Vermersch S, et al. Mesothelioma in children and adolescents: the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) contribution. Eur J Cancer. 2020;140:63-70.

exposures similar to those achieved at 2 mg/kg (or 200 mg) Q3W in adults and served as the basis for approval of a pediatric indication in advanced (unresectable or metastatic) melanoma; Stage IIB, IIC, or III melanoma in adolescents who have undergone complete resection; and in relapsed or refractory cHL.

Figure 16. Pembrolizumab Predicted Exposure for Pediatrics and Adults Following 2 mg/kg Q3W and 200 mg Q2W Dosing Regimens



Additionally, the pediatric dosing regimen of 2 mg/kg Q3W is also supported by the low incidence of positive immunogenicity status after pembrolizumab treatment in KEYNOTE-051 pediatric participants (1.6%), which is comparable with that in adults (2.1%), and had no impact on pembrolizumab exposure.

Literature information on pemetrexed show that PK concentrations and body surface area adjusted clearance observed in pediatric patients after monotherapy dosing are comparable to the values observed in adults (refer to Alimta PI and EPAR).

Contrary to pemetrexed, carboplatin pharmacokinetics are not similar between adult and pediatric populations. As such, dosing adjustments based on body weight and renal function have been used to ensure pediatric patients reach AUC exposures associated with safety in children. Overall, literature information on the chemotherapy components pemetrexed and carboplatin show that these agents are able to be used in pediatric patients to reach PK exposures similar to those in adults.

As far as differences in drug metabolizing pathways between adult and pediatric populations, there are known differences on the metabolism of small molecule drugs and on the metabolism of mAbs between these 2 populations. However, the probability of DDI between pembrolizumab and small molecule drug remains low, given that the differences in metabolic pathways of these drugs between pediatric and adult populations (ie, pembrolizumab eliminated by catabolism and small molecules are eliminated by CYP mediated biotransformation) are not expected. Hence, it is reasonable to assume that there will be no meaningful impact of the coadministration of chemotherapy on the pharmacokinetics of pembrolizumab in the population of pediatrics with MPM aged 12 years and older.

Pembrolizumab PK data included in previous submissions show pembrolizumab pharmacokinetics are consistent across different cancer indications. Moreover, the potential of DDI between biologics such as pembrolizumab and small molecule drugs such as chemotherapy is negligible. Biologics are administered parenterally, which precludes the potential for absorption interaction. The CYP system and other commonly used metabolic pathways are not involved in metabolism of biologics and are not generally induced/inhibited by them; therefore, the potential for metabolism or elimination-based DDIs is also negligible. In agreement with this understanding, data from adult patients with NSCLC treated with pembrolizumab in combination with carboplatin and pemetrexed in KEYNOTE-021 Cohort G showed no meaningful effect of pemetrexed and carboplatin on the pharmacokinetics of pembrolizumab.

Given that pembrolizumab drug concentrations in the MPM pediatric population treated with pembrolizumab are not expected to be impacted by the coadministration of pemetrexed and carboplatin, and the similarity of pembrolizumab drug concentrations across different indications, it is reasonable to assume PK concentrations in pediatric patients with MPM will be similar to the drug concentrations observed in pediatric participants from KEYNOTE-051.

Hence, the results from the model-based PK analysis for the pediatric population in KEYNOTE-051 and the selected dose of 2 mg/kg can also be applied to the adolescent MPM population.

(3) similar exposure-response for efficacy

Due to the limited number of pediatric patients with mesothelioma, no information has been provided on the exposure-response relationship in paediatric patients with mesothelioma.

Data previously submitted in the context of cHL EoI (EPAR EMEA/H/C/3820/II/090) showed that the exposure-response relationship and PK profile are similar in adult and pediatric patients (from 3 years of age). Moreover, considering that consistent flat exposure-response relationships are seen for pembrolizumab in multiple tumor types and pharmacokinetics are not meaningfully different among tumor types, the dosing regimen of pembrolizumab is expected to be similar across all indications in pediatrics (similar to adults).

Supportive studies

Efficacy results from the supportive studies KEYNOTE-A17 and the Phase 2 portion of KEYNOTE-483 were included to provide supportive efficacy of pembro combo intervention in advanced MPM.

KEYNOTE-A17

A Phase Ib Clinical Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Cisplatin and Pemetrexed in Treatment-naive Participants with Advanced Malignant Pleural Mesothelioma.

This was a multicenter, open-label, non-randomized, phase 1b study to evaluate the safety, tolerability, and preliminary efficacy of pembrolizumab in combination with cisplatin and pemetrexed in treatment-naïve, Japanese participants with histologically confirmed diagnosis of advanced/unresectable MPM.

Participants received pembrolizumab 200 mg Q3W in combination with cisplatin 75 mg/m2 Q3W and pemetrexed 500 mg/m2 Q3W for 4-6 cycles followed by monotherapy of pembrolizumab for up to 35 cycles from the first dose of the study intervention in the treatment phase (approximately total 2 years). The administration continued until one of the conditions for discontinuation of study intervention was met.

ELIGIBILITY CRITERIA: The study included Japanese male or female participants at least 20 years of age with histologically confirmed diagnosis of advanced/unresectable MPM; an ECOG PS of 0 or 1; no prior systemic anti-cancer therapy to MPM; and no history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

OBJECTIVES AND ENDPOINTS:

Primary Objective	**Primary Endpoints**
• To evaluate the safety and tolerability of treatment with pembrolizumab in combination with cisplatin and pemetrexed.	• DLT rate • AEs • Discontinuing study intervention due to AEs
Secondary Objective	**Secondary Endpoints**
• To evaluate the preliminary anti-tumor activity (objective response, disease control and DOR by modified RECIST as assessed by the investigator) of pembrolizumab in combination with cisplatin and pemetrexed.	• Objective response: confirmed CR or PR • Disease control: a response of confirmed CR or PR, or SD • DOR: the time from the first documented evidence of objective response (CR or PR) to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was approximately 18 participants. As of the LPLV for this report, 19 participants were allocated and all of them were included in the All Participants as Treated (APaT) population for analysis.

STATISTICAL AND ANALYTICAL METHODS: Efficacy analyses were conducted using the APaT population, which included all participants who received at least 1 dose of study intervention. The DLT was evaluated using the DLT evaluable population, which included APaT participants that met the criteria for DLT evaluability. All other safety analyses were conducted using APaT. The DLT rate and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) were provided. For the efficacy analyses of ORR and DCR, the point estimates and 95% CIs were provided in participants treated with pembrolizumab in combination with cisplatin and pemetrexed, using an exact method based on the binomial distribution.

Participant Disposition

A total of 19 participants were allocated across 4 sites in Japan and received at least 1 dose of study intervention. This comprised the APaT population for the primary efficacy analysis. As of the data cutoff date (21-SEP-2022), 4 (21.1%) participants completed study intervention while 15 (78.9%) discontinued study intervention mostly due to progressive disease (36.8%) and AEs (21.1%).

Demographics and Other Characteristics of the Study Population

Most participants in the APaT population were male (78.9%) and most had an ECOG PS of 1 (89.5%), The median age was 70 years (range: 54 to 78 years).

Efficacy Results

The efficacy analyses were conducted in the APaT population. The following results were observed at FA (data cutoff: 21-SEP-2022) with a median follow-up duration of 20.9 months (range: 4.4 to 33.3 months):

- Pembrolizumab in combination with cisplatin/pemetrexed provided an ORR of 73.7% (95% CI: 48.8, 90.9) and a DCR of 94.7% (95% CI: 74.0, 99.9) as assessed by investigator using mRECIST.
- Responses were durable as 10 (77.9%) participants with confirmed objective responses (CR or PR) had ongoing responses ≥6 months and 5 (43.3%) participants had a DOR ≥18 months. Median DOR was 16.8 months (range: 3.0 to 26.3+ months).

KEYNOTE-483 Phase 2 (see also section 2.4.1)

Participant Disposition

A total of 60 participants (21 in Arm A, 19 in Arm B, and 20 in Arm C) were included in the Phase 2 IA.

A total of 80 participants, with all 60 participants in the IA and all participants included in the pembro mono arm (20 additional participants enrolled after the data cutoff but before the IA) were included and followed per protocol at the Phase 2 FA (data cutoff: 31-JAN-2022).

Demographics and Other Characteristics of the Study Population

Participant demographics were generally balanced between the intervention groups

Efficacy Results

Efficacy analysis at the Phase 2 FA (data cutoff: 31-JAN-2022) was performed on the 60 participants included in the IA.

The following results were observed at FA for the Phase 2 portion of the study:

- The response rates for the pembro combo and chemo groups were numerically higher compared with the pembro mono group.
- Pembro combo and pembro mono provided a numerical improvement in OS compared with chemo.

Table 32. Summary of efficacy results (phase 2 population)

	Arm A (cisplatin/pemetrexed) N=21	Arm B (pembrolizumab + cisplatin/pemetrexed) N=19	Arm C (pembrolizumab monotherapy) N=20
Median PFS, months (95% CI)	6.7 (2.7, 8.4)	6.8 (3.9, 15)	5.3 (2.8, 11.8)
Median OS, months (95% CI)	8.9 (5.3, 12.8)	19.8 (8.4, 41.4)	17.5 (7.4, 33.7)
Response Rate by mRECIST (95% CI)	19% (5%, 42%)	47% (24%, 71%)	13% (4%, 27%)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The current extension of indication is based on the pivotal data derived from study **KEYNOTE-483**. This is a multicenter, open-label, Phase 2/3 randomized study to evaluate the efficacy and safety of pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

The **study population** of KEYNOTE-483 only comprised adult subjects with a median age of 70 years, ranging from 28 to 87 years. Subjects were required to have histologically confirmed MPM. In the study protocol, there was no specification on the diagnostic work-up; it is acknowledged that current guidelines identify in thoracoscopy with confirmatory biopsy the preferable methodology. The approach of the MAH can be considered acceptable assuming a confirmation of diagnosis was obtained. Only subjects with unresectable advanced and/or metastatic disease, unresectable by standard therapies were allowed. Patients eligible to receive either cisplatin- or carboplatin-containing chemotherapy were included, although only an ECOG PS score 0-1 was allowed. The inclusion/exclusion criteria seem overall appropriate for the recruitment of a study population that is representative of unresectable disease in adults. The sought wording of the indication indicates a target population defined by "u*nresectable advanced or metastatic*" disease. "Metastatic" can be considered already included in the "unresectable" definition, and was therefore removed from the wording of indication in alignment with Opdivo/Yervoy and Alimta EU indications.

The planned enrolment total in both Phase 2 and Phase 3 portions of the study was 520 participants. A total of 21 and 19 participants were randomized to chemo (Arm A) and pembro combo (Arm B) groups, respectively, in the Phase 2 before the IA. A total 40 participants were randomized to pembro mono (Arm C) in the Phase 2 portion of the study and were included in the pembro mono population. The Phase 2 IA, based on 16-week disease control rate, was performed in November 2017 and Arm C was discontinued as recommended by CCTG Data and Safety Monitoring Committee due to lower disease control rate compared with Arms A and B. The study continued as a 2-arm trial comparing the pembro combo (Arm B) and chemo (Arm A). The primary endpoint of PFS for the original Phase 2 study became the secondary endpoint of the Phase 3 study and OS was moved to primary endpoint. An additional interim efficacy analysis was conducted on OS, PFS, and ORR during the Phase 3 portion (Phase 3 IA), approximately 11 months after the last participant was randomized (08-NOV-2021, data cutoff: 30-JUL-2021). This IA was the formal testing point for ORR. As of the LPLV, 440 participants were randomized and included in the Phase 3 ITT population for efficacy analysis (222 in the pembro combo group, 218 in the chemo group).

While the Phase 2 portion of study KEYNOTE-483 provided information on the contribution of the tested individual components, i.e. pembrolizumab and pemetrexed/platinum chemotherapy, inference of treatment was derived from the Phase 3 **ITT population,** comprising all randomized participants in the pembro combo and chemo groups from Phase 3 and Phase 2, excluding the 40 participants from Phase 2 that were part of the Phase 2 IA. Important protocol deviations were reported for 24 participants in the Phase 3 ITT population (14 in the pembro combo and 10 in the chemo group) and protocol deviations associated with the pandemic were reported for 102 participants (53 in the pembro combo group and 49 in the chemo group). No participant's data were excluded from analysis due to a protocol deviation, since none of these were considered to be clinically important (ie, did not compromise study analyses pertaining primary efficacy or safety endpoints, or participant's safety).

OS was selected as **primary endpoint**. The analysis of a hard endpoint mitigates the potential bias deriving from the open-label nature of the pivotal study. As secondary endpoints, PFS based on BICR

per mRECIST, confirmed ORR based on BICR per mRECIST, duration of response and QoL indicators were also evaluated.

The **comparator** arm included pemetrexed/platinum chemotherapy. The adopted chemotherapy regimen represents a valid option of treatment in this clinical setting, although the newly licensed immunotherapy based on the nivolumab+ipilimumab combination showed superiority in OS over chemotherapy in patients with an ECOG PS score 0-1, particularly in non-epithelioid MPM. However, KEYNOTE-483 started recruitment in 2016, when the combination nivo/ipi was not approved. Therefore, the comparator is acceptable.

The **sample size** calculation is comprehensible and reproducible. Of the six amendments to the protocol, amendment 2 (11-APR-2018) and amendment 4 (14-APR-2020) affected the sample size and power calculation. The initial sample size, planned for phase II portion of the study was 126 patients (42 per arm). At time of phase II IA, 61 patients were enrolled (21 in Arm A, 19 in Arm B and 21 in Arm C). Then, the sample size calculation for phase III portion of the study was amended twice and increased from 390 patients (Amendment 2) to 440 patients (Amendment 4). As of the FA data cutoff date (16-SEP-2022), 440 patients were randomized in phase III portion of the study (218 in Arm A and 222 in Arm B). The median follow-up duration, defined as the time from randomization to the date of death or the DCO if the participants was still alive, at DCO in the ITT population 17.0 months (range 0.8 to 60.3 months), 17.4 months in the Pembro Combo arm and 16.8 months in the Control arm.

The **randomization** procedures are comprehensible and well described in the study protocol. This study was initially designed as Phase 2 study in which participants were randomized in a 1:1:1 ratio to Arm A (chemo), Arm B (pembro combo), or Arm C (pembro mono). After review of Phase 2 IA results, Arm C was discontinued as recommended by CCTG Data and Safety Monitoring Committee due to lower disease control rate compared with Arms A and B. The study was then adjusted to be a Phase 3 study in which participants were randomized in a 1:1 ratio to Arm A (chemo) or Arm B (pembro combo). Only histological subtype was selected as stratification factor, but participating center was used in the minimization randomization algorithm. In addition to histology, sex is a known prognostic factor in MPM, but it has not been included in the randomisation strategy.

Statistical methods were well reported in the protocol section and in the supplemental SAP (sSAP) dated 05-NOV-2021, which represents its latest version. Overall, statistical methods are considered appropriate: the overall type I error over the primary endpoints (OS) and the key secondary endpoint (PFS and ORR) is strongly controlled at 5% (two-sided), with initially 5% allocated to OS; by using the graphical approach of Mauer and Bretz if OS hypothesis was rejected, the corresponding alpha was reallocated to PFS and ORR; if the PFS hypothesis was rejected, the corresponding alpha was reallocated to ORR; if the ORR hypothesis was rejected, the corresponding alpha was reallocated to PFS.

There were six protocol amendments over the study course, of these Amendment 2 (11-APR-2018) brought the most significant changes, since the study design changed from Phase 2 to Phase 3 trial with OS as primary objective, to support registrational intent. PFS, which was primary objective on Phase 2 became secondary objective on Phase 3 part. Statistical analysis including sample size, power, required number of events, accrual period, OS interim analyses were changed and/or added accordingly. However, with protocol amendment 4 a sample size increase from 390 to 440 and conservative adjustment of OS HR assumptions from 0.65 to 0.70 were introduced in study KEYNOTE-483. The MAH clarified the rationale behind these study modifications as being driven by external data from Keynote-604, a negative trial in the ES-SCLC disease. The impact of such data on the MPM indication is not obvious. However, a sensitivity analysis was conducted and limited to the first 390 patients recruited in the study, which showed consistency with the primary analysis results of KEYONTE-483.

Efficacy data and additional analyses

The current application is based on the final analysis (FA) of study KEYNOTE-483 (DCO: 16-SEP-2022). A total of 440 subjects were allocated between the two treatment arms (Pembro Combo N=222; Control N=218) and constituted the ITT population of the phase 3 study.

At the time of FA, 72.5% of patients in the control arm completed treatment compared to 10.4% in the pembro combo arm. Discontinuation from treatment was more frequent in the experimental than control group (89.6% vs 27.5%), mainly due to progressive disease (61.7% vs 10.9% in the two arms, respectively). This is likely to be associated to the longer treatment course and patient treatment exposure in the experimental than control arm. As expected, also the frequency of discontinuation due to adverse events was higher in the pembro combo than control arm (17.6% vs 8.1%). Discontinuation from trial occurred at higher rate in the control group than the pembro combo arm (84.9% vs 75.7%), with slightly more deaths being reported in the control than pembro combo arm (80.3% vs 75.2%).

Baseline characteristics were overall balanced between groups with the exception of a higher prevalence of patients aged <65 years in the control group (28% vs 18.9%) while the category of 65-74 years of age was more prevalent in the pembro combo arm (52.3% vs 43.6%). The study population mainly included male subjects (75.7%) aged 70 years in median, with those aged ≥75 year-old equally distributed in the two arms (27.9% vs 27.1%). Epithelioid cancer was the prevailing histology (78.4%), and disease was mainly related to asbestos exposure (57.7%). PD-L1 expression was well represented including both CPS≥1 and CPS<1 tumours (59.8% and 30.2% of the ITT, respectively). Platinum use (cisplatin and carboplatin) was almost equally distributed in the ITT (44.1% and 40.9%) and between groups. Also switching from cisplatin to carboplatin was comparable in the pembro combo and control arm (14.4% and 12.4%).

With a median follow-up of 17 months (range: 0.8 to 60.3), the ITT analysis demonstrated a statistically significant superiority of pembro combo compared to control in the **primary endpoint** OS (HR=0.79; 95% CI:0.64,0.98; p=0.0162). However, with a separation of the K-M curves at 18 months and only 1 month gain in median overall survival, the clinical relevance of the treatment benefit in the ITT population appears limited in absolute terms (the median OS was 17.3 months (95% CI: 14.4, 21.3) for the pembro combo group and 16.1 months (95% CI: 13.1, 18.2) for the chemo group).

Among **secondary endpoints**, PFS met statistical significance (HR=0.80; 95% CI:0.65,0.99; p=0.0194), as well as ORR as assessed by BICR that showed improvement in the rate of response for pembro combo (52.3%; 95% CI: 45.5, 59.0) compared to control (28.9%; 95% CI: 23.0, 35.4) (2-sided p-value <0.00001), but a similar duration of response between arms was observed (DoR of 6.9 months, 95% CI: 5.8, 8.3) compared to control (6.8 months; 95% CI: 5.5, 8.5).

For the **exploratory analysis** of response by biomarker, efficacy by PD-L1 level showed consistency of effect by CPS score (≥ or < 1) for both primary (OS) and secondary (PFS, ORR) endpoints. With regard to **PRO**, there were no changes over time for any of the domain scores, inclusive of general quality of life, functioning, and symptom scores in either treatment arm.

Sensitivity analyses planned can be considered adequate and consistent with results from primary analyses, even though analyses of PFS based on censoring rules 1 and 2 did not show statistical significance for both assessment by BICR and by investigator per mRECIST.

The **subgroup analysis** favoured the pembro combo in all the main pre-specified subgroups. Although pembrolizumab exhibited antitumoral activity regardless of histology, as evidenced by the increment in ORR seen in both epithelioid and non-epithelioid subgroups, a lower relative benefit of pembro combo was observed in the epithelioid **histology** group (HR=0.89; 95% CI:0.70,1.13) where the K-M curves

for OS were generally overlapping. In non-epithelioid tumours, the beneficial effect of pembro combo was more evident (HR=0.57, 95% CI 0.36, 0.89) with a net separation of K-M survival curves from the beginning throughout the whole duration of follow-up. This pattern of response reproduces what already observed in epithelioid and non-epithelioid MPM cancer, as previously described for Study CA209743 [EMA/CHMP/260350/2021, EPAR Opdivo/Yervoy WS1881] that was pivotal to the nivolumab+ipilimumab license as first-line treatment of MPM cancer, and as recently also reproduced in the BEAT-meso trial testing standard chemotherapy with or without atezolizumab in the same clinical setting [2024 ASCO Annual Meeting II[20]]. Non-epithelioid tumours generally present with a worse prognosis and response to chemotherapy; and indeed, both treatment arms in study KEYNOTE-483 showed a reduced efficacy in OS than in the epithelioid histology group. Such known difference in response to chemotherapy and prognosis was indeed taken into consideration at the planning stage, with inclusion of histology among stratification factors. However, the advantage of pembro combo emerged clearly in this non-epithelioid group unlike the results achieved in the epithelioid subtype. Although acknowledging the limits of subgroup analysis, histology was the stratification factor of this study, and as described above different results by histology in MPM is supported by external evidence and biological plausibility considerations, thus making the advantage of pembrolizumab in the epithelioid histology highly questionable. Of note this is proposed as an add-on treatment, in contrast to the nivolumab + ipilimumab "chemo-free" indication. Baseline characteristics were generally balanced between the 2 treatment arms within each histological subgroup, and also the next line therapy patterns do not explain the difference in treatment effect size across histologies.

In keeping with this, efficacy by **age** demonstrated a reduced response to treatment in the category of patients aged < 65 years. The assessment of baseline characteristics revealed an imbalance in histology with a higher prevalence of epithelioid tumours in the youngest, which might account for the attenuated effect of the pembro combo relatively to control observed in this age category.

Supportive evidence

Data from the Phase 2 portion of study KEYNOTE-483 and the Phase 1 study KEYNOTE-A17 are presented as supportive evidence of treatment benefit for pembro combo in the intended population. The uncontrolled nature and the primary endpoint (ORR) of KEYNOTE-A17 appears adequate for an early-phase trial but provides very limited value in the demonstration of efficacy of pembro combo in the pursued indication. Indeed, evaluation of MPM based on imaging data is challenging given the lack of clearly demarcated margins of the lesions, so that ORR is not a very reliable endpoint in this setting. The Phase 2 portion of the pivotal KEYNOTE-483 is supposed to generate evidence of the contribution of the individual agents to treatment effect. It is noted that response rate of the pembrolizumab monotherapy was similar to the control arm, while the pembrolizumab combination with chemotherapy showed a more favourable activity. No differences in terms of PFS were observed across treatments. However, as mentioned above, the imaging-based evaluation of MPM lacks robustness, and the OS results on a limited study population is unreliable given the wide confidence intervals. In conclusion, the support coming from KEYNOTE-A17 and the Phase 2 portion of the pivotal KEYNOTE-483 is considered marginal.

Assessment of paediatric data on clinical efficacy

The MAH intended to include in the indication adults and adolescents aged 12 years and older on the basis of an extrapolation of effectiveness from the adult to the paediatric population. The finally approved indication by CHMP does not include adolescents as further described below. The proposed

[20] Popat S, Felip E, Dafni U, et al. BEAT-meso: A randomized phase III study of bevacizumab (B) and standard chemotherapy (C) with or without atezolizumab (A), as first-line treatment (TX) for advanced pleural mesothelioma (PM)—Results from the ETOP 13-18 trial. 2024 ASCO Annual Meeting II, LBA8002 Oral Abstract Section.

dosing regimen of pembrolizumab in adolescents with MPM, to be combined with chemotherapy, is 2 mg/kg Q3W (up to a maximum of 200 mg), which is the same dose approved for pembrolizumab in children with cHL and adolescent with melanoma, while the posology for pembrolizumab in adults is the flat dose already approved in adults for all other indications (200 mg Q3W and 400 mg Q6W). Of note, this would be the first authorization for pembrolizumab in combination with other drug agents in adolescents, as only pembrolizumab monotherapy is approved in the paediatric age so far.

In support of the claimed indication of pembrolizumab in combination with chemotherapy in subjects aged > 12 years, no paediatric data are available. The only existing data are from two adolescents with mesothelioma (but only one pleural) who were treated with pembro as monotherapy. Hence, an extrapolation approach is proposed to support the claimed indication in adolescents. The proposal is based on the MAH's conclusion that the requirements on the use of extrapolation in the development of medicines for paediatrics, as stated in the "Reflection paper on the use of extrapolation in the development of medicines for paediatrics" (EMA/189724/2018), are fulfilled. Specifically, the MAH claims 1) similarity of disease, 2) similarity in pharmacology and 3) similarity in exposure-response for efficacy.

The MAH's conclusion is however only partially shared. One of the main critical aspects of this proposal pertains to the similarity of disease, that remains uncertain (see discussion below).

1) Similarity of mesothelioma disease in adult and paediatric populations

To justify the similarity of disease, the MAH presented the analysis from the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT) which retrospectively reviewed children, adolescents and young adults (<21 year) diagnosed with mesothelial tumours treated between 1987 and 2018[21]. Thirty-three patients were identified, 15 male and 18 female patients. One patient's exposure to asbestos was documented. Primary tumour was mainly in the peritoneum (23 patients). Histology was multicystic mesothelioma of the peritoneum (MCM) (six patients) or malignant mesothelioma (MM) (27 patients). Based on their analysis, it should be noted that the Authors concluded that "*Paediatric seems different from adult counterparts with less male patients, most cases primarily peritoneal and less aggressive behaviour, particularly in peritoneal primary. […] the role of asbestos in the development of paediatric mesothelioma seems unlikely. Interestingly, some reports described the development of mesothelioma in children who previously received radiotherapy for other malignancies, as well as the appearance of a mesothelioma as a second cancer after a Wilms' tumour, specifically, but the majority of cases are probably idiopathic. […]".* Therefore, the similarity in disease appears controversial. This aspect is even more compelling given that efficacy data derived from KEYNOTE-483 mainly refer to asbestos-related disease. Furthermore, in addition to the likely difference in asbestos exposure as risk factor, differences in molecular alterations between adults and pediatrics mesothelioma have been reported in literature, such as inherited BAP1 mutations that could increase risk of mesothelioma in adults but are rare in pediatric patients, in whom different genetic alterations such as ALK gene fusions involving various gene partners including *STRN*, *TPM1*, and *EML4* have been described[22]. This might suggest that mesothelioma in adult and children could be biologically different disease.

In a simplistic approach, one could consider exposure to asbestos a relevant parameter in disease categorisation to distinguish between paediatric and adult cancer. In this context, the subgroup analysis by asbestos exposure showing consistency of effect between groups could be seen as supportive. Whether this aspect can sufficiently substantiate the extrapolation exercise is not obvious. Moreover, the observation of a partial response observed with pembrolizumab monotherapy in the 2

[21] Orbach D, André N, Brecht IB, López Almaraz R, et al. Mesothelioma in children and adolescents: the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) contribution. Eur J Cancer. 2020 Nov;140:63-70.
[22] Argani P, Lian DWQ, Agaimy A, et al.: Pediatric Mesothelioma With ALK Fusions: A Molecular and Pathologic Study of 5 Cases. Am J Surg Pathol 45 (5): 653-661, 2021

patients with mesothelioma recruited in KEYNOTE-051 raises further concerns on the acceptability of an expectedly more toxic combined regimen in the absence of supportive clinical data characterising the safety profile of the pembro combo in adolescents. The uncertainties on safety together with the dubious therapeutic efficacy in the broad population, considering the marginal clinical benefit achieved in the ITT adult population of KEYNOTE-483, makes the B/R balance in adolescents uncertain. The MAH therefore accepted the CHMP recommendation to restrict the indication to adults only.

2) similarity in pharmacology

With regard to similarity in PK data, only 2 adolescents with mesothelioma (only one pleural) were enrolled in study KEYNOTE-051 and received pembrolizumab 2 mg/kg IV q3w as monotherapy (none of them received pembrolizumab in combination with chemotherapy). Considering the paucity of data, no conclusion can be drawn on PK and immunogenicity in adolescents based on data from KEYNOTE-051 and thus similarity in PK data between adults and adolescents is hampered.

The proposed dose of pembrolizumab to be used in adolescents with MPM (2 mg/kg up to a maximum of 200 mg Q3W) is the same already approved in the EU for treatment of pediatric patients aged 3 years and older with relapsed or refractory cHL and for the treatment adolescents aged 12 years and older with melanoma.

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 (EPAR EMEA/H/C/3820/II/090). Data from basket study KEYNOTE-051 showed that exposure parameters following the weight-based regimen of 2 mg/kg Q3W are overall largely similar between the paediatric age groups and similar between paediatrics and adults.

The MAH also claims that observed pembrolizumab exposures from the 2 participants with mesothelioma enrolled in KEYNOTE-051 are within the range observed in other pediatric participants, however, information about these 2 adolescent participants enrolled in KEYNOTE-051 are lacking in terms of observed exposures but also in terms of baseline data (e.g. age, sex, tumor histology, detailed prior medical history including systemic and local treatments for previous tumors, in particular RT that can be risk factor for developing mesothelioma).

The paediatric dosing regimen of 2 mg/kg Q3W is also supported by the low incidence of positive immunogenicity status after pembrolizumab treatment in KEYNOTE-051 paediatric participants (1.6%), which is comparable with that in adults (2.1%), and had no impact on pembrolizumab exposure. Moreover, it is agreed that DDI between pembrolizumab and chemotherapy is unlikely, as no interaction is envisaged between small molecules and MoAb, as already demonstrated in previous indications in adults of pembrolizumab in combination with other agents. Although there is no expected pharmacological interaction between the two chemotherapeutics and pembrolizumab, however the combination platinum-pemetrexed is not authorized in children, thus differences in metabolism of pemetrexed and especially cisplatin in children, potentially impacting the safety profile and its similarity with that of adults, cannot be excluded.

Overall, the conclusion on similar pharmacology between adults and adolescents relies only on data from KEYNOTE-051 (EPAR EMEA/H/C/3820/II/090) in which observed plasma concentrations in paediatric patients with cHL were consistent with predicted plasma concentrations derived from the reference popPK model, further supporting a flat exposure-response relationships across multiple tumour types. No major concerns are raised about this conclusion.

3) similarity in exposure-response for efficacy

Considering that no E-R is available in adolescents with MPM, and that only two adolescents have been treated with pembrolizumab as monotherapy, an indirect conclusion on E-R is drawn by the MAH based on data from cHL patients from KEYNOTE-051 (which were submitted within EMEA/H/C/3829/II/090 procedure). The model-based PK bridging analysis presented at that time 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 would also expect to be similar across all indications in paediatrics (similarly to adults). Hence, the MAH's conclusion could be agreeable. However, the uncertainty on disease similarity impacts also on extrapolation of E-R data.

In conclusion, the currently proposed extrapolation approach lacks appropriate substantiation in some critical requirements. Similarity of disease is not considered sufficiently substantiated and, further, safety data for pembrolizumab in combination with chemotherapy are lacking in this age group. As a result, the final indication was restricted to adults only.

2.4.3. Conclusions on the clinical efficacy

The ITT analysis demonstrated a statistically significant superiority of pembro combo compared to control in OS (HR=0.79; 95% CI:0.64,0.98; p=0.0162). However, with a separation of the K-M curves at 18 months and only 1 month gain in median overall survival, the clinical relevance of the benefit of the addition of pembrolizumab to chemotherapy in the ITT population appears very marginal. Of major concern is the subgroup analysis showing a lower benefit of pembro combo in the epithelioid histology group (HR=0.89; 95% CI:0.70,1.13) where the K-M curves for OS were generally overlapping. Although acknowledging the limited value of subgroup analysis, it must be considered that similar findings by histology in MPM is supported by external consistency in other studies with immunomodulatory treatments and biological plausibility considerations. Given the unfavourable safety profile of an add-on therapy, the indication was restricted to the non-epithelioid subgroup.

For the claimed indication of Keytruda in adolescents, the extrapolation concept as presented by the MAH unsatisfactorily addresses the similarity of disease between adults and adolescents. Although PK extrapolation from adults to adolescents could be considered sufficiently addressed based on KN-051 data, the uncertainty on disease similarity impacts also on extrapolation of E-R data. The uncertainties on safety together with the dubious therapeutic efficacy of pembrolizumab in combination with chemotherapy in the broad population of KEYNOTE-483, makes the B/R balance in adolescents uncertain. The indication was therefore restricted by the MAH to adults only.

2.5. Clinical safety

Introduction

An overview of the safety profile of pembrolizumab in combination with pemetrexed and platinum chemotherapy in the context of its intended use for the first-line treatment of patients with unresectable advanced and/or metastatic MPM are presented for the comparison of the pembro combo safety profile with the chemo safety profile for participants in KEYNOTE-483 conducted within the APaT population (i.e. all randomized participants who received at least 1 dose of study intervention, according to the treatment they actually received). In addition, pooled safety data from studies of pembrolizumab in combination with chemotherapy and as monotherapy are included to enable a comparison of the safety profile (see table below).

Table 33. Safety Datasets

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-483 pembrolizumab + chemotherapy	n=241: Safety data from participants with unresectable advanced and/or metastatic MPM who received pembrolizumab in combination with chemotherapy in KEYNOTE-483	KN483 Pembro+Chemo	pembro combo group
KEYNOTE-483 chemotherapy	n=232: Safety data from participants with unresectable advanced and/or metastatic MPM who received chemotherapy in KEYNOTE-483	KN483 Chemo	chemo group
Pembrolizumab plus chemotherapy	n=3,123: Pooled safety data from participants treated with pembrolizumab plus platinum-based chemotherapy, including 791 participants with NSCLC from KN021, KN189, KN407; 267 participants with HNSCC from KN048; 370 participants with esophageal cancer from KN590; 1379 participants with TNBC from KN355 and KN522; and 307 participants with cervical cancer from KN826.	Pooled Safety Dataset for Pembrolizumab + Chemotherapy	Pooled Pembrolizumab Combination Dataset
Pembrolizumab monotherapy reference safety	n=7,631: Pooled safety data from participants treated with pembrolizumab monotherapy, including 2559 participants with advanced melanoma from KN001, KN002, KN006, KN054, and KN716; 2022 participants with NSCLC from KN001, KN010, KN024, and KN042; 909 participants with HNSCC from KN012, KN040, KN048, and KN055; 636 participants with bladder cancer from KN045 and KN052; 488 participants with RCC from KN564; 475 participants with MSI-H tumors from KN158 and KN164; 389 participants with HL from KN013, KN087, and KN204; 153 participants with MSI-H CRC from KN177.	Pembrolizumab monotherapy Reference Safety Dataset	RSD

CRC=colorectal cancer; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; KN=KEYNOTE; MPM=malignant pleural mesothelioma; MSI-H=microsatellite instability-high; N=number; NSCLC=non-small cell lung cancer; RCC=renal cell carcinoma; RSD=reference safety dataset; TNBC=triple-negative breast cancer.

The studies and database cutoff dates for each aggregate safety dataset are presented in [Appendix 2.7.4-meso1: 1, Appendix 2.7.4-meso1: 2].

Patient exposure

A total of 241 participants in the pembro combo group and 232 participants in the chemo group received at least 1 dose of study intervention in the KEYNOTE-483 Phase 2 and 3 portions of the study. As of the FA data cutoff date (16-SEP-2022), no participants were still receiving study treatment.

Table 34. Summary of Drug Exposure (APaT Population)

	KN483 Pembro + Chemo (N=241)	KN483 Chemo (N=232)	Pooled Safety Dataset for Pembro + Chemo (N=3123)	Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)
Duration On Therapy (days)				
Mean	278.8	95.6	310.1	239.1
Median	211.0	107.0	240.0	176.0
SD	212.32	38.30	245.53	210.22
Range	1.00 to 767.00	1.00 to 192.00	1.00 to 1,732.00	1.00 to 1,157.00
Number of Administrations				
Mean	13.2	5.1	13.7	12.3
Median	10.0	6.0	11.0	9.0
SD	9.53	1.61	10.64	10.12
Range	1.00 to 36.00	1.00 to 8.00	1.00 to 70.00	1.00 to 59.00

Duration of exposure is the time from the first dose date to the last dose date.

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Participants characteristics

Table 35. Participant Characteristics (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
Sex								
Male	181	(75.1)	183	(78.9)	1,042	(33.4)	4,889	(64.1)
Female	60	(24.9)	49	(21.1)	2,081	(66.6)	2,742	(35.9)
Age (Years)								
<65	49	(20.3)	63	(27.2)	2,176	(69.7)	4,524	(59.3)
>=65	192	(79.7)	169	(72.8)	947	(30.3)	3,107	(40.7)
Mean	69.1		68.4		56.6		59.9	
SD	8.4		9.1		12.5		13.4	
Median	70.0		70.0		58.0		62.0	
Range	33 to 86		28 to 87		20 to 94		15 to 94	
Race								
American Indian Or Alaska Native	0	(0.0)	1	(0.4)	55	(1.8)	59	(0.8)
Asian	1	(0.4)	1	(0.4)	686	(22.0)	826	(10.8)
Black Or African American	0	(0.0)	0	(0.0)	108	(3.5)	146	(1.9)
Multiracial	0	(0.0)	0	(0.0)	64	(2.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	2	(0.1)	5	(0.1)
White	193	(80.1)	185	(79.7)	2,088	(66.9)	5,838	(76.5)
Missing	47	(19.5)	45	(19.4)	120	(3.8)	671	(8.8)
Ethnicity								
Hispanic Or Latino	4	(1.7)	6	(2.6)	428	(13.7)	604	(7.9)
Not Hispanic Or Latino	190	(78.8)	179	(77.2)	2,503	(80.1)	6,064	(79.5)
Not Reported	37	(15.4)	40	(17.2)	105	(3.4)	808	(10.6)
Unknown	10	(4.1)	7	(3.0)	66	(2.1)	145	(1.9)
Missing	0	(0.0)	0	(0.0)	21	(0.7)	10	(0.1)

Age Class (Years)								
<65	49	(20.3)	63	(27.2)	2,176	(69.7)	4,524	(59.3)
65-74	126	(52.3)	106	(45.7)	767	(24.6)	2,173	(28.5)
75-84	64	(26.6)	60	(25.9)	175	(5.6)	824	(10.8)
>=85	2	(0.8)	3	(1.3)	5	(0.2)	110	(1.4)
ECOG Performance Status								
[0] Normal Activity	109	(45.2)	107	(46.1)	1,768	(56.6)	4,016	(52.6)
[1] Symptoms, but ambulatory	132	(54.8)	125	(53.9)	1,349	(43.2)	3,440	(45.1)
Other/Missing	0	(0.0)	0	(0.0)	6	(0.2)	175	(2.3)
Geographic Region								
North America	81	(33.6)	82	(35.3)	648	(20.7)	2,669	(35.0)
Western Europe	160	(66.4)	150	(64.7)	1,063	(34.0)	2,856	(37.4)
Rest of the World	0	(0.0)	0	(0.0)	1,412	(45.2)	2,106	(27.6)

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Adverse events

Due to the design of the CCTG database, for discontinuations reported in KEYNOTE-483, only SAEs (regardless of causality) and drug-related AEs were collected (and not regardless of causality or seriousness as in the pooled datasets). Additionally, according to CCTG data entry guidelines, asymptomatic laboratory events (related or unrelated to study treatment) that were not considered clinically significant by the investigator were captured and summarized as laboratory abnormalities and not specific AEs.

Table 36. Adverse Event Summary (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	232	(96.3)	212	(91.4)	3,097	(99.2)	7,375	(96.6)
with no adverse event	9	(3.7)	20	(8.6)	26	(0.8)	256	(3.4)
with drug-related[a] adverse events	217	(90.0)	189	(81.5)	3,020	(96.7)	5,462	(71.6)
with toxicity grade 3-5 adverse events	106	(44.0)	70	(30.2)	2,481	(79.4)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	74	(30.7)	39	(16.8)	2,101	(67.3)	1,208	(15.8)
with serious adverse events	97	(40.2)	44	(19.0)	1,464	(46.9)	2,742	(35.9)
with serious drug-related adverse events	67	(27.8)	19	(8.2)	913	(29.2)	840	(11.0)
who died	17	(7.1)	5	(2.2)	165	(5.3)	346	(4.5)
who died due to a drug-related adverse event	7	(2.9)	2	(0.9)	49	(1.6)	42	(0.6)
discontinued any drug due to an adverse event	83	(34.4)	40	(17.2)	910	(29.1)	1,066	(14.0)
discontinued pembrolizumab	51	(21.2)	0	(0.0)	551	(17.6)	1,066	(14.0)
discontinued any chemotherapy	59	(24.5)	40	(17.2)	636	(20.4)	0	(0.0)
discontinued any drug due to a drug-related adverse event	74	(30.7)	37	(15.9)	754	(24.1)	639	(8.4)
discontinued pembrolizumab	43	(17.8)	0	(0.0)	407	(13.0)	639	(8.4)
discontinued any chemotherapy	52	(21.6)	37	(15.9)	528	(16.9)	0	(0.0)
discontinued any drug due to a serious adverse event	50	(20.7)	10	(4.3)	475	(15.2)	714	(9.4)
discontinued pembrolizumab	43	(17.8)	0	(0.0)	386	(12.4)	714	(9.4)
discontinued any chemotherapy	31	(12.9)	10	(4.3)	307	(9.8)	0	(0.0)

discontinued any drug due to a serious drug-related adverse event	41	(17.0)	7	(3.0)	344	(11.0)	347	(4.5)
discontinued pembrolizumab	35	(14.5)	0	(0.0)	263	(8.4)	347	(4.5)
discontinued any chemotherapy	24	(10.0)	7	(3.0)	213	(6.8)	0	(0.0)

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

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

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

NA=not applicable

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 37. Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN483 Pembro + Chemo	KN483 Chemo	Pooled Safety Dataset for Pembro + Chemo	Pembrolizumab Monotherapy Reference Safety Dataset
Number of subjects exposed	241	232	3123	7631
Total exposure[b] in person-months	2444.78	957.43	29997.14	66840.89
Total events (rate)				
adverse events	2758 (112.81)	1593 (166.38)	66857 (222.88)	76878 (115.02)
drug-related[c] adverse events	1532 (62.66)	1003 (104.76)	40340 (134.48)	24542 (36.72)
toxicity grade 3-5 adverse events	212 (8.67)	123 (12.85)	9671 (32.24)	7463 (11.17)
toxicity grade 3-5 drug-related adverse events	125 (5.11)	57 (5.95)	6954 (23.18)	1770 (2.65)
serious adverse events	196 (8.02)	69 (7.21)	2926 (9.75)	4801 (7.18)
serious drug-related adverse events	117 (4.79)	24 (2.51)	1480 (4.93)	1093 (1.64)
adverse events leading to death	18 (0.74)	5 (0.52)	171 (0.57)	353 (0.53)
drug-related adverse events leading to death	8 (0.33)	2 (0.21)	50 (0.17)	42 (0.06)
adverse events resulting in drug discontinuation	129 (5.28)	55 (5.74)	1115 (3.72)	1165 (1.74)
drug-related adverse events resulting in drug discontinuation	117 (4.79)	50 (5.22)	920 (3.07)	703 (1.05)
serious adverse events resulting in drug discontinuation	69 (2.82)	13 (1.36)	542 (1.81)	753 (1.13)
serious drug-related adverse events resulting in drug discontinuation	57 (2.33)	8 (0.84)	390 (1.30)	363 (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 time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.

[c] 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.

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

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Adverse Events

Table 38. Participants With Adverse Events by Decreasing Incidence (Incidence ⩾ 10% in One or More Treatment Groups) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	232	(96.3)	212	(91.4)	3,097	(99.2)	7,375	(96.6)
with no adverse events	9	(3.7)	20	(8.6)	26	(0.8)	256	(3.4)
Fatigue	148	(61.4)	141	(60.8)	1,200	(38.4)	2,368	(31.0)
Nausea	128	(53.1)	109	(47.0)	1,696	(54.3)	1,534	(20.1)
Constipation	77	(32.0)	51	(22.0)	1,110	(35.5)	1,179	(15.5)
Diarrhoea	74	(30.7)	34	(14.7)	1,079	(34.6)	1,678	(22.0)
Dyspnoea	69	(28.6)	51	(22.0)	431	(13.8)	1,130	(14.8)
Vomiting	63	(26.1)	37	(15.9)	887	(28.4)	945	(12.4)
Pyrexia	54	(22.4)	23	(9.9)	634	(20.3)	934	(12.2)
Stomatitis	54	(22.4)	42	(18.1)	453	(14.5)	201	(2.6)
Decreased appetite	52	(21.6)	48	(20.7)	855	(27.4)	1,312	(17.2)

Cough	42	(17.4)	27	(11.6)	658	(21.1)	1,392	(18.2)
Rash maculo-papular	42	(17.4)	20	(8.6)	160	(5.1)	295	(3.9)
Pruritus	40	(16.6)	11	(4.7)	469	(15.0)	1,435	(18.8)
Non-cardiac chest pain	34	(14.1)	22	(9.5)	39	(1.2)	84	(1.1)
Abdominal pain	32	(13.3)	11	(4.7)	325	(10.4)	671	(8.8)
Peripheral sensory neuropathy	32	(13.3)	21	(9.1)	393	(12.6)	83	(1.1)
Lacrimation increased	31	(12.9)	18	(7.8)	127	(4.1)	55	(0.7)
Back pain	28	(11.6)	14	(6.0)	369	(11.8)	847	(11.1)
Dysgeusia	28	(11.6)	32	(13.8)	329	(10.5)	150	(2.0)
Embolism	28	(11.6)	21	(9.1)	37	(1.2)	33	(0.4)
Insomnia	28	(11.6)	12	(5.2)	405	(13.0)	528	(6.9)
Oedema peripheral	28	(11.6)	16	(6.9)	358	(11.5)	630	(8.3)
Arthralgia	27	(11.2)	2	(0.9)	665	(21.3)	1,436	(18.8)
Dizziness	24	(10.0)	16	(6.9)	367	(11.8)	564	(7.4)
Headache	22	(9.1)	15	(6.5)	577	(18.5)	946	(12.4)
Hypothyroidism	22	(9.1)	4	(1.7)	439	(14.1)	937	(12.3)
Urinary tract infection	17	(7.1)	8	(3.4)	347	(11.1)	511	(6.7)
Upper respiratory tract infection	14	(5.8)	2	(0.9)	311	(10.0)	514	(6.7)
Alopecia	13	(5.4)	8	(3.4)	1,099	(35.2)	118	(1.5)
Myalgia	9	(3.7)	3	(1.3)	363	(11.6)	575	(7.5)
Anaemia	7	(2.9)	0	(0.0)	1,705	(54.6)	982	(12.9)
Platelet count decreased	6	(2.5)	1	(0.4)	377	(12.1)	95	(1.2)
Alanine aminotransferase increased	4	(1.7)	0	(0.0)	566	(18.1)	572	(7.5)
Aspartate aminotransferase increased	4	(1.7)	0	(0.0)	492	(15.8)	538	(7.1)
Rash	3	(1.2)	2	(0.9)	644	(20.6)	1,175	(15.4)
Neutrophil count decreased	2	(0.8)	0	(0.0)	623	(19.9)	53	(0.7)
Asthenia	0	(0.0)	0	(0.0)	662	(21.2)	880	(11.5)
Hypokalaemia	0	(0.0)	1	(0.4)	334	(10.7)	324	(4.2)
Leukopenia	0	(0.0)	0	(0.0)	367	(11.8)	52	(0.7)
Mucosal inflammation	0	(0.0)	0	(0.0)	366	(11.7)	111	(1.5)
Neuropathy peripheral	0	(0.0)	0	(0.0)	467	(15.0)	146	(1.9)
Neutropenia	0	(0.0)	0	(0.0)	1,111	(35.6)	82	(1.1)
Thrombocytopenia	0	(0.0)	0	(0.0)	572	(18.3)	117	(1.5)
Weight decreased	0	(0.0)	0	(0.0)	367	(11.8)	628	(8.2)
White blood cell count decreased	0	(0.0)	0	(0.0)	466	(14.9)	70	(0.9)

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

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

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

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

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 39. participants with AEs by toxicity grade

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	232	(96.3)	212	(91.4)	3,097	(99.2)	7,375	(96.6)
Grade 1	14	(5.8)	29	(12.5)	57	(1.8)	1,028	(13.5)
Grade 2	112	(46.5)	113	(48.7)	559	(17.9)	2,833	(37.1)
Grade 3	76	(31.5)	62	(26.7)	1,589	(50.9)	2,731	(35.8)
Grade 4	13	(5.4)	3	(1.3)	727	(23.3)	438	(5.7)
Grade 5	17	(7.1)	5	(2.2)	165	(5.3)	345	(4.5)
with no adverse events	9	(3.7)	20	(8.6)	26	(0.8)	256	(3.4)

Drug-related Adverse Events

Table 40. Participants With Drug-Related Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN483 Pembro + Chemo	KN483 Chemo	Pooled Safety Dataset for Pembro + Chemo	Pembrolizumab Monotherapy Reference Safety

							Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	217	(90.0)	189	(81.5)	3,020	(96.7)	5,462	(71.6)
with no adverse events	24	(10.0)	43	(18.5)	103	(3.3)	2,169	(28.4)
Fatigue	120	(49.8)	121	(52.2)	1,040	(33.3)	1,476	(19.3)
Nausea	119	(49.4)	104	(44.8)	1,513	(48.4)	675	(8.8)
Diarrhoea	56	(23.2)	22	(9.5)	748	(24.0)	904	(11.8)
Vomiting	50	(20.7)	32	(13.8)	695	(22.3)	248	(3.2)
Stomatitis	49	(20.3)	42	(18.1)	409	(13.1)	103	(1.3)
Decreased appetite	40	(16.6)	42	(18.1)	665	(21.3)	525	(6.9)
Constipation	37	(15.4)	29	(12.5)	509	(16.3)	184	(2.4)
Pruritus	35	(14.5)	8	(3.4)	347	(11.1)	1,143	(15.0)
Rash maculo-papular	34	(14.1)	17	(7.3)	140	(4.5)	237	(3.1)
Peripheral sensory neuropathy	29	(12.0)	21	(9.1)	371	(11.9)	35	(0.5)
Lacrimation increased	28	(11.6)	17	(7.3)	94	(3.0)	22	(0.3)
Dysgeusia	27	(11.2)	31	(13.4)	295	(9.4)	79	(1.0)
Hypothyroidism	18	(7.5)	3	(1.3)	382	(12.2)	810	(10.6)
Paraesthesia	18	(7.5)	8	(3.4)	141	(4.5)	63	(0.8)
Arthralgia	17	(7.1)	0	(0.0)	315	(10.1)	661	(8.7)
Pyrexia	17	(7.1)	9	(3.9)	291	(9.3)	314	(4.1)
Tinnitus	17	(7.1)	16	(6.9)	74	(2.4)	7	(0.1)
Dyspnoea	16	(6.6)	6	(2.6)	116	(3.7)	232	(3.0)
Oedema peripheral	15	(6.2)	10	(4.3)	134	(4.3)	126	(1.7)
Dyspepsia	14	(5.8)	8	(3.4)	137	(4.4)	44	(0.6)
Alopecia	13	(5.4)	7	(3.0)	1,072	(34.3)	57	(0.7)
Dry skin	12	(5.0)	3	(1.3)	120	(3.8)	218	(2.9)
Febrile neutropenia	12	(5.0)	3	(1.3)	250	(8.0)	0	(0.0)
Conjunctivitis	11	(4.6)	16	(6.9)	50	(1.6)	31	(0.4)
Hypoacusis	10	(4.1)	13	(5.6)	16	(0.5)	3	(0.0)
Epistaxis	7	(2.9)	4	(1.7)	155	(5.0)	6	(0.1)
Anaemia	6	(2.5)	0	(0.0)	1,466	(46.9)	234	(3.1)
Headache	6	(2.5)	3	(1.3)	191	(6.1)	250	(3.3)
Platelet count decreased	5	(2.1)	0	(0.0)	363	(11.6)	43	(0.6)
Alanine aminotransferase increased	4	(1.7)	0	(0.0)	454	(14.5)	336	(4.4)
Aspartate aminotransferase increased	4	(1.7)	0	(0.0)	386	(12.4)	312	(4.1)
Myalgia	4	(1.7)	2	(0.9)	271	(8.7)	312	(4.1)
Neutrophil count decreased	2	(0.8)	0	(0.0)	605	(19.4)	34	(0.4)
Rash	2	(0.8)	1	(0.4)	496	(15.9)	884	(11.6)
Blood creatinine increased	1	(0.4)	0	(0.0)	211	(6.8)	105	(1.4)
Asthenia	0	(0.0)	0	(0.0)	522	(16.7)	491	(6.4)
Leukopenia	0	(0.0)	0	(0.0)	345	(11.0)	32	(0.4)
Mucosal inflammation	0	(0.0)	0	(0.0)	333	(10.7)	57	(0.7)
Neuropathy peripheral	0	(0.0)	0	(0.0)	410	(13.1)	54	(0.7)
Neutropenia	0	(0.0)	0	(0.0)	1,076	(34.5)	49	(0.6)
Thrombocytopenia	0	(0.0)	0	(0.0)	536	(17.2)	56	(0.7)
Weight decreased	0	(0.0)	0	(0.0)	189	(6.1)	148	(1.9)
White blood cell count decreased	0	(0.0)	0	(0.0)	444	(14.2)	34	(0.4)

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

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

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

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 41. Participants With Drug-Related Adverse Events by Maximum Toxicity Grade

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	217	(90.0)	189	(81.5)	3,020	(96.7)	5,462	(71.6)
Grade 1	28	(11.6)	51	(22.0)	145	(4.6)	1,947	(25.5)
Grade 2	115	(47.7)	99	(42.7)	774	(24.8)	2,307	(30.2)
Grade 3	57	(23.7)	35	(15.1)	1,424	(45.6)	1,027	(13.5)
Grade 4	10	(4.1)	2	(0.9)	628	(20.1)	139	(1.8)
Grade 5	7	(2.9)	2	(0.9)	49	(1.6)	42	(0.6)
with no adverse events	24	(10.0)	43	(18.5)	103	(3.3)	2,169	(28.4)

Grade 3-5 Adverse Events

Table 42. Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	106	(44.0)	70	(30.2)	2,481	(79.4)	3,514	(46.0)
with no adverse events	135	(56.0)	162	(69.8)	642	(20.6)	4,117	(54.0)
Fatigue	18	(7.5)	18	(7.8)	159	(5.1)	166	(2.2)
Febrile neutropenia	14	(5.8)	3	(1.3)	259	(8.3)	11	(0.1)
Anaemia	7	(2.9)	0	(0.0)	621	(19.9)	275	(3.6)
Dyspnoea	6	(2.5)	12	(5.2)	50	(1.6)	145	(1.9)
Neutrophil count decreased	2	(0.8)	0	(0.0)	443	(14.2)	10	(0.1)
Neutropenia	0	(0.0)	0	(0.0)	727	(23.3)	21	(0.3)
Thrombocytopenia	0	(0.0)	0	(0.0)	202	(6.5)	23	(0.3)
White blood cell count decreased	0	(0.0)	0	(0.0)	218	(7.0)	5	(0.1)

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

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

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

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

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Grade 3 to 5 Drug-related Adverse Events

Table 43. Participants With Grade 3-5 Drug-related Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	74	(30.7)	39	(16.8)	2,101	(67.3)	1,208	(15.8)
with no adverse events	167	(69.3)	193	(83.2)	1,022	(32.7)	6,423	(84.2)
Fatigue	17	(7.1)	14	(6.0)	133	(4.3)	75	(1.0)
Febrile neutropenia	12	(5.0)	3	(1.3)	245	(7.8)	0	(0.0)
Anaemia	6	(2.5)	0	(0.0)	525	(16.8)	33	(0.4)
Neutrophil count decreased	2	(0.8)	0	(0.0)	428	(13.7)	6	(0.1)

Neutropenia	0	(0.0)	0	(0.0)	710	(22.7)	13	(0.2)
Thrombocytopenia	0	(0.0)	0	(0.0)	186	(6.0)	11	(0.1)
White blood cell count decreased	0	(0.0)	0	(0.0)	211	(6.8)	2	(0.0)

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

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

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

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Adverse reactions in section 4.8 of the SmPC

Section 4.8 of the SmPC is updated to include the KEYNOTE-483 population into the current 'pembrolizumab in combination with chemotherapy' pooled dataset. In addition to KEYNOTE-483, this dataset includes all pembrolizumab plus chemotherapy combination studies with indications currently approved in the EU as well as studies KEYNOTE-A18 and KEYNOTE-868, currently under assessment in the EU. As a part of this update, adverse events were evaluated that included assessment of any potential clinically meaningful imbalances between treatment groups and assessment of any potential biologic plausibility for an association with exposure to pembrolizumab in combination with chemotherapy. The appropriate frequency categories for the events were determined according to MedDRA v27.0 definitions. Of note, the frequencies included are based on all reported Adverse Drug Reactions, regardless of the investigator assessment of causality.

The table below encompasses the adverse reactions included in Table 2 of the SmPC with related frequency categories and incidence percentages from the latest pooled dataset from combination therapy (pembrolizumab plus chemotherapy) studies as follows:

• Non-small cell lung cancer: KEYNOTE-021 (Cohorts A, C, and G), KEYNOTE-189, KEYNOTE-407 and KEYNOTE-671

• Head and neck squamous cell carcinoma: KEYNOTE-048

• Gastric, oesophageal or gastroesophageal cancer: KEYNOTE-590, KEYNOTE-811 and KEYNOTE-859

• Triple negative breast cancer: KEYNOTE-355 and KEYNOTE-522

• Cervical cancer: KEYNOTE-826 and KEYNOTE-A18

• Biliary tract cancer: KEYNOTE-966

• Endometrial cancer: KEYNOTE-868

• Malignant pleural mesothelioma: KEYNOTE-483

Table 44. Adverse Reactions in Patients Treated With Pembrolizumab in Combination With Chemotherapy (APaT Population)

		Combination Therapy (N=6334)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.7% (424)	233
Blood and lymphatic system disorders			
Very common	Anaemia	51.4% (3255)	1136
Very common	Neutropenia	23.1% (1462)	885
Very common	Thrombocytopenia	12.7% (804)	241
Common	Febrile Neutropenia	5.1% (324)	313
Common	Leukopenia	9.2% (584)	234
Common	Lymphopenia	3.2% (200)	91
Uncommon	Haemolytic Anaemia[a]	0.1% (8)	7
Uncommon	Eosinophilia	0.7% (45)	4
Rare	Immune Thrombocytopenia	0.05% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	7.1% (449)	77
Rare	Sarcoidosis	0.03% (2)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	13.5% (856)	18
Common	Adrenal Insufficiency[d]	1.1% (68)	27
Common	Hyperthyroidism[e]	5.7% (359)	8
Common	Thyroiditis[f]	1.1% (72)	7
Uncommon	Hypophysitis[g]	0.7% (43)	23
Rare	Hypoparathyroidism	0.03% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.8% (747)	222
Very common	Decreased Appetite	26.5% (1681)	119
Common	Hyponatraemia	8.2% (521)	188
Common	Hypocalcaemia	4.6% (290)	44
Uncommon	Type 1 Diabetes Mellitus[h]	0.3% (20)	19
Psychiatric disorders			
Very common	Insomnia	10.8% (682)	9

Nervous system disorders			
Very common	Neuropathy Peripheral	13.6% (861)	57
Very common	Headache	13.8% (874)	20
Very common	Dizziness	10.0% (636)	15
Common	Dysgeusia	8.6% (544)	3
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Epilepsy	0.1% (7)	3
Uncommon	Lethargy	0.99% (63)	2
Rare	Myasthenic Syndrome[j]	0.08% (5)	5
Rare	Guillain-Barre Syndrome[k]	0.06% (4)	4
Rare	Myelitis	0.02% (1)	1
Rare	Optic Neuritis	0.02% (1)	1
Rare	Meningitis (Aseptic)	0.02% (1)	1
Eye disorders			
Common	Dry Eye	3.0% (188)	1
Uncommon	Uveitis[l]	0.2% (12)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	3.9% (244)	56
Uncommon	Myocarditis[n]	0.2% (11)	9
Uncommon	Pericardial Effusion	0.4% (26)	10
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.8% (431)	176
Uncommon	Vasculitis[o]	0.6% (35)	6
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	12.3% (779)	83
Very common	Cough	15.1% (958)	5
Common	Pneumonitis[p]	3.9% (244)	89
Gastrointestinal disorders			
Very common	Diarrhoea	35.4% (2242)	244
Very common	Nausea	52.4% (3318)	194
Very common	Vomiting	27.8% (1762)	188
Very common	Abdominal Pain[q]	18.9% (1194)	82
Very common	Constipation	32.2% (2041)	23
Common	Colitis[r]	2.7% (168)	79
Common	Gastritis[s]	2.0% (128)	9
Common	Dry Mouth	4.4% (279)	1
Uncommon	Pancreatitis[t]	0.4% (27)	20
Uncommon	Gastrointestinal Ulceration[u]	0.4% (24)	4
Rare	Pancreatic Exocrine Insufficiency	(0)	0
Rare	Small Intestinal Perforation	0.03% (2)	2
Rare	Coeliac Disease	(0)	0
Hepatobiliary disorders			
Common	Hepatitis[v]	1.0% (65)	47
Rare	Cholangitis Sclerosing[w]	0.03% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Rash[x]	20.4% (1289)	7
Very common	Alopecia	22.9% (1451)	6
Very common	Pruritus[y]	14.1% (893)	6
Common	Severe Skin Reactions[z]	2.5% (157)	130
Common	Dermatitis	1.5% (93)	4
Common	Erythema	3.3% (206)	3
Common	Dry Skin	5.3% (333)	2
Common	Dermatitis Acneiform	2.1% (134)	2
Common	Eczema	1.2% (76)	1
Uncommon	Psoriasis	0.6% (37)	5
Uncommon	Lichenoid Keratosis[aa]	0.1% (8)	1
Uncommon	Vitiligo[bb]	0.6% (35)	0
Uncommon	Papule	0.2% (11)	0
Rare	Stevens-Johnson Syndrome	0.05% (3)	3

Rare	Erythema Nodosum	0.06% (4)	0
Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[cc]	13.4% (848)	42
Very common	Arthralgia	15.8% (1000)	40
Common	Myositis[dd]	8.9% (566)	24
Common	Pain In Extremity	7.2% (459)	12
Common	Arthritis[ee]	1.6% (99)	9
Uncommon	Tenosynovitis[ff]	0.3% (20)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (200)	102
Uncommon	Nephritis[gg]	0.7% (42)	24
Uncommon	Cystitis Noninfective	0.3% (18)	0
General disorders and administration site conditions			
Very common	Fatigue	36.1% (2289)	274
Very common	Asthenia	17.0% (1077)	164
Very common	Pyrexia	17.8% (1128)	48
Very common	Oedema[hh]	13.3% (840)	26
Common	Influenza Like Illness	2.8% (175)	2
Common	Chills	3.0% (190)	0
Investigations			
Very common	Alanine Aminotransferase Increased	16.8% (1067)	180
Very common	Aspartate Aminotransferase Increased	16.5% (1042)	151
Common	Blood Bilirubin Increased	4.7% (296)	50
Common	Blood Alkaline Phosphatase Increased	6.6% (418)	45
Common	Blood Creatinine Increased	9.9% (624)	32
Common	Hypercalcaemia	1.7% (107)	22

Uncommon	Amylase Increased	0.6% (40)	10

Every participant is counted a single time for each applicable row.

a. Haemolytic Anaemia (Autoimmune Haemolytic Anaemia, Coombs Negative Haemolytic Anaemia, Haemolytic Anaemia)

b. Infusion Reactions (Anaphylactic Reaction, Cytokine Release Syndrome, Drug Hypersensitivity, Hypersensitivity, Infusion Related Hypersensitivity Reaction, Infusion Related Reaction, Serum Sickness)

c. Hypothyroidism (Autoimmune Hypothyroidism, Hypothyroidism, Immune-Mediated Hypothyroidism)

d. Adrenal Insufficiency (Addison's Disease, Adrenal Insufficiency)

e. Hyperthyroidism (Graves' Disease, Hyperthyroidism)

f. Thyroiditis (Autoimmune Thyroiditis, Immune-Mediated Thyroiditis, Silent Thyroiditis, Thyroid Disorder, Thyroiditis, Thyroiditis Acute)

g. Hypophysitis (Hypophysitis, Hypopituitarism)

h. Type 1 Diabetes Mellitus (Diabetic Ketoacidosis, Type 1 Diabetes Mellitus)

i. Encephalitis (Encephalitis, Encephalitis Autoimmune)

j. Myasthenic Syndrome (Myasthenia Gravis, Myasthenic Syndrome)

k. Guillain-Barre Syndrome (Demyelinating Polyneuropathy, Guillain-Barre Syndrome)

l. Uveitis (Iridocyclitis, Iritis, Uveitis)

m. Cardiac Arrhythmia (Including Atrial Fibrillation) (Arrhythmia, Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, Atrioventricular Block, Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block, Cardiac Flutter, Electrocardiogram Qt Prolonged, Electrocardiogram Repolarisation Abnormality, Extrasystoles, Heart Rate Irregular, Sinus Arrhythmia, Sinus Bradycardia, Sinus Node Dysfunction, Sinus Tachycardia, Supraventricular Extrasystoles, Supraventricular Tachycardia, Ventricular Arrhythmia, Ventricular Extrasystoles, Ventricular Tachycardia)

n. Myocarditis (Autoimmune Myocarditis, Myocarditis)

o. Vasculitis (Central Nervous System Vasculitis, Vasculitis)

p. Pneumonitis (Autoimmune Lung Disease, Immune-Mediated Lung Disease, Interstitial Lung Disease, Organising Pneumonia, Pneumonitis)

q. Abdominal Pain (Abdominal Discomfort, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper)

r. Colitis (Autoimmune Colitis, Colitis, Colitis Microscopic, Enterocolitis, Immune-Mediated Enterocolitis)

s. Gastritis (Gastritis, Gastritis Erosive, Immune-Mediated Gastritis)

t. Pancreatitis (Pancreatitis, Pancreatitis Acute)

u. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)

v. Hepatitis (Autoimmune Hepatitis, Drug-Induced Liver Injury, Hepatitis, Immune-Mediated Hepatitis)

w. Cholangitis Sclerosing (Cholangitis Sclerosing, Immune-Mediated Cholangitis)

x. Rash (Genital Rash, Rash, Rash Erythematous, Rash Follicular, Rash Macular, Rash Maculo-Papular, Rash Papular, Rash Pruritic, Rash Vesicular)

y. Pruritus (Pruritus, Pruritus Genital, Urticaria)

z. Severe Skin Reactions (Cutaneous Vasculitis, Dermatitis Bullous, Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Erythema Multiforme, Pemphigoid, Pruritus, Rash, Rash Erythematous, Rash Maculo-Papular, Rash Pruritic, Rash Pustular, Stevens-Johnson Syndrome, Toxic Skin Eruption)

aa. Lichenoid Keratosis (Lichen Planus, Lichenoid Keratosis)

bb. Vitiligo (Skin Depigmentation, Skin Hypopigmentation, Vitiligo)

cc. Musculoskeletal Pain (Back Pain, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness, Torticollis)

dd. Myositis (Myalgia, Myopathy, Myositis, Polymyalgia Rheumatica, Rhabdomyolysis)

ee. Arthritis (Arthritis, Immune-Mediated Arthritis, Joint Effusion, Joint Swelling, Polyarthritis)

ff. Tenosynovitis (Synovitis, Tendon Pain, Tendonitis, Tenosynovitis)

gg. Nephritis (Autoimmune Nephritis, Immune-Mediated Nephritis, Nephritis, Nephrotic Syndrome, Tubulointerstitial Nephritis)

hh. Oedema (Eyelid Oedema, Face Oedema, Fluid Retention, Generalised Oedema, Lip Oedema, Localised Oedema, Oedema, Oedema Peripheral, Periorbital Oedema)

Database cutoff date for KN483: 19SEP2022

The list of studies and database cutoff dates for the aggregate safety dataset within this table are provided in the appendix of the memorandum in support of SmPC section 4.8.

Serious adverse event/deaths/other significant events

SAE

Table 45. Participants With Serious Adverse Events by Decreasing Incidence (Incidence ⩾ 1% in One or More Treatment Groups) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	97	(40.2)	44	(19.0)	1,464	(46.9)	2,742	(35.9)
with no adverse events	144	(59.8)	188	(81.0)	1,659	(53.1)	4,889	(64.1)
Febrile neutropenia	12	(5.0)	3	(1.3)	217	(6.9)	8	(0.1)
Pneumonia	10	(4.1)	5	(2.2)	146	(4.7)	272	(3.6)
Diarrhoea	8	(3.3)	3	(1.3)	47	(1.5)	70	(0.9)
Pneumonitis	8	(3.3)	0	(0.0)	55	(1.8)	136	(1.8)

Anaemia	7	(2.9)	0	(0.0)	86	(2.8)	65	(0.9)
Sepsis	7	(2.9)	2	(0.9)	44	(1.4)	56	(0.7)
Platelet count decreased	6	(2.5)	1	(0.4)	19	(0.6)	0	(0.0)
Abdominal pain	5	(2.1)	2	(0.9)	9	(0.3)	43	(0.6)
Embolism	5	(2.1)	6	(2.6)	8	(0.3)	13	(0.2)
Nausea	5	(2.1)	1	(0.4)	28	(0.9)	30	(0.4)
Pyrexia	5	(2.1)	2	(0.9)	73	(2.3)	79	(1.0)
Vomiting	5	(2.1)	0	(0.0)	41	(1.3)	32	(0.4)
Alanine aminotransferase increased	4	(1.7)	0	(0.0)	12	(0.4)	16	(0.2)
Aspartate aminotransferase increased	4	(1.7)	0	(0.0)	11	(0.4)	17	(0.2)
Colitis	4	(1.7)	0	(0.0)	28	(0.9)	71	(0.9)
Dyspnoea	4	(1.7)	4	(1.7)	18	(0.6)	91	(1.2)
Acute kidney injury	3	(1.2)	1	(0.4)	56	(1.8)	65	(0.9)
Atrial fibrillation	3	(1.2)	1	(0.4)	13	(0.4)	28	(0.4)
Device related infection	3	(1.2)	1	(0.4)	11	(0.4)	5	(0.1)
Urinary tract infection	3	(1.2)	0	(0.0)	33	(1.1)	67	(0.9)
Fatigue	2	(0.8)	3	(1.3)	14	(0.4)	22	(0.3)
Myocardial infarction	2	(0.8)	3	(1.3)	12	(0.4)	23	(0.3)
Pleural effusion	2	(0.8)	2	(0.9)	31	(1.0)	88	(1.2)
Confusional state	0	(0.0)	3	(1.3)	4	(0.1)	22	(0.3)
Neutropenia	0	(0.0)	0	(0.0)	50	(1.6)	3	(0.0)
Pulmonary embolism	0	(0.0)	0	(0.0)	43	(1.4)	78	(1.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	43	(1.4)	10	(0.1)

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

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

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

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

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 46. Participants With Serious Drug-Related Adverse Events by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (APaT Population in Arms A and B)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	241		232		473	
with one or more adverse events	67	(27.8)	19	(8.2)	86	(18.2)
with no adverse events	174	(72.2)	213	(91.8)	387	(81.8)
Febrile neutropenia	10	(4.1)	3	(1.3)	13	(2.7)
Pneumonitis	8	(3.3)	0	(0.0)	8	(1.7)
Diarrhoea	7	(2.9)	2	(0.9)	9	(1.9)
Anaemia	6	(2.5)	0	(0.0)	6	(1.3)
Nausea	5	(2.1)	1	(0.4)	6	(1.3)
Platelet count decreased	5	(2.1)	0	(0.0)	5	(1.1)
Sepsis	5	(2.1)	1	(0.4)	6	(1.3)
Vomiting	5	(2.1)	0	(0.0)	5	(1.1)
Alanine aminotransferase increased	4	(1.7)	0	(0.0)	4	(0.8)
Aspartate aminotransferase increased	4	(1.7)	0	(0.0)	4	(0.8)
Colitis	4	(1.7)	0	(0.0)	4	(0.8)
Pneumonia	3	(1.2)	1	(0.4)	4	(0.8)
Acute kidney injury	2	(0.8)	1	(0.4)	3	(0.6)
Adrenal insufficiency	2	(0.8)	0	(0.0)	2	(0.4)
Arthralgia	2	(0.8)	0	(0.0)	2	(0.4)
Fatigue	2	(0.8)	3	(1.3)	5	(1.1)
Lipase increased	2	(0.8)	0	(0.0)	2	(0.4)
Neutrophil count decreased	2	(0.8)	0	(0.0)	2	(0.4)
Pancreatitis	2	(0.8)	0	(0.0)	2	(0.4)
Abdominal pain	1	(0.4)	1	(0.4)	2	(0.4)
Atrial fibrillation	1	(0.4)	0	(0.0)	1	(0.2)
Blood alkaline phosphatase increased	1	(0.4)	0	(0.0)	1	(0.2)
Blood creatinine increased	1	(0.4)	0	(0.0)	1	(0.2)
Bone marrow failure	1	(0.4)	0	(0.0)	1	(0.2)
Cardiac arrest	1	(0.4)	0	(0.0)	1	(0.2)
Cardiac failure	1	(0.4)	0	(0.0)	1	(0.2)
Decreased appetite	1	(0.4)	0	(0.0)	1	(0.2)
Dehydration	1	(0.4)	2	(0.9)	3	(0.6)
Diabetes mellitus	1	(0.4)	0	(0.0)	1	(0.2)
Dyspnoea	1	(0.4)	0	(0.0)	1	(0.2)
Embolism	1	(0.4)	2	(0.9)	3	(0.6)
Gamma-glutamyltransferase increased	1	(0.4)	0	(0.0)	1	(0.2)
Hypertension	1	(0.4)	0	(0.0)	1	(0.2)
Hypophysitis	1	(0.4)	0	(0.0)	1	(0.2)
Myelitis	1	(0.4)	0	(0.0)	1	(0.2)
Nephritis	1	(0.4)	0	(0.0)	1	(0.2)
Osteitis	1	(0.4)	0	(0.0)	1	(0.2)
Peripheral motor neuropathy	1	(0.4)	0	(0.0)	1	(0.2)
Peripheral sensory neuropathy	1	(0.4)	0	(0.0)	1	(0.2)
Pruritus	1	(0.4)	0	(0.0)	1	(0.2)
Pulmonary oedema	1	(0.4)	0	(0.0)	1	(0.2)
Purpura	1	(0.4)	0	(0.0)	1	(0.2)
Seizure	1	(0.4)	0	(0.0)	1	(0.2)
Skin infection	1	(0.4)	0	(0.0)	1	(0.2)
Stevens-Johnson syndrome	1	(0.4)	0	(0.0)	1	(0.2)
Sudden death	1	(0.4)	0	(0.0)	1	(0.2)
Tubulointerstitial nephritis	1	(0.4)	0	(0.0)	1	(0.2)
Uveitis	1	(0.4)	0	(0.0)	1	(0.2)
Vasculitis	1	(0.4)	0	(0.0)	1	(0.2)
Vertigo	1	(0.4)	0	(0.0)	1	(0.2)
Atrial flutter	0	(0.0)	1	(0.4)	1	(0.2)
Confusional state	0	(0.0)	1	(0.4)	1	(0.2)
Enterocolitis infectious	0	(0.0)	1	(0.4)	1	(0.2)
Myocardial infarction	0	(0.0)	2	(0.9)	2	(0.4)
Pyrexia	0	(0.0)	1	(0.4)	1	(0.2)
Stress cardiomyopathy	0	(0.0)	1	(0.4)	1	(0.2)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 16SEP2022

Deaths

A total of 17 participants (7.1%) in the pembro combo group and 5 participants (2.2%) in the chemo group had fatal AEs. When adjusted for exposure, those were 0.74 vs 0.52 events/100 person-months. Of those, a total of 7 participants (2.9%) in the pembro combo group and 2 participants (0.9%) in the chemo group had fatal drug-related AEs. When adjusted for exposure, whose were 0.33 vs 0.21 events/100 person-months.

Of note, in KEYNOTE-483, the terms "death" or "sudden death" were reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term in a participant with comorbidities and confounding factors that led to death. Also, due to CCTG database conventions, some deaths due to progressive disease were coded as "ill-defined disorder."

Table 47. Participants With Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups of KN-483) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	17	(7.1)	5	(2.2)	165	(5.3)	346	(4.5)
with no adverse events	224	(92.9)	227	(97.8)	2,958	(94.7)	7,285	(95.5)
Sepsis	4	(1.7)	2	(0.9)	10	(0.3)	11	(0.1)
Assisted suicide	2	(0.8)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiac arrest	2	(0.8)	0	(0.0)	10	(0.3)	9	(0.1)
Ill-defined disorder	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
Death	1	(0.4)	0	(0.0)	19	(0.6)	49	(0.6)
Dyspnoea	1	(0.4)	0	(0.0)	1	(0.0)	5	(0.1)
Febrile neutropenia	1	(0.4)	0	(0.0)	1	(0.0)	1	(0.0)
Mesothelioma	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial infarction	1	(0.4)	1	(0.4)	4	(0.1)	6	(0.1)
Pleural effusion	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.0)
Sudden death	1	(0.4)	0	(0.0)	1	(0.0)	2	(0.0)
Haemorrhage intracranial	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.0)
Neoplasm malignant	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)

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

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

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

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

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 48. Participants With Drug-Related Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups of KN-483) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	7	(2.9)	2	(0.9)	49	(1.6)	42	(0.6)
with no adverse events	234	(97.1)	230	(99.1)	3,074	(98.4)	7,589	(99.4)
Sepsis	3	(1.2)	1	(0.4)	5	(0.2)	1	(0.0)
Cardiac arrest	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	1	(0.4)	0	(0.0)	1	(0.0)	5	(0.1)
Febrile neutropenia	1	(0.4)	0	(0.0)	1	(0.0)	0	(0.0)
Sudden death	1	(0.4)	0	(0.0)	1	(0.0)	2	(0.0)
Myocardial infarction	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.0)

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

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

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

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

Database cutoff date for KN483: 16SEP2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Adverse Events of Special Interest (AEOSI)

AEOSI are immune-mediated events and infusion-related reactions causally associated with pembrolizumab.

Table 49. Adverse Event Summary for AEOSI (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	64	(26.6)	16	(6.9)	1,092	(35.0)	2,082	(27.3)
with no adverse event	177	(73.4)	216	(93.1)	2,031	(65.0)	5,549	(72.7)
with drug-related[a] adverse events	54	(22.4)	11	(4.7)	963	(30.8)	1,808	(23.7)
with toxicity grade 3-5 adverse events	16	(6.6)	2	(0.9)	334	(10.7)	534	(7.0)
with toxicity grade 3-5 drug-related adverse events	15	(6.2)	2	(0.9)	303	(9.7)	467	(6.1)
with serious adverse events	23	(9.5)	0	(0.0)	259	(8.3)	517	(6.8)
with serious drug-related adverse events	21	(8.7)	0	(0.0)	236	(7.6)	455	(6.0)
who died	0	(0.0)	0	(0.0)	10	(0.3)	13	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	9	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	17	(7.1)	1	(0.4)	234	(7.5)	360	(4.7)
discontinued pembrolizumab	17	(7.1)	0	(0.0)	180	(5.8)	360	(4.7)
discontinued any chemotherapy	4	(1.7)	1	(0.4)	119	(3.8)	0	(0.0)
discontinued any drug due to a drug-related adverse event	17	(7.1)	1	(0.4)	229	(7.3)	353	(4.6)
discontinued pembrolizumab	17	(7.1)	0	(0.0)	176	(5.6)	353	(4.6)
discontinued any chemotherapy	4	(1.7)	1	(0.4)	117	(3.7)	0	(0.0)
discontinued any drug due to a serious adverse event	15	(6.2)	0	(0.0)	148	(4.7)	228	(3.0)
discontinued pembrolizumab	15	(6.2)	0	(0.0)	135	(4.3)	228	(3.0)
discontinued any chemotherapy	4	(1.7)	0	(0.0)	65	(2.1)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	15	(6.2)	0	(0.0)	144	(4.6)	226	(3.0)
discontinued pembrolizumab	15	(6.2)	0	(0.0)	132	(4.2)	226	(3.0)
discontinued any chemotherapy	4	(1.7)	0	(0.0)	63	(2.0)	0	(0.0)

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

For KN483, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included. For all other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

NA=not applicable

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 50. Participants With Adverse Events of Special Interest by AEOSI Category (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	64	(26.6)	16	(6.9)	1,092	(35.0)	2,082	(27.3)
with no adverse events	177	(73.4)	216	(93.1)	2,031	(65.0)	5,549	(72.7)

Adrenal Insufficiency	**2**	**(0.8)**	**1**	**(0.4)**	**42**	**(1.3)**	**74**	**(1.0)**
Arthritis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**0**	**(0.0)**
Colitis	**6**	**(2.5)**	**0**	**(0.0)**	**84**	**(2.7)**	**159**	**(2.1)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.2)**	**5**	**(0.1)**
Gastritis	**2**	**(0.8)**	**2**	**(0.9)**	**76**	**(2.4)**	**57**	**(0.7)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**6**	**(0.1)**
Hepatitis	**0**	**(0.0)**	**0**	**(0.0)**	**40**	**(1.3)**	**80**	**(1.0)**
Hyperthyroidism	**4**	**(1.7)**	**2**	**(0.9)**	**173**	**(5.5)**	**398**	**(5.2)**
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**1**	**(0.0)**
Hypophysitis	**1**	**(0.4)**	**0**	**(0.0)**	**28**	**(0.9)**	**52**	**(0.7)**
Hypothyroidism	**22**	**(9.1)**	**4**	**(1.7)**	**439**	**(14.1)**	**939**	**(12.3)**
Infusion Reactions	**14**	**(5.8)**	**4**	**(1.7)**	**247**	**(7.9)**	**165**	**(2.2)**
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**8**	**(0.1)**
Myelitis	**1**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myocarditis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.3)**	**9**	**(0.1)**
Myositis	**1**	**(0.4)**	**0**	**(0.0)**	**13**	**(0.4)**	**34**	**(0.4)**
Nephritis	**2**	**(0.8)**	**0**	**(0.0)**	**26**	**(0.8)**	**37**	**(0.5)**
Nephritis	**2**	**(0.8)**	**0**	**(0.0)**	**26**	**(0.8)**	**37**	**(0.5)**
Optic Neuritis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Pancreatitis	**2**	**(0.8)**	**0**	**(0.0)**	**16**	**(0.5)**	**28**	**(0.4)**
Pneumonitis	**12**	**(5.0)**	**0**	**(0.0)**	**125**	**(4.0)**	**324**	**(4.2)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**20**	**(0.3)**
Severe Skin Reactions	**7**	**(2.9)**	**3**	**(1.3)**	**96**	**(3.1)**	**130**	**(1.7)**
Thyroiditis	**0**	**(0.0)**	**0**	**(0.0)**	**41**	**(1.3)**	**74**	**(1.0)**
Thyroiditis	**0**	**(0.0)**	**0**	**(0.0)**	**41**	**(1.3)**	**74**	**(1.0)**
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**11**	**(0.4)**	**34**	**(0.4)**
Uveitis	**2**	**(0.8)**	**1**	**(0.4)**	**4**	**(0.1)**	**25**	**(0.3)**
Vasculitis	**2**	**(0.8)**	**0**	**(0.0)**	**23**	**(0.7)**	**5**	**(0.1)**

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.

Database cutoff date for KN483: 16SEP2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 51. Participants With Adverse Events of Special Interest by Maximum Toxicity Grade (APaT Population)

	KN483 Pembro + Chemo		KN483 Chemo		Pooled Safety Dataset for Pembro + Chemo		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	241		232		3,123		7,631	
with one or more adverse events	64	(26.6)	16	(6.9)	1,092	(35.0)	2,082	(27.3)
Grade 1	13	(5.4)	6	(2.6)	254	(8.1)	495	(6.5)
Grade 2	35	(14.5)	8	(3.4)	504	(16.1)	1,053	(13.8)
Grade 3	16	(6.6)	2	(0.9)	281	(9.0)	458	(6.0)
Grade 4	0	(0.0)	0	(0.0)	43	(1.4)	63	(0.8)
Grade 5	0	(0.0)	0	(0.0)	10	(0.3)	13	(0.2)
with no adverse events	177	(73.4)	216	(93.1)	2,031	(65.0)	5,549	(72.7)

Table 52. Participants With Adverse Events of Special Interest by Outcome (APaT Population)

	Outcome	KN483 Pembro + Chemo n	KN483 Pembro + Chemo (%)	KN483 Chemo n	KN483 Chemo (%)	Pooled Safety Dataset for Pembro + Chemo n	Pooled Safety Dataset for Pembro + Chemo (%)	Pembrolizumab Monotherapy Reference Safety Dataset n	Pembrolizumab Monotherapy Reference Safety Dataset (%)
Participants in population		241		232		3123		7631	
With one or more AEOSI	**Overall**	**64**	**(26.6)**	**16**	**(6.9)**	**1059**	**(33.9)**	**2082**	**(27.3)**
	Fatal	0	(0.0)	0	(0.0)	9	(0.8)	13	(0.6)
	Not Resolved	26	(40.6)	3	(18.8)	344	(32.5)	905	(43.5)
	Resolving	0	(0.0)	0	(0.0)	124	(11.7)	181	(8.7)
	Unknown	0	(0.0)	0	(0.0)	3	(0.3)	30	(1.4)
	Sequelae	0	(0.0)	0	(0.0)	38	(3.6)	67	(3.2)
	Resolved	38	(59.4)	13	(81.3)	541	(51.1)	886	(42.6)

Table 53. Time to Onset and Duration of AEOSI (APaT Population)

	KN483 Pembro + Chemo	KN483 Chemo	Pooled Safety Dataset for Pembro + Chemo	Pembrolizumab Monotherapy Reference Safety Dataset
Participants in population	241	232	3123	7631
Participants with AEOSI, n (%)	64 (26.6)	16 (6.9)	1092 (35.0)	2082 (27.3)
Time to Onset of First AEOSI[a] (day)				
Mean (SD)	122.3 (136.4)	65.3 (45.4)	123.9 (133.8)	118.5 (121.5)
Median	70.0	60.0	83.0	78.0
Range	2 to 639	5 to 133	1 to 878	1 to 796
Total number of episodes of AEOSI	89	18	1749	2956
Average number of episodes of AEOSI per participant	1.4	1.1	1.6	1.4
Episode Duration[b] (day)				
Median	40.0	17.0	58.0	105.0
Range	1 to 1836+	1 to 815+	1 to 1748+	1 to 1915+

Laboratory findings

The percentage of participants with the most frequently reported laboratory abnormalities were generally similar between the pembro combo group and the chemo group. The most frequently reported Grade 3 to 4 laboratory abnormalities were generally similar between the pembro combo group and chemo groups, except anemia (22.1% vs 12.4%), leukocytes decreased (16.2% vs 7.5%), lymphocytes decreased (25.7% vs 14.9%), neutrophils decreased (27.4% vs 18.6%), and potassium decreased (8.1% vs 0%), which were reported at higher rates in the pembro combo group compared with the chemo group.

No participant met the predetermined laboratory criteria for potential DILI (ALT or AST $\geq 3 \times$ ULN, bilirubin $\geq 2 \times$ ULN, and alkaline phosphatase $< 2 \times$ ULN).

Safety in special populations

Table 54. Adverse Event Summary by Age Category (<65, ⩾ 65 Years) (APaT Population)

	KN483 Pembro + Chemo				KN483 Chemo				Pooled Safety Dataset for Pembro + Chemo				Pembrolizumab Monotherapy Reference Safety Dataset			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	49		192		63		169		2,176		947		4,524		3,107	
with one or more adverse events	48	(98.0)	184	(95.8)	58	(92.1)	154	(91.1)	2,158	(99.2)	939	(99.2)	4,364	(96.5)	3,011	(96.9)
with no adverse event	1	(2.0)	8	(4.2)	5	(7.9)	15	(8.9)	18	(0.8)	8	(0.8)	160	(3.5)	96	(3.1)
with drug-related[a] adverse events	42	(85.7)	175	(91.1)	54	(85.7)	135	(79.9)	2,107	(96.8)	913	(96.4)	3,231	(71.4)	2,231	(71.8)
with toxicity grade 3-5 adverse events	18	(36.7)	88	(45.8)	20	(31.7)	50	(29.6)	1,723	(79.2)	758	(80.0)	1,917	(42.4)	1,597	(51.4)
with toxicity grade 3-5 drug-related adverse events	9	(18.4)	65	(33.9)	11	(17.5)	28	(16.6)	1,466	(67.4)	635	(67.1)	629	(13.9)	579	(18.6)
with serious adverse events	13	(26.5)	84	(43.8)	12	(19.0)	32	(18.9)	939	(43.2)	525	(55.4)	1,457	(32.2)	1,285	(41.4)
with serious drug-related adverse events	8	(16.3)	59	(30.7)	5	(7.9)	14	(8.3)	593	(27.3)	320	(33.8)	451	(10.0)	389	(12.5)
who died	3	(6.1)	14	(7.3)	1	(1.6)	4	(2.4)	74	(3.4)	91	(9.6)	158	(3.5)	188	(6.1)
who died due to a drug-related adverse event	2	(4.1)	5	(2.6)	0	(0.0)	2	(1.2)	20	(0.9)	29	(3.1)	21	(0.5)	21	(0.7)
discontinued drug due to an adverse event	12	(24.5)	71	(37.0)	9	(14.3)	31	(18.3)	575	(26.4)	335	(35.4)	554	(12.2)	512	(16.5)
discontinued drug due to a drug-related adverse event	12	(24.5)	62	(32.3)	9	(14.3)	28	(16.6)	499	(22.9)	255	(26.9)	333	(7.4)	306	(9.8)
discontinued drug due to a serious adverse event	6	(12.2)	44	(22.9)	1	(1.6)	9	(5.3)	272	(12.5)	203	(21.4)	366	(8.1)	348	(11.2)
discontinued drug due to a serious drug-related adverse event	6	(12.2)	35	(18.2)	1	(1.6)	6	(3.6)	212	(9.7)	132	(13.9)	177	(3.9)	170	(5.5)

[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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN483: 16SEP2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 55. Adverse Event Summary by Age Category (<65, 65-74, 75-84, ⩾ 85 Years) (APaT Population)

	KN483 Pembro + Chemo								KN483 Chemo								Pooled Safety Dataset for Pembro + Chemo							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	49		126		64		2		63		106		60		3		2,176		767		175		5	
with one or more adverse events	48	(98.0)	121	(96.0)	61	(95.3)	2	(100.0)	58	(92.1)	100	(94.3)	52	(86.7)	2	(66.7)	2,158	(99.2)	760	(99.1)	174	(99.4)	5	(100.0)
with no adverse event	1	(2.0)	5	(4.0)	3	(4.7)	0	(0.0)	5	(7.9)	6	(5.7)	8	(13.3)	1	(33.3)	18	(0.8)	7	(0.9)	1	(0.6)	0	(0.0)
with drug-related[a] adverse events	42	(85.7)	116	(92.1)	57	(89.1)	2	(100.0)	54	(85.7)	86	(81.1)	47	(78.3)	2	(66.7)	2,107	(96.8)	742	(96.7)	167	(95.4)	4	(80.0)
with toxicity grade 3-5 adverse events	18	(36.7)	56	(44.4)	30	(46.9)	2	(100.0)	20	(31.7)	27	(25.5)	21	(35.0)	2	(66.7)	1,723	(79.2)	608	(79.3)	145	(82.9)	5	(100.0)
with toxicity grade 3-5 drug-related adverse events	9	(18.4)	40	(31.7)	23	(35.9)	2	(100.0)	11	(17.5)	15	(14.2)	12	(20.0)	1	(33.3)	1,466	(67.4)	520	(67.8)	111	(63.4)	4	(80.0)
with serious adverse events	13	(26.5)	54	(42.9)	28	(43.8)	2	(100.0)	12	(19.0)	18	(17.0)	13	(21.7)	1	(33.3)	939	(43.2)	418	(54.5)	103	(58.9)	4	(80.0)
with serious drug-related adverse events	8	(16.3)	38	(30.2)	19	(29.7)	2	(100.0)	5	(7.9)	6	(5.7)	8	(13.3)	0	(0.0)	593	(27.3)	256	(33.4)	61	(34.9)	3	(60.0)
who died	3	(6.1)	9	(7.1)	5	(7.8)	0	(0.0)	1	(1.6)	3	(2.8)	1	(1.7)	0	(0.0)	74	(3.4)	56	(7.3)	31	(17.7)	4	(80.0)
who died due to a drug-related adverse event	2	(4.1)	3	(2.4)	2	(3.1)	0	(0.0)	0	(0.0)	1	(0.9)	1	(1.7)	0	(0.0)	20	(0.9)	18	(2.3)	8	(4.6)	3	(60.0)
discontinued drug due to an adverse event	12	(24.5)	46	(36.5)	23	(35.9)	2	(100.0)	9	(14.3)	19	(17.9)	11	(18.3)	1	(33.3)	575	(26.4)	260	(33.9)	71	(40.6)	4	(80.0)
discontinued drug due to a drug-related adverse event	12	(24.5)	40	(31.7)	20	(31.3)	2	(100.0)	9	(14.3)	16	(15.1)	11	(18.3)	1	(33.3)	499	(22.9)	205	(26.7)	47	(26.9)	3	(60.0)
discontinued drug due to a serious adverse event	6	(12.2)	26	(20.6)	16	(25.0)	2	(100.0)	1	(1.6)	7	(6.6)	2	(3.3)	0	(0.0)	272	(12.5)	148	(19.3)	51	(29.1)	4	(80.0)
discontinued drug due to a serious drug-related adverse event	6	(12.2)	20	(15.9)	13	(20.3)	2	(100.0)	1	(1.6)	4	(3.8)	2	(3.3)	0	(0.0)	212	(9.7)	100	(13.0)	29	(16.6)	3	(60.0)

	Pembrolizumab Monotherapy Reference Safety Dataset							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	4,524		2,173		824		110	
with one or more adverse events	4,364	(96.5)	2,097	(96.5)	805	(97.7)	109	(99.1)
with no adverse event	160	(3.5)	76	(3.5)	19	(2.3)	1	(0.9)
with drug-related[a] adverse events	3,231	(71.4)	1,552	(71.4)	594	(72.1)	85	(77.3)
with toxicity grade 3-5 adverse events	1,917	(42.4)	1,071	(49.3)	457	(55.5)	69	(62.7)
with toxicity grade 3-5 drug-related adverse events	629	(13.9)	391	(18.0)	163	(19.8)	25	(22.7)
with serious adverse events	1,457	(32.2)	839	(38.6)	387	(47.0)	59	(53.6)
with serious drug-related adverse events	451	(10.0)	265	(12.2)	105	(12.7)	19	(17.3)
who died	158	(3.5)	113	(5.2)	63	(7.6)	12	(10.9)
who died due to a drug-related adverse event	21	(0.5)	13	(0.6)	7	(0.8)	1	(0.9)
discontinued drug due to an adverse event	554	(12.2)	327	(15.0)	168	(20.4)	17	(15.5)
discontinued drug due to a drug-related adverse event	333	(7.4)	206	(9.5)	92	(11.2)	8	(7.3)
discontinued drug due to a serious adverse event	366	(8.1)	214	(9.8)	120	(14.6)	14	(12.7)
discontinued drug due to a serious drug-related adverse event	177	(3.9)	113	(5.2)	52	(6.3)	5	(4.5)

[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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN483: 16SEP2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 56. Adverse Event Summary by Sex (Male, Female) (APaT Population)

	KN483 Pembro + Chemo				KN483 Chemo				Pooled Safety Dataset for Pembro + Chemo				Pembrolizumab Monotherapy Reference Safety Dataset			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	181		60		183		49		1,042		2,081		4,889		2,742	
with one or more adverse events	174	(96.1)	58	(96.7)	169	(92.3)	43	(87.8)	1,035	(99.3)	2,062	(99.1)	4,711	(96.4)	2,664	(97.2)
with no adverse event	7	(3.9)	2	(3.3)	14	(7.7)	6	(12.2)	7	(0.7)	19	(0.9)	178	(3.6)	78	(2.8)
with drug-related[a] adverse events	160	(88.4)	57	(95.0)	149	(81.4)	40	(81.6)	996	(95.6)	2,024	(97.3)	3,457	(70.7)	2,005	(73.1)
with toxicity grade 3-5 adverse events	85	(47.0)	21	(35.0)	56	(30.6)	14	(28.6)	814	(78.1)	1,667	(80.1)	2,265	(46.3)	1,249	(45.6)
with toxicity grade 3-5 drug-related adverse events	59	(32.6)	15	(25.0)	30	(16.4)	9	(18.4)	641	(61.5)	1,460	(70.2)	814	(16.6)	394	(14.4)
with serious adverse events	76	(42.0)	21	(35.0)	36	(19.7)	8	(16.3)	562	(53.9)	902	(43.3)	1,797	(36.8)	945	(34.5)
with serious drug-related adverse events	51	(28.2)	16	(26.7)	15	(8.2)	4	(8.2)	320	(30.7)	593	(28.5)	566	(11.6)	274	(10.0)
who died	14	(7.7)	3	(5.0)	4	(2.2)	1	(2.0)	98	(9.4)	67	(3.2)	240	(4.9)	106	(3.9)
who died due to a drug-related adverse event	5	(2.8)	2	(3.3)	2	(1.1)	0	(0.0)	32	(3.1)	17	(0.8)	27	(0.6)	15	(0.5)
discontinued drug due to an adverse event	59	(32.6)	24	(40.0)	31	(16.9)	9	(18.4)	308	(29.6)	602	(28.9)	695	(14.2)	371	(13.5)
discontinued drug due to a drug-related adverse event	52	(28.7)	22	(36.7)	28	(15.3)	9	(18.4)	231	(22.2)	523	(25.1)	418	(8.5)	221	(8.1)
discontinued drug due to a serious adverse event	37	(20.4)	13	(21.7)	9	(4.9)	1	(2.0)	199	(19.1)	276	(13.3)	473	(9.7)	241	(8.8)
discontinued drug due to a serious drug-related adverse event	30	(16.6)	11	(18.3)	6	(3.3)	1	(2.0)	125	(12.0)	219	(10.5)	233	(4.8)	114	(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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN483: 16SEP2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 57. Adverse Event Summary by ECOG Status Category (0, 1) (APaT Population)

	KN483 Pembro + Chemo				KN483 Chemo				Pooled Safety Dataset for Pembro + Chemo				Pembrolizumab Monotherapy Reference Safety Dataset			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	109		132		107		125		1,768		1,349		4,016		3,440	
with one or more adverse events	103	(94.5)	129	(97.7)	93	(86.9)	119	(95.2)	1,756	(99.3)	1,335	(99.0)	3,883	(96.7)	3,324	(96.6)
with no adverse event	6	(5.5)	3	(2.3)	14	(13.1)	6	(4.8)	12	(0.7)	14	(1.0)	133	(3.3)	116	(3.4)
with drug-related[a] adverse events	93	(85.3)	124	(93.9)	82	(76.6)	107	(85.6)	1,727	(97.7)	1,287	(95.4)	3,072	(76.5)	2,295	(66.7)
with toxicity grade 3-5 adverse events	46	(42.2)	60	(45.5)	17	(15.9)	53	(42.4)	1,390	(78.6)	1,085	(80.4)	1,540	(38.3)	1,866	(54.2)
with toxicity grade 3-5 drug-related adverse events	30	(27.5)	44	(33.3)	10	(9.3)	29	(23.2)	1,227	(69.4)	870	(64.5)	623	(15.5)	555	(16.1)
with serious adverse events	39	(35.8)	58	(43.9)	11	(10.3)	33	(26.4)	754	(42.6)	704	(52.2)	1,157	(28.8)	1,491	(43.3)
with serious drug-related adverse events	24	(22.0)	43	(32.6)	5	(4.7)	14	(11.2)	493	(27.9)	417	(30.9)	442	(11.0)	381	(11.1)
who died	7	(6.4)	10	(7.6)	1	(0.9)	4	(3.2)	51	(2.9)	113	(8.4)	93	(2.3)	237	(6.9)
who died due to a drug-related adverse event	4	(3.7)	3	(2.3)	1	(0.9)	1	(0.8)	22	(1.2)	27	(2.0)	13	(0.3)	29	(0.8)
discontinued drug due to an adverse event	34	(31.2)	49	(37.1)	10	(9.3)	30	(24.0)	525	(29.7)	384	(28.5)	515	(12.8)	522	(15.2)
discontinued drug due to a drug-related adverse event	32	(29.4)	42	(31.8)	9	(8.4)	28	(22.4)	471	(26.6)	283	(21.0)	379	(9.4)	247	(7.2)
discontinued drug due to a serious adverse event	17	(15.6)	33	(25.0)	2	(1.9)	8	(6.4)	238	(13.5)	236	(17.5)	296	(7.4)	397	(11.5)

discontinued drug due to a serious drug-related adverse event	15	(13.8)	26	(19.7)	1	(0.9)	6	(4.8)	198	(11.2)	146	(10.8)	184	(4.6)	156	(4.5)

[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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN483: 16SEP2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 58. Adverse Event Summary by Region (EU, Ex-EU) (APaT Population)

	KN483 Pembro + Chemo				KN483 Chemo				Pooled Safety Dataset for Pembro + Chemo				Pembrolizumab Monotherapy Reference Safety Dataset			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	160		81		150		82		1,118		2,005		2,856		4,775	
with one or more adverse events	152	(95.0)	80	(98.8)	133	(88.7)	79	(96.3)	1,105	(98.8)	1,992	(99.4)	2,745	(96.1)	4,630	(97.0)
with no adverse event	8	(5.0)	1	(1.2)	17	(11.3)	3	(3.7)	13	(1.2)	13	(0.6)	111	(3.9)	145	(3.0)
with drug-related[a] adverse events	138	(86.3)	79	(97.5)	116	(77.3)	73	(89.0)	1,070	(95.7)	1,950	(97.3)	2,018	(70.7)	3,444	(72.1)
with toxicity grade 3-5 adverse events	64	(40.0)	42	(51.9)	35	(23.3)	35	(42.7)	876	(78.4)	1,605	(80.0)	1,251	(43.8)	2,263	(47.4)
with toxicity grade 3-5 drug-related adverse events	44	(27.5)	30	(37.0)	15	(10.0)	24	(29.3)	727	(65.0)	1,374	(68.5)	447	(15.7)	761	(15.9)
with serious adverse events	55	(34.4)	42	(51.9)	26	(17.3)	18	(22.0)	549	(49.1)	915	(45.6)	1,019	(35.7)	1,723	(36.1)
with serious drug-related adverse events	36	(22.5)	31	(38.3)	9	(6.0)	10	(12.2)	340	(30.4)	573	(28.6)	332	(11.6)	508	(10.6)
who died	12	(7.5)	5	(6.2)	3	(2.0)	2	(2.4)	57	(5.1)	108	(5.4)	126	(4.4)	220	(4.6)
who died due to a drug-related adverse event	6	(3.8)	1	(1.2)	1	(0.7)	1	(1.2)	12	(1.1)	37	(1.8)	13	(0.5)	29	(0.6)
discontinued drug due to an adverse event	55	(34.4)	28	(34.6)	19	(12.7)	21	(25.6)	388	(34.7)	522	(26.0)	400	(14.0)	666	(13.9)
discontinued drug due to a drug-related adverse event	50	(31.3)	24	(29.6)	16	(10.7)	21	(25.6)	323	(28.9)	431	(21.5)	260	(9.1)	379	(7.9)
discontinued drug due to a serious adverse event	31	(19.4)	19	(23.5)	6	(4.0)	4	(4.9)	199	(17.8)	276	(13.8)	264	(9.2)	450	(9.4)
discontinued drug due to a serious drug-related adverse event	26	(16.3)	15	(18.5)	3	(2.0)	4	(4.9)	142	(12.7)	202	(10.1)	140	(4.9)	207	(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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN483: 16SEP2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Safety in paediatric patients

In addition to the adult population, the MAH is seeking an indication for pembrolizumab in combination with platinum and pemetrexed for first line advanced malignant pleural mesothelioma including **adolescent (i.e. from 12 to 18 years of age)**. In order to support an **extrapolation** of data from the adult to the paediatric population, pembrolizumab safety data comparison between paediatric and adult participants has been presented. Safety profile of **pembrolizumab monotherapy** in the paediatric patient population aged 9 months to 17 years in KEYNOTE-051 (N=173; of those N=108 are adolescents aged 12-17) compared to the adult patient population in the EU RSD (N = 7631) is summarized in the tables below.

The median exposure to pembrolizumab was lower in the paediatric as compared to the adult dataset (2.1 vs 5.8 months on therapy, 4 vs 9 median cycles).

Table 59. Participant characteristics (APaT population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
Sex				
Male	88	(50.9)	4,889	(64.1)
Female	85	(49.1)	2,742	(35.9)
Age (Years)				
6 months - <2 years	3	(1.7)	0	(0.0)
2 - 5 years	23	(13.3)	0	(0.0)
6 - 9 years	26	(15.0)	0	(0.0)
10 - 13 years	39	(22.5)	0	(0.0)
14 - 17 years	82	(47.4)	2	(0.0)
>= 18 years	0	(0.0)	7,629	(100.0)
Mean	11.7		59.9	
SD	4.7		13.4	
Median	13.0		62.0	
Range	1 to 17		15 to 94	
Race				
American Indian Or Alaska Native	1	(0.6)	59	(0.8)
Asian	24	(13.9)	826	(10.8)
Black Or African American	15	(8.7)	146	(1.9)
Multiracial	14	(8.1)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	5	(0.1)
White	118	(68.2)	5,838	(76.5)
Missing	1	(0.6)	671	(8.8)
Ethnicity				
Hispanic Or Latino	22	(12.7)	604	(7.9)
Not Hispanic Or Latino	133	(76.9)	6,064	(79.5)
Not Reported	14	(8.1)	808	(10.6)
Unknown	4	(2.3)	145	(1.9)
Missing	0	(0.0)	10	(0.1)
Age Class (Years)				
<65	173	(100.0)	4,524	(59.3)
65-74	0	(0.0)	2,173	(28.5)
75-84	0	(0.0)	824	(10.8)
>=85	0	(0.0)	110	(1.4)
ECOG Performance Scale				
[0] Normal Activity	0	(0.0)	4,016	(52.6)
[1] Symptoms, but ambulatory	0	(0.0)	3,440	(45.1)
Other/Missing	0	(0.0)	175	(2.3)
Missing	173	(100.0)	0	(0.0)
Geographic Region				
North America	54	(31.2)	2,669	(35.0)
Western Europe	69	(39.9)	2,856	(37.4)
Rest of the World	50	(28.9)	2,106	(27.6)

Database cutoff date for KN051: 18JAN2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 60. Adverse Event Summary (APaT population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	105	(97.2)	168	(97.1)	7,375	(96.6)
with no adverse event	3	(2.8)	5	(2.9)	256	(3.4)
with drug-related[a] adverse events	63	(58.3)	99	(57.2)	5,462	(71.6)

with toxicity grade 3-5 adverse events	47	(43.5)	80	(46.2)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	8	(7.4)	13	(7.5)	1,208	(15.8)
with serious adverse events	41	(38.0)	68	(39.3)	2,742	(35.9)
with serious drug-related adverse events	11	(10.2)	16	(9.2)	840	(11.0)
who died	3	(2.8)	5	(2.9)	346	(4.5)
who died due to a drug-related adverse event	1	(0.9)	1	(0.6)	42	(0.6)
discontinued drug due to an adverse event	8	(7.4)	11	(6.4)	1,066	(14.0)
discontinued drug due to a drug-related adverse event	7	(6.5)	7	(4.0)	639	(8.4)
discontinued drug due to a serious adverse event	5	(4.6)	8	(4.6)	714	(9.4)
discontinued drug due to a serious drug-related adverse event	4	(3.7)	4	(2.3)	347	(4.5)

[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.

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 61. Exposure-adjusted Adverse Event Summary (including multiple occurrence of event) (APaT population)

	Event Count and Rate (Events/100 person-months)[a]	
	All Pediatrics Population KN051 (Pembro Monotherapy)	Pembrolizumab Monotherapy Reference Safety Dataset
Number of subjects exposed	173	7631
Total exposure[b] in person-months	1103.34	66840.89
Total events (rate)		
adverse events	2082 (188.70)	76878 (115.02)
drug-related[c] adverse events	375 (33.99)	24542 (36.72)
toxicity grade 3-5 adverse events	225 (20.39)	7463 (11.17)
toxicity grade 3-5 drug-related adverse events	17 (1.54)	1770 (2.65)
serious adverse events	124 (11.24)	4801 (7.18)
serious drug-related adverse events	23 (2.08)	1093 (1.64)
adverse events leading to death	5 (0.45)	353 (0.53)
drug-related adverse events leading to death	1 (0.09)	42 (0.06)
adverse events resulting in drug discontinuation	11 (1.00)	1165 (1.74)
drug-related adverse events resulting in drug discontinuation	7 (0.63)	703 (1.05)
serious adverse events resulting in drug discontinuation	8 (0.73)	753 (1.13)
serious drug-related adverse events resulting in drug discontinuation	4 (0.36)	363 (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 time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.
[c] 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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN051: 18JAN2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 62. Participants With Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	105	(97.2)	168	(97.1)	7,375	(96.6)
with no adverse events	3	(2.8)	5	(2.9)	256	(3.4)
Pyrexia	33	(30.6)	57	(32.9)	934	(12.2)
Headache	27	(25.0)	43	(24.9)	946	(12.4)

Vomiting	27	(25.0)	51	(29.5)	945	(12.4)
Abdominal pain	24	(22.2)	39	(22.5)	671	(8.8)
Constipation	22	(20.4)	33	(19.1)	1,179	(15.5)
Diarrhoea	22	(20.4)	32	(18.5)	1,678	(22.0)
Nausea	22	(20.4)	33	(19.1)	1,534	(20.1)
Cough	21	(19.4)	35	(20.2)	1,392	(18.2)
Fatigue	20	(18.5)	32	(18.5)	2,368	(31.0)
Arthralgia	19	(17.6)	25	(14.5)	1,436	(18.8)
Anaemia	16	(14.8)	36	(20.8)	982	(12.9)
Back pain	16	(14.8)	19	(11.0)	847	(11.1)
Lymphocyte count decreased	14	(13.0)	22	(12.7)	130	(1.7)
White blood cell count decreased	13	(12.0)	19	(11.0)	70	(0.9)
Chest pain	12	(11.1)	14	(8.1)	341	(4.5)
Pain in extremity	12	(11.1)	21	(12.1)	506	(6.6)
Alanine aminotransferase increased	11	(10.2)	20	(11.6)	572	(7.5)
Aspartate aminotransferase increased	11	(10.2)	22	(12.7)	538	(7.1)
Asthenia	11	(10.2)	19	(11.0)	880	(11.5)
Decreased appetite	11	(10.2)	22	(12.7)	1,312	(17.2)
Dizziness	11	(10.2)	13	(7.5)	564	(7.4)
Dyspnoea	11	(10.2)	16	(9.2)	1,130	(14.8)
Hypertension	11	(10.2)	15	(8.7)	416	(5.5)
Hypothyroidism	11	(10.2)	15	(8.7)	937	(12.3)
Nasopharyngitis	11	(10.2)	14	(8.1)	469	(6.1)
Pruritus	11	(10.2)	20	(11.6)	1,435	(18.8)
Rhinitis	11	(10.2)	17	(9.8)	153	(2.0)
Upper respiratory tract infection	11	(10.2)	16	(9.2)	514	(6.7)
Nasal congestion	10	(9.3)	14	(8.1)	201	(2.6)
Platelet count decreased	10	(9.3)	16	(9.2)	95	(1.2)
Sinus tachycardia	10	(9.3)	13	(7.5)	47	(0.6)
Weight decreased	10	(9.3)	12	(6.9)	628	(8.2)
Hypophosphataemia	9	(8.3)	11	(6.4)	168	(2.2)
Blood creatinine increased	8	(7.4)	12	(6.9)	358	(4.7)
Hyponatraemia	8	(7.4)	13	(7.5)	387	(5.1)
Myalgia	8	(7.4)	8	(4.6)	575	(7.5)
Pleural effusion	8	(7.4)	10	(5.8)	204	(2.7)
Rash	8	(7.4)	14	(8.1)	1,175	(15.4)
Hypoalbuminaemia	7	(6.5)	11	(6.4)	209	(2.7)
Hypokalaemia	7	(6.5)	9	(5.2)	324	(4.2)
Neutrophil count decreased	7	(6.5)	11	(6.4)	53	(0.7)
Dry skin	6	(5.6)	9	(5.2)	394	(5.2)
Haemoglobin decreased	6	(5.6)	7	(4.0)	46	(0.6)
Hyperglycaemia	6	(5.6)	9	(5.2)	360	(4.7)
Hyperthyroidism	6	(5.6)	7	(4.0)	398	(5.2)
Hyperuricaemia	6	(5.6)	6	(3.5)	119	(1.6)
Hypocalcaemia	6	(5.6)	8	(4.6)	137	(1.8)
Hypotension	6	(5.6)	9	(5.2)	197	(2.6)
Insomnia	6	(5.6)	7	(4.0)	528	(6.9)
Oropharyngeal pain	6	(5.6)	11	(6.4)	260	(3.4)
Proteinuria	6	(5.6)	10	(5.8)	80	(1.0)
Blood alkaline phosphatase increased	5	(4.6)	9	(5.2)	322	(4.2)
Rash maculo-papular	5	(4.6)	12	(6.9)	295	(3.9)
Rhinorrhoea	5	(4.6)	10	(5.8)	149	(2.0)
Seizure	4	(3.7)	9	(5.2)	40	(0.5)
Oedema peripheral	3	(2.8)	6	(3.5)	630	(8.3)
Pneumonia	3	(2.8)	7	(4.0)	487	(6.4)
Urinary tract infection	3	(2.8)	3	(1.7)	511	(6.7)
Dry mouth	0	(0.0)	0	(0.0)	388	(5.1)

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.

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 63. Participants With Anaemia Adverse Events (Incidence > 0% in One or More Treatment Groups) By System Organ Class and Preferred Term (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	22	(20.4)	43	(24.9)	1,036	(13.6)
with no adverse events	86	(79.6)	130	(75.1)	6,595	(86.4)
Blood and lymphatic system disorders	**16**	**(14.8)**	**36**	**(20.8)**	**990**	**(13.0)**
Anaemia	16	(14.8)	36	(20.8)	982	(12.9)
Anaemia macrocytic	0	(0.0)	0	(0.0)	1	(0.0)
Microcytic anaemia	0	(0.0)	0	(0.0)	4	(0.1)
Normochromic normocytic anaemia	0	(0.0)	0	(0.0)	1	(0.0)
Normocytic anaemia	0	(0.0)	0	(0.0)	2	(0.0)
Investigations	**6**	**(5.6)**	**8**	**(4.6)**	**55**	**(0.7)**
Haematocrit decreased	0	(0.0)	1	(0.6)	6	(0.1)
Haemoglobin decreased	6	(5.6)	7	(4.0)	46	(0.6)
Red blood cell count decreased	0	(0.0)	0	(0.0)	5	(0.1)

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.

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 64. Participants With Neutropenia/Lymphopenia Adverse Events (Incidence > 0% in One or More Treatment Groups) By System Organ Class and Preferred Term (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	25	(23.1)	35	(20.2)	335	(4.4)
with no adverse events	83	(76.9)	138	(79.8)	7,296	(95.6)

Blood and lymphatic system disorders	**5**	**(4.6)**	**8**	**(4.6)**	**172**	**(2.3)**
Febrile neutropenia	1	(0.9)	2	(1.2)	11	(0.1)
Lymphopenia	1	(0.9)	1	(0.6)	93	(1.2)
Neutropenia	3	(2.8)	5	(2.9)	82	(1.1)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Neutropenic sepsis	0	(0.0)	0	(0.0)	1	(0.0)
Investigations	**20**	**(18.5)**	**29**	**(16.8)**	**175**	**(2.3)**
Lymphocyte count decreased	14	(13.0)	22	(12.7)	130	(1.7)
Neutrophil count decreased	7	(6.5)	11	(6.4)	53	(0.7)

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.

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 65. Participants With Thrombocytopenias Adverse Events (Incidence > 0% in One or More Treatment Groups) By System Organ Class and Preferred Term (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	12	(11.1)	19	(11.0)	213	(2.8)
with no adverse events	96	(88.9)	154	(89.0)	7,418	(97.2)
Blood and lymphatic system disorders	**3**	**(2.8)**	**4**	**(2.3)**	**124**	**(1.6)**
Immune thrombocytopenia	1	(0.9)	1	(0.6)	8	(0.1)
Thrombocytopenia	2	(1.9)	3	(1.7)	117	(1.5)
Investigations	**10**	**(9.3)**	**16**	**(9.2)**	**95**	**(1.2)**
Platelet count decreased	10	(9.3)	16	(9.2)	95	(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.

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 66. Participants With Drug-Related Adverse Events (Incidence >1% in pediatric dataset) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	99	(57.2)	5,462	(71.6)
with no adverse events	74	(42.8)	2,169	(28.4)
Fatigue	14	(8.1)	1,476	(19.3)
Anaemia	13	(7.5)	234	(3.1)
Pyrexia	13	(7.5)	314	(4.1)
Lymphocyte count decreased	12	(6.9)	64	(0.8)
Aspartate aminotransferase increased	11	(6.4)	312	(4.1)
Diarrhoea	11	(6.4)	904	(11.8)
Hypothyroidism	10	(5.8)	810	(10.6)
Rash maculo-papular	10	(5.8)	237	(3.1)
Alanine aminotransferase increased	9	(5.2)	336	(4.4)
Nausea	9	(5.2)	675	(8.8)
White blood cell count decreased	8	(4.6)	34	(0.4)
Abdominal pain	7	(4.0)	147	(1.9)
Hyperthyroidism	7	(4.0)	352	(4.6)
Asthenia	6	(3.5)	491	(6.4)
Arthralgia	4	(2.3)	661	(8.7)
Decreased appetite	4	(2.3)	525	(6.9)
Erythema	4	(2.3)	98	(1.3)
Hypertension	4	(2.3)	44	(0.6)
Neutrophil count decreased	4	(2.3)	34	(0.4)
Platelet count decreased	4	(2.3)	43	(0.6)
Proteinuria	4	(2.3)	24	(0.3)
Pruritus	4	(2.3)	1,143	(15.0)
Rash	4	(2.3)	884	(11.6)
Back pain	3	(1.7)	82	(1.1)
Blood alkaline phosphatase increased	3	(1.7)	118	(1.5)
Blood bilirubin increased	3	(1.7)	71	(0.9)
Blood creatinine increased	3	(1.7)	105	(1.4)
Cough	3	(1.7)	232	(3.0)
Dry skin	3	(1.7)	218	(2.9)
Headache	3	(1.7)	250	(3.3)

Neutropenia	3	(1.7)	49	(0.6)
Night sweats	3	(1.7)	57	(0.7)
Pneumonitis	3	(1.7)	268	(3.5)
Weight decreased	3	(1.7)	148	(1.9)
Alopecia	2	(1.2)	57	(0.7)
Blood lactate dehydrogenase increased	2	(1.2)	15	(0.2)
Bone pain	2	(1.2)	28	(0.4)
Colitis	2	(1.2)	121	(1.6)
Conjunctivitis	2	(1.2)	31	(0.4)
Dermatitis allergic	2	(1.2)	8	(0.1)
Dyspnoea	2	(1.2)	232	(3.0)
Gastrooesophageal reflux disease	2	(1.2)	19	(0.2)
Haematuria	2	(1.2)	9	(0.1)
Hypoalbuminaemia	2	(1.2)	23	(0.3)
Hypocalcaemia	2	(1.2)	34	(0.4)
Hypomagnesaemia	2	(1.2)	37	(0.5)
Myalgia	2	(1.2)	312	(4.1)
Nasal congestion	2	(1.2)	25	(0.3)
Pain	2	(1.2)	47	(0.6)
Skin hypopigmentation	2	(1.2)	41	(0.5)
Thyroiditis	2	(1.2)	49	(0.6)
Vomiting	2	(1.2)	248	(3.2)

Table 67. Participants With Grade 3-5 Adverse Events (Incidence >1% in paediatric group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	80	(46.2)	3,514	(46.0)
with no adverse events	93	(53.8)	4,117	(54.0)
Anaemia	15	(8.7)	275	(3.6)
Lymphocyte count decreased	10	(5.8)	33	(0.4)
Abdominal pain	7	(4.0)	65	(0.9)
Neutrophil count decreased	6	(3.5)	10	(0.1)
Device related infection	5	(2.9)	9	(0.1)
Pleural effusion	5	(2.9)	73	(1.0)
Vomiting	5	(2.9)	52	(0.7)
Alanine aminotransferase increased	4	(2.3)	97	(1.3)
Aspartate aminotransferase increased	4	(2.3)	95	(1.2)
Back pain	4	(2.3)	72	(0.9)
Hypokalaemia	4	(2.3)	70	(0.9)
Nausea	4	(2.3)	58	(0.8)
Dyspnoea	3	(1.7)	145	(1.9)
Fatigue	3	(1.7)	166	(2.2)
Haemoglobin decreased	3	(1.7)	4	(0.1)
Headache	3	(1.7)	19	(0.2)
Platelet count decreased	3	(1.7)	10	(0.1)
Pneumonia	3	(1.7)	270	(3.5)
Pyrexia	3	(1.7)	33	(0.4)
Seizure	3	(1.7)	13	(0.2)
Sepsis	3	(1.7)	60	(0.8)
Wound infection	3	(1.7)	7	(0.1)
Anxiety	2	(1.2)	6	(0.1)
Disseminated intravascular coagulation	2	(1.2)	4	(0.1)
Dysphagia	2	(1.2)	31	(0.4)
Febrile neutropenia	2	(1.2)	11	(0.1)
Flank pain	2	(1.2)	9	(0.1)
Hemiparesis	2	(1.2)	3	(0.0)
Hyperkalaemia	2	(1.2)	30	(0.4)
Hypertension	2	(1.2)	148	(1.9)

Hypoalbuminaemia	2	(1.2)	33	(0.4)
Hyponatraemia	2	(1.2)	169	(2.2)
Hypophosphataemia	2	(1.2)	52	(0.7)
Muscular weakness	2	(1.2)	25	(0.3)
Pain in extremity	2	(1.2)	22	(0.3)
Pneumonitis	2	(1.2)	97	(1.3)
Spinal cord compression	2	(1.2)	19	(0.2)
Tonsillitis	2	(1.2)	0	(0.0)
White blood cell count decreased	2	(1.2)	5	(0.1)

Table 68. Participants With Grade 3-5 Drug-Related Adverse Events (Incidence >0% in pediatric group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	13	(7.5)	1,208	(15.8)
with no adverse events	160	(92.5)	6,423	(84.2)
Lymphocyte count decreased	4	(2.3)	9	(0.1)
Anaemia	2	(1.2)	33	(0.4)
Aspartate aminotransferase increased	1	(0.6)	47	(0.6)
Dyspnoea	1	(0.6)	22	(0.3)
Gastric ulcer	1	(0.6)	1	(0.0)
Hypertension	1	(0.6)	15	(0.2)
Myelitis	1	(0.6)	1	(0.0)
Neutrophil count decreased	1	(0.6)	6	(0.1)
Photosensitivity reaction	1	(0.6)	0	(0.0)
Pneumonitis	1	(0.6)	91	(1.2)
Pruritus	1	(0.6)	13	(0.2)
Pulmonary oedema	1	(0.6)	0	(0.0)
Pyrexia	1	(0.6)	7	(0.1)

Table 69. Participants With Adverse Events Resulting in Death Up to 90 Days of Last Dose (Incidence >0% in pediatric group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	5	(2.9)	346	(4.5)
with no adverse events	168	(97.1)	7,285	(95.5)
Adenocarcinoma gastric	1	(0.6)	1	(0.0)
Blood creatinine increased	1	(0.6)	0	(0.0)
Immune thrombocytopenia	1	(0.6)	0	(0.0)
Pulmonary oedema	1	(0.6)	1	(0.0)
Sepsis	1	(0.6)	11	(0.1)

In the paediatric group, **pulmonary edema** is the only AE resulting in death considered drug-related by the investigator.

Table 70. Participants With Serious Adverse Events Up to 90 Days of Last Dose (Incidence >1% in the pediatric Group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	68	(39.3)	2,742	(35.9)
with no adverse events	105	(60.7)	4,889	(64.1)
Pyrexia	11	(6.4)	79	(1.0)
Pleural effusion	5	(2.9)	88	(1.2)
Pneumonia	5	(2.9)	272	(3.6)
Device related infection	4	(2.3)	5	(0.1)
Vomiting	4	(2.3)	32	(0.4)
Pneumonitis	3	(1.7)	136	(1.8)
Seizure	3	(1.7)	15	(0.2)
Sepsis	3	(1.7)	56	(0.7)
Acute kidney injury	2	(1.2)	65	(0.9)
Dyspnoea	2	(1.2)	91	(1.2)
Headache	2	(1.2)	8	(0.1)
Hypertension	2	(1.2)	2	(0.0)
Nausea	2	(1.2)	30	(0.4)
Wound infection	2	(1.2)	6	(0.1)

Table 71. Participants With Drug-related Serious Adverse Events Up to 90 Days of Last Dose (Incidence >1% in pediatric group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	16	(9.2)	840	(11.0)
with no adverse events	157	(90.8)	6,791	(89.0)
Pyrexia	4	(2.3)	22	(0.3)
Hypertension	2	(1.2)	0	(0.0)
Adrenal insufficiency	1	(0.6)	25	(0.3)
Alanine aminotransferase increased	1	(0.6)	12	(0.2)
Diaphragmatic hernia	1	(0.6)	0	(0.0)
Dyspnoea	1	(0.6)	10	(0.1)
Enterocolitis infectious	1	(0.6)	1	(0.0)
Gastric ulcer	1	(0.6)	1	(0.0)
Gastrooesophageal reflux disease	1	(0.6)	1	(0.0)
Myelitis	1	(0.6)	1	(0.0)
Oedema peripheral	1	(0.6)	1	(0.0)
Photosensitivity reaction	1	(0.6)	0	(0.0)
Pleural effusion	1	(0.6)	10	(0.1)
Pneumonitis	1	(0.6)	129	(1.7)
Pruritus	1	(0.6)	1	(0.0)
Pulmonary oedema	1	(0.6)	0	(0.0)
Thyroiditis	1	(0.6)	5	(0.1)

Table 72. Participants With AEs Resulting in Treatment Discontinuation (Incidence >0% in pediatric group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	11	(6.4)	1,066	(14.0)
with no adverse events	162	(93.6)	6,565	(86.0)
Pneumonitis	2	(1.2)	115	(1.5)
Adenocarcinoma gastric	1	(0.6)	1	(0.0)
Aspartate aminotransferase increased	1	(0.6)	28	(0.4)
Astrocytoma	1	(0.6)	0	(0.0)
Blood creatinine increased	1	(0.6)	6	(0.1)
Hypertension	1	(0.6)	0	(0.0)
Myelitis	1	(0.6)	1	(0.0)
Oral lichenoid reaction	1	(0.6)	0	(0.0)
Pulmonary oedema	1	(0.6)	0	(0.0)
Sepsis	1	(0.6)	10	(0.1)

Table 73. Participants With Drug-related Adverse Events Resulting in Treatment Discontinuation (Incidence >0% in pediatric group) By Decreasing Frequency of Preferred Term (APaT Population)

	All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)
Participants in population	173		7,631	
with one or more adverse events	7	(4.0)	639	(8.4)
with no adverse events	166	(96.0)	6,992	(91.6)
Pneumonitis	2	(1.2)	113	(1.5)
Aspartate aminotransferase increased	1	(0.6)	25	(0.3)
Hypertension	1	(0.6)	0	(0.0)
Myelitis	1	(0.6)	1	(0.0)
Oral lichenoid reaction	1	(0.6)	0	(0.0)
Pulmonary oedema	1	(0.6)	0	(0.0)

Table 74. Adverse Event Summary AEOSI (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	27	(25.0)	35	(20.2)	2,082	(27.3)
with no adverse event	81	(75.0)	138	(79.8)	5,549	(72.7)
with drug-related[a] adverse events	20	(18.5)	23	(13.3)	1,808	(23.7)
with toxicity grade 3-5 adverse events	4	(3.7)	4	(2.3)	534	(7.0)
with toxicity grade 3-5 drug-related adverse events	3	(2.8)	3	(1.7)	467	(6.1)
with serious adverse events	6	(5.6)	7	(4.0)	517	(6.8)
with serious drug-related adverse events	4	(3.7)	4	(2.3)	455	(6.0)
who died	0	(0.0)	0	(0.0)	13	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	13	(0.2)
discontinued drug due to an adverse event	3	(2.8)	3	(1.7)	360	(4.7)
discontinued drug due to a drug-related adverse event	3	(2.8)	3	(1.7)	353	(4.6)
discontinued drug due to a serious adverse event	2	(1.9)	2	(1.2)	228	(3.0)
discontinued drug due to a serious drug-related adverse event	2	(1.9)	2	(1.2)	226	(3.0)

[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.

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 75. Exposure-adjusted Adverse Event Summary (Including Multiple Occurrences of Events) AEOSI (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]	
	All Pediatrics Population KN051 (Pembro Monotherapy)	Pembrolizumab Monotherapy Reference Safety Dataset
Number of subjects exposed	173	7631
Total exposure[b] in person-months	1103.34	66840.89
Total events (rate)		
adverse events	45 (4.08)	2956 (4.42)
drug-related[c] adverse events	29 (2.63)	2524 (3.78)
toxicity grade 3-5 adverse events	4 (0.36)	610 (0.91)
toxicity grade 3-5 drug-related adverse events	3 (0.27)	529 (0.79)
serious adverse events	8 (0.73)	578 (0.86)
serious drug-related adverse events	5 (0.45)	510 (0.76)
adverse events leading to death	0 (0.00)	13 (0.02)
drug-related adverse events leading to death	0 (0.00)	13 (0.02)
adverse events resulting in drug discontinuation	3 (0.27)	368 (0.55)
drug-related adverse events resulting in drug discontinuation	3 (0.27)	361 (0.54)
serious adverse events resulting in drug discontinuation	2 (0.18)	234 (0.35)
serious drug-related adverse events resulting in drug discontinuation	2 (0.18)	232 (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 time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.
[c] 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.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN051: 18JAN2022.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 76. Participants With Adverse Events of Special Interest by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) By AEOSI Category (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)
Participants in population	108		173		7,631	
with one or more adverse events	27	(25.0)	35	(20.2)	2,082	(27.3)
Grade 1	9	(8.3)	14	(8.1)	495	(6.5)
Grade 2	14	(13.0)	17	(9.8)	1,053	(13.8)
Grade 3	4	(3.7)	4	(2.3)	458	(6.0)
Grade 4	0	(0.0)	0	(0.0)	63	(0.8)
Grade 5	0	(0.0)	0	(0.0)	13	(0.2)
with no adverse events	81	(75.0)	138	(79.8)	5,549	(72.7)
Adrenal Insufficiency	**1**	**(0.9)**	**1**	**(0.6)**	**74**	**(1.0)**
Arthritis	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**
Colitis	**3**	**(2.8)**	**3**	**(1.7)**	**159**	**(2.1)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**
Gastritis	**3**	**(2.8)**	**3**	**(1.7)**	**57**	**(0.7)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(0.1)**
Hepatitis	**0**	**(0.0)**	**0**	**(0.0)**	**80**	**(1.0)**

Hyperthyroidism	**6**	**(5.6)**	**7**	**(4.0)**	**398**	**(5.2)**
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Hypophysitis	**0**	**(0.0)**	**0**	**(0.0)**	**52**	**(0.7)**
Hypothyroidism	**11**	**(10.2)**	**15**	**(8.7)**	**939**	**(12.3)**
Infusion Reactions	**4**	**(3.7)**	**6**	**(3.5)**	**165**	**(2.2)**
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**
Myelitis	**1**	**(0.9)**	**1**	**(0.6)**	**3**	**(0.0)**
Myocarditis	**0**	**(0.0)**	**0**	**(0.0)**	**9**	**(0.1)**
Myositis	**0**	**(0.0)**	**0**	**(0.0)**	**34**	**(0.4)**
Nephritis	**0**	**(0.0)**	**0**	**(0.0)**	**37**	**(0.5)**
Optic Neuritis	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Pancreatitis	**0**	**(0.0)**	**0**	**(0.0)**	**28**	**(0.4)**
Pneumonitis	**4**	**(3.7)**	**5**	**(2.9)**	**324**	**(4.2)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**20**	**(0.3)**
Severe Skin Reactions	**1**	**(0.9)**	**1**	**(0.6)**	**130**	**(1.7)**
Thyroiditis	**2**	**(1.9)**	**2**	**(1.2)**	**74**	**(1.0)**
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**34**	**(0.4)**
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**25**	**(0.3)**
Vasculitis	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a system organ class is counted a single time for that system organ class.

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

Only the highest reported grade of a given adverse event is counted for the individual participant.

Grades are based on NCI CTCAE version 4.

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

Database cutoff date for KN051: 18JAN2022.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in an appendix of the Rationale for Treatment in Pediatric Patients.

Table 77. Participants With Adverse Events of Special Interest by Outcome (Incidence > 0% in One or More Treatment Groups) (APaT Population)

		Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)		All Pediatrics Population KN051 (Pembro Monotherapy)		Pembrolizumab Monotherapy Reference Safety Dataset	
	Outcome	n	(%)	n	(%)	n	(%)
Participants in population		108		173		7631	
With one or more AEOSI	**Overall**	**27**	**(25.0)**	**35**	**(20.2)**	**2082**	**(27.3)**
	Fatal	0	(0.0)	0	(0.0)	13	(0.6)
	Not Resolved	13	(48.1)	16	(45.7)	905	(43.5)
	Resolving	2	(7.4)	3	(8.6)	181	(8.7)
	Unknown	1	(3.7)	1	(2.9)	30	(1.4)
	Sequelae	1	(3.7)	1	(2.9)	67	(3.2)
	Resolved	10	(37.0)	14	(40.0)	886	(42.6)

Table 78. Time to Onset and Duration of AEOSI (APaT Population)

	Pediatrics Population Aged 12-18 KN051 (Pembro Monotherapy)	All Pediatrics Population KN051 (Pembro Monotherapy)	Pembrolizumab Monotherapy Reference Safety Dataset
Participants in population	108	173	7631
Participants with AEOSI, n (%)	27 (25.0)	35 (20.2)	2082 (27.3)
Time to Onset of First AEOSI[a] (day)			
Mean (SD)	122.9 (176.1)	114.9 (159.2)	118.5 (121.5)
Median	44.0	48.0	78.0
Range	1 to 720	1 to 720	1 to 796
Total number of episodes of AEOSI	37	45	2956
Average number of episodes of AEOSI per participant	1.4	1.3	1.4
Episode Duration[b] (day)			
Median	211.0	211.0	105.0
Range	1 to 2298+	1 to 2298+	1 to 1915+

There are **no** paediatric patients who have received **pembrolizumab in combination** with chemotherapy or other drugs in the context of clinical trials.

In the **post-marketing setting**, a search of the Applicant's global safety database to investigate available information of treatment with pembrolizumab in combination with platinum-doublet chemotherapy in the paediatric population, identified reports through 29-NOV-2023, including interventional study cases, non-interventional study cases, literature reports, and spontaneous cases for patients ≤18 years of age. A total of 9 individual case safety reports were identified and summarized in the table below. No new safety concerns were identified from these 9 cases.

Table 79. Postmarketing Reports of Children Treated with Pembrolizumab in Combination with Pemetrexed and Cisplatin/Carboplatin Chemotherapy

Reported indication	Reported Adverse Events
Neoplasm of thymus	Malignant neoplasm progression Metastases to bone Neoplasm of thymus Hepatic lesion Peritoneal lesion Spinal pain Bone lesion
Nasopharyngeal cancer	Hyperpyrexia Hyperpyrexia Product use in unapproved indication
Lung adenocarcinoma	Off label use
Thymic carcinoma	Off label use
Metastatic melanoma	Death Product availability issue Product dose omission issue
Lung adenocarcinoma Stage IV	Product use issue
Pancreatic carcinoma	Off label use
Squamous cell carcinoma of cervix	Urogenital fistula Thyroiditis Adrenal disorder
Cervical carcinoma	Product use in unapproved indication

Safety related to drug-drug interactions and other interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. Drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of cytochrome P450 enzymes, other enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, the use of systemic corticosteroids or other immunosuppressants before the start of pembrolizumab treatment should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab treatment to treat immune-mediated adverse reactions, and corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy.

Discontinuation due to adverse events

Due to the design of the CCTG database, for discontinuations reported in KEYNOTE-483, only SAEs (regardless of causality) and drug-related AEs were collected. For the studies in the Pooled Pembrolizumab Combination dataset and RSD, all AEs that led to discontinuation, regardless of causality or seriousness, were included.

Events resulting in discontinuation of any study intervention was reported in 34.4% and 17.2% of participants in the pembro combo and chemo groups, respectively. The most commonly reported events resulting in any study intervention discontinuation (incidence ≥3%) were: fatigue (5.8%), nausea (3.7%), and pneumonitis (3.3%) for pembro combo; fatigue (3.9%), nausea (3%), and tinnitus (3%) for chemo combo.

The percentage of participants with events leading to discontinuation of any study intervention was similar between the pembro combo group (34.4%) and the Pooled Pembrolizumab Combination dataset (29.1%).

Pneumonitis was the only event with an incidence ≥3% that led to discontinuation of pembrolizumab in the pembro combo group and was similar with the Pooled Pembrolizumab Combination dataset. Pneumonitis is a known AEOSI for pembrolizumab.

The percentage of participants with events resulting in discontinuation of all treatments 9.5% in the pembro combo group vs 6.5% in the chemo group.

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2022 through 03-SEP-2023. No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The safety profile of pembrolizumab in combination with pemetrexed and platinum (cisplatin or carboplatin) chemotherapy was assessed in participants from KEYNOTE-483 in the context of its intended use for the first-line treatment of unresectable advanced and/or metastatic MPM. N=241 patients received at least 1 dose of study intervention in the pembro combo arm vs n=232 in the placebo + chemo arm. Pembrolizumab was administered in combination with 6 cycles of chemotherapy and then continued as monotherapy for maximum 2 years. For contextualization, side by side safety data were provided from the reference pembrolizumab combination dataset (n=3123) and the reference pembrolizumab monotherapy dataset (n=7631).

In KN-483 study, the median duration of therapy was longer in the pembro combo group compared with the chemo group (211 days vs 107 days), consistent to the differences in treatment duration (i.e. maximum 35 cycles in the pembrolizumab in the experimental arm and 6 cycles of chemo in the chemotherapy group). The median duration of exposure in the pembro combo group of KN-483 study was however slightly shorter compared with the 240 days in the Pooled Pembrolizumab Combination dataset, which likely reflect the overall poor prognosis of patients with advanced MPM, although the fraction of patients with exposure longer than 6 months was overall similar (about 60%).

While baseline patient's characteristics were overall balanced between treatment arms within KN-483, more participants in the pembro combo group of this study compared with the Pooled Pembrolizumab Combination dataset were male (75.1% vs 33.4%, respectively) and ≥65 years of age (79.7% vs 30.3%, respectively), which is expected from a population of patients with MPM.

In KN-483, some safety data were collected differently as compared to most of other Keytruda sponsored clinical trials, due to the design of the CCTG database, as only SAEs and drug-related AEs were collected for treatment discontinuations, and as asymptomatic laboratory events were not captured as specific AEs if considered not clinically significant by the investigator. This approach however still allows an appropriate evaluation of safety.

The percentages of participants with adverse events were higher in the pembro combo group compared with the chemo group of KN-483 (drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, drug-related SAEs, and events leading to discontinuation), although differences are reduced when adjusted for exposure.

A general higher incidence of the most common AEs is seen in the pembro combo arm as compared to the chemo arm of KN-483. AEs are however in line with the expected toxicity of the chemotherapy combination and pembrolizumab. A higher risk difference was observed with the pembro combo group for the AEs of diarrhea, pyrexia, pruritus, arthralgia, vomiting, constipation, rash maculo-papular, abdominal pain, and insomnia. In both treatment arms, most AEs were grade 2 and 3, but in a similar percentage (approximately 40% and 30%, respectively). The AEs profile of the pembro combo arm seems in general similar to the Pooled pembrolizumab combination Dataset, with few differences compatible with pemetrexed use in KN-483 as well as with the underlining mesothelioma disease.

In KN-483, most common drug-related AEs (>20%) were fatigue, nausea, diarrhoea, vomiting and stomatitis in the pembro combo group, while they were fatigue and nausea in the chemo group. There were more G3-4 drug-related AEs in the experimental arm and more G1 in the control arm. Overall, drug-related AEs in the pembro combo group were consistent with the Pooled Pembrolizumab Combination dataset. It is noted that some AE frequencies (eg, anemia, neutropenia, and thrombocytopenia) were reported less frequently in the pembro combo group compared with the Pooled Pembro Combo dataset, but this was likely due to different CCTG data entry guidelines specific for KN-483 study.

The most frequently reported Grade 3 to 5 AEs (all causality and drug-related) (incidence ≥5%) were fatigue and febrile neutropenia in the pembro combo group, and fatigue in the chemo group. The incidence of febrile neutropenia in the pembro combo group was however lower than in the pooled pembro plus chemo reference dataset.

The incidence of SAE and drug-related SAE was higher in the pembro combo group than in the placebo combo group of KN-483 (40.2% vs 19%; 27.8% vs 8.2%), although similar to the pooled pembro combo dataset. Febrile neutropenia was the most common SAE in the pembro-combo arm (5%). The types of SAEs reported in the pembro combo group were generally consistent with the established profile of pembrolizumab and the known safety profile of the individual chemotherapy agents.

More deaths due to AEs (17 vs 5, i.e. 7.1% vs 2.2%) and due to drug-related AEs (7 vs 2, i.e. 2.9% vs 0.9%) were recorded in the pembro arm as compared to the control arm of KN-483 study. The difference between treatment arms was reduced when adjusted for exposure, although remained slightly higher in the pembro combo arm rather than in the pooled combo safety dataset. It could be speculated one of the reasons of this finding being the higher median age in the pembro combo arm of KN-483 study, due to a general worse tolerability observed across clinical trials with pembrolizumab when combined with chemotherapy in older patients. Deaths considered due to treatment-related AEs in KN-483 were sepsis (n=3), dyspnoea, febrile neutropenia and sudden death (1 each) in the pembro combo group, with sepsis and myocardial infarction (1 each) in the chemo group. It is noted a quite higher incidence of sepsis as death-related AEs in the pembro combo arm as compared to all other datasets, although generally AEs that led to death in the pembro combo group were generally consistent with the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

With regard to AEOSI, the overall percentage of participants with, the frequency, severity and duration of AEOSI, were similar between the pembro combo group and the Pooled Pembrolizumab Combination dataset. The AEOSI categories with the highest percentage of participants in the pembro combo group were hypothyroidism (9.1%), infusion reactions (5.8%), and pneumonitis (5%), at similar percentages

in the Pooled Pembrolizumab Combination dataset. In the pembro combo arm of KN-483, most AEOSI were grade 2, approximately 60% resolved. No deaths due to AEOSI have been reported. No new indication-specific immune-mediated event causally associated with pembrolizumab was identified.

No specific concern is raised based on the analysis of laboratory findings. The most frequently reported laboratory abnormalities (including Grade 3 or 4 events) in the pembro combo group generally reflected the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components. There were no new safety concerns based on laboratory abnormalities.

Treatment discontinuation due to AEs was more common in the pembro combo arm than in the chemo arm (34.4% vs 17.2% for discontinuation of any treatment), mostly related to fatigue, nausea and pneumonitis in the experimental arm.

Safety was also assessed in selected subgroups of participants. In the pembro combo arm of KN-483, a higher percentage of participants who were ≥65 years old had Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, SAEs and drug-related SAEs, and discontinuation due to AEs, as compared to younger patients <65 years. The same was not clearly observed in the chemo arm Within patients ≥65 years, similar incidences were reported in the two subgroups 65-74 and 75-84 years. There were only 5 patients aged ≥85 years enrolled in KN-483 to draw any conclusion in this subset. The overall safety summary in patients ≥65 years in the pembro combo arm appears similar to the pembro combo pooled dataset.

The AE summary profile based on sex was generally similar between male and female participants in the pembro combo group, with the exception of a higher percentage of males with Grade 3 to 5 AEs compared to female, and a higher percentage of female with treatment discontinuation due to drug-related AEs as compared to males. However, overall the safety appears similar to the pooled combo dataset.

The AE profile based on ECOG status in the pembro combo group was generally consistent between ECOG PS 0 and 1. Differences between ECOG 0 and 1 were more evident in the control group rather than in the experimental group of KN-483.

With regard to geographic region, the AE profile based on region was generally consistent between participants in the EU and ex-EU in the pembro combo group. However, given the study was only conducted in France, Italy, and Canada, the observed differences based on region should be interpreted with caution.

Assessment of paediatric data on clinical safety

Due to the MAH's request to include adolescent (12-18 years) in the sought indication for pembrolizumab in combination with platinum and pemetrexed for first line advanced malignant pleural mesothelioma, the available pembrolizumab monotherapy safety data in the paediatric population (N=173 from KN-051 study, age interval 9 months-17 years; of those N=108 are adolescents aged 12-17) were presented in comparison to the safety profile from adults (n = 7631).

While pembrolizumab is already authorised in children from 3 years of age in cHL, and in adolescent in melanoma, as monotherapy, the sought indication in MPM will be the first one for pembrolizumab in combination with chemotherapy under the age of 18. It should be noted, however, that pembrolizumab has never been administered in combination with another agent in the paediatric population including in adolescent, in the context of clinical trials. The only data mentioned in the dossier in this regard are related to postmarketing reports of n=9 children that have received pembrolizumab in combination with cisplatin/carboplatin and pemetrexed chemotherapy. According to

the MAH, no new safety concerns were identified on review of these 9 cases. However, the information provided, in one table, are extremely limited and lack of details on AEs. Further heterogeneity in this group of patients is due to the age range (from 2 years and above) and the different tumor types. Thus, such data does not allow to draw any conclusion on the feasibility of combining pembrolizumab and chemotherapy in pediatric/adolescent patients from a safety perspective.

Median exposure to pembrolizumab in KN-051 was shorter in the pediatric than in the reference adult dataset (2.1 vs 5.8 months on therapy). Overall incidence of AEs, SAE, discontinuation and deaths due to AE are similar in adolescents and adults treated with pembrolizumab monotherapy. Pyrexia, headache, vomiting, abdominal pain and constipation were the most common AEs in adolescents, occurring at higher incidence in adolescents rather than in adults. In the paediatric population, it was observed a higher incidence of haematological toxicity as compared to adults. While the incidence of anaemia as AE between adolescents and adults was similar (14.8% vs 13%), haemoglobin decreased was more common in adolescents (5.6% vs 0.7%). Also, decrease in lymphocytes and neutrophil counts was also far more common in adolescents rather than adults (18.5% vs 2.3%), febrile neutropenia is however less than 1% (0.1% vs 0.9%) and no cases of febrile neutropenic sepsis were recorded. Also decreased platelets/thrombocytopenia were more common in adolescents rather than adults.

In the overall paediatric population, anaemia and lymphocyte count decrease were the most common all causality grade 3-5 AEs (8.7% and 5.8% respectively) as well as the most common drug related AEs (1.2% and 2.3%, respectively), quite higher than in the adult dataset. Taking into account that the sought indication in adolescent is in combination with chemotherapy drugs, having known myelosuppressive toxicity, the lack of safety data for pembrolizumab plus chemotherapy in adolescents is a concern for the sought indication. The MAH has withdrawn the indication in adolescent.

With regard to AEs leading to death, those were less common in paediatric than in adults (2.9% vs 4.5%). The only fatal AE considered drug related by investigator was pulmonary edema. This is however not listed as ADR in Keytruda SmPC.

Pyrexia was the most common SAE (6.4% vs 1%) and drug-related SAE (2.3% vs 0.3%) in the paediatric population, more common than in adults. As in adults, also in paediatrics pneumonitis was the most common AE and drug-related AE leading to treatment discontinuation.

Incidence of AEOSI appears overall lower in paediatrics than in adults, although differences are very limited when adjusting for exposure. It is reassuring that most AEOSI in paediatrics were low grade (G1-2). Lower rate of hypothyroidism, pneumonitis and severe skin reaction were recorded in paediatric compared to adult patients, while infusion reactions were a bit more common in children. Immunological events related to pembrolizumab appear similar in adolescents and adults in terms of incidence, type of AEOSI, severity and resolution, with the exception of shorter median time to onset of first AEOSI but longer median duration of AEOSI in adolescent as compared to adults.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of pembrolizumab in combination with platinum and pemetrexed as first line treatment for adult patients with advanced/malignant pleural mesothelioma in KEYNOTE-483 study was consistent with the established safety profile of pembrolizumab and of the individual chemotherapy components. As expected, the addition of pembrolizumab partly increased the toxicity of chemotherapy, however the safety of pembrolizumab in combination is already well described in the SmPC and considered manageable in clinical practice. No new safety signals were identified.

With regard to the sought indication in adolescent, for pembrolizumab monotherapy the most common AEs are slightly different in adolescents as compared to adults, although the overall incidence of AEs is similar. AEOSI related to pembrolizumab appear similar in adolescent and adults in incidence, type, severity and resolution, with the exception of shorter median time to onset of first AEOSI but longer median duration of AEOSI in adolescent as compared to adults. Somewhat more frequent incidence of decreased haemoglobin, lymphocytes and neutrophil counts and decreased platelets is reported in adolescents, which is of note considering the combination with myelotoxic chemotherapy. The main issue for the sought indication is the complete lack of safety data of pembrolizumab in combination with chemotherapy in adolescents, as paediatric patients have only been treated with pembrolizumab as monotherapy in clinical trials. The MAH has withdrawn the indication in adolescent.

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 submit 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 45.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 45.0 with the following content:

Safety concerns

Table 80. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions
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 81. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Mediated Adverse Reactions		
Immune-mediated adverse reactions	Routine risk minimisation measures: ▪ The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: ▪ Patient card	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor 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).
	Routine risk minimisation measures:	Routine pharmacovigilance activities

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	▪ 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	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 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 proposed revision does not contain significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

3.1.2. Available therapies and unmet medical need

Malignant pleural mesothelioma (MPM) is a rare disease of the elderly population. The treatment decision making process considers factors such as staging, histology, age, PS, comorbidities and the patient's preferences[23]. A multimodality approach including surgery, or palliative care, or systemic therapy only are the available options for MPM management. In subjects candidate for a non-surgical approach, pemetrexed-platinum chemotherapy has long been the standard-of-care as a first line treatment[22] [24] . Nivolumab–ipilimumab is a new first-line option for unresectable MPM, that was licensed based on the supportive data from the CheckMate 743 study, demonstrating improvement in OS with nivolumab–ipilimumab over cisplatin/carboplatin and pemetrexed chemotherapy. However, a difference in treatment effect was observed between the epithelioid and non-epithelioid histology, mostly attributable to the known reduced response to chemotherapy in non-epithelioid tumours that

[23] Popat S, Baas P, Faivre-Finn C, et al; ESMO Guidelines Committee. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022 Feb;33(2):129-142.
[24] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21(14):2636-2644

translated in a larger immunotherapy OS benefit considering that the performance of nivolumab–ipilimumab was similar regardless of histology[22] [25] [26]. Prognosis, however, remains poor in advanced MPM, leading to need for effective treatments.

3.1.3. Main clinical studies

The current application is supported by data from the phase 2/3 study KEYNOTE-483, an open-label, multicentre, Phase 2/3 randomized study of pembrolizumab plus chemotherapy versus chemotherapy alone in participants with MPM receiving first-line treatment for unresectable advanced and/or metastatic disease. The study was sponsored and conducted by the Canadian Cancer Trial Group (CCTG).

This study was initially designed as Phase 2 study in which participants were randomized in a 1:1:1 ratio to Arm A (chemo), Arm B (pembro combo), or Arm C (pembro mono). The study was then adjusted to be a Phase 3 study in which participants were randomized into 1 of 2 arms in a 1:1 ratio to Arm A (chemo) or Arm B (pembro combo).

3.2. Favourable effects

- The ITT analysis of the phase 3 part demonstrated a statistically significant superiority of pembro combo compared to control in the primary endpoint OS (HR=0.79; 95% CI:0.64,0.98; p=0.0162), as well as in the secondary endpoints PFS (HR=0.80; 95% CI:0.65,0.99; p=0.0194), and ORR as assessed by BICR (52.3%; 95% CI: 45.5, 59.0) compared to control (28.9%; 95% CI: 23.0, 35.4) (2-sided p-value <0.00001)..
- In the non-epithelioid subgroup, median OS gain was 4.1 months (HR=0.57; 95% CI: 0.36, 0.89), median PFS gain was 2.6 months (HR=0.47; 95% CI: 0.29, 0.77) and ORR by BICR was improved for pembro combo (41%; 95% CI: 27, 57) compared to control (6%; 95%: 1, 17).

3.3. Uncertainties and limitations about favourable effects

- The clinical relevance of the treatment benefit in the ITT population appears limited in absolute terms (1 month gain in median OS).
- Subgroup analysis based on histology was not adjusted for multiplicity, however, non-epithelioid histology was a stratification factor.

3.4. Unfavourable effects

- In the pembro + chemo arm (n=241) generally higher toxicity was observed as compared to the chemo arm (n=232): drug-related AE (90% vs 81.5%), G3-5 AE (44% vs 30.2%), drug-related G3-5 AE (30.7% vs 16.8%), SAE (40.2% vs 19%), drug-related SAE (27.8% vs 8.2%), death (7.1% vs 2.2%), drug-related death (2.9% vs 0.9%), discontinuation due to AE of any treatment (34.4% vs 17.2%) and of any chemotherapy (24.5% vs 15.9%). When adjusted for exposure (longer in the pembro arm due to protocol-defined continuation of pembrolizumab after 6 cycles of chemotherapy) difference between arms appears more limited. Overall incidence of AEs of the

[25] EPAR Opdivo/Yervoy WS-1881.
[26] Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021;397(10272):375-386.

pembro+chemo arm of KN-483 appear however overall similar to the pooled pembro+chemo reference safety dataset (n=3123).

- In the pembro+chemo arm, most common AEs (>20%) were fatigue (61.4%), nausea (53.1%), constipation (32%), diarrhoea (30.7%), dysponea (29.6%), vomiting (26.1%), pyrexia (22.4%), stomatitis (22.4%), and decreased appetite (21.6%); while in the chemo arm those were fatigue (61.4%), nausea (47%), constipation and dyspnea (22% each), decreased appetite (20.7%). Those AEs are consistent with safety profile of each drug and disease setting. In both arms, most AEs were G2 and G3. The AE types and incidences in the pembro combo arm of KN-483 are similar to the combo reference dataset.
- Most common G3-5 AEs (>5%) were fatigue (7.5%) and febrile neutropenia (5.8%) in the pembro combo arm and fatigue (7.8%) and dyspnea (5.2%) in the control arm of KN-483. Febrile neutropenia was the only SAE ≥5% occurring in the pembro combo arm.
- Most common cause of death due to AE was sepsis in both treatment arms (4 cases in pembro combo arm, 1.7%; 2 cases in the control arm, 0.9%). Sepsis (3 cases), cardiac arrest, dyspnea, febrile neutropenia and sudden death (1 case each) were considered treatment-related deaths in the pembro+chemo arm.
- Most common (>5%) AEOSI occurring in the pembro combo arm of KN-483 were hypothyroidism (9.1%), infusion reactions (5%) and pneumonitis (5%). The overall type, frequency, severity and duration of AEOSI were similar to the Pooled Pembrolizumab Combination dataset.
- Higher toxicity was reported in patients ≥65 years as compared to younger <65 years. The overall safety summary in patients ≥65 years in the pembro combo arm appears however similar to the pembro combo pooled dataset.

3.5. Uncertainties and limitations about unfavourable effects

n/a

3.6. Effects Table

Table 82. Effects Table for Keytruda in combination platinum and pemetrexed in unresectable non-epithelioid MPM (Study KEYNOTE-481, data cut-off: 16-SEP-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	duration of survival from randomization to death regardless of cause	months (95 % CI)	12.3 (8.7, 21.2)	8.2 (5.8, 9.8)	Subgroup analysis not adjusted for multiplicity. Stratified subgroup Primary analysis in ITT was statistically significant but considered of limited clinical relevance	Section 2.4
PFS	duration of survival without progression from randomization to PD or death whichever occurred first	months (95 % CI)	7.1 (4.5, 9.8)	4.5 (4.0, 6.4)		
Unfavourable Effects						
	Grade 3-5 AEs	%	44	30.2	Worse safety of the combination/toxicity consistent with each agent of the combination, no new unexpected safety findings	Section 2.5
	SAEs		40.2	19		
	Deaths		7.1	2.2		
	Discontinuation due to AE (any drug)		34.4	17.2		

Abbreviations: AE: adverse event; SAE: serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The phase 3 portion of the RCT KEYNOTE-483 demonstrated a statistically significant superiority in the primary endpoint OS of pembrolizumab in combination with platinum-pemetrexed chemotherapy vs chemotherapy alone for the treatment of unresectable MPM in 1L setting. From a statistical perspective, the currently generated evidence are supportive of a successful demonstration of superiority of pembro combo vs chemotherapy alone in the ITT population. However, with a clear separation of the K-M curves only at 18 months and only 1 month gain in median overall survival, and no gain in median PFS, the clinical relevance of the results appears limited in absolute terms. A lower benefit of the pembro combo was observed in the epithelioid histology group where the K-M curves for OS were generally overlapping. On the contrary, in the subgroup of patients with non-epithelioid histology, better HRs in terms of OS (0.57, 95%CI 0.36, 0.89), PFS (0.47, 95%CI 0.29, 0.77) as well as larger delta ORR (35.2%) was noticed. In line with external data (BEAT-Meso), KEYNOTE-483 demonstrates reduced additional benefit in the epithelioid subtype compared to the non-epithelioid counterpart. Specifically, response to pembro combo trended toward a similar direction in the two histology subgroups (19.8 vs 12.3 months in median OS in the epithelioid and non-epithelioid tumours). However, response to chemotherapy was histology-dependent, and this clearly resembles the expectedly poorer prognosis and stronger chemosensitivity of the epithelioid (18.2 months in median OS, 7.4 months in median PFS, 36.1% in ORR in the control arm) compared to the non-epithelioid subtype (8.2 months in median OS, 4.5 months in median PFS, 6.1% in ORR in the control arm). It can therefore be concluded that the observed inconsistency of effect by histology seems to be primarily ascribed to the disparity between groups in the performance of the control arm and chemotherapy component of the pembro combo treatment, rather than a differential antitumoral activity of pembrolizumab. This finding is similar to what has been seen when immune-checkpoint inhibitors were compared to, rather than added to, chemotherapy (Checkmate-734). In the case of KEYNOTE-483, there is therefore biological plausibility for a differential add-on effect of pembrolizumab depending on histology, due to different response to chemotherapy. This is a largely established aspect that was taken into consideration by the Applicant at study planning stage, with the inclusion of histology among the stratification factors of KEYNOTE-483.

Pre-specification, replication and plausibility are key elements in the definition of credibility of the observed subgroup analysis by histology, which therefore appears of appropriate robustness to support regulatory decisions (scenario 2, EMA/CHMP/539146/2013).

Overall, the safety profile of pembrolizumab in combination with platinum and pemetrexed emerged from KEYNOTE-483 study was consistent with the established safety profile of pembrolizumab and of the individual chemotherapy components. As expected, the addition of pembrolizumab partly increase the toxicity of chemotherapy, however the safety of pembrolizumab in combination is already well described in SmPC and managed in clinical practice. No new safety signals were identified.

3.7.2. Balance of benefits and risks

A statistically significant survival advantage, although very limited in absolute terms, was achieved with the addition of pembrolizumab to standard chemotherapy in study KEYNOTE-483 for 1L MPM in the ITT population. As the measured effect on OS as well as PFS is near-exclusively seen in the smaller

non-epithelioid subgroup, evidence of add-on efficacy in patients with epithelioid disease is considered not sufficient to justify the added toxicity of pembrolizumab in this larger subgroup of patients. A restriction of the indication to the non-epithelioid histology was therefore agreed, where the beneficial effect of pembro combo was more evident with a net separation of K-M survival curves from the beginning throughout the whole duration of follow-up, and is considered to outweigh the additional toxicity, resulting in a positive benefit/risk balance.

3.7.3. Additional considerations on the benefit-risk balance

n/a

3.8. Conclusions

The overall B/R of Keytruda is positive.

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 and IIIB

Extension of indication to include in combination with pemetrexed and platinum chemotherapy the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma for Keytruda, based on final results from study KEYNOTE-483; this is a multicenter, open-label, Phase 2/3 randomized study to evaluate the efficacy and safety of pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with unresectable advanced or metastatic malignant pleural mesothelioma (MPM). As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 45.0 of the RMP has also been submitted.

Amendments to the marketing authorisation

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

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

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of KEYTRUDA in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness of patients and/or their caregivers on the signs and symptoms relevant to the early recognition/identification of the potential immune-mediated adverse reactions (imARs).

The MAH shall ensure that in each Member State where KEYTRUDA is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe and use KEYTRUDA have access to/are provided with the patient educational material.

The patient educational material should contain:

- The patient card

The patient card shall contain the following key elements:

- Description of the main signs or symptoms of the imARs and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first
- The importance of carrying the patient card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).

The card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with KEYTRUDA.

5. Re-examination of the CHMP opinion of 14 November 2024

Following the CHMP conclusion that Keytruda was not approvable in the subgroup of patients with

epithelioid disease considering:

A statistically significant survival advantage, although very limited in absolute terms, was achieved with the addition of pembrolizumab to standard chemotherapy in study KEYNOTE-483 for 1L MPM in the ITT population. As the measured effect on OS as well as PFS is near-exclusively seen in the smaller non-epithelioid subgroup, evidence of add-on efficacy in patients with epithelioid disease is considered not sufficient to justify the added toxicity of pembrolizumab in this larger subgroup of patients. A restriction of the indication to the non-epithelioid histology was therefore agreed, where the beneficial effect of pembro combo was more evident with a net separation of K-M survival curves from the beginning throughout the whole duration of follow-up, and is considered to outweigh the additional toxicity, resulting in a positive benefit/risk balance.

The MAH submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the MAH

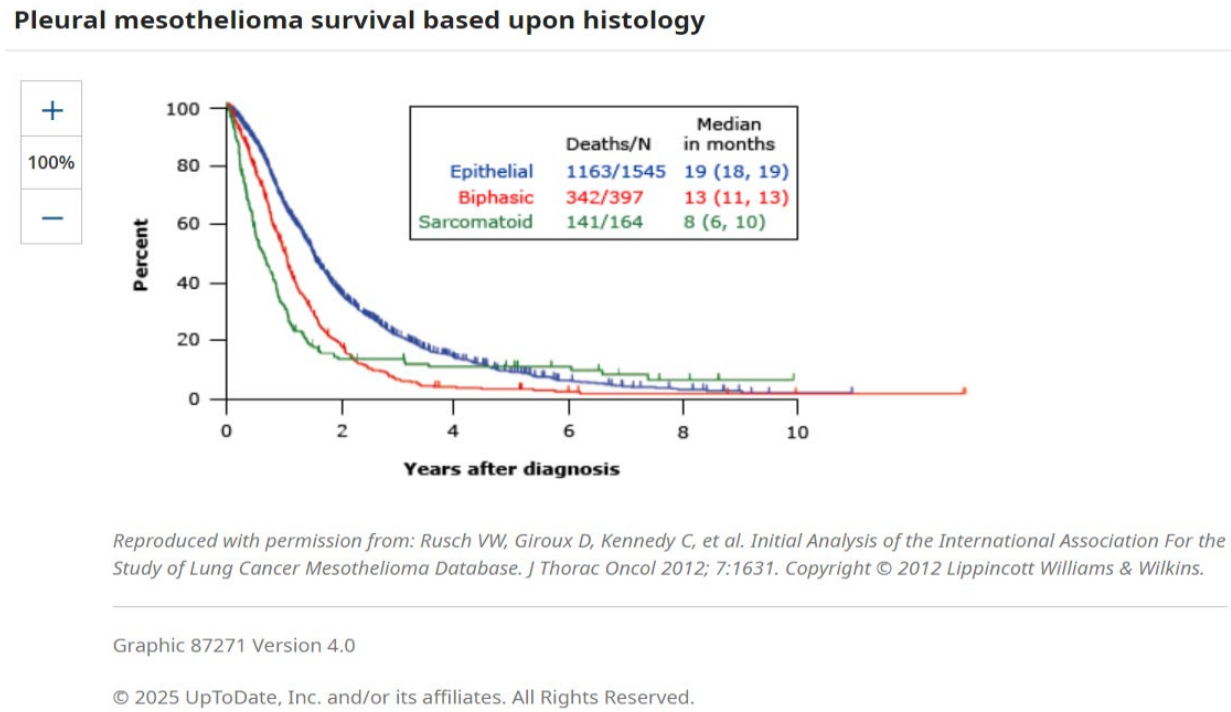
The MAH presented in writing and at an oral explanation arguments refuting the grounds for a restricted indication. The MAH argumentation was as follows:

Disease and heterogeneity in epithelioid histology

Although it cannot be dismissed that biological plausibility may exist to account for the varying effects of Keytruda across different histological types, this differential treatment effect may also stem from the heterogeneity within the epithelioid subgroup which could potentially exhibit different levels of benefit to immunotherapy among its subtypes. For instance, certain subtypes previously categorized as epithelioid, such as transitional and pleomorphic, have now been reclassified as sarcomatoid. In the context of the molecular heterogeneity of epithelial MPM, another study has recognized two unique epithelioid MPM subtypes that exhibit different gene expression profiles and prognostic outcomes. Additional research is necessary to determine which specific subgroup within the epithelioid population may derive greater benefits from the chemotherapy or chemo-immunotherapy combination, although the existing data on this matter is constrained.

The heterogeneity of the disease in terms of the histological subtypes and molecular characteristics is reflected, e.g., in differential effects of chemotherapy, since chemotherapy is more active against epithelioid disease, and has very limited activity in non-epithelioid disease. Difference in the efficacy of chemotherapy is a factor resulting in different prognosis between patients in the epithelioid subgroup treated with chemotherapy and patients in the non-epithelioid subgroups treated with chemotherapy (see figure below).

Figure 17. Pleural mesothelioma survival based upon histology



Reproduced with permission from: Rusch VW, Giroux D, Kennedy C, et al. Initial Analysis of the International Association For the Study of Lung Cancer Mesothelioma Database. J Thorac Oncol 2012; 7:1631. Copyright © 2012 Lippincott Williams & Wilkins.

Graphic 87271 Version 4.0

Additionally, the classification of histological subtype can be complex and it is essential to rely on expert, trained pathologists for accurate subtype identification. The existing histological classification is based solely on morphological descriptions, which may vary between different readers. One of the key challenges in classifying the subtype of mesothelioma is the morphological spectrum of this disease which is a continuum from epithelioid to spindle cells. Due to its pluripotential nature, mesothelioma tissue from the same patient may contain several different morphological architectural subtypes on the basis of how the cells arrange themselves and invade nearby tissues. Particularly, epithelioid mesothelioma may contain different percentages of some of these architectural subtypes: accordingly, different biopsies from the same patient may reveal different histologies, evidence of plasticity of these tumors and polyclonal origin of several of these malignancies. This intra-patient tumor heterogeneity in the epithelioid subgroup may impact the treatment benefit observed in this subgroup at large.

In this context, it was observed that out of 120 patients in the KEYNOTE-483 trial who underwent a central review of their histology, 20 patients had their histological classifications corrected centrally. Please note that the central review was performed retrospectively and did not impact on the primary OS analysis.

These findings underscore the difficulties associated with histological classification in MPM and suggest that imposing restrictions on treatment indication by subgroups based on histology may not be justified.

Overview of efficacy

Phase 3 efficacy results from KEYNOTE-483 show that pembrolizumab in combination with pemetrexed and platinum chemotherapy provides statistically significant and clinically meaningful improvement in OS, PFS and ORR by BICR per mRECIST when compared with pemetrexed/platinum chemotherapy alone in previously untreated participants with unresectable advanced and/or metastatic MPM. This is the only contemporaneous study that has demonstrated statistical and clinically meaningful results in the three key efficacy endpoints (OS, PFS and ORR).

Table 83. Efficacy results in KEYNOTE-483 (cut-off date 16 Sep 2022)

Endpoint	Pembrolizumab 200 mg every 3 weeks + Pemetrexed + Platinum Chemotherapy (n=222)	Pemetrexed + Platinum Chemotherapy (n=218)
OS		
Number (%) of patients with event	167 (75%)	175 (80%)
Hazard ratio* (95% CI)	0.79 (0.64, 0.98)	
p-Value†	0.0162	
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
PFS‡		
Number (%) of patients with event	190 (86%)	166 (76%)
Hazard ratio* (95% CI)	0.80 (0.65, 0.99)	
p-Value†	0.0194	
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Objective response rate‡		
ORR % (95% CI)	53% (46, 59)	29% (23, 36)
Response duration‡§		
Median in months (range)	6.9 (1.2+, 38.9+)	6.8 (1.4+, 25.1+)

* Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by histological subtype at randomisation (epithelioid vs. other subtypes)
† One-sided p-Value based on stratified log-rank test.
‡ Assessed by BICR using mRECIST
- Based on patients with a best objective response as confirmed complete or partial response; n=117 for patients in the pembrolizumab combination arm; n=64 for patients in the chemotherapy arm

Overall Survival

At final analysis, pembro combo provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy alone. The HR was 0.79 (95% CI: 0.64, 0.98; p-value: 0.0162, 1-sided p-value boundary=0.0204), with a reduction of 21% in the risk of death. The median OS was 17.3 months (95% CI: 14.4, 21.3) for the pembro combo group and 16.1 months (95% CI: 13.1, 18.2) for the control group, reflecting the overlapped OS KM curves until approximately Month 16, when they showed sustained separation in favour of pembro combo (see Figure 8).

Although the study was not powered to detect subgroup level treatment benefit, improvement in OS with pembro combo was generally consistent across most predefined subgroups when compared with the overall population. An improved OS was observed in both epithelioid and non-epithelioid histological subtypes; the improvement was more prominent in the non-epithelioid histological subtype (HR: 0.57 [95% CI: 0.36, 0.89]) compared with the epithelioid subtype (HR:0.89 [95% CI; 0.70, 1.13]) (see Figure 14 and Figure 15).

Results of the exploratory subgroup analyses should be interpreted with caution in absence of prespecified formal comparison of subgroups.

Progression-free Survival by BICR per mRECIST

At the final analysis, pembro combo provided a statistically significant and clinically meaningful improvement in PFS by BICR per mRECIST when compared with chemotherapy alone. The HR was 0.80 (95% CI: 0.65, 0.99; 1-sided *p*-value: 0.0194), with a 20% reduction in the risk of disease progression or death. The KM curves showed sustained separation starting at approximately Month 10 in favor of pembro combo. Both the epithelioid and non-epithelioid histological subtypes had a PFS

HR<1; the non-epithelioid histological subtype had a numerically more prominent improvement (HR: 0.47 [95% CI; 0.29, 0.77]) compared with the epithelioid subtype (HR: 0.92 [95% CI:0.73, 1.17]). Results of the exploratory subgroup analyses should be interpreted with caution.

Objective Response Rate (mRECIST by BICR)

The confirmed ORR was higher in the pembro combo group (52.3% [95% CI: 45.5, 59.0]) compared with the control group (28.9% [95% CI: 23.0, 35.4]), reflecting a clinically meaningful and statistically significant difference of 23.5% (95% CI: 14.6, 32.0; p<0.00001, 1-sided p-value boundary=0.0075 after the OS hypothesis was rejected and 30% of the alpha reallocated to the ORR hypothesis). Improvement in ORR with the pembro combo compared with the control was consistent across most predefined subgroups when compared with the overall population, including the non-epithelioid and epithelioid histological subtypes (ORR differences: 35.2 [95% CI: 19.2, 50.7] and 19.6 [95% CI: 9.1, 29.6] respectively).

Replication and plausibility of effects in epithelioid group

Results from KEYNOTE-483 are externally validated since the OS benefit observed in participants with epithelioid histology treated with pembro combo was comparable to the OS benefit observed with the nivolumab/ipilimumab (nivo+ipi) combination on the same patient population.

The combination therapy nivo+ipi in CheckMate-743 (CM743) showed an overall clinically relevant improvement in the ITT in OS of 4.0 months (HR = 0.74 [95% CI: 0.61, 0.89], stratified log-rank test p value=0.0020). This combination also showed an improved OS for both histologies included (below table). In non-epithelioid patients (n=134) the reported improvement in OS was larger compared to that reported in epithelioid patients (n=471), i.e. median OS of 8.80 (95% CI: 7.62, 11.76) months and of 16.23 months (95% CI: 14.09, 19.15) for the chemotherapy arm (non-epithelioid and epithelioid subgroup respectively) vs. 16.89 months (95% CI: 11.83, 25.20) and 18.73 (95% CI: 17.05, 21.72) for the nivo+ipi combination arm [HR = 0.46 (95% CI: 0.31, 0.70) vs. HR = 0.85 (95% CI: 0.68, 1.06)], (non-epithelioid and epithelioid subgroup respectively). Notably, the OS benefit observed in the epithelioid subgroup of CheckMate-743 did not correlate with any improvement in PFS (HR 1.14; 95% CI 0.92-1.41) or ORR (38.6% for nivolumab/ipilimumab compared to 47.2% for the chemotherapy arm) [Table 84]. In contrast, the epithelioid subgroup in KEYNOTE-483 showed a favorable trend in PFS for the pembrolizumab combination, achieving an HR of 0.92 (95% CI: 0.73, 1.17). Additionally, the ORR as assessed by BICR was significantly greater for the pembrolizumab combination in the epithelioid subtype, recording an ORR of 55.7%, which reflects an increase of 19.6% over the control arm. The 95% confidence interval for the difference in ORR did not include 0% (95% CI: 9.1; 29.6), indicating a treatment benefit associated with the pembrolizumab combination in this specific histological type.

Table 84. Efficacy results by histology (CM743 / CA209743)

	Epithelioid (n = 471)		Non-epithelioid (n = 134)	
	nivolumab + ipilimumab (n = 236)	chemotherapy (n = 235)	nivolumab + ipilimumab (n = 67)	chemotherapy (n = 67)
Overall survival				
Events	157	164	43	55
Hazard ratio (95% CI)[a]	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Median (months) (95% CI)	18.73 (17.05, 21.72)	16.23 (14.09, 19.15)	16.89 (11.83, 25.20)	8.80 (7.62, 11.76)
Rate (95% CI) at 24 months	41.2 (34.7, 47.6)	31.8 (25.7, 38.1)	39.5 (27.5, 51.2)	9.7 (3.8, 18.9)
Progression-free survival				
Hazard ratio (95% CI)[a]	1.14 (0.92, 1.41)		0.58 (0.38, 0.90)	
Median (months) (95% CI)	6.18 (5.49, 7.03)	7.66 (7.03, 8.31)	8.31 (3.84, 11.01)	5.59 (5.13, 7.16)
Overall response rate (95% CI)[b]	38.6% (32.3, 45.1)	47.2% (40.7, 53.8)	43.3% (31.2, 56.0)	26.9% (16.8, 39.1)
Duration of response Median (months) (95% CI)[c]	8.44 (7.16, 14.59)	6.83 (5.59, 7.13)	24.02 (8.31, N.A.)	4.21 (2.79, 7.03)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Confidence interval based on the Clopper and Pearson method
[c] Median computed using Kaplan-Meier method

Despite the similar data in OS and lack of clinically meaningful results in PFS and ORR in the epithelioid group in the CheckMate-743, the CHMP did not consider it warranted to exclude these patients, as the results were still positive for the combination (see EPAR Opdivo/Yervoy EMEA/H/C/WS1881, CHMP opinion 22/04/2021).

The importance of precedent in the authorization of new medicinal products cannot be overstated. It provides the foundation for a consistent, fair, transparent, and predictable regulatory process. In the realm of medicinal product regulation within the European Union, the reliance on established precedents is fundamental to the integrity and efficacy of the decision-making process. Precedent, in this context, refers to the principles, decisions, and practices established in previous authorizations that guide current and future evaluations.

Precedents ensure that health regulatory authorities maintain a consistent approach when assessing new medicinal products. By adhering to established benchmarks and criteria derived from former approvals, regulators can provide a stable and predictable framework for pharmaceutical companies. This consistency helps in maintaining public trust and industry confidence in the regulatory system.

When regulatory decisions are grounded in historical context, stakeholders, including applicants and the public, can better understand the rationale behind approvals or rejections. This transparency is essential for fostering an equitable regulatory environment where similar cases are treated similarly, thus upholding the principles of justice and impartiality.

For pharmaceutical companies, a predictable regulatory landscape is invaluable. By understanding the precedents that guide regulatory decisions, companies can more effectively navigate the complex pathways of drug development and authorization. This predictability encourages innovation, as

companies can invest in research and development with greater confidence in the regulatory process and its outcomes.

The approval of pembrolizumab in combination with chemotherapy for an unrestricted histology indication would ensure alignment with precedent while also allowing for an additional option for physicians to use this combination in the epithelioid histology, where there is an unmet medical need for more active treatments, especially in patients with high tumor burden.

Clinical value of efficacy results in epithelioid group

Malignant pleural mesothelioma shares characteristics with other solid tumors, such as lung cancer, where continuous tumor progression and the prevalence of symptoms are significant concerns for patients. Upon diagnosis, MPM is recognized as a highly symptomatic (dyspnea, pain in the chest, fatigue) and aggressive cancer, presenting considerable treatment challenges.

The combination of pembrolizumab with chemotherapy produced a rapid and sustained antitumor activity in more than 50% of patients within the epithelioid group, with an ORR difference of almost 20% (55.7% vs 36.1% pembro combo and chemotherapy alone, respectively). This reduction in the tumor burden was shown in a context of a randomized clinical trial where per inclusion criteria there had to be measurable disease at enrollment and responses were measured by a blinded independent central review. Moreover, in the overall population, only 4.1% of participants in the pembro combo group had a best overall response of progressive disease. Tumor shrinkage is usually associated with an improvement in symptoms in those patients with a considerable tumor burden. Importantly, despite the fact that KEYNOTE-483 was not designed to show differences in subgroups and considering that epithelioid histology displays longer survival than the non-epithelioid, OS and PFS outcomes in the epithelioid subgroup showed a favorable HR in both endpoints, pointing out a potential benefit in time-to-event endpoints for some patients in this histology subgroup. The efficacy of the combination of pembrolizumab and chemotherapy in KEYNOTE-483 did not produce any deterioration in health-related quality of life (QoL), as evaluated by the EORTC QLQ-C30 (GHS/QoL, physical functioning, and dyspnea) and EORTC QLQ-LC13 (chest pain and cough domains) scores. Furthermore, the proportion of participants who "improved" relative to baseline was higher in the pembro combo group compared with the chemo group for the GHS/QoL, physical functioning and disease-related symptoms scores.

In particular, the efficacy of the combination of pembrolizumab and chemotherapy has translated into a moderate improvement in chest pain score relative to the baseline (95% CI excluded zero) in the epithelioid subgroup. In the control arm, chest pain score was stable relative to the baseline (95% CI included 0). Difference in LS mean was directionally in favor of the combination of pembrolizumab and chemotherapy (-1.73; 95% CI: -6.61, 3.14), although it did not reach statistical significance (nominal p value =0.48).

These results should be considered in the light of the available efficacy data for epithelioid MPM patients.

The Phase 3 MAPS study showed improved median OS for patients with unresectable epithelioid MPM when bevacizumab was added to a cisplatin/pemetrexed regimen and followed by maintenance bevacizumab compared with cisplatin/pemetrexed alone (HR=0.82; 95% CI 0.64-1.00) . However, bevacizumab is not currently considered SOC, is not approved for MPM by major health authorities such as the FDA, Health Canada, or EMA, and its use in patients with MPM varies across global regions.

In a Phase 2 study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma, an objective response rate of 34.2% (95% CI 23.7–46.0%) was achieved in patients with epithelioid or mixed histotype only.

The BEAT-meso study, a randomized Phase 3 study of bevacizumab and standard chemotherapy with or without atezolizumab, as first-line treatment for advanced pleural mesothelioma, reported an OS HR of 1.01 (95% CI: 0.77-1.32) for epithelioid histology.

Nivolumab plus ipilimumab combination approved in 2021 in EU as first-line therapy regardless of histology, showing an OS HR in the epithelioid histology of 0.85 (95% CI: 0.68, 1.06) with no meaningful differences in ORR and PFS between nivolumab plus ipilimumab compared with cisplatin/carboplatin plus pemetrexed (ORR of 40% vs 43% and median PFS of 6.8 months vs 7.2 months); 18% of participants in the nivolumab plus ipilimumab group had a best overall response of progressive disease compared with 5% in the chemotherapy group.

Based on these data, in epithelioid MPM patients with heavy tumor burden, disease-related symptoms, and/or rapidly progressive disease, for whom a prompt treatment response is needed, pembro combo would be the preferred option due to the better antitumor activity along with the positive outcomes in PFS and OS of this combination as compared to chemotherapy and other available therapies.

Overview of safety

The results from KEYNOTE-483 demonstrate that pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with previously untreated advanced and/or metastatic MPM has a manageable safety profile that is generally consistent with the known safety profile of pembrolizumab in combination with pemetrexed/platinum chemotherapy in thoracic malignancies. The frequency and severity of AEOSI among participants treated with pembrolizumab in combination with pemetrexed/platinum chemotherapy in KEYNOTE-483 were also consistent with this combination therapy in thoracic malignancies. No new safety concerns were identified. The majority (79.3%) of the participants in KEYNOTE-483 had epithelioid mesothelioma; the safety profile of pembrolizumab in combination with pemetrexed/platinum chemotherapy in patients with epithelioid mesothelioma is consistent with the overall population of KEYNOTE-483, with no new safety concerns in patients with epithelioid mesothelioma.

Whereas the percentages of participants with some categories of adverse events were higher in the pembro combo group compared with the control group of KEYNOTE-483; Grade 3 to 5 AEs (44% vs 30.2%), drug-related Grade 3 to 5 AEs (30.7% vs 16.8%), SAEs (40.2% vs 19.0%), drug-related SAEs (27.8% vs 8.2%), and events leading to discontinuation of any drug (34.4% vs 17.2%), the median duration of therapy was longer in the pembro combo group (211.0 days) compared with the control group (107.0 days), which allowed for a longer duration of collection of AEs in the pembro combo group. Therefore, when adjusted for exposure, the rates of AEs in each category in KEYNOTE-483 were comparable between the pembro combo and control groups.

Overall occurrence of imAEs was infrequent with pembrolizumab, a single immune-checkpoint-inhibitor (ICPI), in combination with chemotherapy in KEYNOTE-483. In contrast, imAE have occurred at higher frequencies with dual ICPIs (nivolumab administered in combination with ipilimumab, compared with nivolumab as monotherapy) . In a meta-analysis of 8 clinical trials of 1727 patients with advanced cancers, the combination of nivolumab with ipilimumab was associated with substantially higher treatment-related toxicity and discontinuations compared with nivolumab alone . Moreover, a higher frequency as compared to chemotherapy alone, of Grade 3-4 AEs, SAEs and AEs leading to discontinuation were reported for the combination of nivolumab with ipilimumab in the treatment of mesothelioma, as described in the EPAR - Assessment Report for the CheckMate-743 study. The following is described in the safety discussion and conclusion sections of the EPAR - Assessment Report for the CheckMate-743 study:

"Frequencies of grade 3-4 all-causality AEs were higher with nivolumab plus ipilimumab (53.0%) compared to chemotherapy (42.6%). The overall frequency of all-causality SAEs and drug-related SAEs was higher with nivolumab plus ipilimumab (54.7% | 21.3%) compared to chemotherapy (25.4% | 7.7%). Grade 3-4 all causality SAEs were also more frequent for the nivolumab plus ipilimumab arm (34.3%) compared to the chemotherapy arm (19.0%). In the same way, the frequency of grade 3-4 drug-related SAEs was higher in the nivolumab plus ipilimumab arm (15.3%) compare to the chemotherapy arm (6.0%). A higher proportion of subjects in the nivolumab plus ipilimumab arm than in the chemotherapy arm presented any-grade all-causality AEs leading to discontinuation (29.3% vs. 20.4%), grade 3-4 all-causality AEs leading to discontinuation (19.7% vs. 9.9%), any-grade drug-related AEs leading to discontinuation (23.0% vs 15.8%) and grade 3-4 drug-related AEs leading to discontinuation (15.0% vs. 7.4%)."

"The combination treatment appears to be less well tolerated than chemotherapy as grade 3-4 all-causality AEs, all-causality and drug-related SAE (any-grade and grade 3-4), and all-causality and drug-related AEs leading to discontinuation (any-grade and grade 3-4) were reported more frequently with the nivolumab plus ipilimumab compared to chemotherapy. As expected, select AEs, IMAEs and OESIs also occurred more frequently with nivolumab plus ipilimumab compared to chemotherapy."

Based on the totally of data from CheckMate-743, a positive opinion was recommended by the CHMP for the combination of nivolumab with ipilimumab in the treatment of mesothelioma regardless of histology.

Clinical experience with Pembrolizumab plus chemotherapy and nivolumab plus ipilimumab

The combination regimens studied in KEYNOTE-483 and CHECKMATE-743 have unique safety profiles likely due to differences in their mechanism of action as combination regimens, which are important factors for thoracic oncologists to consider when individualizing the patient's optimal therapeutic plan based on clinical experience.

Conclusions

KEYNOTE-483 is the only contemporary study which demonstrated statistically significant superiority over SoC in the three key efficacy endpoints; primary endpoint OS (HR=0.79; 95% CI: 0.64, 0.98; p=0.0162), secondary endpoints PFS (HR=0.80; 95% CI: 0.65, 0.99; p=0.0194) and ORR (52.3%; 95% CI: 45.5, 59.0 and 28.9%; 95% CI: 23.0, 35.4; pembro combo and chemotherapy alone respectively)

Subgroup analyses were strictly exploratory and not powered to detect treatment effect, however they indicated benefit of the pembro combo with respect to all 3 key efficacy endpoints (OS, PFS by BICR, and ORR by BICR) in the epithelioid histology.

- OS HR favored pembro combo (HR 0.89; 95% CI: 0.70, 1.13)
- PFS HR favored pembro combo (HR 0.92; 95% CI: 0.73, 1.17)
- ORR difference of 23.5% (95% CI: 14.6, 32.0) (ORR 55.7% and 36.1%, pembro combo and chemotherapy respectively).

The KEYNOTE-483 study demonstrated significant tumor burden reduction for epithelioid patients with measurable disease at enrollment, as assessed by a blinded independent review. This tumor shrinkage, which may be associated with symptom improvement in patients with considerable tumor burden,

along with the OS and PFS results, might offer a major therapeutic advantage over available therapies in epithelioid MPM.

The treatment of pembrolizumab with chemotherapy did not negatively impact health-related quality of life (QoL), pointing out a tolerable and manageable safety profile that is generally consistent with the known safety profiles of pembrolizumab and pemetrexed/platinum chemotherapy. In addition, moderate improvement in chest pain was also observed in favor of the combination of pembrolizumab and chemotherapy.

Results from the study KEYNOTE-483, should be considered in the light of the totality of the data in the treatment of MPM, contemplating the clinical experience and reported efficacy and safety data from clinical studies of the current therapeutic armamentarium. Both, combination of ICPI and chemotherapy-based regimens, have a different safety profile and mechanism of action, with no clear efficacy/safety advantages over pembro combo. Consistency with prior regulatory precedents which show similar benefit-risk discussion is beneficial for different stakeholders in the decision-making process of medicinal products regulations.

The MAH considers that a restricted indication is not justified or warranted and would deny treatment with pembro combo for an important group of patients in need of new therapies, who could benefit from this combination. Instead, the MAH proposes to include the results of exploratory subgroup analyses by histology in section 5.1 of the SmPC for transparency to prescribers to make an informed treatment decision.

In summary, pembrolizumab plus chemotherapy would provide an alternative treatment option for MPM patients with epithelioid histology and would allow providers to individualize the patient's optimal therapeutic plan among a panel of treatment combinations of distinct mechanistic, safety, and clinical activity profiles with careful thought of physician preferences, and patient-related consideration such as disease burden, rate of tumor growth, presence of tumor-related symptoms, and patient underlying comorbidities.

5.2. Discussion and overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the MAH.

Of note, the requirement for fair, transparent, and consistent regulation is completely agreed. However, it is not agreed that differential outcomes of KN483 and CM743 are inconsistent or reflect the application of different standards. KN483 is an add-on study to an active chemotherapy background, whereas CM743 is a substitution study where immune therapy is compared to chemotherapy. The evaluation of efficacy metrics must be viewed in this light.

The MAH argues for a positive B/R for pembrolizumab in the first-line treatment of adults with unresectable malignant pleural mesothelioma in combination with pemetrexed and platinum chemotherapy. According to the MAH this is regardless of histology, thereby challenging the CHMP opinion stating that this is only for patients with non-epithelioid histology.

The MAH begins by noting the heterogeneity of the disease in terms of the histological subtypes and molecular characteristics. This is reflected, e.g., in differential effects of chemotherapy, which is more active against epithelioid disease, and has very limited activity in non-epithelioid disease. Differences in the efficacy of chemotherapy is a factor resulting in different prognosis (see Figure 17. Pleural mesothelioma survival based upon histology).

The MAH also notes that the histological classification of mesothelioma may not be straightforward, as

illustrated by a considerable proportion of disease being differently classified by local and central review.

However, it is acknowledged that the known difference in response to chemotherapy and prognosis was taken into consideration at the planning stage, with inclusion of histology as a stratification factor.

On the data pivotal to the claim

The pivotal trial for this application, KN-483, is an academic study conducted by the CCTG, open-label, Phase 2/3, randomized, in patients with previously untreated unresectable MPM to investigate the add-on of pembrolizumab to pemetrexed/platinum chemotherapy.

440 participants were included starting with 2016 and randomised 1:1. between pembrolizumab plus chemotherapy or chemotherapy alone.

The OS result of the final analysis (cut-off 16-SEP-2022) in the ITT population was statistically significant with HR 0.79 (95% CI: 0.64, 0.98; 1-sided p-value: 0.0162, 1-sided p-value boundary=0.0204). This is plausible based on prolonged PFS and increased ORR. Results in the ITT population are given in Table 25. Analysis of Overall Survival (Phase 3 ITT population).

Histology was a stratification factor, which confirms the importance of histology for understanding efficacy and gives a high a-priori weight to the subgroup analysis by histology. As already noted, baseline characteristics were generally balanced within each histological subgroup.

The different prognosis in epithelioid and non-epithelioid disease is evident in Table 30. OS as well as PFS are approximately twice as long for epithelioid disease in the control arm. The different prognosis is at least partly driven by the differential activity of chemotherapy in the epithelioid and non-epithelioid subgroups. Moreover, the activity of chemotherapy in non-epithelioid disease is near absent in the present study (ORR 6%), whereas a substantial proportion of patients with epithelioid disease respond to therapy (ORR 36%).

The add-on of pembrolizumab results in an increase of objective responses by 20 percentage units (ORR 56%). Although pembrolizumab exhibits antitumoral activity regardless of histology, a lower relative benefit of pembro combo was observed in the epithelioid **histology** group (HR=0.89; 95% CI:0.70,1.13) where the K-M curves for OS were generally overlapping. In non-epithelioid tumours, the beneficial effect of pembro combo is more evident (HR=0.57, 95% CI 0.36, 0.89) with a net separation of K-M survival curves from the beginning throughout the whole duration of follow-up. This pattern of response reproduces what was already observed in epithelioid and non-epithelioid MPM cancer (see below).

External data to support the activity of checkpoint inhibition regardless of histology

The biological activity and clinical benefit of checkpoint inhibition has external support through the CheckMate-743 study, where a combination of nivolumab+ipilimumab was compared to chemotherapy. OS was longer with checkpoint inhibition than with chemotherapy alone, regardless of histology. Moreover, the activity of checkpoint inhibition was similar regardless of histology (see Table 84).

Median PFS and OS for patients treated with checkpoint inhibition are similar regardless of histology. Differences in relative efficacy are due to the greater activity of chemotherapy in epithelioid disease.

The CheckMate-743 study supports that histology is mainly a modifier of the antitumoral activity of chemotherapy rather than checkpoint inhibition. Of note, this was a substitution study, testing immune-checkpoint inhibitors as alternative to chemotherapy, which needs to be considered when evaluating the relevance of the observed benefit. Thus, the CheckMate-743 study supported a CHMP

positive opinion for nivolumab+ipilimumab regardless of histology (see EPAR Opdivo/Yervoy EMEA/H/C/WS1881, CHMP opinion 22/04/2021).

Subsequently, activity as well as the prolonged OS of checkpoint inhibition for patients with non-epithelioid tumours seen in CheckMate-743 was replicated with the add-on of pembrolizumab to chemotherapy in the Keynote-483 study. A differential antitumoral activity of chemotherapy was also observed in KN-483.

The safety profile of pembrolizumab as add-on to chemotherapy

The safety profile of pembro combo in KN-483 was generally consistent with the safety profile from other studies with pembro-chemotherapy combination. As expected, the addition of pembrolizumab increases the toxicity of chemotherapy, although no new safety concerns emerged. The add-on of a PD-1 inhibitor to chemotherapy has shown an acceptable and manageable safety profile across a broad range of solid tumours, including mesothelioma. The CHMP grounds for refusal of use in patients with epithelioid tumours is based on the lack of a relevant benefit to compensate for the added toxicity, and not on any specific safety concerns.

The clinical benefit of adding pembrolizumab to chemotherapy

Adding pembrolizumab to chemotherapy in patients with malignant pleural mesothelioma resulted in a statistically significant increase in OS, although very limited in absolute terms and near-exclusively seen in the non-epithelioid subgroup.

Conclusion

The pivotal KN-483 study demonstrated a statistically significant OS benefit in the ITT population (HR 0.79; 95% CI 0.69-0.98). The add-on activity as well as an increment in OS was most pronounced in the smaller non-epithelioid subgroup (OS HR=0.57; 95%, CI 0.36, 0.89).

The activity and benefit of checkpoint inhibition regardless of histological subgroup is consistent with findings from the CheckMate-743 study, which also showed a differential response to chemotherapy between the two histology subgroups.

The safety profile of adding pembrolizumab to chemotherapy is in line with what has been seen in the treatment of numerous solid tumours in advanced stage and is acceptable in this context. There are no new safety concerns. However, in the epithelioid subgroup, the added toxicity of pembrolizumab compares unfavourably to the marginal benefit observed that appears neither clinically relevant nor statistically compelling despite the larger size of this subgroup (471 vs 134 patients).

Based on these considerations, the MAH's position is not agreed, and a restriction of the applied indication of pembrolizumab in combination with chemotherapy for the first line treatment of unresectable malignant pleural mesothelioma to the subgroup with non-epithelioid histology is sufficiently justified.

The B/R for the first-line treatment of adults with unresectable malignant pleural mesothelioma in combination with pemetrexed and platinum chemotherapy is positive in the subgroup of patients with non-epithelioid histology.

5.3. Update of the Product information

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

6. Benefit-risk balance

6.1. Therapeutic Context

6.1.1. Disease or condition

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

6.1.2. Available therapies and unmet medical need

Malignant pleural mesothelioma (MPM) is a rare disease. The treatment decision making process considers factors such as staging, histology, age, PS, comorbidities and the patient's preferences. A multimodality approach including surgery, or palliative care, or systemic therapy only are the available options for MPM management. In subjects that are candidates for a non-surgical approach, pemetrexed-platinum chemotherapy has long been the standard-of-care as a first line treatment. Nivolumab–ipilimumab is a relatively new first-line option for unresectable MPM regardless of underlying histology (epithelioid or non-epithelioid). This was approved based on the supportive data from the CheckMate 743 study, demonstrating improvement in OS with nivolumab–ipilimumab over cisplatin/carboplatin and pemetrexed chemotherapy regardless of histology (see EPAR Opdivo/Yervoy EMEA/H/C/WS1881, CHMP opinion 22/04/2021). Prognosis remains poor in advanced MPM, leading to the need for effective treatments.

6.1.3. Main clinical studies

The current application is supported by data from the phase 2/3 study KEYNOTE-483, an open-label, multicentre, randomized study of pembrolizumab plus chemotherapy versus chemotherapy alone in participants with MPM receiving first-line treatment for unresectable advanced and/or metastatic disease. The study was sponsored and conducted by the Canadian Cancer Trial Group (CCTG).

In the Phase 3 portion of the study in which participants were randomized into 1 of 2 arms in a 1:1 ratio to Arm A (chemo) or Arm B (pembro + chemo).

6.2. Favourable effects

- The type 1 error controlled ITT analysis of the phase 3 part demonstrated a statistically significant superiority of pembro combo compared to control in the primary endpoint OS (HR=0.79; 95% CI:0.64,0.98; p=0.0162), as well as in the secondary endpoints PFS (HR=0.80; 95% CI:0.65,0.99; p=0.0194), and ORR as assessed by BICR (52.3%) compared to control (28.9%) (2-sided p-value <0.00001).

  OS in the non-epithelioid histology subgroup (n=134) showed a HR=0.57; 95% CI 0.36, 0.89.

  Thus, improved median OS was observed with pembro combo vs chemotherapy in the non-epithelioid subgroup of 12.3 vs 8.2 months.

- The ORR by BICR in the pembro combo versus chemotherapy arm was 41.3% vs 6.1% in the non-epithelioid subgroup.

- PFS in the non-epithelioid histology subgroup was HR=0.47 (95% CI: 0.29, 0.77). In the non-epithelioid subgroup median PFS comparatively between arms was 7.1 vs 4.5.

6.3. Uncertainties and limitations about favourable effects

- The results of the subgroup analysis by histology are exploratory and not type 1 error controlled, however, histology was a stratification factor and baseline characteristics were balanced within each histological subgroup.

6.4. Unfavourable effects

- In the pembro + chemo arm (n=241) generally higher toxicity was observed as compared to the chemo arm (n=232): drug-related AE (90% vs 81.5%), G3-5 AE (44% vs 30.2%), SAE (40.2% vs 19%), drug-related SAE (27.8% vs 8.2%), death (7.1% vs 2.2%), drug-related death (2.9% vs 0.9%), discontinuation due to AE of any treatment (34.4% vs 17.2%) and of any chemotherapy (24.5% vs 15.9%). When adjusted for exposure (longer in the pembro arm due to protocol-defined continuation of pembrolizumab after 6 cycles of chemotherapy) the difference between arms appears more limited. The overall incidence of AEs of the pembro+chemo arm of KN-483 appears similar to the pooled pembro+chemo reference safety dataset (n=3123).
- In the pembro+chemo arm, the most common AEs (>20%) were fatigue (61.4%), nausea (53.1%), constipation (32%), diarrhoea (30.7%), dyspnoea (29.6%), vomiting (26.1%), pyrexia (22.4%), stomatitis (22.4%), and decreased appetite (21.6%); while in the chemo arm those were fatigue (61.4%), nausea (47%), constipation and dyspnoea (22% each), decreased appetite (20.7%). In both arms, most AEs were G2 and G3. The AE types and incidences in the pembro combo arm of KN-483 are similar to the combo reference dataset.
- The most common G3-5 AEs (>5%) were fatigue (7.5%) and febrile neutropenia (5.8%) in the pembro combo arm and fatigue (7.8%) and dyspnoea (5.2%) in the control arm of KN-483. Febrile neutropenia was the only SAE ≥5% occurring in the pembro combo arm.
- The most common cause of death due to AE was sepsis in both treatment arms (4 cases in pembro combo arm, 1.7%; 2 cases in the control arm, 0.9%).
- The most common (>5%) AEOSI occurring in the pembro combo arm of KN-483 were hypothyroidism (9.1%), infusion reactions (5%) and pneumonitis (5%). The overall type, frequency, severity and duration of AEOSI were similar to the Pooled Pembrolizumab Combination dataset.

6.5. Uncertainties and limitations about unfavourable effects

N/A

6.6. Effects Table

Table 85 Effects Table for Keytruda in combination platinum and pemetrexed in unresectable non-epithelioid MPM (Study KEYNOTE-481, data cut-off: 16-SEP-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	duration of survival from randomization	months	12.3 (8.7, 21.2)	8.2 (5.8, 9.8)	Subgroup analysis not adjusted for multiplicity.	Section 2.4

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	to death regardless of cause	(95 % CI)			Stratified subgroup Primary analysis in ITT was statistically significant but considered of limited clinical relevance	
PFS	duration of survival without progression from randomization to PD or death whichever occurred first	mon ths (95 % CI)	7.1 (4.5, 9.8)	4.5 (4.0, 6.4)		
Unfavourable Effects						
	Grade 3-5 AEs	%	44	30.2	Worse safety of the combination/toxicity consistent with each agent of the combination, no new unexpected safety findings	Section 2.5
	SAEs		40.2	19		
	Deaths due to AEs		7.1	2.2		
	Discontinuation due to AE (any drug)		34.4	17.2		

Abbreviations: AE: adverse event; SAE: serious adverse event

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The pivotal KN-483 study demonstrated a statistically significant OS benefit in the ITT population. However, these results are considered of limited clinical relevance since there is a separation of the K-M curves only at 18 months with only 1 month gain in median overall survival, and no gain in median PFS. The add-on activity as well as increment in OS was most pronounced in the smaller non-epithelioid subgroup, while only modest activity with marginally increased OS was seen in the larger epithelioid subgroup that was not statistically compelling despite the size of the subgroup. Thus, clinical benefit cannot be inferred in the sought wider indication, independent of histology. The differential activity based on histology is consistent with findings from the CheckMate-743 study.

The safety profile of adding pembrolizumab to chemotherapy is in line with what has been seen in the treatment of numerous solid tumours in advanced stage and is considered manageable in clinical practice. There are no new safety concerns. However, the observed toxicity of adding pembrolizumab to chemo outweighs the insufficient efficacy seen in the epithelioid subgroup.

Based on these considerations, the MAH's position is not agreed and the restriction of the applied indication of pembrolizumab in combination with chemotherapy for the first line treatment of unresectable pleural mesothelioma to the subgroup of patients with non-epithelioid histology is justified (see also section 3.7.1).

6.7.2. Balance of benefits and risks

The benefit/risk balance of pembrolizumab in combination with platinum/pemetrexed in first line unresectable malignant pleural mesothelioma is therefore considered positive only in the subgroup of patients with non-epithelioid histology (see also 3.7.2).

6.7.3. Additional considerations on the benefit-risk balance

n/a

6.8. Conclusions

The overall B/R of Keytruda is positive.

7. Recommendations following re-examination

Final outcome

Based on the arguments of the MAH and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion 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 and IIIB

Extension of indication to include in combination with pemetrexed and platinum chemotherapy the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma for Keytruda, based on final results from study KEYNOTE-483; this is a multicenter, open-label, Phase 2/3 randomized study to evaluate the efficacy and safety of pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with unresectable advanced or metastatic malignant pleural mesothelioma (MPM). As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 45.0 of the RMP has also been submitted.

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 and IIIB and to the Risk Management Plan are recommended.