Amsterdam, 18 September 2025
EMADOC-1700519818-2228659
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMA/X/0000248795

Note

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

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List of abbreviations

Abbreviation	Definition
%CV	percent coefficient of variation
α	Allometric exponent
1L	first line
AUC	area under the curve
ADA	antidrug antibodies
ADME	Absorption, distribution, metabolism, and elimination
AE	adverse event
AEOSI	adverse event of special interest
AS	Active substance
AUC	Area under the concentration-time curve
BLA	biologics license application
BLQ	below the limit of quantification
BTC	biliary tract cancer
CDE	Centre of Drug Evaluation
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum serum concentration
C_{trough}	trough serum concentration
CV	Coefficient of variation (%)
DDI	drug-drug interaction
dMMR	deficient mismatch repair
DOR	duration of response
DP	drug product
DS	drug substance
E-R	exposure-response
EC50	effective concentration
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EQ-5D-5L	EuroQol 5-dimension 5-level Questionnaire

Abbreviation	Definition
E-R	Exposure-response
EU	European Union
F	bioavailability
FA	final analysis
Fc	fragment crystallizable
FDA	Food and Drug Administration
GC	gastric cancer
G-CSF	granulocyte colony-stimulating factor
GM	geometric mean
GMR	geometric mean ration
HC	Health Canada
HER	human epidermal growth factor receptor
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
IgG4	immunoglobulin G4
IL-2	Interleukin 2
ITT	Intent-to-Treat
IV	intravenous
Ka	absorption rate constant
KM	Kaplan-Meier
M&S	modeling and simulation
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	microsatellite instability-high
NI	noninferiority
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	Pharmacodynamics
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1

Abbreviation	Definition
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PMBCL	primary mediastinal B-cell lymphoma
PMDA	Pharmaceuticals and Medical Device Agency
PP	per protocol
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
RSD	reference safety dataset
RSE	Relative standard error
SC	subcutaneous
SmPC	Summary of Product Characteristics
sSAP	supplemental statistical analysis plan
SD	safety dataset
SAE	serious adverse event
TDPK	Time-dependent pharmacokinetic
TMB-H	tumor mutational burden-high
TNBC	triple negative breast cancer
TNF	tumor necrosis factor
TPS	tumor proportion score
UC	urothelial carcinoma
US	United States
USPI	United States Prescribing Information
V	volume
VAS	visual analog scale
Vc	Central volume of distribution

1. Executive Summary

On 18 September 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Keytruda (pembrolizumab).

The CHMP adopted a new pharmaceutical form, solution for injection, associated with two new strengths (790 mg and 395 mg) and a new route of administration, subcutaneous use.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

The indications included in the current application are all the approved indications for Keytruda in the adult population (i.e. excluding the paediatric indications).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Information on the product

Product data	
Product name	Keytruda
Active substance	pembrolizumab
INN or common name	pembrolizumab
Applicant	Merck Sharp & Dohme B.V.
EMA Product Number	EMEA/H/C/003820
ATC code and Pharmacotherapeutic group	L01FF02
Pharmaceutical form(s) and strength (s)	solution for injection, 790 mg and 395 mg
Packaging	Vial
Package size(s)	1 vial
Route of administration	subcutaneous use
Device or diagnostic	Not applicable
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Final indication	<u>Melanoma</u> KEYTRUDA as monotherapy is indicated for the treatment of adults with advanced (unresectable or metastatic) melanoma. KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage IIB, IIC or III melanoma and who have undergone complete resection (see section 5.1). <u>Non-small cell lung carcinoma (NSCLC)</u> KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1). KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection

and platinum-based chemotherapy (for selection criteria, see section 5.1).

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PDL1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

Malignant pleural mesothelioma (MPM)

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

Classical Hodgkin lymphoma (cHL)

KEYTRUDA as monotherapy is indicated for the treatment of adults with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1).

Product data	
	KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see section 5.1). <u>Head and neck squamous cell carcinoma (HNSCC)</u> KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1). KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy (see section 5.1). <u>Renal cell carcinoma (RCC)</u> KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1). KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1). KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, see section 5.1). <u>Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers</u> *Colorectal cancer (CRC)* KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings: - first-line treatment of metastatic colorectal cancer; - treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy. *Non-colorectal cancers* KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with: - advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any

setting and who are not candidates for curative surgery or radiation;

- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10 (see section 5.1).

Triple-negative breast cancer (TNBC)

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence (see section 5.1).

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease (see section 5.1).

Endometrial carcinoma (EC)

KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Cervical cancer

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of

Product data	
	persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1. Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1). Biliary tract carcinoma (BTC) KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

2.2. Scientific advice and protocol assistance

Scientific advice and protocol assistance

The MAH received scientific advices from the CHMP on 25 Jul 2019 (EMEA/H/SA/2437/27/2019/I), 15 September 2022 (EMA/SA/0000095182), 22 June 2023 (EMA/SA/0000136666), 20 July 2023 (EMA/SA/0000137910), 22 February 2024 (EMA/SA/0000161394) and 30 January 2025 (EMA/SA/0000230344). The scientific advices pertained to quality, non-clinical, and clinical aspects.

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
25/07/2019	Quality	EMEA/H/SA/2437/27/2019/I / Sheila Killalea and Stephan Lehr	Chemical, Pharmaceutical and Biological development
15/09/2022	Non-clinical and clinical	EMA/SA/0000095182 / Brigitte Schwarzer-Daum and Silvijus Abramavicius	The Scientific Advice pertained to the following clinical, and non-clinical aspects: • The proposed non-clinical package for the finished product and novel excipient to support the extension for the subcutaneous route of administration • The overall design of a proposed phase 3 study MK-3475A-D77 and specifically the patient population, stratification factors, and endpoints; the safety data collection strategy; the statistical assumptions and analyses; and the dose selection strategy • The proposed approach to bridge the subcutaneous route to all approved IV indications
20/07/2023	Clinical	EMA/SA/0000137910 / Serena Marchetti and Andrea Laslop	Design of the phase 2 cross-over trial MK-3475A-F11, evaluating patient preference between pembrolizumab SC and pembrolizumab IV, in particular, the primary endpoints, the use of an electronic version of the Patient Preference Questionnaire (PPQ), statistical considerations and inclusion of study results in the SmPC.

2.3. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (1) - Extensions of marketing authorisations.

2.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0096/2023 on the granting of a (product-specific) waiver.

2.5. Information on orphan market exclusivity

2.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure Tibsovo, Pemazyre, Vyloy and Ziihera.

2.6. Patient experience data

Table 1: Patient experience data relevant to the application

Patient experience data submitted with this application				Section where discussed (if applicable)
☒	Patient experience data submitted by the applicant:			
	☒	Clinical outcome assessments (COAs) such as		
		☒	Patient-reported outcomes (PRO)	6.2.2
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	☐	CHMP early dialogue with patient organisations		
	☐	Third party interventions from patients and patient groups		
	☐	Other (such as medical literature, summaries/analysis from patient engagement activities - please specify)		

2.7. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur:	Paolo Gasparini
Co-Rapporteur:	n/a

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

PRAC Rapporteur:	Bianca Mulder
PRAC Co-Rapporteur:	n/a

The application was received by the EMA on	31 Jan 2025
The procedure started on	20 Feb 2025
The CHMP Rapporteur's first Assessment Report was received on	12 May 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	19 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 June 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	26 Aug 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 Sept 2025
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	12 Sept 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion on	18 September 2025
The CHMP adopted a report on similarity of Keytruda with on	18 September 2025

2.8. Final CHMP outcome

2.8.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 9.3 of this report.

2.8.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 9.4 of this report.

2.8.3. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Keytruda (790 mg and 395 mg) solution for injection and a new route of administration (subcutaneous use) is favourable in the following indication(s):

Melanoma

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

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage IIB, IIC or III melanoma and who have undergone complete resection (see section 5.1).

Non small cell lung carcinoma (NSCLC)

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1).

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (for selection criteria, see section 5.1).

KEYTRUDA as monotherapy is indicated for the first line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non squamous non small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab paclitaxel, is indicated for the first line treatment of metastatic squamous non small cell lung carcinoma in adults.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non small cell lung carcinoma in adults whose tumours express PD L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

Malignant pleural mesothelioma (MPM)

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

Classical Hodgkin lymphoma (cHL)

KEYTRUDA as monotherapy is indicated for the treatment of adults with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum containing chemotherapy (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10 (see section 5.1).

Head and neck squamous cell carcinoma (HNSCC)

KEYTRUDA as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1.

KEYTRUDA, as monotherapy or in combination with platinum and 5 fluorouracil (5 FU) chemotherapy, is indicated for the first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a CPS ≥ 1 (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a ≥ 50% TPS and progressing on or after platinum containing chemotherapy (see section 5.1).

Renal cell carcinoma (RCC)

KEYTRUDA, in combination with axitinib, is indicated for the first line treatment of advanced renal cell carcinoma in adults (see section 5.1).

KEYTRUDA, in combination with lenvatinib, is indicated for the first line treatment of advanced renal cell carcinoma in adults (see section 5.1).

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, see section 5.1).

Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers

Colorectal cancer (CRC)

KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- first line treatment of metastatic colorectal cancer;
- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine based combination therapy.

Non-colorectal cancers

KEYTRUDA as monotherapy is indicated for the treatment of the following MSI H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD L1 with a CPS ≥ 10 (see section 5.1).

Triple negative breast cancer (TNBC)

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence (see section 5.1).

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease (see section 5.1).

Endometrial carcinoma (EC)

KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation.

Cervical cancer

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD L1 with a CPS ≥ 1

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD L1 with a CPS ≥ 1 (see section 5.1).

Biliary tract carcinoma (BTC)

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

2.8.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

2.8.5. Other conditions and requirements of the marketing authorisation

2.8.5.0. Periodic safety update reports

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.

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

2.8.6.0. 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.

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.

2.8.6.1. 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.

2.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

3. Introduction

3.1. Therapeutic Context

Immunotherapy has changed the treatment paradigm for numerous cancers. Its use has been evaluated firstly in melanoma and NSCLC, and subsequently in several malignancies at first in the advanced/metastatic setting and then also in early-stage disease.

To date, Keytruda (pembrolizumab), an anti-PD1 mAb, is approved in the EU as monotherapy or in combination with chemotherapy or other agents (i.e. ADC, TKI, antiangiogenics, RT) in 14 tumor types and in both early and metastatic disease settings. The currently approved regimen for treatment with pembrolizumab is administration by IV The currently recommended dose of Keytruda in adults is either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) administered as an IV infusion over 30 minutes. Patients should be treated with Keytruda until disease progression or unacceptable toxicity, or up to a maximum duration of therapy if specified for an indication (usually 1 or 2 years).

According to the Applicant, the subcutaneous (SC) route could offer increased convenience, time saving, and the potential to improve the quality of life for patients and reduce chair time in the hospital compared to the IV route, while providing clinical benefits comparable to IV product.

The new formulation for the SC route of administration is for the doses of395 mg Q3W and 790 mg Q6W. Timing of administration is approximately 1 minute and 2 minutes, respectively, as compared to 30 minutes of the IV infusion. The SC injection should be administered in the abdomen or thigh. The SC injection should be administered by a healthcare professional only.

The Applicant is requesting the use of the SC formulation to all the currently approved indications for Keytruda IV in adults. The two currently approved paediatric indications in melanoma and Hodgkin lymphoma are not covered by this line extension.

3.2. Aspects of development

The development of a SC version of pembrolizumab is based on the extensive pembrolizumab IV program. These data have indicated that both PK and immunogenicity are generally consistent across tumor types, stage of disease, and between monotherapy and combination treatment. Furthermore, the exposure-response relationship of pembrolizumab for both efficacy and safety are shown to be flat in the clinically studied >5-fold dose/exposure range from 2 mg/kg Q3W to 10 mg/kg Q2W in NSCLC and melanoma, and it was also observed to be flat for other indications.

The pivotal study MK-3475A-D77 was designed with PK primary endpoints to evaluate the noninferiority of pembrolizumab administered SC compared to IV. MK-3475A-D77 included a population that comprised adult participants with treatment-naïve metastatic NSCLC. This setting was justified by the Applicant as this is the most common malignancy and pembrolizumab has changed the treatment paradigm for NSCLC. MK-3475A-D77 included a population that comprised adult participants with treatment-naïve metastatic NSCLC.

As the active ingredient in MK-3475A is identical to the approved pembrolizumab IV product, the Applicant considered that demonstration of noninferiority of the systemic drug exposure after SC administration provides evidence that efficacy similar to pembrolizumab IV will be maintained. A lower Cmax at steady state is expected after SC administration compared with IV administration and would therefore be expected to have a similar systemic safety profile to that for the currently

approved IV product. Further, according to the Applicant, establishing PK NI and comparable efficacy and safety in NSCLC allows bridging to other approved pembrolizumab indications.

To support the development of MK-3475A, the reference PK model was expanded to characterize the pembrolizumab PK profile after SC administration of MK-3475A using pooled data from MK-3475A-C18 and MK-3475A-D77.

The PK of MK-5180 (berahyaluronidase alfa) was characterized in healthy volunteers in ALT-BB4-01 study, and plasma MK-5180 concentrations were then evaluated following SC administration of MK-3475A in MK-3475A-C18 and MK-3475A-D77 studies.

To justify the dose of MK-3475A, PK exposure-matching principles were used to bridge the proposed pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A dosing regimens to the currently approved pembrolizumab IV dosing regimens across indications, based on data from MK-3475A-D77 and MK-3475A-C18 studies.

The clinical immunogenicity of pembrolizumab after SC administration as MK-3475A and pembrolizumab IV administration was assessed in MK-3475A-C18 and MK-3475A-D77 studies.

Of note, an earlier development program was initiated to examine the use of pembrolizumab administered subcutaneously without MK-5180 (KEYNOTE-A86 study), which was however deprioritized in favor of MK-3475A, since the addition of MK-5180 would allow for both Q3W and Q6W SC administration as well as delivery in a single injection.

3.3. Description of the product

MK-3475A is pembrolizumab with MK-5180.

Pembrolizumab (MK-3475) is a potent and highly selective anti-PD-1 humanized IgG4/kappa isotype mAb which blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T-cells.

MK-5180 is a novel variant of human hyaluronidase PH20 called berahyaluronidase alfa, which acts as a permeation enhancer. The addition of MK-5180 allows for the administration of pembrolizumab via SC administration in 1 injection for both Q3W and Q6W dosing regimens.

3.4. Inspection issues

3.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

3.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

3.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

4. Quality aspects

4.1. Introduction

With this extension application, the MAH seeks approval of a subcutaneous (SC) formulation of Keytruda (pembrolizumab) as an alternative formulation/route of administration to that of pembrolizumab IV. In this SC formulation, pembrolizumab is co-formulated with recombinant berahyaluronidase alfa (MK-5180), a novel excipient added to the fully formulated pembrolizumab as a permeation enhancer. Keytruda subcutaneous finished product (FP) is presented as a solution for injection containing 165 mg/mL pembrolizumab as active substance (AS).

Other ingredients are: recombinant berahyaluronidase alfa, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, sucrose, polysorbate 80 (E433), and water for injections.

Keytruda SC finished product is available in two presentations:

- KEYTRUDA 395 mg solution for injection

  2.4 mL of solution in a Type I glass vial with a grey chlorobutyl stopper and an aluminium seal with a yellow coloured flip-off cap, containing 395 mg pembrolizumab.

- KEYTRUDA 790 mg solution for injection

  4.8 mL of solution in a Type I glass vial with a grey chlorobutyl stopper and an aluminium seal with a light green coloured flip-off cap, containing 790 mg pembrolizumab.

4.2. Active substance

4.2.1. General information

Pembrolizumab 165 mg/mL active substance (AS) is identical to the approved pembrolizumab 25 mg/mL AS, except for the higher protein concentration and addition of L-methionine to the formulation as an antioxidant. Pembrolizumab 165 mg/mL AS manufacturing process is identical to the registered AS manufacturing process of pembrolizumab 25 mg/mL up to and including the ultrafiltration/diafiltration (UF/DF) process step, followed by the high concentration ultrafiltration step to generate a high concentration product required for the pembrolizumab 165 mg/mL formulation.

Pembrolizumab 165 mg/mL AS at room temperature is a clear to opalescent liquid. The colour of the solution at room temperature is colourless to slightly yellow. There is no change to other physicochemical, biological and immunochemical properties of pembrolizumab due to the pembrolizumb 165 mg/mL AS formulation.

4.2.2. Manufacture, characterisation, and process controls

4.2.2.0. Manufacturer(s)

Pembrolizumab 165 mg/mL is manufactured at two approved AS manufacturing sites: Samsung Biologics Co., South Korea (SBL).

Description of manufacturing process and process controls

Detailed information on the AS manufacture is provided for both sites.

Briefly, the AS is expressed by means of Chinese hamster ovary (CHO) cell line and the manufacturing process is achieved in two main parts:

a) the upstream process that includes inoculum growth and cellular expansion up to the production bioreactor;

b) the downstream process that purifies the antibody by sequential chromatography and viral inactivation steps up to an ultrafiltration/diafiltration (UF/DF) unit to concentrate and exchange the buffer to obtain the final AS.

Noteworthy, the process up to the above-described stage is exactly the same as that already approved to produce pembrolizumab 25 mg/mL for IV formulation. Additional steps have been implemented to produce AS at 165 mg/mL for the new SC formulation, the first of which is a high concentration ultrafiltration (HC UF) to further concentrate the product pool. During the operation of the formulation unit, formulation buffer is added. Finally, the formulated AS is filtered, dispensed into bags, frozen and stored.

Importantly, Critical Process Parameters (CPPs) with corresponding ranges, as well as Non-critical Process Parameters - Key Operating Parameters (KOPs), Non-Key Operating parameters (NKOPs), In-Process Control (IPC) and Key Process Attribute (KPA) are appropriately provided as part of the overall control strategy along the different stages of the entire process.

Control of materials

The MAH has provided the list of the materials intended to be used for the manufacture of pembrolizumab AS 165 mg/mL for SC presentation. In general, sufficient details on this regard are available. The pembrolizumab 165 mg/mL AS manufacturing process uses the same Master Cell Bank (MCB) and Working Cell Banks (WCB) as the pembrolizumab 25 mg/mL AS manufacturing process. Consequently, no critical issues have been identified in this regard.

It should be noted that all materials, solutions and reagents in the manufacturing process of pembrolizumab 165 mg/mL up to the UF/DF stage are the same as those used for the already licensed production of pembrolizumab 25 mg/mL. All the other information specific for the additional final steps planned for AS at 165 mg/mL, which include high concentration ultrafiltration and the new formulation for active substance SC version, is satisfactorily presented.

Regarding the expression vector and the cell bank system (MCB/WCB/PPCB) together with all related information, nothing changes with respect to what has already been authorised for the AS at 25 mg/mL.

4.2.2.1. Control of critical steps and intermediates

The proposed critical process parameters monitoring plan, as well the control of bioburden, endotoxin, and other in-process controls is adequate to control the different process steps foreseen for pembrolizumab 165 mg/mL AS manufacturing process. In this regard, all tests related to the proposed critical process parameters monitoring plan have been adequately verified or validated, thereby providing an overview of the results (from three independent lots) and, where relevant, a reference to the European Pharmacopoeia.

4.2.2.2. Process validation and/or evaluation

Pembrolizumab 165 mg/mL AS manufacturing process was successfully validated during the Process Performance Qualification (PPQ) campaign with the execution of 3 consecutive lots.

Supporting studies were completed for the clearance of process related impurities, reuse of the membrane for the AS process, resin lifetime, process hold times, and reprocessing. The active substance manufacturing process has been validated adequately.

4.2.2.3. Manufacturing process development

A comprehensive analytical comparability study was performed between pembrolizumab 165 mg/mL AS and pembrolizumab 25 mg/mL AS through comparison of release results, comparison of extended characterization test results, comparison of stability profiles, and comparison of forced degradation profiles.

In addition, process comparability was successfully demonstrated between the two AS manufacturing sites. The results demonstrated that the AS obtained from each process is comparable. Small differences were found between the different manufacturing processes that are explained and not regarded inconsistent with considering the processes comparable.

4.2.2.4. Characterization

The structure of Pembrolizumab 165 mg/mL was evaluated using a comprehensive list of biochemical, biophysical and functional characterisation techniques in order to define primary and high order structures, thermal stability, Glycosylation, Molecular size heterogeneity, Post-translational modifications, charge profile and biological activities.

Overall, the data provided in the Characterisation section indicate that pembrolizumab 165 mg/mL AS exhibits properties representative of a hinge-modified IgG4 and shares essentially the same quality attributes as pembrolizumab 25 mg/mL AS.

As a whole, the characterisation of pembrolizumab 165 mg/mL is considered sufficient.

4.2.3. Specification

The specifications are in line with ICH Q6B and Ph. Eur. 2031 monoclonal antibodies for human use and are considered acceptable for routine control of Pembrolizumab 165 mg/mL AS.

The release and stability specification is established to assure the identity, potency, strength, quality and purity. Specification for release and stability testing of pembrolizumab 165 mg/mL AS include tests for appearance, clarity, colour, pH, osmolality, protein concentration, purity, identity, potency, host cell protein, bacterial endotoxins, and bioburden.

4.2.3.0. Analytical procedures and reference standards

The methods are sufficiently described, and validation reports have been properly provided for review.

Standard compendial methods are used for appearance, bacterial endotoxin, bioburden and pH and are in line with the relevant Ph. Eur.

The non-compendial methods used for release and stability testing of pembrolizumab 165 mg/mL AS are identical to the methods used for pembrolizumab 25 mg/mL AS except with an extra dilution step for samples due to the higher concentration of pembrolizumab 165 mg/mL AS, and two methods which are newly developed. As for most methods, changes from the pembrolizumab 25 mg/mL AS method are limited to sample preparation for the higher concentration pembrolizumab 165 mg/mL

AS formulation, therefore, the validation approach taken was to evaluate elements of method performance specific for pembrolizumab 165 mg/mL AS and leveraged other elements from the validation of the methods for pembrolizumab 25 mg/mL AS.

4.2.3.1. Justification of specification

For the Justification of specification, the overall approach is endorsed.

4.2.3.2. Batch analysis

Batch analysis data on a sufficient number of batches are provided with satisfactory results.

4.2.4. Stability

A shelf life of 60 months is proposed for pembrolizumab 165 mg/mL AS when stored at -40°C / ambient humidity, based on stability studies performed in accordance with ICH guidelines. The studies have been conducted in containers representative of the AS container closure system.

The batches utilised in stability studies are AS batches manufactured at the intended commercial manufacturing facility, at the intended commercial manufacturing-scale.

Real-time stability data at the long-term storage condition of -40ºC are available for the AS batches. All results meet the proposed acceptance criteria. The study is ongoing up to the intended 60 months. In addition, stability data under intermediate (-20°C), accelerated (5°C), and stressed conditions (25ºC) have been provided.

Regarding stability studies results, no trends were observed for the parameters tested at long term condition and a slight increase in protein concentrations is observed at accelerated conditions. All results are below the commercial acceptance criteria. No significant trends were observed for the parameters tested.

Photostability data was generated during formulation development and is representative of pembrolizumab 165 mg/mL AS under stress conditions and confirmed the inherent light sensitivity of the pembrolizumab 165 mg/mL formulation.

Based on the stability data provided the proposed shelf life of 60 months for pembrolizumab 165 mg/mL AS when stored at -40°C / ambient humidity, is acceptable.

4.3. Finished medicinal product

4.3.1. Description of the product and pharmaceutical development

4.3.1.0. Description of the product

The finished product (FP), 165 mg/mL pembrolizumab,

is available as a single-use vial solution for injection for subcutaneous (SC) administration in two presentations: 790 mg pembrolizumab and 395 mg pembrolizumab. The composition of both finished product presentations is the same. The composition includes a novel excipient, recombinant berahyaluronidase alfa. The other excipients include L-histidine, L-histidine hydrochloride monohydrate, L-methionine, sucrose, polysorbate 80 and water for injections.

There are no excipients of human or animal origin used in the manufacturing of the drug product.

Both FP presentations are supplied in Type I clear tubing glass vial with a chlorobutyl stopper, and an aluminum seal with a plastic flip-off cap.

Berahyaluronidase alfa is considered a novel excipient and more information is provided in Section 'Novel Excipient' of this report.

4.3.1.1. Pharmaceutical development

The formulation development for the SC formulation with berahyaluronidase alfa leveraged pembrolizumab IV (Keytruda) and was subsequently refined through development of pembrolizumab SC. The studies conducted confirmed the final commercial finished product composition.

A characterization of formulations containing varied concentrations of pembrolizumab and berahyaluronidase alfa was performed. There are no changes observed in pembrolizumab attributes compared to the controls (without berahyaluronidase alfa).

Two manufacturing sites have been used to manufacture pembrolizumab SC injection, one site for clinical manufacturing and one site for commercial manufacturing. The sequence of unit operations remained unchanged throughout development of the FP manufacturing process.

An integrated control strategy (ICS) for the FP manufacturing processes is based on scientific and risk-based approaches involving in-depth product and process understanding.

Controls were identified and developed for each quality attribute based on the criticality of the attribute to safety and efficacy. The extractables and leachables safety assessment of the container closure components has shown no risk to patient based on a dose and the analytical studies performed. The compatibility of the FP formulation with primary packaging materials was adequately demonstrated.

4.3.1.2. Control of excipients

The excipients and measures for their control in the FP are adequately described.

4.3.2. Manufacture of the product and process controls

4.3.2.0. Manufacture

Name, address and responsibilities of the manufacturers and the facilities involved in the manufacturing, testing and batch release of the finished product have been provided. FP release is performed by Merck Sharp & Dohme B.V., Netherlands. Based on the supporting documents provided, GMP compliance concerning the listed manufacturer is found acceptable in the context of the present procedure.

Detailed information on the manufacturing process as well as the batch formula and batch size proposed for finished product have been provided and found adequate.

The proposed batch size is adequately supported by the FP PPQ exercise, based on consecutive batches at commercial scale.

The manufacturing process is well described and includes the following steps: thaw-formulate-fill-packaging. The information has been provided as a narrative description and flow-chart. Process controls

Information and justification of the applied controls of the process parameters have been adequately provided.

4.3.2.1. Process validation / verification

The process validation strategy for the finished product is based on a life-cycle management approach that includes the process design stage and process qualification stage. The process design is described, while the process qualification stage was carried out by producing at least three consecutive PPQ batches of pembrolizumab 790 mg and 395 mg at the commercial manufacturing site, which confirmed the proposed manufacturing process. Completion of the PPQ has been appropriately documented. The validation of the sterilization and aseptic manufacturing equipment/process, sterile filtration, and shipping of the finished product has been provided.

4.3.3. Product specification

Specification and acceptance criteria for release and stability testing of the pembrolizumab SC injection FP is presented and include tests for appearance, clarity, colour, identity, pH, polysorbate 80, L-Methionine, osmolality, particulate matter, extractable volume, protein concentration, purity, potency of pembrolizumab, enzyme activity, bacterial endotoxins, sterility and container closure integrity testing.

The provided specifications and acceptance criteria for release and stability testing of pembrolizumab SC injection FP are acceptable, showing an adequate control of the product quality.

Regarding product related impurities, the approach and the employed methods to address possible heterogenic protein-protein interactions between berahyaluronidase alfa and pembrolizumab molecules are considered correct. In this regard, the Applicant has provided a detailed summary of results of the above-mentioned analyses. The data, considered as a whole, support the conclusion that there are no distinguishable protein-protein interactions that influence the structure or lead to the aggregation of hyaluronidase alfa or pembrolizumab.

The description of the strategy followed to evaluate Elemental Impurities appears to be overall correct. In this regard, the Applicant appropriately provided the risk assessment in line with the ICH Q3D Guideline for Elemental Impurities, that also includes the calculations that support the conclusions regarding the non-exceedance of the relevant PDE limits.

Finally, the Applicant states that the risk for potential formation of nitrosamines or cross-contamination with nitrosamine impurities is negligible for Keytruda FP SC, and the relevant risk assessment was provided in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products.

4.3.3.0. Analytical procedures and reference standards

All methods are well described and suitable for their intended use. Furthermore, all analytical procedures intended for the control of Keytruda SC FP (165 mg/mL) were properly validated according to ICH Q2 (R2), with validation summaries made available for reference and review. For compendial procedures, the reference to respective Ph. Eur. monograph is given.

The reference standard used for finished product (pembrolizumab (+) berahyaluronidase alfa) testing is the same reference standard used for testing pembrolizumab 165mg/mL active substance, except for determination of berahyaluronidase alfa. Sufficient information was also provided on the FP calibration standard used for the determination of the activity of

berahyaluronidase alfa, including the qualification strategy, periodic re-qualification and the plan for the introduction of a new standard.

4.3.3.1. Batch analysis

The FP Batch analysis lists batches of both vial images (790 mg and 395 mg) produced at the different FP production sites (clinical and commercial).

Satisfactory data have been obtained from all these batches and are provided to demonstrate consistency in FP manufacturing.

4.3.3.2. Container closure

Pembrolizumab subcutaneous (SC) injection, 790 mg and 395 mg is packaged in a Type I glass vial, closed with a chlorobutyl rubber stopper and an aluminum seal with a plastic flip-off cap. The vial presentation is secondary packaged in a paperboard folding carton to protect the product from light and ensure adequate product handling protection.

4.3.4. Stability of the product

The shelf-life of 24 months is proposed for the Keytruda SC FP (790 mg and 395 mg) when stored at the recommended long-term storage condition of 2-8 °C (5°C), protected from light.

The stability studies are performed in accordance with ICH guidelines, using the same container closure system as the commercial product. The outcome of the in-use stability studies on the FP justifies the following storage conditions: 8h at room temperature, or up to 24 h at refrigerated temperature (2-8 ºC), or 8 h at room temperature followed by storage at refrigerated temperature for 16 h, totalling 24 h of cumulative storage time.

The shelf-life of 24 months proposed for the Keytruda SC finished product when stored at the recommended long-term storage condition of 2-8 °C (5°C) is acceptable.

4.3.5. Post approval change management protocol(s)

The Applicant provided the protocol for the production and qualification of future WCB additional MK-5180 CHO WCBs for commercial use. The protocol proposed for the qualification of the WCB is considered adequate. The Applicant also submitted two Post Approval Change Management Protocols (PACMPs).

4.3.6. Adventitious agents

Results generated by the complementary approaches for the approved pembrolizumab 25 mg/mL marketing application are applicable to the pembrolizumab 165 mg/mL AS manufacturing process.

Section 3.2.A.2 present the results specific to pembrolizumab 165 mg/mL AS.

In summary, viral safety regarding pembrolizumab 165 mg/mL has been demonstrated.

4.3.7. Novel excipient

The novel enzyme berahyaluronidase alfa is a variant of mature wild-type human hyaluronidase. (PH20), an endoglycosidase, with three changes:

1. The structural domain of PH20 (T306 – I326) is replaced with corresponding human Hyal-1 domain (S323 – T343), which has 15 amino acid substitutions compared to PH20. This is listed as S304-T324 in the fully engineered sequence.

2. 2 amino acids from PH20 are deleted from the N-terminus (L1, N2).

3. 41 amino acids from PH20 are deleted from the C-terminus (L434-474).

Berahyaluronidase alfa is composed of 431 amino acids and it is heterogeneously N-glycosylated at 6 N-glycosylation sites. The theoretical average molecular weight derived from the non-glycosylated amino acid sequence is 49220.59 Daltons (Da). The molecular weight range of intact glycosylated berahyaluronidase alfa is 54.3 to 58.3 kDa. The complete amino acid sequence includes six intrachain disulfide bonds between cystine residues.

The secondary structure of berahyaluronidase alfa is primarily composed of alpha-helix and random coil as indicated in homology modeling and confirmed by far-ultraviolet circular dichroism (CD).

Berahyaluronidase alfa is manufactured at the currently approved manufacturing site. Valid GMP certificates and QP declarations of GMP compliance of drug establishments are provided for the manufacturing and testing sites of berahyaluronidase alfa.

Berahyaluronidase alfa is expressed in Chinese hamster ovary (CHO) cell line. Manufacture is initiated from one vial of the WCB.

The manufacturing process includes inoculum growth and expansion starting from cells of a WCB followed by expansion in shake flasks and rocker bag. The cell suspension from the rocker bag is used to inoculate the production bioreactor. When the harvest criteria have been reached, the contents of the bioreactor are clarified using depth filtration followed by 0.2-µm filtration.

The clarified harvest product is further processed through Ultrafiltration Diafiltration 1 (UF/DF-1), Viral inactivation (VI), Anion exchange chromatography (AEX-1), Intermediate depth filtration (Int. DF), Anion-exchange chromatography (AEX-2), Multimodal exchange chromatography (MMC), Viral filtration, and Ultrafiltration diafiltration 2 (UF/DF-2) was used to concentrate and exchange the product into a formulation buffer. The formulated product is filtered, dispensed into the storage container, frozen, and stored.

The berahyaluronidase alfa is frozen and stored at -70 ± 10 ºC.

Reprocessing is foreseen and validated for two steps: viral filtration and final filtration.

The source, history and control of cell banks are well described. The MCB and WCB lot are identified as of CHO origin, monoclonal, sterile and free of adventitious agents of both viral and non-viral origin. The banks are stable as demonstrated by LIVCA batch characterization. The MCB and WCB were characterized for identity and viral contamination, and the results are compliant to ICH Q5A guideline.

The Applicant provided information regarding the quality and control of the raw materials and prepared solutions used in the manufacture of the berahyaluronidase alfa. No raw materials of human or animal origin are used in the berahyaluronidase alfa manufacturing process.

The information provided on CPP and IPCs identified for the manufacturing process are considered adequate. During the process validation, CQA, CPP, PP and IPC have been monitored, and all the results were compliant with the pre-set acceptance criteria.

A total of three consecutive berahyaluronidase alfa PPQ batches were manufactured. These PPQ results demonstrate that the facility, the manufacturing personnel, and the manufacturing process

can reliably and consistently produce berahyaluronidase alfa that meets the predefined acceptance criteria. Extractable & Leachable evaluation and shipping validation supported a good state of control.

Manufacturing process development

The manufacturing process for berahyaluronidase alfa was developed in stages. The initial process was used to produce material for development studies, formal stability studies, and clinical trials. The berahyaluronidase alfa process was subsequently transferred to commercial process site to produce material for development studies, stability studies, process performance qualification and commercial supply.

The data provided demonstrates the comparability in process performance between sites and WCB changes in the berahyaluronidase alfa process through visual evaluation of the key performance attributes and in-process intermediate product quality. Based on the process comparability assessment, the manufacturing process as implemented at the commercial process site is comparable to the clinical process.

The changes introduced to the manufacturing process post-PPQ are deemed acceptable and justified by validation studies.

Batches manufactured were used in the phase I study to evaluate the tolerance, safety and pharmacokinetics of berahyaluronidase alfa in healthy volunteers. Summaries of analytical method validations and verifications are provided. All non-compendial release and stability analytical methods have been validated according to current ICH guidelines. Method verification was completed for compendial methods. The applicant's conclusions are considered acceptable. The changes introduced in the analytical methods during development are also deemed acceptable.

Specification and acceptance criteria for release and stability testing of berahyaluronidase alfa is presented and include tests for appearance, clarity, color, identity, protein concentration, enzyme activity, purity, residual HPC, residual host cell DNA, pH, osmolality, bioburden, bacterial endotoxin.

The specifications are considered adequately justified.

Berahyaluronidase alfa is filled into single-use bottles equipped with a screw cap closure containing a silicone liner. Bottles and closures are received sterile and ready to use. The filled bottles are transferred to a freezer and held until further processing. Suitability of the container closure system was demonstrated.

Supportive data up to 36 months have been provided (formal stability study). All the data provided comply with the specification ranges and no significant trends have been observed. The results from the accelerated stability condition supports temperature excursions for the enzyme of up to 1-month (30 days) at 5 °C.

The long-term storage stability data supports the long-term storage condition of -70 °C based on real time stability data. An initial shelf-life of 36-months at -70 °C is proposed based upon real time stability data. Batches used to generate data for stability studies supporting the shelf-life were manufactured using the commercial scale and process.

4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The Applicant has submitted an extension application to the current Keytruda Marketing authorisation (EU/1/15/1024/002-003) to add a new route of administration for subcutaneous use

(SC), a new pharmaceutical form solution for injection and two new strengths 395 mg and 790 mg (EU/1/15/1024/004-005).

The new formulation for the SC route of administration contains a higher concentration of pembrolizumab, in comparison with the IV formulation, and is prepared along with a novel variant of human hyaluronidase excipient which functions as a permeation enhancer to enable dosing of higher injection volumes by SC route.

The manufacturing process of pembrolizumab 165 mg/mL active substance is identical to the registered manufacturing process of pembrolizumab 25 mg/mL active substance up to and including the ultrafiltration/diafiltration (UF/DF) process step, followed by the high concentration ultrafiltration step to generate a high concentration product required for the pembrolizumab 165 mg/mL formulation.

The finished product composition is 165 mg/mL pembrolizumab and berahyaluronidase alfa in L-histidine, L-histidine hydrochloride monohydrate, L-methionine, sucrose, and polysorbate 80. The finished product is a single-use vial provided at two doses as solution for injection for subcutaneous (SC) administration: 790 mg pembrolizumab and 395 mg pembrolizumab. The composition of both finished product doses is the same. The Applicant claims a shelf life of 24 months when stored at the recommended storage condition of 2°C to 8°C and protected from light The manufacturing process has been validated.

The pembrolizumab 165 mg/mL AS will be stored frozen. The pembrolizumab 165 mg/mL AS at room temperature is a clear to opalescent liquid. The colour of the solution at room temperature is colourless to slightly yellow. There is no change to other physicochemical, biological and immunochemical properties of pembrolizumab due to the pembrolizumb 165 mg/mL AS formulation.

The pembrolizumab 165 mg/mL AS manufacturing process was initially successfully validated during the process performance qualification (PPQ) campaign

A detailed comparison of the AS production processes implemented at the approved manufacturing sites was provided. The general approach for the validation exercise is considered acceptable.

Apart from change in AS/FP concentration, a main change is represented by the formulation variation, to introduce L-methionine as antioxidant and to introduce the novel excipient recombinant berahyaluronidase, to facilitate delivery at the site of SC injection.

A full dossier for berahyaluronidase was presented and assessed, reporting full and adequate information on manufacturing, process development and validation, characterization, control, container closure system and stability of this novel excipient.

Overall, based on the quality data provided, Keytruda SC can be considered approvable.

5. Non-clinical aspects

5.1. Introduction

The development of the subcutaneous (SC) formulation of pembrolizumab, MK-3475A, is primarily based on the existing non-clinical data supporting the IV formulation of pembrolizumab, supplemented with additional studies to support the new subcutaneous route of administration.

In the area of pharmacodynamics, primary in vitro studies were conducted to assess the immunogenicity potential of MK-5180 by evaluating its effects on immune cell stimulation and by characterising its enzymatic activity using an established colourimetric assay. Complementary in vivo studies were conducted in mice using dye dispersion methods to investigate the ability of the compound to enhance tissue permeation following subcutaneous administration. No secondary pharmacodynamic studies were performed.

Safety pharmacology assessments were designed to evaluate the potential effects of MK-5180 on cardiovascular, respiratory and neurobehavioural functions. These assessments were integrated with repeated dose toxicity studies in well-characterised animal models to ensure that the compound did not cause adverse effects in these critical systems. In terms of pharmacokinetics, a number of bioanalytical methods were developed and validated to monitor MK-5180 in plasma following both intravenous and subcutaneous administration in animal models. Although the absorption of MK--5180 has been characterised, studies on its distribution, metabolism, excretion and potential drug-drug interactions have not been performed.

The toxicology component of the non-clinical programme included single and repeated dose studies in rats and monkeys conducted under GLP conditions. These studies provided insight into the tolerability of MK-5180 and supported the selection of appropriate doses for further development. In addition, extensive reproductive and developmental toxicity studies were conducted in rats and rabbits covering fertility, early embryonic development, embryo-fetal development and pre- and postnatal development. Genotoxicity and carcinogenicity studies were not performed because current regulatory guidelines for anticancer agents do not require these evaluations. In addition, local tolerability was assessed in a minipig study, while antigenicity, immunotoxicity and potential addiction studies were either included in repeat-dose studies or deemed unnecessary. Similarly, studies were not performed to assess metabolites, impurities and phototoxicity, the latter in accordance with guidance for biopharmaceuticals.

Comparative exposure analyses were performed between preclinical and clinical SC administration. Additional studies included PK and toxicokinetic evaluations of MK-3475A and its components, in vitro immunogenicity assays, and in vivo dye dispersion studies.

5.2. Analytical methods

Exploratory ECL based immunoassays were used to quantify pembrolizumab concentrations in rat plasma and monkey serum in SC PK studies in rat and monkey, PK008MK3475. A validated ECL-based immunoassay was used to quantify pembrolizumab concentrations in cynomolgus monkey serum to support TT #21-1002, a GLP MK-3475A SC tolerability study in cynomolgus monkeys.

Table 2 Bioanalytical Assay Methods for Pembrolizumab Concentration

Validation Report Number	PK008MK3475[a]	PK008MK3475[a]	PPD Project REKZ2[b]
Bioanalytical Method Reference	NA	NA	ICD 573.1 version 1.01
Activity	Exploratory	Exploratory	Full validation

Species	Rat/Sprague Dawley	Monkey	Monkey
Analyte	Pembrolizumab	Pembrolizumab	Pembrolizumab
Matrix	Plasma	Serum	Serum
Method	ECL	ECL	ECL
Capture Reagent	Biotinylated goat anti-human IgG Fc gamma specific	Biotinylated mouse anti-human IgG kappa chain	Biotinylated recombinant human PD-1 chimera Fc
Detection Reagent	SULFO-TAG labeled mouse anti-human IgG	SULFO-TAG labeled mouse anti-human IgG	SULFO-TAG labeled mouse anti-human IgG4
Regression Model	NA	NA	four-parameter logistic
Range of Quantitation (ng/mL)	MCD=78 ng/mL	MCD=27.4 ng/mL	100 to 6500 ng/mL
Minimum Required Dilution	NA	NA	1:100
Standard Inter-Day Accuracy Range (% Bias)	NA	NA	- 3.78 to 4.24
Standard Inter-Day Precision Range (% CV)	NA	NA	1.57 to 3.70
QC Nominal Concentration (ng/mL)	NA	NA	100, 200, 300, 2000, 5000, 5500, and 6500 ng/mL
QC Inter-day Accuracy Range (% Bias)	NA	NA	- 1.63 to 4.54
QC Inter-day Precision Range (% CV)	NA	NA	4.73 to 9.04
QC Intra-day Accuracy Range (% Bias)	NA	NA	- 3.71 to 11.1
QC Intra-day Precision Range (% CV)	NA	NA	2.32 to 8.76
Matrix LTS (at 70/80 °C)	NA	NA	1247 days
Dilution Linearity	NA	NA	1,000,000 ng/mL diluted five-fold
Interference from MK-5180	NA	NA	MK-3475A coformulation performed acceptably in the assay

CV=coefficient of variation; ECL=electrochemiluminescence; Fc=fragment crystallizable; IgG=immunoglobulin G; LTS=long term stability; MCD=minimum detectable concentration; NA=not applicable; PD-1=programmed cell death protein 1; pembrolizumab=MK-3475, SCH900475, and Org 307488-0; QC=quality control; SULFO-TAG=ruthenylated.

[a] PK008MK3475 [Ref. 4.2.2.2: PK008MK3475].

[b] Validation of an Electrochemiluminescence (ECL) Method for the Quantitation of Pembrolizumab in Cynomolgus Monkey Serum REKZ2 [Ref. 4.2.2.1: REKZ2]; Addendum 1 REKZ5 [Ref. 4.2.2.1: 06DWYS]; Addendum 2 effect of MK-5180 on pembrolizumab quantitation REKZ7 [Ref. 4.2.2.1: 06DWYTS]; Addendum 3 LTS at - 70/- 80 ºC REKZ3 [Ref. 4.2.2.1: VRREKZ3ADDEND3MK3475].

Table 3 Bioanalytical Assay Methods for MK-5180 Concentration

Validation Report Number	WuXi AppTec Study No. 891-0006-IM[a]	WuXi AppTec Study No. 891-0009-IM[b]	WuXi AppTec Study No. 891-0019-IM[c]	WuXi AppTec Study No. 891-0023-IM[d]	Charles River Study No. VR-20229779 andAmendment 1[e]
Bioanalytical Method Reference	891-0006-AM.	891-0009-VM	891-0019-VM.	891-0023-VM	AP.20229779.IC.01 through AP.20229779.IC.07
Activity	Full validation	Full validation and long term stability amendment	Full validation	Full validation	Full validation and long term stability amendment
Species	Rat	Rat	Rat	Rabbit	Monkey
Analyte	Hyaluronidase activity	MK-5180	MK-5180	MK-5180	Hyaluronidase activity
Matrix	Plasma	Plasma	Plasma	Plasma	Plasma
Method	ELISA (hyaluronan enzymatic degradation)	ELISA immunoassay	ECL	ELISA immunoassay	ELISA (hyaluronan enzymatic degradation)
Regression Model	Logistic (auto-estimate) model with weighting factor $1/Y^2$	Logistic (auto-estimate) model with weighting factor $1/Y^2$	Logistic (auto-estimate) model with weighting factor $1/Y^2$	Logistic (auto-estimate) model with weighting factor $1/Y^2$	5 parameter logistic model, with a weighting factor of 1.

Validation Report Number	WuXi AppTec Study No. 891-0006-IM[a]	WuXi AppTec Study No. 891-0009-IM[b]	WuXi AppTec Study No. 891-0019-IM[c]	WuXi AppTec Study No. 891-0023-IM[d]	Charles River Study No. 20229779[e]
Range of Quantitation (ng/mL)	3.00 to 404	3.00 to 100	2.00 to 250	2.00 to 100	10 to 150 in reaction buffer 800 to 12,000 in neat plasma
Minimum Required Dilution	1:4	1:5	1:4	1:5	1:80
Standard Inter-Day Accuracy Range (%Bias)	- 5.2 to 6.2	- 2.0 to 3.0	- 5.5 to 6.3	- 0.5 to 2.0	- 5 to 8
Standard Inter-Day Precision Range (% CV)	2.5 to 11.8	3.3 to 6.3	3.7 to 9.1	3.3 to 8.9	4 to 9
QC Nominal Concentration (ng/mL)	3.00, 9.00, 35.0, 303, and 404	3.00, 9.00, 18.0, 75.0, and 100.0	2.00, 6.00, 24.0, 190, and 250	2.00, 5.00, 15.0, 75.0, and 100	10, 30, 60, 90, 150 ng/mL in reaction buffer
QC Intra-day Accuracy Range (%Bias)	- 16.7 to 16.9	- 8.9 to 12.2	- 20.4 to 16.0	- 11.6 to12.0	- 32 to -4
QC Intra-day Precision Range (%CV)	0.3 to 22.8	0.4 to 9.7	0.8 to 16.7	0.2 to 12.1;	1 to 22
QC Inter-day Accuracy Range (%Bias)	- 3.0 to 7.7	- 0.5 to 3.1	- 5.6 to 3.5	- 5.0 to 2.5	- 23 to -10
QC Inter-day Precision Range (%CV)	9.3 to 17.9	5.6 to 7.7%	8.5 to 16.7	5.4 to 8.5	8 to - 18
Matrix LTS (at ≤ - 60 °C)	111 days	369 days	216 days	87 days	4 months and 3 days at -80°C

Dilution Linearity	Dilution factor was validated up to 10,100. No hook effect was observed at concentrations of 202,000 and 4040 ng/mL.	Dilution factor was validated up to 40,000. No hook effect was observed at concentrations of 500,000 and 50,000 ng/mL.	A 500,000 ng/mL QC can be accurately diluted 100,000 fold	Dilution factor was validated up to 32,000. No hook effect was observed at concentrations 96,000 ng/mL and 2400 ng/mL.	Dilution linearity demonstrated for MK5180 dilutions of 20- to 1000-fold in reaction buffer

CV=coefficient of variation; ECL=electrochemiluminescence; ELISA=enzyme linked immunosorbent assay; HRP=horseradish peroxidase; LTS=long term stability; mAb=monoclonal antibody; MK5180=ALT-B4, a modified hyaluronidase; pAb=polyclonal antibody; PC=positive control; QC=quality control; TMB=tetramethylbenzidine.

[a] Validation of an ELISA Method for Measuring the Concentration of Alt-B4 in Rat Plasma (K2EDTA), 891-0006-IM amendment 1 [Ref. 4.2.2.1: VRMK5180].

[b] Validation of an ELISA Method for Measuring Alt-B4 Concentration in Rat Plasma 891-0009 Amendment 1 [Ref. 4.2.2.1: VR8910009IMAMEND1MK5180].

[c] Validation of an Electrochemiluminescence (ECL) Method for Measuring Alt-B4 Concentration in Rat Plasma, 891-0019-IM [Ref. 4.2.2.1: VR8910019IMMK5180].

[d] Validation of an ELISA Method For Measuring Alt-B4 Concentration in Rabbit Plasma, 891-0023-IM [Ref. 4.2.2.1: VR8910023IMMK5180].

[e] Validation of an Enzyme-Linked Immunosorbent Assay (ELISA) Method for the Determination of Hyaluronidase Activity in Cynomolgus Monkey Plasma VR-20229779, [Ref. 4.2.2.1: VR20229779].

Table 4 Bioanalytical Assay Methods for Anti-MK-5180 Antibodies

Validation Report Number	**WuXi AppTec Study No. 891-0027-IM[a]**	**WuXi AppTec Study No. 891-0029-IM[b]**
Bioanalytical Method Reference	891-0027-VM	891-0029-VM
Activity	Full validation	Full validation
Species	Rat	Rabbit
Analyte	Anti-MK-5180 antibodies	Anti-MK-5180 antibodies
Matrix	Plasma	Plasma
Method	ELISA	ELISA
PC		
Minimum Required Dilution	50	50
Sensitivity (ng/mL)	3.380	5.984
Drug Tolerance of Screening Assay	2000 ng/mL of anti-MK-5180 antibody positive control tolerated 2 µg/mL of MK-5180 500 ng/mL of anti-MK-5180 antibody positive control tolerated 1 µg/mL of MK-5180 20 ng/mL of anti-MK-5180 antibody positive control tolerated 0.1 µg/mL of MK-5180	2000 ng/mL of anti-MK-5180 mAb tolerated 8 µg/mL of MK-5180 500 ng/mL of anti-MK-5180 mAb tolerated 2 µg/mL of MK-5180 20 ng/mL of anti-MK-5180 mAb tolerated 0.1 µg/mL of MK-5180
PC Nominal Concentration (ng/mL)	20, 500, 2000	20, 500, 2000
PC Intra-day Precision Range, without drug (%CV)	1.7 to 12.5	1.9 to 7.8

Validation Report Number	**WuXi AppTec Study No. 891-0027-IM[a]**	**WuXi AppTec Study No. 891-0029-IM[b]**

PC Inter-day Precision Range, without drug (%CV)	15.73.1 to 19.5	8.4 to 12.7
PC Intra-day Precision Range of % Inhibition, with drug (%CV)	0.5 to 5.1	0.3 to 10.6
PC Inter-day Precision Range of % Inhibition, with drug (%CV)	1.8 to 8.6	0.8 to 11.0

CV=coefficient of variation; ELISA=enzyme linked immunosorbent assay; HRP=horseradish peroxidase; mAb=monoclonal antibody PC=positive control. MK-5180=ALT-B4, a modified hyaluronidase; TMB=tetramethylbenzidine.

[a] Validation of an ELISA Method for Detecting Anti-Alt-B4 Antibodies in Rat Plasma, 891-0027-IM

[b] Validation of an ELISA Method for Detecting Anti-Alt-B4 Antibodies in Rabbit Plasma, 891-0029-IM

5.3. Pharmacology

5.3.1. Pharmacodynamics

5.3.1.0. Primary pharmacodynamics

The immunogenicity potential of MK-5180 was assessed by its ability to stimulate CD4+ and CD8+ T cells. In an *in vitro* study, MK-5180 was compared to rHuPH20 at concentrations of 1.5 µg/mL and 15 µg/mL (n = 10 per concentration). Stimulation Index (SI) values remained below 2, the threshold for a positive immunogenic response, in the majority of replicates for both rHuPH20 and MK-5180. In particular, MK-5180 showed SI values below 2 in all CD4+ T cell replicates and in all but one CD8+ T cell replicate at the higher dose of 15 µg/ml.

In vivo, MK-5180 was evaluated for its permeation enhancing effects in a novel dye dispersion study in female BALB/c nude mice. MK-5180 was administered either sequentially or co-formulated with trypan blue dye. The results showed that the diffusion of the dye increased with higher doses of MK-5180, with maximum diffusion observed when the dye was injected shortly after MK-5180. These results support the potential of MK-5180 as a permeation enhancer for drug delivery applications. Both pembrolizumab and MK-5180 showed no significant adverse effects in safety pharmacology evaluations.

5.3.1.1. Secondary pharmacodynamics

No secondary pharmacodynamic studies have been conducted with pembrolizumab with MK-5180 and with MK-3475A.

5.3.1.2. Safety pharmacology

MK-5180 showed no changes in ECG, respiratory function or CNS activity at doses up to 2 mg/kg in monkeys and rats (approximately 1400 times the anticipated clinical dose of 192 U/kg). A GLP tolerability study of MK-3475A showed that the combination of pembrolizumab and MK-5180 was well tolerated at a dose of 50 mg/kg pembrolizumab and 4.1 µg/kg MK-5180 (approximately three times the clinical dose of 192 U/kg). See toxicity section.

Both pembrolizumab and MK-5180 showed no significant adverse effects in safety pharmacology evaluations.

5.3.1.3. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interactions studies with MK-5180 or MK-3475A have been conducted.

5.3.2. Pharmacokinetics

Previous non-clinical data demonstrated that the pharmacokinetic and toxicokinetic parameters of MK-3475 were consistent with those of a monoclonal antibody, with exposure increasing with dose and independent of sex (see Keytruda EPAR).

5.3.2.0. Absorption

Two studies compared the exposure of different pembrolizumabformulations administered SCto rats (PK008MK3475/15-M46-6966) and cynomolgus monkeys (PK008MK3475/15-M100-7090). The bioavailability of the SC pembrolizumab formulations was also investigated. In the rat study (15-M46-6966), no adverse reactions were observed, and pembrolizumab exhibited linear pharmacokinetics following SC administration. Bioavailability ranged from 82.7% to 94.4% for the clinical formulation63.3% to 92.3% for the lead formulation. In the non-human primate study (15-M100-7090), no clinical signs related to the test article were observed, and pembrolizumab showed linear pharmacokinetics following SC administration with no adverse reactions in cynomolgus monkeys.

PK studies for MK-5180 (ALT-B4) were performed in rats (Study Report PK001MK5180/2519133) and monkeys (Study Report PK002MK5180/2089034).

In rats after a single IV dose of MK-5180(1 mg/kg 124,000 U/kg), the blood concentration decreased with a half-life of approximately 7 minutes. Total clearance was 4.3 mL/min/kg, slower than hepatic blood flow (55.2 mL/min/kg) while the volume of distribution at steady state was 34.6 mL/kg, which is less than the total body water content of rats (668 mL/kg). These results suggest that MK-5180remains predominantly in the blood with limited tissue distribution.

In monkeys, MK-5180was rapidly eliminated after IV administration (t½ 0.3–0.87 h across doses of 3–30 mg/kg). No clear dose-dependence was observed in PK parameters. A secondary plasma concentration peak was noted in some animals, suggesting possible saturable elimination. However, interpretation is limited by the small number of animals (n=3) and by the presence of baseline hyaluronidase activity (4.27 to 13.9 µg/mL), which was not subtracted from post-dose concentrations, potentially affecting accuracy of AUC, clearance and volume of distribution.

Following SC administration (1, 3, 10 and 30 mg/kg), MK-5180was absorbed rapidly (Tmax 0.25–1 h), but systemic exposure was low and non-dose-proportional, especially below 30 mg/kg. Plasma concentrations declined quickly and returned close to baseline within 4 hours.

5.3.2.1. Distribution

The previous data provided for the initial application does cover the new posology of the extension (see Keytruda EPAR). No additional studies are needed.

5.3.2.2. Metabolism

Non-clinical studies assessing the metabolism of pembrolizumab, following SC administration have not been conducted. Similarly, no metabolism studies have been conducted for MK-5180 or MK-

3475A. The previous data provided for the initial application does cover the new posology of the extension.

5.3.2.3. Excretion

No non-clinical studies have been conducted to assess the excretion of pembrolizumab following SC administration. Similarly, no excretion studies have been performed for MK-5180 or MK-3475A.

5.3.2.4. Pharmacokinetic drug interactions

No non-clinical studies have been conducted to assess the drug-drug interactions of pembrolizumab following SC administration. No drug interaction studies have been conducted for MK-5180 or MK-3475A.

5.3.2.5. Other pharmacokinetic studies

Pharmacokinetic and toxicokinetic evaluations of pembrolizumab were conducted in Cynomolgus monkeys (see Keytruda EPAR). In agreement with ICH S6 no standard ADME studies have been performed. Likewise, no other PK studies were performed following SC administration of pembrolizumab. Similarly, no drug interactions studies have been conducted for MK-5180 or MK-3475A.

5.4. Toxicology

5.4.1. Single-dose toxicity

There were no single-dose toxicity studies conducted with the subcutaneous formulation of pembrolizumab. The toxicity of pembrolizumab (IV formulation - Keytruda) was evaluated in cynomolgus monkeys (see Keytruda EPAR).

A new single dose study (TT #19-7846/891-0003-TX) was conducted in rats to evaluate the toxicity and reversibility of MK-5180 following SC or IV administration with a 7-day treatment free period. Doses of 0, 0.04, 0.2 and 2 mg/kg were tested. The study monitored mortality, clinical signs, body weight, food consumption, haematology, coagulation, serum chemistry, urinalysis, organ weights and pathology. No mortality or adverse effects were observed, and there were no MK-5180-related changes in any clinical or pathological parameters. The NOAEL was 2 mg/kg (approximately 1400 times the anticipated clinical dose of 192 U/kg), indicating that MK-5180 is well tolerated at the highest dose tested. No acute toxicity studies have been conducted with MK-3475A.

5.4.2. Repeat-dose toxicity

No pivotal repeat-dose toxicity studies have been conducted with the subcutaneous formulation of pembrolizumab.

Three new studies were conducted to further evaluate the toxicity of MK-5180.

A 29-day GLP study (TT #20-7838/891-0004-TX) in Sprague-Dawley rats showed that MK-5180 was well tolerated at doses up to 2 mg/kg/dose with no treatment-related toxicological findings. Systemic exposure was confirmed only at the highest dose, while pharmacokinetic data at 0.04 and 0.2 mg/kg were unreliable due to sensitivity limitations of the assay. The NOAEL was established at 2 mg/kg, but the lack of dose proportionality makes interpretation of the pharmacokinetics at lower doses difficult.

In a second study (TT #22-7821/891-0017-TX), MK-5180 was administered in Sprague-Dawley rats by SC injection once a week for up to 26 weeks at doses of 0, 0.04, 0.2 and 2 mg/kg/dose, followed by a four-week recovery period. The treatment was well tolerated with no mortality or adverse effects in clinical signs, injection site reactions, body weight, food consumption, ophthalmology, clinical pathology or general pathology. All changes observed were reversible by the end of the recovery period. The presence of ADA in all MK-5180 treated groups was associated with a decrease in systemic exposure at 2 mg/kg/dose after 26 weeks of repeated dosing. The NOAEL was determined to be 2 mg/kg/dose with a corresponding Cmax of 8.66 ng/ml in males, while systemic exposure was undetectable in females after the last dose.

In addition, results from study report TT#20-7837/20219-234 in Cynomolgus monkeys confirmed that MK-5180 was well tolerated at the doses tested (0.04, 0.2 and 2 mg/kg/dose) with only transient fibrinogen elevation in females at 2 mg/kg/dose and minimal to mild mixed cell inflammation, hemorrhage, and/or regionally extensive myocyte degeneration at the administration site at all dose levels on Day 30, both of which had resolved by the end of the recovery period (14-day treatment free period) by Day 42 (28+14 days). Without bioanalytical and toxicokinetic evaluation data, this conclusion was made based on dose formulation analysis results, which reflected that the animals were exposed at the intended dose levels of 0.04, 0.2, and 2 mg/kg/dose. Under the study conditions, the NOAEL for MK-5180 was considered 2 mg/kg/dose (approximately 1400 times the anticipated clinical dose of 192 U/kg).

The four-week subcutaneous tolerability study in cynomolgus monkeys (TT #21-1002) evaluated the safety and pharmacokinetics of MK-3475A administered weekly. The study showed no significant adverse effects with minimal post-mortem findings. There was a significant increase in drug exposure after repeated dosing: AUC0-168h increased from 83,700 h*µg/mL on Day 1 to 206,000 h*µg/mL on Day 15 and Cmax increased from 573 µg/mL to 1450 µg/mL. Systemic exposure to pembrolizumab exceeded the predicted clinical AUC by ≥3- to 6-fold at the tested dose, while MK-5180 remained undetectable. No relevant sex differences were observed. The increased dosing frequency (Q1W vs Q3W/Q6W clinically) provides an additional safety margin.

5.4.3. Genotoxicity

No mutagenicity studies have been performed for pembrolizumab, MK-5180 and MK-3475A.

5.4.4. Carcinogenicity

Carcinogenicity studies have not been performed for pembrolizumab, MK-5180 and MK-3475A.

5.4.5. Developmental and reproductive toxicity

No dedicated reproductive toxicity studies were conducted at the time of MAA with Keytruda (pembrolizumab), as the potential risk to reproduction is well established from literature data (see Keytruda EPAR).

A new study (TT #22-7808/891-0011-DR) was performed to evaluate the effects of MK-5180 on fertility and early embryonic development in rats when administered once daily via SC injection. The study demonstrated that MK-5180 was well tolerated in both male and female rats at doses up to 18 mg/kg/day (>9000-fold higher than the anticipated clinical dose of 192 U/kg), with no treatment-related mortality or adverse effects on clinical signs, body weight, food consumption, or fertility parameters. While an increase in abnormal sperm morphology was observed at ≥6 mg/kg/day (approximately 4375-fold higher than the anticipated clinical dose of 192 U/kg), it was deemed not

biologically significant due to its limited magnitude and lack of impact on male reproductive indices. The NOAEL was established at 18 mg/kg/day, with systemic exposures (Cmax and AUC0-24h) of 89.0 ng/mL and 312 h*ng/mL in males (Day 63) and 27.7 ng/mL and 174 h*ng/mL in females (Day 14), respectively. Reproductive and developmental toxicity studies have not been performed with MK-3475A because of the known risk to pregnancy from the pembrolizumab component of the drug.

The Embryo-Fetal Development Toxicity of MK-5180 was assessed in rats and rabbits.

In the rat studies, the once daily SC injection administration of MK-5180 at doses ranging from 2 to 18 mg/kg/day from GD 6 to 17 during an exploratory study (TT #21-7814/891-0012-DR) showed that there were no mortalities, and all animals survived to necropsy. No MK-5180-related clinical signs were observed, with alopecia noted as an incidental finding. Maternal body weight, gravid uterine weight, and absolute weight gain showed no treatment-related effects. A slight reduction in food consumption (−2.3% to −9.7%) was observed in the high-dose group, but this effect was not directly linked to MK-5180, as similar reductions were seen prior to the treatment. Embryo-fetal development endpoints, such as corpora lutea count, implantation sites, fetal sex ratio, fetal weight, crown-rump length, and placental morphology, showed no treatment-related changes. No malformations or variations were observed during fetal external examination, and no gross abnormalities were found in the pregnant females during necropsy. In the subsequent confirmatory GLP-compliant study in Rats (TT #22-7809/891-0013-DR), once daily SC injections of MK-5180 to pregnant female rats during the organogenesis period (GD 6 to 17) at doses of 2, 6, and 18 mg/kg/day were well tolerated and didn't result in any treatment-related mortality, or any test article-related changes in clinical signs, body weight, and food consumption. In addition, no test article-related embryo-fetal developmental toxicity was noted at any dose level. Toxicokinetic analysis showed that Tmax values ranged from 0.5 to 4 h post-dose and that systemic exposure to MK-5180 (AUC0-24h and Cmax) increased proportionally with dose, from 2 to 18 mg/kg/day at GD 6. However, repeated SC administration resulted in a decrease in systemic exposure at all dose levels based on AUC0-24h values. Therefore, under the conditions of the study, the NOAEL of MK-5180 for both maternal and embryo-fetal developmental toxicity was considered to be 18 mg/kg/day (corresponding maternal mean Cmax and AUC0-24h values on GD 17 was 61.5 ng/mL and 282 h*ng/mL, respectively).

To assess the toxicity of MK-5180 for embryo-fetal development in rabbits, a SC injection dose-ranging study and a confirmatory study were also performed.

The Dose Range Finding Study in Rabbits (TT #23-7821/891-0020-DR) was administered SC injection once daily at doses of 0, 0.99, 2.88 and 8.64 mg/kg/day and covered early pregnancy to late fetal development from GD 6 to 19. Based on the results, there were no MK-5180-related maternal deaths or spontaneous abortions. No significant clinical signs or changes in body weight were observed, except for slight decreases in food consumption in the highest dose group (8.64 mg/kg/day), which were transient and not toxicologically significant. In addition, a slight decrease in embryo-fetal survival was observed at the highest dose (8.64 mg/kg/day, 6300-fold the anticipated clinical dose of 192 U/kg), particularly with a reduction in the number of live male fetuses (mean number of live male fetuses decreased from 4.7 in the control group to 2.5 in the highest dose group). The number of live fetuses also decreased (mean 7.3 in the high dose group versus 8.1 in the controls). In addition, there was an increase in early resorptions and post-implantation losses (27.2% in the high-dose group versus 24.2% in the controls). However, these effects were not considered to be directly related to MK-5180 due to the lack of a dose-response relationship and similar poor pregnancy outcomes in the controls, suggesting that the findings may be incidental. In terms of pregnancy parameters, there were no significant effects on the number of corpora lutea,

embryo or foetal implants, or fetal weight and size. No abnormalities were observed in fetal development, external morphology or placental examination in any of the treatment groups.

Toxicokinetically, systemic exposure to MK-5180 increased dose-proportionally, with AUC0-24h values ranging from 210 to 6290 h*ng/mL as the dose increased from 0.99 to 8.64 mg/kg/day. Plasma concentrations peaked approximately 1 to 2 hours (median Tmax) after dosing on day 6. However, at the highest dose (8.64 mg/kg/day, ~6299-fold the anticipated clinical dose of 192 U/kg), plasma levels decreased with repeated dosing and some animals had undetectable levels by GD 19. At the two lower doses (0.99 and 2.88 mg/kg/day, ~700-fold and 2100-fold the anticipated clinical dose of 192 U/kg, respectively), most animals had MK-5180 concentrations below the limit of quantification at GD 19, except for one animal in the 2.88 mg/kg/day group which had trace levels of MK-5180 at 2- and 4-hours post-dose (2.48 and 2.25 ng/mL, respectively).

The embryo-fetal development confirmatory study TT #23-7820/891-0021-DR in rabbits showed that MK-5180 was rapidly absorbed after once daily SC injection, with a dose-dependent increase in systemic exposure at GD 6, followed by a marked decrease in exposure at GD 19 at lower doses, probably due to the development of ADAs. The NOAEL for maternal toxicity was 8.64 mg/kg/day, while the NOAEL for embryo-fetal developmental toxicity was 0.99 mg/kg/day (~700-fold the anticipated clinical dose of 192 U/kg respectively). Significant reductions in mean fetal weight (up to 8.08%) and crown-rump length (up to 3.75%) were observed at 2.88 and 8.64 mg/kg/day (2100-fold and 6299-fold the anticipated clinical dose of 192 U/kg, respectively) and were considered adverse and related to MK-5180. Visceral abnormalities included supernumerary pulmonary fissures at 8.64 mg/kg/day (~6299-fold the anticipated clinical dose of 192 U/kg), and skeletal abnormalities such as asymmetry and incomplete ossification of the sternebrae and shortened thoracolumbar vertebrae were also observed at this dose.

Reproductive and developmental toxicity studies have not been conducted with MK-3475A since pregnancy risk has been identified for the pembrolizumab component of MK-3475A. Based on the mechanism of action of pembrolizumab, which involves inhibition of the PD-1/PD-L1 pathway, an important regulator of pregnancy maintenance through induction of maternal immune tolerance to fetal tissue, MK-3475A may cause fetal harm if administered to a pregnant patient.

The potential maternal and developmental toxicity of MK-5180 was evaluated following once daily SC administration to pregnant and lactating female rats (F0) from gestation day (GD) 6 to lactation day (LD) 21 (TT #22-7820/8891-0014-DR), and systemic exposure in both dams and their offspring (F1) was measured. No mortality or treatment-related clinical signs were observed in either F0 or F1 animals. Maternal body weight, food consumption, pregnancy outcome and offspring developmental milestones were unaffected by treatment. In addition, no adverse effects were observed on functional developmental endpoints, including reflexes, motor activity and cognitive performance, and no signs of reproductive or developmental toxicity were reported.

These findings are further supported by the toxicokinetic results, which showed systemic exposure in F0 dams with rapid absorption (Tmax 0.5-2 h) and a more than dose-proportional increase in exposure, indicating non-linear pharmacokinetics. At the highest dose level (18 mg/kg/day, 13,000-fold the anticipated clinical dose of 192 U/kg), maternal Cmax and AUC0-24h values reached 223 ng/mL and 750 h*ng/mL, respectively, on LD 21, with no evidence of drug accumulation over the dosing period (162,000-fold and 546,000-fold the anticipated clinical dose of 192 U/kg). Importantly, plasma concentrations in F1 pups were below the lower limit of quantitation (BLQ) at both PND 4 and PND 21, indicating negligible systemic exposure in the offspring.

Taken together, the absence of maternal toxicity, the absence of developmental or functional adverse effects in F1 animals, and the minimal transfer of ALT-B4 to the offspring support the

conclusion that 18 mg/kg/day (13,000-fold the anticipated clinical dose of 192 U/kg) represents the NOAEL for both maternal and developmental toxicity under the conditions of this study.

5.4.6. Toxicokinetic and exposure margins

Rats (Sprague Dawley): In a 1-month study, once weekly SC administration of MK-5180 at 0.04, 0.2, and 2 mg/kg showed measurable systemic exposure only at the highest dose (2 mg/kg; ~1400-fold anticipated clinical dose). Tmax was 0.5 h post-dose and plasma levels were undetectable by 8 h, indicating rapid elimination. No sex differences or accumulation were observed with repeated dosing over 22 days. Lower doses showed minimal exposure, complicated by assay limitations. In a 26-week study (TT #22-7821/891-0017-TX), systemic exposure remained measurable at 2 mg/kg with a Tmax of 0.5 h, but drug levels were undetectable by day 176. AUC and Cmax were minimal at 0.2 mg/kg and negligible after repeated dosing, suggesting reduced bioavailability over time. Two additional studies (TT #22-7808/891-0011-DR and TT #22-7809/891-0013-DR) evaluated reproductive/developmental toxicity (2, 6, 18 mg/kg). Exposure increased with dose (Tmax: 0.5-2 h) but decreased with time, probably due to the formation of anti-drug antibodies (ADA).

Rabbits (New Zealand White): In a dose-ranging study, systemic exposure was dose-dependent. At 8.64 mg/kg/day (~6300-fold the clinical dose), plasma levels decreased over time, with some animals having undetectable levels by the end of gestation. Lower doses resulted in concentrations largely below the limit of quantitation, indicating poor absorption or rapid clearance.

A subsequent developmental study confirmed rapid absorption (Tmax: 0.8-2 h), dose-dependent exposure, and decreasing plasma levels with repeated dosing - again suggesting ADA-mediated clearance. Exposure remained dose proportional at the highest dose.

Monkeys (Cynomolgus): In a 28-day repeat-dose study with a 14-day recovery, systemic exposure was confirmed, though PK profiles differed significantly from rodents.

In a combination study with pembrolizumab, monkeys received weekly IV. doses of 0.004 mg MK-5180 + 50 mg pembrolizumab. A 2.5-fold increase in MK-5180 exposure was observed by day 15, with Tmax reduced from 75.8 h to 42.8 h, indicating accelerated absorption. Systemic exposure exceeded that observed in human trials.

5.4.7. Local tolerance

Local tolerability has been evaluated in several non-clinical studies. In rabbits (study report TT #16-7110), the SC injection formulation of pembrolizumab was well tolerated with minimal injection site reactions observed, comparable to the control group. No gross or histomorphological changes were associated with pembrolizumab SC. In a separate study (TT #19-7845/2089-031), the tolerability of MK-5180 was evaluated in 5-month-old male minipigs administered SC injection at doses of 0.04, 0.2 and 2 mg/kg. No local toxicity associated with MK-5180 was observed. A mild, isolated erythema at the 0.04 mg/kg dose (~3 times the anticipated clinical dose of 192 U/kg) resolved by day 3 and was not dose related. Overall, MK-5180 was well tolerated locally and systemically at all doses tested. In addition, the local tolerability of MK-3475A was further evaluated in a once weekly SC injection repeat dose study in cynomolgus monkeys (Study Report TT #21-1002). Minimal changes at the injection sites and in the draining lymph nodes, consistent with the volume of the SC formulation, were not attributed to MK-3475A. Overall, the formulation demonstrated acceptable local tolerability at the SC injection sites.

5.4.8. Other toxicity studies

There were no antigenicity/immunogenicity studies conducted with the SC formulation of pembrolizumab. MK-5180 induced ADA responses in all rats during the 26-week repeated dose SC toxicity study, as expected for biotherapeutics in non-human species. While systemic exposure was confirmed at 2 mg/kg (~1400 times the anticipated clinical dose of 192 U/kg), ADA formation decreased exposure over time without associated toxicological findings. No hypersensitivity or anaphylactic reactions were observed. Immunogenicity observed in rats is not considered clinically relevant. In the repeat dose local tolerability study (TT #21-1002), no findings were observed that would suggest antigenicity associated with MK-3475A. Therefore, immunogenicity assessments were not considered necessary and were not performed. The general toxicology study design for anticancer products is considered sufficient to assess immunotoxic potential and support marketing authorisation in accordance with ICH Guideline S9. Additional immunotoxicology studies were not performed. Repeated dose studies in cynomolgus monkeys and rats with pembrolizumab and MK-5180 showed no evidence of autoimmune, inflammatory or lymphoid tissue effects. The combination of haematological, organ weight and histopathological assessments provided strong evidence that MK-3475A is not associated with immunotoxicity concerns. Specific animal studies to assess abuse potential were not considered necessary and given the nature of this molecule, there were no studies conducted assessing the toxicity of metabolites. No impurity studies were conducted with the SC formulation of pembrolizumab and no non-clinical studies were conducted with individual impurities as they were qualified at the levels specified in the toxicity studies conducted with the various batches/lots of MK 3475A. This is acceptable. Finally, no phototoxicity studies were conducted with the SC formulation of pembrolizumab, MK-5180 or MK-3475A. Based on the recommendations in ICH Guidance S10 (Photosafety Evaluation of Pharmaceuticals), phototoxicity testing does not apply to peptides, proteins, antibody drug conjugates, or oligonucleotides. Therefore, the evaluation of MK-5180 and MK-3475A for phototoxicity risk was not conducted.

5.4.9. Ecotoxicity/environmental risk assessment

Pembrolizumab is a humanized monoclonal antibody (mAb; protein) and berahyaluronidase alfa is a variant of human hyaluronidase (endoglycosidase) enzyme. In line with EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), proteins are exempted of environmental risk assessment.

Pembrolizumab and berahyaluronidase alfa are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Pembrolizumab and berahyaluronidase alfa are not expected to pose a risk to the environment.

5.5. Overall discussion and conclusions on non-clinical aspects

The lack of new pharmacodynamic studies for the SC formulation of pembrolizumab is considered acceptable as its mechanism of action is unchanged from the approved IV formulation. Given the established pharmacodynamic profile of the IV formulation and the non-inferiority demonstrated in the pivotal D77 clinical study, no additional pharmacodynamic bridging studies are required to support the SC formulation.

PD in vitro studies with pembrolizumab IV and MK-5180 support their favourable safety and efficacy profiles. Pembrolizumab works primarily by activating T cells to enhance immune responses, while MK-5180 offers an improved enzymatic profile with minimal immunogenicity, suggesting that both may be valuable therapeutic options with different mechanisms of action and complementary benefits. The immunogenicity results showed low stimulation index values (below

2), indicating minimal potential for immune response induction, making MK-5180 a safe therapeutic option. In addition, MK-5180 demonstrated significantly improved catalytic efficiency compared to rHuPH20, with almost 2-fold higher catalytic efficiency. Kinetic parameters such as k_{cat} and k_{cat}/K_M showed that MK-5180 may be a more efficient alternative in clinical applications, potentially offering better pharmacokinetic properties while maintaining favourable enzymatic characteristics.

The non-clinical pharmacokinetic and toxicokinetic data for pembrolizumab (MK-3475) and its components are consistent with the expected behaviour of monoclonal antibodies and support the proposed posology extension. Pembrolizumab exhibited dose-dependent pharmacokinetics consistent with target-mediated disposition and ADA-related effects, with limited distribution mainly confined to the plasma compartment. SC administration demonstrated high bioavailability and linear pharmacokinetics in both rats and monkeys with no adverse findings reported. For MK-5180, IV administration resulted in rapid systemic clearance and limited tissue distribution. The pharmacokinetic profile was consistent across doses, although the presence of endogenous hyaluronidase activity (measured prior to IV dosing) and the small sample size limit the robustness of the conclusions. MK-5180 shows low immunogenicity and superior enzymatic efficiency compared to rHuPH20, suggesting its suitability as a permeation enhancer.

Pharmacokinetic studies indicate predictable, dose-proportional exposure for pembrolizumab and MK-5180, with limited tissue distribution and no adverse effects. The absence of metabolic interactions and acceptable safety pharmacology results further support a positive non-clinical benefit-risk assessment. After SC administration, systemic exposure to MK-5180 was low and not dose-proportional. Absorption was rapid, but no clear elimination phase was observed, and plasma concentrations returned to baseline levels within 4 hours. Pharmacokinetic parameters could not be reliably determined due to limited sampling and the absence of baseline hyaluronidase measurements in animals prior to SC dosing. As systemic exposure of MK-5180 is not required for its intended local effect at the SC injection site, the low bioavailability is considered acceptable. The applicant also referred to alignment with other marketed monoclonal antibodies co-formulated with hyaluronidase. While the issue is not fully resolved, no follow-up questions are raised as there is no further impact on the B/R, SmPC or RMP.

The overall non-clinical development program provides a comprehensive safety and pharmacokinetic profile for MK-3475A. In line with scientific advice received from the CHMP in September 2022 (EMA/SA/0000095182), the existing non-clinical safety package for MK-3475A is considered acceptable to support the line extension for the SC route of administration. Although single-dose toxicity studies with the SC formulation are not available, this is mitigated by robust safety data from repeated-dose studies with the IV formulation of pembrolizumab and studies with MK-5180. These studies, conducted in relevant species, showed no significant systemic or local toxicity at exposures well above those expected clinically. Repeated dose toxicity studies of pembrolizumab in cynomolgus monkeys up to 6 months showed no significant target organ toxicity at doses up to 200 mg/kg, with immune-related findings (e.g. mild inflammation, inguinal swelling) not associated with adverse outcomes. A NOAEL of 200 mg/kg was identified, providing a 94-fold margin of exposure to the clinical dose of 2 mg/kg.

The lack of specific carcinogenicity, genotoxicity and reproductive toxicity studies is acceptable based on ICH S6(R1) and ICH S9 guidelines, given the biological nature of the product and its intended use in oncology. In addition, the reproductive risk is already recognised in the current SmPC for pembrolizumab IV and is considered class-related based on its mechanism of action. As the reproductive risk is primarily driven by pembrolizumab and this risk is already defined and managed, no additional DART studies are considered necessary for MK-3475A. Reproductive

toxicity studies have been conducted for the novel excipient MK-5180. In rats, a fertility and embryonic development study showed no adverse effects at doses up to 18 mg/kg/day (NOAEL), >9000-fold the expected clinical dose. A slight increase in abnormal sperm morphology was observed at ≥6 mg/kg/day but was not considered biologically significant. Embryo-fetal development studies in rats and rabbits showed no major treatment-related effects, although slight reductions in fetal weight and skeletal abnormalities were observed in rabbits at higher doses. The NOAELs were 18 mg/kg/day (rats) and 0.99 mg/kg/day (rabbits) for embryo-fetal toxicity.

Overall, no new safety concerns have emerged from the non-clinical programme and the existing data, together with the known safety profile of pembrolizumab, are considered sufficient to support the ongoing clinical development of MK-3475A, including the SC route of administration.

In terms of toxicokinetic and exposure margins, MK-5180 showed rapid absorption and dose-proportional exposure across species, with systemic levels decreasing over time due to likely ADA formation. Significant exposure was only achieved at high doses, and prolonged administration led to reduced bioavailability, particularly in rodents and rabbits.

ERA

Pembrolizumab and berahyaluronidase alfa are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, pembrolizumab and berahyaluronidase alfa are not expected to pose a risk to the environment.

5.5.1. Conclusions

The non-clinical data package provides sufficient support for the pharmacodynamic and pharmacokinetic properties of the products under investigation.

The non-clinical safety profile of MK-3475A is well supported by data from the marketed IV formulation (pembrolizumab), supplemented by specific SC toxicity studies and evaluations of the novel excipient MK-5180.

6. Clinical aspects

6.1. Introduction

6.1.1. GCP aspects

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

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

Based on the review of clinical data, the CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

6.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
Phase 1 studies				
MK-3475A-C18 (ongoing)	**Arm 1**: 46 allocated/ 46 treated Gender: 33Male/13Female Median age: 61.0 years	Nonrandomized, sequential, multicenter, bioavailability and safety study of MK-3475A Primary Endpoint(s): **Arms 1 and 2**: •Ctrough •Cmax •Tmax •AUC •F **Arm 3**: •Ctrough •Cmax •Tmax •AUC •Safety **Arm 4**: •Ctrough •Cmax •AUC	**Arm 1 (Q6W)**: Cycle 1: MK-3475A 650mg SC, Cycle 2: pembrolizumab 400mg IV, Cycle 3: 650 mg SC, Cycles 4-18: pembrolizumab 400mg IV; with or without standard of care therapy, as appropriate for the indication [a,b,c]	unresectable, advanced melanoma, metastatic NSCLC, or advanced or metastatic RCC
	Arm 2: 44 allocated/ 44 treated Gender: 26Male/18Female Median age: 66.5 years		**Arm 2 (Q6W)**: Cycle 1: MK-3475A 650mg SC, Cycle 2: pembrolizumab 400mg IV, Cycle 3: 650 mg SC, Cycles 4-18: pembrolizumab 400mg IV; with or without standard of care therapy, as appropriate for the indication [a,b,c]	
	Arm 3: 6 allocated/ 6 treated Gender: 6Male/0Female Median age: 68.0 years		**Arm 3 (Q6W)**: Cycle 1: MK-3475A 790 mg SC with standard of care chemotherapy, Cycles 2-18: pembrolizumab 400mg IV[c]	

	Arm 4: 44 allocated/44 treated Gender: 22Male/22Female Median age: 60.0 years		**Arm 4 (Q3W)**: Cycles 1-35: MK-3475A 395 mg SC	
ALT-BB4-01 (completed)	**Part I**: 290 allocated/282 completed Gender: 96Male/148Female Median age: 34.0 years **Part II-A**: 23 allocated/23 completed Gender: 8Male/15Female Median age: 41.0 years **Part II-B**: Study group: 172 allocated/142 treated Gender: 62Male/80Female Median age: 34.0 years **Control group**: 87 allocated/72 treated Gender: 24Male/48Female Median age: 34.0 years	Tolerance, safety and pharmacokinetics of ALT-BB4 (a drug product containing ALT-B4, also known as MK-5180) Primary endpoint(s): **Part I:** Incidence rate of drug allergy following ID injection of MK-5180 **Part II:** Safety and tolerability following SC injection of MK-5180	**Part I**: Single dose of ALT-BB4 and comparator (0.9% NaCl) 0.02 mL **Part II-A**: Single dose of ALT-BB4 1 mL **Part II-B**: Single dose of ALT-BB4 (study group) or comparator (0.9% NaCl) (control group) 1 mL	healthy volunteers
Phase 2 studies				
MK-3475A-F11 (ongoing)	**Arm A**: 63 randomized/63 treated Gender: 39Male/24Female Median age: 61.0 years **Arm B**: 69 randomized/69 treated Gender: 44Male/25Female Median age: 65.0 years	Randomized, cross-over, multicenter, open-label study of MK-3475A Primary endpoint(s): Participant preference assessed by response of MK-3475A SC on PPQ question 1	Treatment Crossover Period: **Arm A**: MK-3475A 395 mg SC Q3W for 3 cycles followed by pembrolizumab IV 200 mg Q3W for 3 cycles **Arm B**: pembrolizumab 200 mg IV Q3W for 3 cycles followed by MK-3475A 395 mg SC Q3W for 3 cycles Treatment Continuation Period: Participants continued their preferred intervention for up to a total of 17 cycles (for adjuvant melanoma and RCC participants) or 35	resected Stage IIB, IIC, III melanoma, intermediate-high or high risk resected RCC, or newly diagnosed, untreated Stage IV NSCLC with a PD-L1 TPS ≥50%

			cycles (for metastatic NSCLC participants)	
Phase 3 studies				
MK-3475A-D77 (ongoing) **pivotal**	**Arm 1**: 251 randomized/ 251 treated Gender: 182Male/69Female Median age: 65.0 years **Arm 2**: 126 randomized/ 126 treated Gender: 86Male/40Female Median age: 66.0 years	Randomized, active-controlled, parallel-group, multisite, open-label study of MK-3475A versus pembrolizumab IV, with chemotherapy Primary endpoint(s): •Cycle 1 $AUC_{0\text{-}6\ wks}$ •Steady-state (Cycle 3) C_{trough}	**Arm 1**: MK-3475A 790 mg SC Q6W for up to 18 cycles in combination with platinum doublet chemotherapy[c] **Arm 2**: Pembrolizumab 400 mg IV Q6W for up to 18 cycles in combination with platinum doublet chemotherapy[c]	metastatic squamous or nonsquamous NSCLC

AUC = area under the curve; C = concentration; CL = clearance; F = bioavailability; ID = intradermally; IV = intravenous; Ka = absorption rate; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; PPQ = Patient Preference Questionnaire; Q3W = every 3 weeks; Q6W = every 6 weeks; RCC = renal cell carcinoma; SC = subcutaneous; Tmax = time of maximum; Vc = central volume of distribution

a For participants in Arm 1, MK-3475A concentration was 165 mg/mL. For participants in Arm 2, MK-3475A concentration was 130 mg/mL

b For participants with RCC, SOC included axitinib; for participants with NSCLC, SOC included platinum doublet chemotherapy

c For participants with nonsquamous NSCLC, platinum doublet chemotherapy included 4 infusions of pemetrexed with investigator's choice of cisplatin or carboplatin, followed by pemetrexed maintenance until a discontinuation criterion was met. For participants with squamous NSCLC, platinum doublet chemotherapy included 4 infusions of carboplatin with investigator's choice of paclitaxel or nab-paclitaxel.

6.2. Clinical pharmacology

6.2.1. Methods

A bioanalytical method based on electrochemiluminescence (ECL) for the quantification of pembrolizumab (MK-3475) in human serum was previously developed and validated to support multiple submissions of pembrolizumab IV program. In the same way, ECL-based immunoassays for the detection of pembrolizumab ADA and pembrolizumab NAb in human serum were previously developed and validated at PPD and WuXi.

A new ECL-based immunoassay was developed and validated to support the assessment of MK-5180 human plasma concentrations in clinical studies and an ECL-based assay was developed and validated for the detection of anti-MK-5180 antibodies at PPD (report: 08GQZM) and at the Keyfron Bio site (report: 08Q69I). All serum pembrolizumab samples from studies MK-3475A-C18, and MK-3475A-D77 were assayed at PPD using a 3rd generation assay. Samples from MK-3475A-D77 in China were analyzed using the 3rd generation assay in place at WuXi. Samples from the ALT-BB4-01 study were analyzed at Keyfron Bio. Validation parameters for the quantification of MK-5180 in plasma were described in reports 08MSKL and relative addendum 1 and 2 (08PD7B and 08Q42X, performed at PPD) and S21111 (performed at Keyfron Bio, Republic of Korea). Specifically, in ALT-BB4-01 clinical study, method S21111 was used whereas for the MK-3475A-C18 and MK-3475A-D77 studies the method 08MSKL was used.

As with pembrolizumab, a multi-tier testing strategy was used to detect and characterize anti-MK-5180 antibodies but no NAb assessment was performed.

6.2.2. Pharmacokinetics

6.2.2.0. Introduction

To support the use of a SC formulation of pembrolizumab co-formulated with MK-5180 (berahyaluronidase alfa) as an alternative route of administration to pembrolizumab IV (Keytruda) for solid tumour indications in adults, the MAH conducted a pivotal study: MK-3475A-D77 and two main supportive studies: MK-3475A-C18 and ALT-BB4-01.

MK-3475A-D77 provided data to demonstrate PK NI of the Proposed SC formulation with respect to the already authorized IV formulation.

In addition, a Phase 2 Study MK-3475A-F11 was performed to evaluate patient reported preference for subcutaneous pembrolizumab co-formulated with hyaluronidase (MK-3475A) over intravenous pembrolizumab formulation in participants with multiple tumor types.
Moreover, two additional studies were included in the submitted dossier and were part of an earlier development program begun to evaluate the use of pembrolizumab SC administered without the berahyaluronidase alpha: KEYNOTE-555 and KEYNOTE-A86.
These two last studies have been only briefly in the specific section dedicated to the description of bioavailability of SC formulation versus the IV one.

6.2.2.1. Evaluation and qualification of models

For this submission and to support the development of MK-3475A (pembrolizumab with MK-5180), the reference population PK analysis of pembrolizumab (report 04M52F) was expanded using SC pooled data from study MK-3475A-C18 (Arms 1, 2 and 3) and from pivotal study MK-3475A-D77, to characterize pembrolizumab PK after SC administration of MK-3475A (report 08QL4V).

Report 08QL4V was the final popPK model describing pembrolizumab PK after either IV and SC administration and was essentially used to derive model-based individual exposure estimates representing the dual primary endpoints and also model-based individual exposure estimates which are the secondary endpoints in the Phase 3 NI study.

The development of this final IV and SC expanded model was done by building other interim models used to characterize the pembrolizumab PK profile after SC administration of MK-3475A and estimate the SC bioavailability of pembrolizumab for two different formulation strengths (130 mg/mL and 165 mg/mL) based on data from the Phase 1 study MK-3475A-C18, initially for an interim analysis (interim data from Arm1 and Arm 2, report 08NTM7), and then expanded with data from a final analysis (final data from Arms 1 to 4, report 08PH8G), while an earlier popPK was also developed to characterize the PK of pembrolizumab administered subcutaneously without MK-5180 using serum concentration data from 32 subjects from KEYNOTE-555 Cohort A (report 05MV7X). This model expands the reference PK model using serum concentration data from 32 subjects from KEYNOTE-555 Cohort A with the aim to characterize the PK profile of pembrolizumab after subcutaneous (SC) administration without MK-5180 and to specifically estimate the relative bioavailability at 2 distinct SC formulation strengths (130 mg/mL and 165 mg/mL).

Evaluation of the final Model

PcVPCs were performed for all data to assess the robustness of the final Pop PK model.

Dataset

A total of **377 subjects from Study D77 and 96 subjects from Study C18** were present in the source dataset.

Table 6. Number of individuals included in the PK analysis set

Study	PK Database (N)	Flagged (N)	Included Individuals (N; %)
MK-3475A-D77	377	4	373 (98.94%)
MK-3475A-C18	96	0	96 (100%)
Total	473	4	469 (99.15)

Source: [08QL4V: analysis-adnmpkpm]
Abbreviations: PK = pharmacokinetics.

A summary of the number of observations included in the final analysis dataset is shown below.

Table 7. Number of PK observations included in the PK analysis set

Study	Total number of observations	Number (%) excluded based on flag[a]	Number (%) of Pre-dose BLQ	Number (%) of Post-dose BLQ	Number (%) of outliers[b]	Number (%) of observations available for PK analysis
MK-3475A-D77	4388	96 (2.19%)	349 (7.95%)	3 (0.07%)	13 (0.30%)	3927 (89.49%)
MK-3475A-C18	2298	8 (0.35%)	93 (4.05%)	0 (0%)	8 (0.35%)	2189 (95.26%)
Total	6686	104 (1.56%)	442 (6.61%)	3 (0.04%)	21 (0.31%)	6116 (91.47%)

Source: [08QL4V: analysis-adnmpkpm]
Abbreviations: BLQ = below limit of quantification; PK = pharmacokinetics.
[a]The rationale for exclusion of individual records is provided in [Appendix 2].
[b]Individual records identified as outliers (|CWRES|>6) are listed in [Appendix 3] and the results of the sensitivity analysis are provided in [Appendix 7].

Available serum concentration data from 373 subjects in MK-3475A-D77 and from 96 subjects in MK-3475A-C18, providing a total of 6116 observations, were used in the PK modelling analysis.

Methods

Non-linear mixed-effects modelling was applied to the pooled Phase 1 study (MK-3475A-C18 Arm 1, Arm 2, and Arm 3) and Phase 3 study (MK-3475A-D77) data informed by the reference IV PK model based on historical IV pembrolizumab data.

Typical values of the base model and goodness-of-fit plots are presented in the table and figure below respectively:

Table 8. Base Model Parameter Estimates

Parameter	Model excluding outliers		
	Estimate	%RSE	%CV
Ka (day-1)	0.303	2.88	48.02
F	0.599	1.65	14.21
Corr (ω2Ka, ω2F)	R = 36.3	26.2	
Residual error IV SC	 0.174 0.192	 4.2 3.09	

The updated population PK model was able to describe pembrolizumab PK after either IV or SC administrations. The estimated bioavailability of pembrolizumab SC was 59.9% (95% confidence interval [CI]: 58% - 62%, CV (%): 14%) and the estimated absorption rate constant was 0.32 /day (95% CI: 0.30 /day - 0.34 /day, CV (%): 47%).

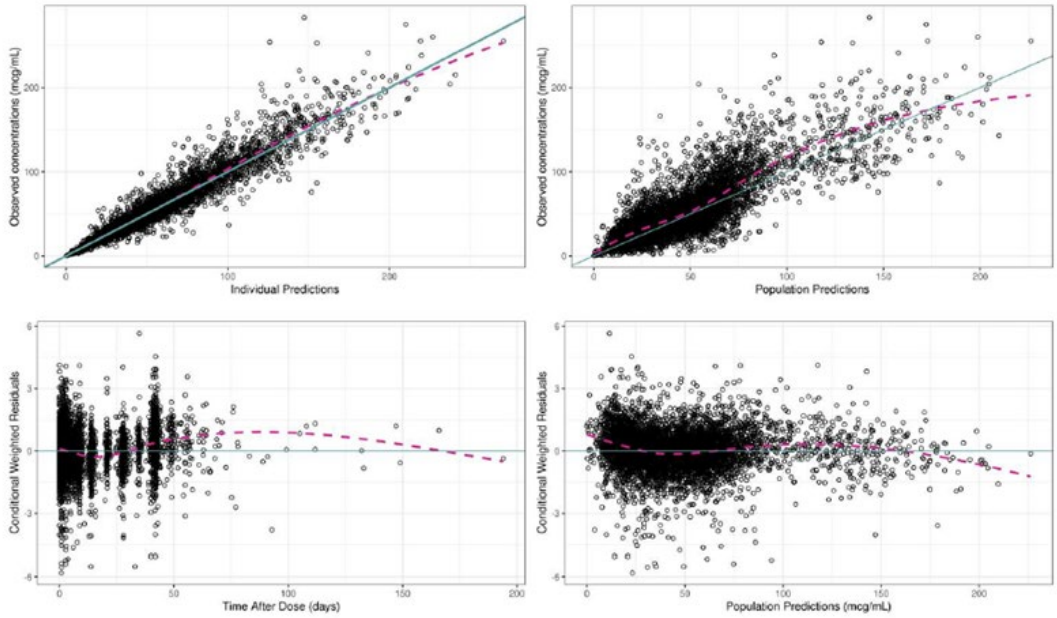
The adequacy of the structural model was assessed by different model diagnotics including: OFV, Precision of parameter estimates, GOF diagnostic plots, Observed concentrations versus population

(PRED) and individual (IPRED) model predictions, Population (CWRES) and individual (IWRES) conditional weighted residuals versus time and model predictions.

Stability of models was assessed based on standard criteria including GOF plots, Prediction-corrected visual predictive check (pcVPC) and/or bootstrap analysis.

Precision of parameter estimates are reported in above table as relative standard errors, which are within 30% and considered reasonable. Plots of conditional weighted residuals versus population predictions and versus time after first dose are presented in the below figure.

Figure 1. Base Model Goodness of Fit



Open circles represent pembrolizumab observed and predicted concentrations; green line represents the identity line; dashed red line represents the loess regression line.

Model parameter estimates of the final combined SC and IV population PK model are presented in the following table.

Table 9. Final parameter estimates of the combined SC and IV population PK model and bootstrap results

Parameter	Estimate	%RSE[a]	%CV[b]	%Shrinkage	Bootstrap	Bootstrap 95% CI	
Estimated parameters using MK-3475A-D77 and MK-3475A-C18 data							
Ka (day-1)	0.322	3.25	46.9%	23.3%	0.322	0.302	0.343
F	0.599	1.65	14.2%	32.9%	0.599	0.580	0.619
Corr (ω2Ka, ω2F)	0.089 (R = 33.7)	28.49	-	-	0.089	0.041	0.135
Sex effect on Ka	-0.192	25.87	-	-	-0.192	-0.280	-0.089
Residual error							
IV	0.174	4.21	-	10.6%	0.174	0.160	0.188
SC	0.192	3.09	-		0.191	0.180	0.203
Fixed parameters from reference IV model							
CL (L/day)	0.28	-	30.6%	21.3%	-	-	
Q (L/day)	0.89	-			-	-	
Vc (L)	3.53	-	19.1%	38.5%	-	-	
Vp (L)	2.75	-			-	-	
Maximum effect of time on CL	-0.218	-	79.4%	24.4%	-	-	
TI50 (days)	65.5	-	-	-	-	-	
Hill coefficient	2.99	-	-	-	-	-	
a for CL and Q (allometric scaling factor)	0.534	-	-	-	-	-	
a for Vc and Vp (allometric scaling factor)	0.514	-	-	-	-	-	
Albumin effect on CL	-0.849	-	-	-	-	-	
eGFR effect on CL	0.123	-	-	-	-	-	
Sex effect on CL	-0.162	-	-	-	-	-	
Baseline ECOG effect on CL	-0.0697	-	-	-	-	-	
Baseline tumor size effect on CL	0.0933	-	-	-	-	-	

Parameter	Estimate	%RSE[a]	%CV[b]	%Shrinkage	Bootstrap	Bootstrap 95% CI
Bilirubin effect on CL	-0.0488	-	-	-	-	-
Albumin effect on Vc	-0.233	-	-	-	-	-
Sex effect on Vc	-0.131	-	-	-	-	-
Tumor type effect (NSCLC vs other) on Vc	-0.059	-	-	-	-	-

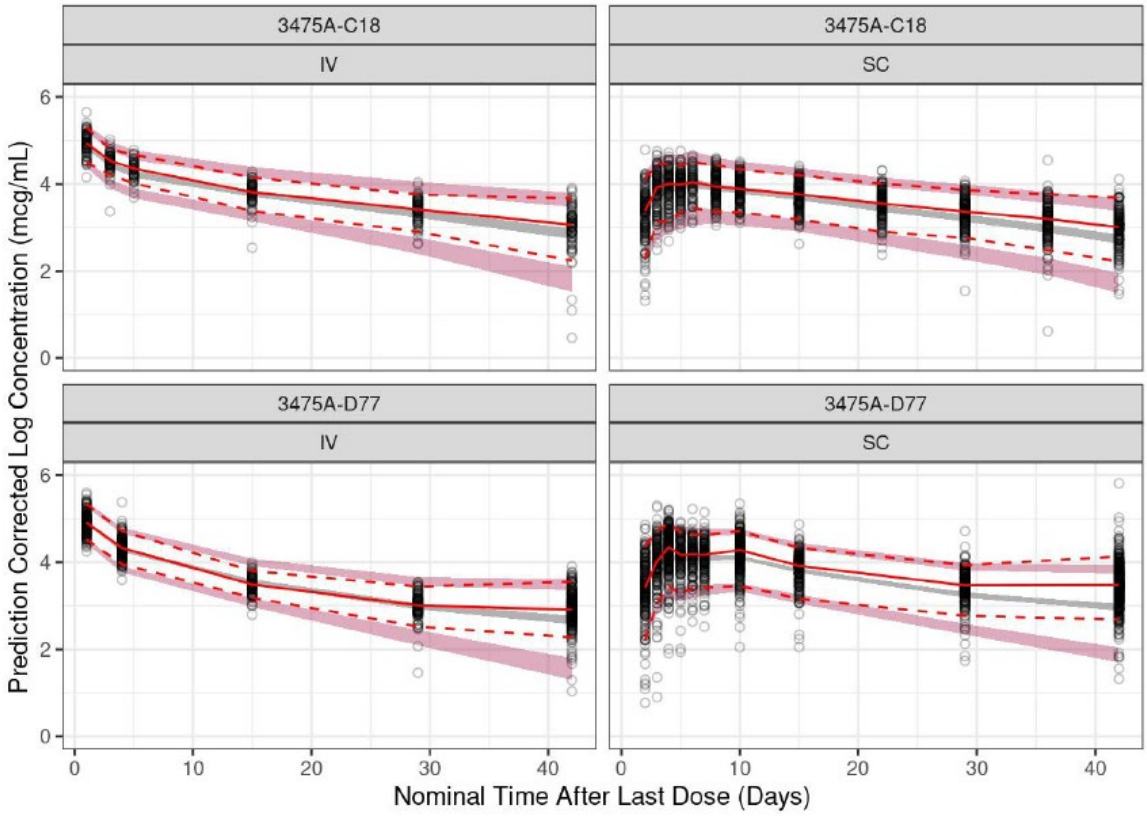
[a]: The RSE of parameter estimate is calculated as 100 × (SE / typical value); the RSE of correlation between random effects is calculated as 100 × (SE / variance estimate).

[b]: Estimates for exponential random effects are presented in % CV and, based on the estimated variances, are calculated as $\sqrt{}$(exp [variance] - 1) × 100, if variance ≥0.15; otherwise, $\sqrt{}$(variance) × 100. Estimates for additive random effects (Imax) are calculated as $\sqrt{}$(variance) /|typical value of fixed effect| × 100. The % CV for bioavailability was calculated as √(variance) × F1 × (1-F1) × 100 since the random effect was additive in the logit scale.

Abbreviation: CV, coefficient of variation of between-subject distributions of parameters; eGFR, estimated glomerular filtration rate; NSCLC, non-small cell lung cancer; RSE, relative standard error; Ka: absorption rate constant; F: bioavailability; CL: clearance; Vc: volume of distribution in the central compartment; Q: intercompartmental clearance; Vp: volume of distribution of the peripheral compartment; TI50, time at which 50% of the maximum effect on clearance has been achieved

The ability of the final combined SC and IV PK model to describe pembrolizumab PK after IV or SC administration as MK-3475A was evaluated by pcVPC plots based on 1000 simulations. pcVPC plots stratified by study and route of administration are displayed in the below figure.

Figure 2. pcVPC plots stratified by study and route of administration



Note: The black circles are the prediction-corrected observed concentrations. The red lines are the 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations. The colored bands are the 90% confidence intervals for the simulated 50th (gray), 5th, and 95th (pink).

6.2.2.1.1. Population Pharmacokinetics

During model development, the absorption phase PK parameters i.e. first-order absorption rate constant (Ka) and bioavailability (F) for SC administration were estimated from the SC data collected, while all model parameters describing systemic PK (including fixed effects, random effects, and covariate effects) were fixed from the reference IV PK model based on historical IV data.
Finally, for the combined IV and SC model, the absorption phase for SC administration was characterized by first order absorption rate constant (Ka) and bioavailability (F) parameters. Distribution and elimination phases were described by a two-compartment model with time-dependent clearance and a fixed effect of body weight, as established historically in the reference pembrolizumab PK model
The adequacy of the structural model was assessed by different model diagnostics and overall, the updated/expanded model seems to adequately describe the shape of observed IV and SC serum concentration, indeed, the model well centred the absorption phase of the SC route.

6.2.2.2. Absorption

The PK profile of MK-5180 (berahyaluronidase alfa) has been evaluated in study in ALT-BB4-01 (Part II) as secondary endpoint (the primary endpoint of that study was safety and tolerability and was evaluated in Part I of the study).

In part I enrolled subjects were intradermally administered into the right or left forearm with investigational product (MK-5180 1,500 IU/mL) or comparator (normal saline 0.9% NaCl).

Eligible subjects for Part II-A of the study will be enrolled only subjects with a drug allergy test negative in the Part I.

The part I is designed as a multicenter, 2-arms, randomised (1:1), double blind, placebo-controlled, intradermal injection study; the part II-A was a single centre, single arm, open-label, SC injection; the Part II-B was a multicenter, 2-arms, randomised (2:1), double-blind, placebo-controlled, SC injection study.

The primary objective is to evaluate the allergic reactivity, safety and tolerability of ALT-BB4; the secondary objective was to evaluate the PK profile of SC single dose of ALT-BB4. Among the exploratory objective was the evaluation of the immunogenicity.

The primary PK endpoints in Part II were Cmax, AUClast, T1/2 and Tmax; the secondary endpoints were baseline-adjusted Cmax, AUClast, t1/2 and Tmax. Results indicate that after a single SC dose of 1,500 IU, 21 out of 23 subjects showed concentrations below the **LLO**Q, whereas two subjects had concentrations above the L**LO**Q

Samples for evaluation of MK-5180 were also collected in all Arms of study C18 (pre-dose 0 to 3 hours before MK-3475A administration on C1D1 and C3D1 and on D2 and D3 of C1 and C3 at any time), as well as in Study D77 (PK sampling for determination of berahyaluronidase alfa were collected at predose and post-dose D1 and 42).

The SC formulations used (130 mg/mL and 165 mg/mL) in study C18 and D77 contained 2000 U/mL of berahyaluronidase alfa while that used in study ALT-BB4-01 contained 1,500 IU.

In C18, MK-5180 PK samples were available from 140 subjects. 9 out of 706 samples included in the PK evaluation contained concentrations above the detection level of the assay (lower limit of quantification [LLOQ] = 0.313 ng/mL). These samples were from 2 subjects for whom baseline MK-5180 concentrations (Cycle 1 Day 1 Predose) were already above the detection level of the assay, which were considered attributable to pre-existing matrix interference, hence post-dose MK-5180 concentrations in these subjects are not considered reliable.

In D77, MK-5180 PK samples were available from 226 subjects. 9 out of 640 samples included in the PK evaluation contained concentrations above the detection level of the assay (lower limit of quantification [LLOQ] =0.313 ng/mL). These samples were from 3 subjects for whom baseline MK-5180 concentrations (Cycle 1 Day 1 Predose) were already above the detection level of the assay, which could be attributable to pre-existing matrix interference, hence post-dose MK-5180 concentrations in these subjects are not considered reliable. Thus, there were no subjects with only post-dose samples containing measurable MK-5180 concentrations (i.e., above the detection level of the assay).

Bioavailability

Available PK data from the FIH, Phase 1 study MK-3475A-C18, was used to estimate the bioavailability of pembrolizumab when administered SC as MK-3475A to enable Phase 3 dose selection and further clinical development.

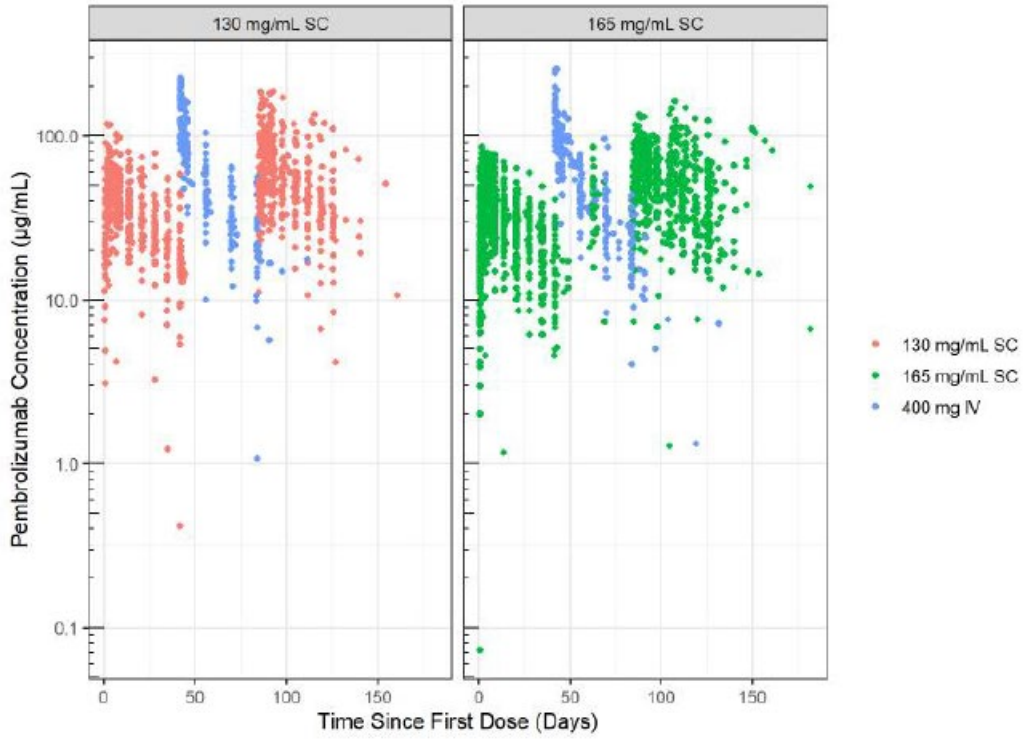
Primary objectives of this Phase 1 non-randomized, multicenter, open-label study in patients were to characterize the PK profile of pembrolizumab, particularly during the absorption phase, following SC administration of MK-3475A and to estimate the bioavailability of pembrolizumab following SC injection of 2 different formulations of MK-3475A, differing in the strength of pembrolizumab SC solution (i.e., 165 mg/mL or 130 mg/mL).

The 2000 U/mL concentration of MK-5180 was chosen to maintain consistency with marketed mAbs formulated with hyaluronidase. RITUXAN HYCELA (rituximab, Roche), HERCEPTIN HYLECTA (trastuzumab and hyaluronidase, Genentech) and DARZALEX FASPRO (daratumumab and hyaluronidase, Janssen) all contain 2000 U/mL of hyaluronidase. The enzyme activity of MK-5180 is comparable to the marketed rPH20, HYLENEX recombinant (hyaluronidase human injection, Halozyme Therapeutics) present in these other products.

The selected dose of 650 mg assumes ~65%bioavailability for the SC formulation based on data from the previous pembrolizumab SC development study KEYNOTE-555 and is expected to have comparable exposures relative to the IV dose of 400 mg Q6W.

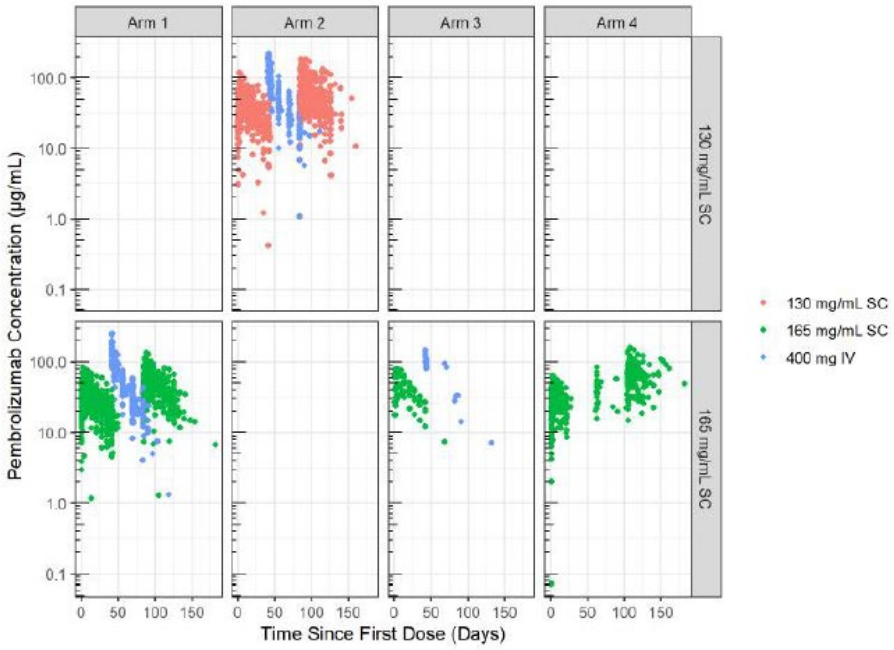
Scatter plots of observed pembrolizumab serum concentrations versus time since first dose (semi-log) stratified by formulation and treatment arm did not reveal any major differences in the PK profiles between the 130 mg/mL and 165 mg/mL SC formulation strengths.

Figure 3. Observed pembrolizumab serum concentrations versus time since first dose (semi-log) stratified by formulation



Source: mk3475_c18_pk_data_eda_v20.Rmd → mk3475_c18_pk_data_eda_v20.html
Note: Colors of circles represent different formulation and route of administration.
Abbreviations: IV=intravenous; SC=subcutaneous
Data cutoff date: 24-JUN-2024

Figure 4. Observed pembrolizumab serum concentrations versus time since first dose (semi-log) stratified by treatment arm and formulation

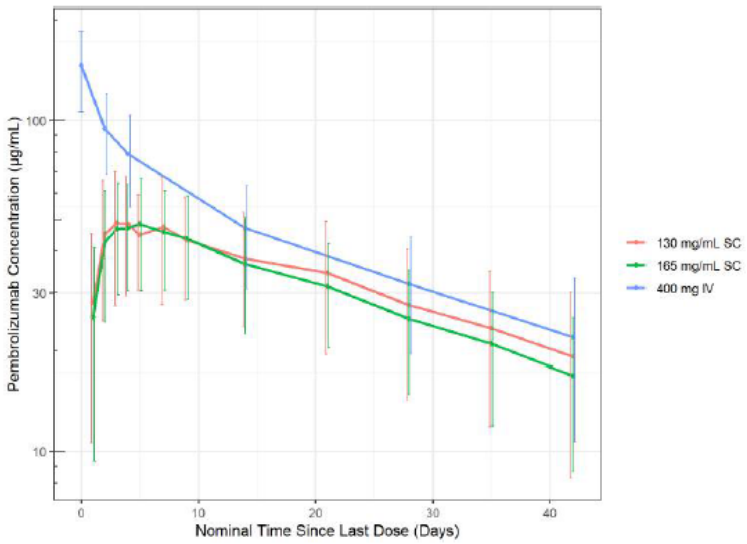


Source: mk3475_c18_pk_data_eda_v20.Rmd → mk3475_c18_pk_data_eda_v20.html
Note: Colors of circles represent different formulation and route of administration.
Abbreviations: IV=intravenous; SC=subcutaneous
Data cutoff date: 24-JUN-2024

The median observed Tmax in Cycle 1 across all arms was estimated to be 4 days (range: 1 to 35 day).

The mean observed SC and IV profiles are generally consistent except for the distinct absorption phase associated to the SC administration.

Figure 5. Observed mean PK profiles for SC and IV (semi-log)



Source: mk3475_c18_pk_data_eda_v20.Rmd → mk3475_c18_pk_data_eda_v20.html
Note: Colors of lines represent different formulation and route of administration. Data and error bars represent arithmetic mean ± SD. In Arms 1, 2, and 3, MK-3475A SC injection was given at pembrolizumab 650 mg Q6W in Cycle 1 and IV pembrolizumab was given at 400 mg Q6W in Cycle 2.
Abbreviations: IV=intravenous; PK=pharmacokinetic; SC=subcutaneous; SD=standard deviation
Data cutoff date: 24-JUN-2024

A population PK analysis approach (report 08PH8G) with nonlinear mixed-effects modeling was applied to characterize the PK of pembrolizumab following SC administration of MK-3475A in all treatment arms. (see section "evaluation and qualification of models" for a detailed description of population PK analysis)

The mean bioavailability of pembrolizumab administered SC as MK-3475A (all arms), assessed using this PK model-based analysis, is estimated to be **61.1%** (CV%: 22.4%) and mean absorption rate constant is estimated to be 0.301/day (CV%: 43.7%). This is in line with the estimated value estimated with the final model 08QL4V (60%; CV%: 14%) and similar with the BA observed for other monoclonal antibodies after SC administration (Zhao et al, 52-80%; Davis et al, 2024, 50-85%).

The bioavailability for pembrolizumab SC without berahyaluronidase was also evaluated in Study Keynote-555 (see further below). The updated/expanded population PK model (**05MV7X**) was used to simultaneously describe pembrolizumab PK after IV or SC administrations. The BA of pembrolizumab SC without berahyaluronidase is similar (66%; 95% CI: 58% to 74 %) to that estimated with berahyaluronidase.

Table 10. Summary statistics of model-based individual PK exposures of cycle 1 following the administration of 650 mg Q6W SC in Arm 1 and 2

Pembrolizumab Pharmacokinetic Parameter	Arm 1 (165 mg/ml)				Arm 2 (130 mg/ml)			
	N	Mean (SD)	Median (range)	GM (CV%)	N	Mean (SD)	Median (range)	GM (CV%)
C_{max} (µg/mL)	46	47.8 (15.5)	44.5 (19.4, 79.6)	45.2 (36.5%)	44	52.4 (16.8)	51.2 (23.5, 112)	49.9 (32.7%)
C_{trough} (µg/mL)	46	15.4 (6.84)	15.1 (3.76, 36.1)	13.9 (51.0%)	44	17.0 (8.72)	16.0 (0.595, 44.4)	14.4 (80.0%)
$AUC_{0\text{-}6wks}$ (µg·day/mL)	46	1249 (397)	1280 (562, 2382)	1185 (34.9%)	44	1355 (479)	1287 (529, 2648)	1277 (36.4%)
T_{max} (day)	46	5.91 (2.04)	6.00 (3.00, 10.0)	5.59 (35.1%)	44	5.50 (1.92)	5.00 (2.00, 10.0)	5.20 (35.0%)

$AUC_{0\text{-}6wks}$=area under the concentration-time curve for 0 to 6 weeks; C_{trough}=concentration at the end of the dosing interval; C_{max}=maximum concentration; CV%=percent coefficient of variation; GM=geometric mean; N=number of subjects with available information; Q6W= every 6 week; SC=subcutaneous; SD=standard deviation; T_{max}= time to maximum concentration.
[PC18V01MK3475A: adam-adnmpkpm]

Table 11. Statistics of Model-based Individual PK Exposures of Cycle 1 and Cycle 6 Following Administration of 395 mg Q3W SC in Arm 4

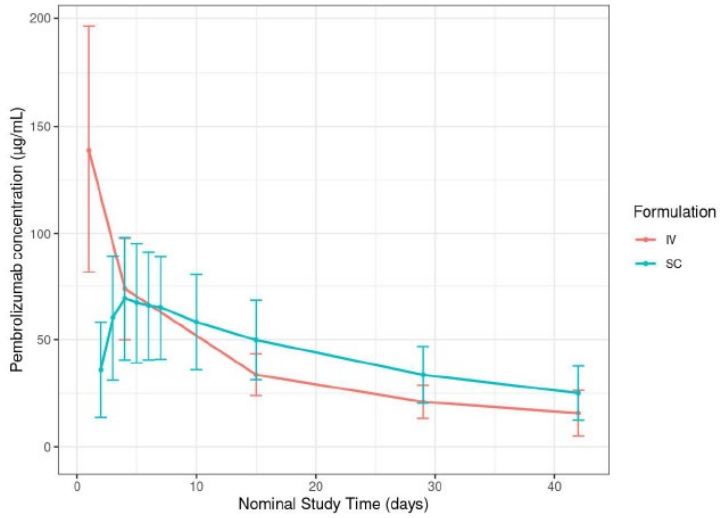
Summary Statistics of Model-based Individual Pharmacokinetic Exposures of Pembrolizumab in Cycle 1 and Cycle 6 Following Administrations of Pembrolizumab 395 mg Q3W SC as MK-3475A in Arm 4

Pembrolizumab Pharmacokinetic Parameter	Cycle 1				Cycle 6 (steady-state)			
	N	Mean (SD)	Median (range)	GM (CV%)	N	Mean (SD)	Median (range)	GM (CV%)
C_{max} (µg/mL)	44	35.3 (12.3)	34.1 (10.6, 63.7)	33.0 (40.6%)	44	81.7 (28.8)	80.7 (30.9, 162)	76.5 (39.0%)
C_{trough} (µg/mL)	44	21.4 (6.75)	21.2 (9.73, 40.5)	20.3 (34.2%)	44	53.6 (22.2)	54.6 (21.7, 123)	49.0 (45.8%)
$AUC_{0\text{-}3wks}$ (µg·day/mL)	44	578 (186)	567 (192, 979)	546 (36.7%)	44	1439 (528)	1446 (604, 3050)	1343 (39.9%)
T_{max} (day)	44	5.48 (2.14)	5.00 (2.00, 10.0)	5.11 (38.9%)	44	4.18 (1.21)	4.00 (2.00, 8.00)	4.02 (28.6%)

$AUC_{0\text{-}3wks}$=area under the concentration-time curve for 0 to 3 weeks; C_{trough}=concentration at the end of the dosing interval; C_{max}=maximum concentration; CV%=percent coefficient of variation; GM=geometric mean; N=number of subjects with available information; Q3W= every 3 week; SC=subcutaneous; SD=standard deviation; T_{max}= time to maximum concentration.
[PC18V01MK3475A: adam-adnmpkpm]

In the **pivotal study D77,** the mean observed SC and IV pembrolizumab PK profiles for treatment Cycle 1 in MK-3475A-D77 are shown in the figure below:

Figure 6. Observed SC and IV pembrolizumab mean PK profiles for treatment Cycle 1 in MK-3475A-D77



Source: [08QL4V: analysis-adnmpkpm]
Error bars represent the standard deviation of concentrations. "SC" and "IV" represent the observed mean PK profile after the first pembrolizumab 790 mg Q6W SC dose and 400 mg Q6W IV dose. Based on data from all 373 subjects included in the PK analysis.

Median observed Tmax with SC pembrolizumab given as MK-3475A was 4 days (range: 1 to 35 days). Median model-predicted Tmax with SC pembrolizumab given as MK-3475A was 5 days (range: 2 to 15 days). The median model-predicted accumulation ratio for 790 mg Q6W SC was estimated to be 1.61 (range: 1.05- 2.24).
Detailed information about this study is reported in section "Main study" considering that it is the pivotal study for this line extension to establish NI respect to IV formulation.

6.2.2.3. Distribution

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

6.2.2.4. Metabolism

Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

6.2.2.5. 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.

6.2.2.6. Dose proportionality and time dependency

Exposure to intravenous pembrolizumab as expressed by peak concentration (Cmax) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2.1-fold.

Model-predicted PK exposures at 395 mg Q3W SC were consistent with 790 mg Q6W SC with both regimens given as MK-3475A and no meaningful difference in bioavailability or absorption rate was found between the 130 mg/mL and 165 mg/mL MK-3475A SC formulation strengths.

6.2.2.7. Pharmacokinetics in the target population

Pivotal study D77 has been conducted in patients with NSCLC and results are reported in section 6.3.

6.2.2.8. Special populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range: 15-94 years), gender, race, mild or moderate renal impairment, mild or moderate hepatic impairment and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. Pembrolizumab exposure with weight-based dosing at 2 mg/kg bw every 3 weeks in paediatric patients (≥ 3 to 17 years) are comparable to those of adults at the same dose.

Of note, after forward inclusion and backward elimination, sex on Ka was identified as a significant (p value= 0.0004) covariate in the combined SC and IV population PK model, with 19.2% lower Ka in female subjects. However, this effect was considered as not clinically significant.

6.2.2.9. Pharmacokinetic interaction studies

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected. The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab 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 to treat immune-mediated adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

Exposure relevant for safety evaluation

As per Study D77, after 790 mg Q6Q SC, the median Cycle 1 AUC0-6weeks is 1711.63 µg·day/mL and the median Cycle 1 Cmax is 70.02 µg/mL. At steady state, the median AUC (cycle 3) is 2772 µg·day/mL and Cmax (cycle 3) is 100 µg/mL.

Model-based steady-state (Cycle 3) Ctrough showed noninferiority of pembrolizumab 790 mg Q6W administered SC as MK-3475A compared with IV administration of pembrolizumab 400 mg Q6W and prespecified sensitivity analysis of observed steady-state (Cycle 3) Ctrough were consistent with the primary analysis of model-based steady-state (Cycle 3) Ctrough.

6.2.3. Pharmacodynamics

6.2.3.0. Mechanism of action

KEYTRUDA is a humanised monoclonal antibody which binds to the programmed cell 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

6.2.3.1. Immunological events

The development of ADA against pembrolizumab and MK-5180 and the effect on PK have been analysed in the pivotal study D77, in C18 and in ALT-BB4-01 studies (only against MK-5180 for study ALT-BB4-01). The primary basis to evaluate the immunogenicity for MK-3475A is the pivotal Study D77 (below table). Moreover, for study D77 the effect of ADA on efficacy and safety has been also investigated.

Table 12. Summary of subject immunogenicity results in study MK-3475A-D77

Pembrolizumab Therapy			
Immunogenicity status	**Total**	**MK-3475A SC with Chemotherapy**	**MK-3475 IV with Chemotherapy**
Assessable subjects[a]	349	230	119
Inconclusive subjects[b]	24	19	5
Evaluable subjects[c]	**325**	**211**	**114**
Negative[d]	319 (98.2%)	206 (97.6%)	113 (99.1%)
Non-Treatment emergent positive[d]	2 (0.6%)	2 (0.9%)	0
Neutralizing negative	2 (0.6%)	2 (0.9%)	0
Neutralizing positive	0	0	0
Treatment emergent positive[d]	4 (1.2%)	3 (1.4%)	1 (0.9%)
Neutralizing negative	3 (0.9%)	2 (0.9%)	1 (0.9%)
Neutralizing positive	1 (0.3%)	1 (0.5%)	0
a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level. c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent. d: Denominator was total number of evaluable subjects.			

Data source: [PD77V01MK3475A: adam-adadapm]

Results from D77 suggest that, although the SC route of administration is potentially more immunogenic than IV administration, the observed increment is minimal with 3 out of 211 patients **(1.4%)** treated with MK-3475A SC developing treatment emergent pembrolizumab ADA versus 1 out of 114 patients (0.9%) treated with MK-3475 IV. One subject (0.5%) with TE ADA treated with MK-3475A SC had Nab, whereas the subject with TE ADA in IV arm had no Nab. The incidence of ADA for subcutaneous injection is within that observed for IV injection ranging from 1.8 to 2.1%. No evidence of an effect of ADA on PK is observed with comparable exposure in patients ADA positive and ADA negative and it is in line with that observed in patients treated with MK-3475 IV. The effect of ADA on efficacy was also evaluated revealing that the ORR in ADA positive participants is 66.7% (95% CI: 9.4, 99.2) versus 47.1% (95% CI: 40.1, 54.1) in ADA negative participants. Although the efficacy seems not be impacted by the presence of ADA. No clear conclusion can be drawn, considering the low number of ADA positive participants and the wide range of variability. The same can be concluded on the effect of ADA on safety.

Regarding MK-5180, the incidence of TE ADA is **1.5%** (3 out of 194) if considering subject with at least one pre-treatment or post-dose sample positive in the confirmatory assay; among these 3 participants, 1 was a TE positive ADA (negative at pre-dose and positive at Cycle 3 day 1) and 2 participants were treatment boosted ADA since were positive also pre-dose. It is of note that none of these ADA positive participants showed MK-5180 plasma concentrations; whereas participants

showing MK-5180 plasma concentrations did not develop ADA. Due to the fact that participants ADA positive did not show MK-5180 plasma concentrations, no evaluation of effect of ADA on PK can be done. Regarding the effect on efficacy, the ORR was 50.0% (95% CI: 42.6, 57.4) for ADA negative participants and 66.7% (95% CI: 9.4, 99.2) for ADA positive participants.
As supportive evidence on low immunogenicity of MK-3475A and MK-5180, ADA were also evaluated in study C18. One subject (**0.8%**) showed TE positive pembrolizumab ADA with no neutralizing activity and no effect on PK. Regarding MK-5180, 2 subjects showed TE positive ADA (**1.6%**); the neutralizing activity has not been evaluated and these subjects did not have MK-5180 plasma concentrations therefore the effect on PK cannot be evaluated.
The development of ADA against MK-5180 was also evaluated in study ALT-BB4-01, however no samples were confirmed positive.

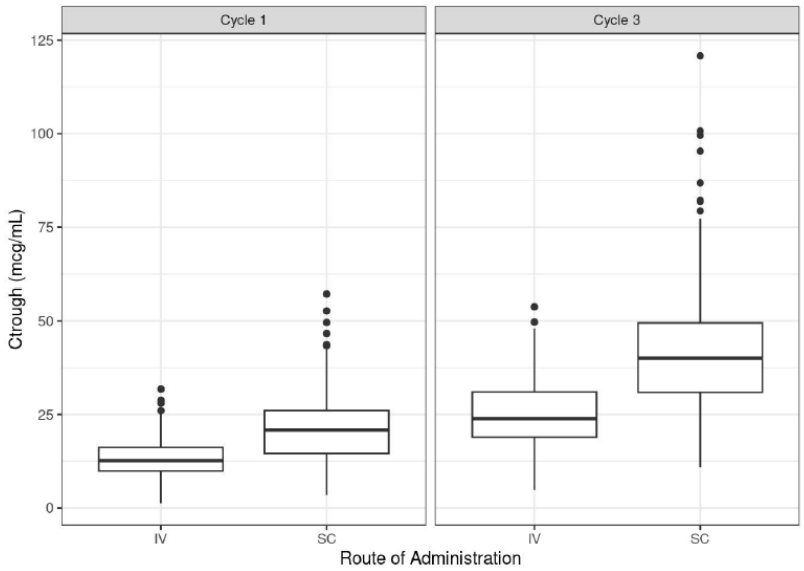
6.2.4. Dose selection and therapeutic window

Modelling and simulation approaches have been used to select the Q6W dose for the pivotal phase 3 study D77 and also to select an appropriate Q3W SC dosing regimen for use in MK-3475A-C18 Arm 4 and then to support bridging with the Q3W dosing regimen as an alternative recommended dose.

Initially, in Study MK-3475A-C18, the dose of 650 mg Q6W was selected assuming ~65% bioavailability for the SC formulation based on data from the previous pembrolizumab SC development study KEYNOTE-555 and expected to have comparable exposures relative to the IV dose of 400 mg Q6W based on literature data (Zhao, L., et al 2013). The observed PK data for pembrolizumab 650 mg Q6W administered SC as MK-3475A from the Phase 1 study, MK-3475A-C18 (interim data from Arms 1 and 2), were used to inform a model to characterize the PK of pembrolizumab after both SC and IV administration (popPK report 08NTM7).

Simulations using the SC and IV PK model (08NTM7) were performed to select the optimal dose of pembrolizumab 790 mg Q6W administered SC as MK-3475A for the Phase 3 study, targeting consistency of the pembrolizumab SC PK exposure profile with that of the approved 400 mg Q6W IV dose and also to select an appropriate Q3W SC dosing regimen for use in MK-3475A-C18 Arm 4, targeting consistency of the Q3W SC PK exposure profile with that of 790 mg Q6W SC dosing regimen.
Observed PK data from the pivotal phase 3 study D77 were used to confirm the selected dose of 790 mg Q6W for SC administration and the 395 mg Q3W SC regimen was finally evaluated in MK-3475A-C18 Arm 4 and used to validate model-based predictions of PK profiles for pembrolizumab 395 mg Q3W administered SC.
The model-based predictions of PK profiles for pembrolizumab 395 mg Q3W administered SC as MK-3475A were validated by observed data in Arm 4 of MK-3475A-C18, using a modelling and simulation approach as described in the M&S Report 08NTYM.
Simulation from this report was substantially used to compare exposures between Q3W and Q6W SC dosing regimens of MK-3475A and to compare exposures between SC and IV dosing regimens with the aim to bridge the proposed pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A dosing regimens to the currently approved pembrolizumab IV dosing regimens (200 mg Q3W and 400 mg Q6W).

Figure 7. Box plots of Ctrough and Cmax for cycle 1 and 3 (IV and SC)



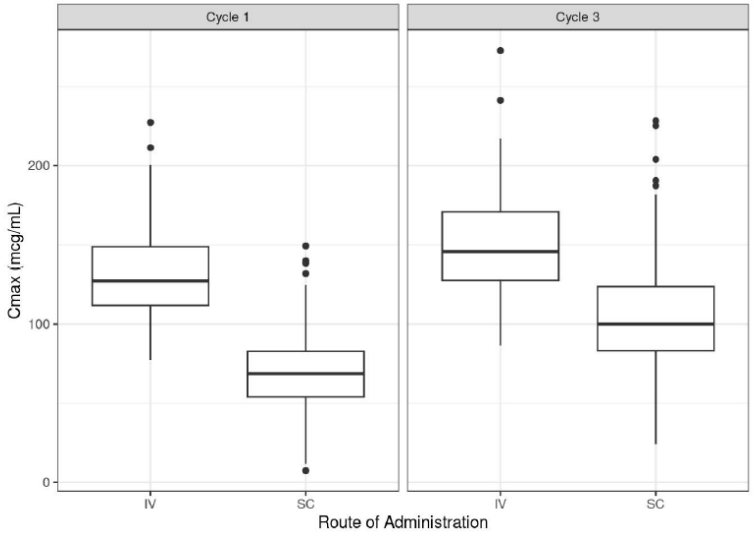
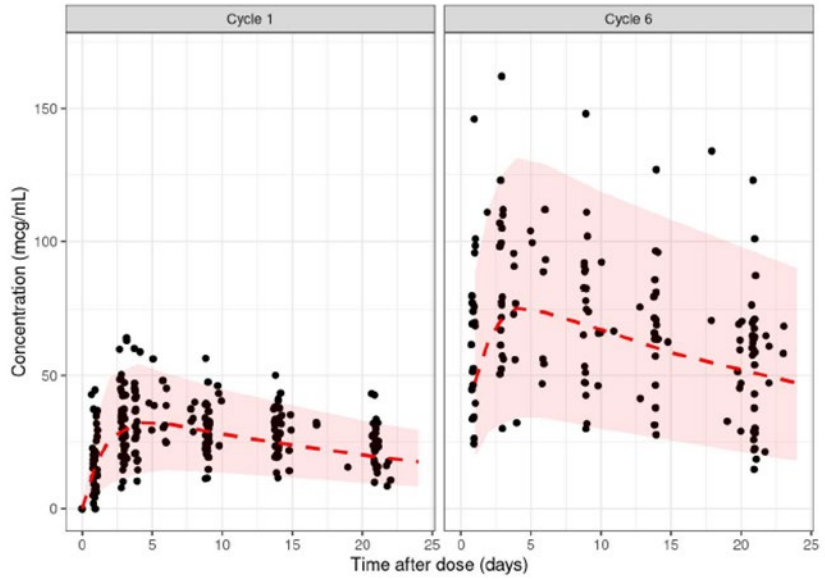
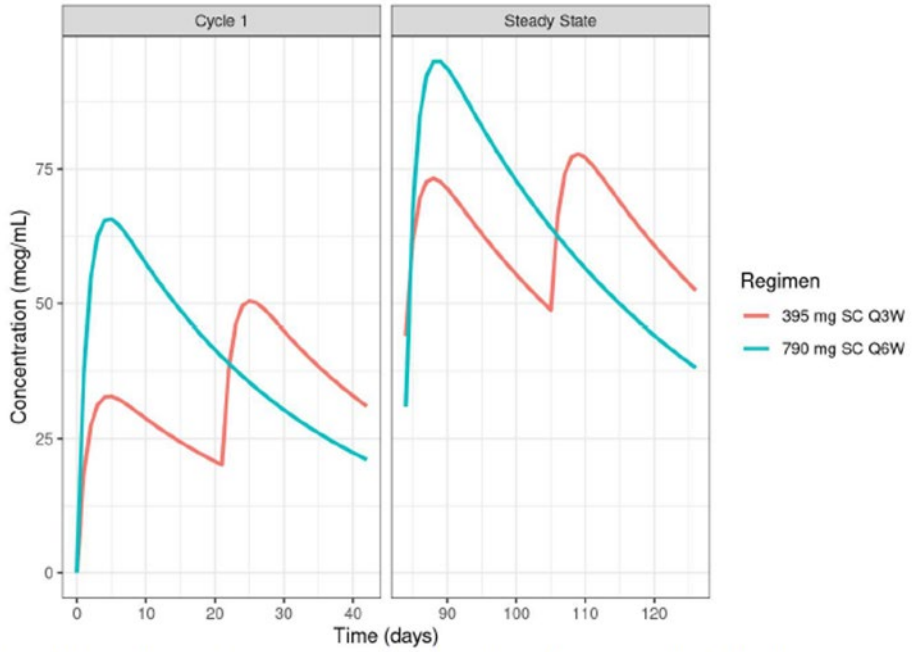


Figure 8. Observed PK data from Arm 4 overlaid on model PK profile in cycle 1 and at steady-state



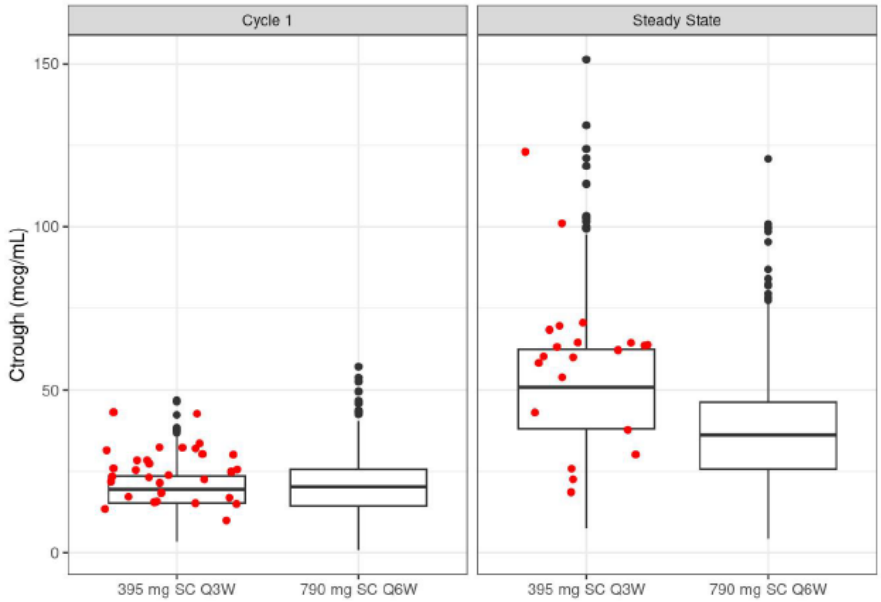
Notes: Black dots represent the observed concentration data at 395 mg Q3W SC given as MK-3475A from MK-3475A-C18 Arm 4 (n=44). Dashed red line represents the median PK profile of 343 participants from Phase 1 MK-3475A-C18 (Arms 1 to 3, n=96) and Phase 3 MK-3475A-D77 (n=247, SC arm) at 395 mg Q3W SC based on PK simulations using individual post-hoc estimates from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. Shaded areas represent the 90% prediction interval of the PK profiles of 343 participants as described above. a) After 1st dose with prediction intervals calculated for a single dose (0-24 days); b) at steady state, 16-18 weeks, prediction intervals are shown up to 24 days after last dose. Observed data represented by black dots are shown up to 24 days after the last dose.
Abbreviations: PK = pharmacokinetic; Q3W = every 3 weeks.
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]
Observed Data Source: [PC18V01MK3475A: adam-adnmpkpm]

Figure 9. Model predicted mean PK profiles



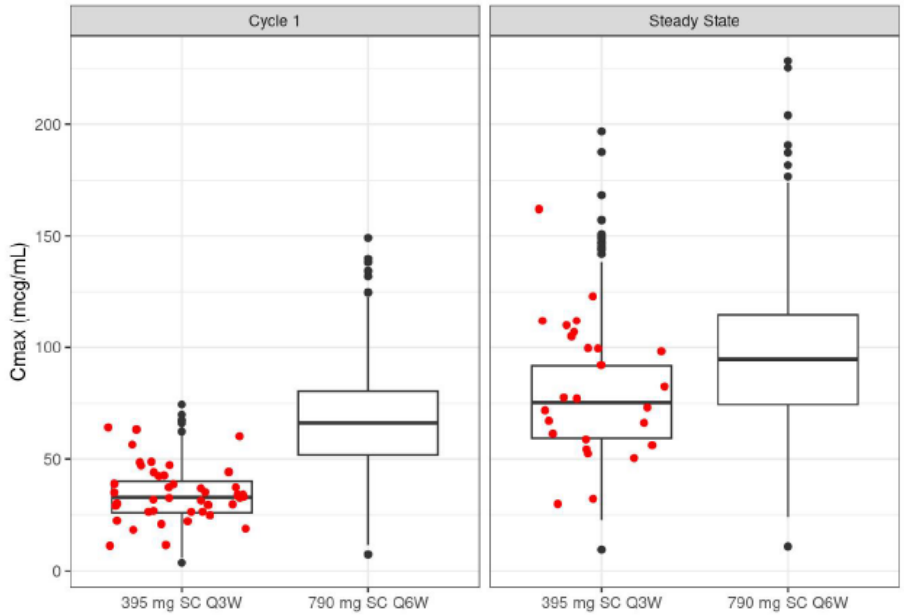
Note: Model-predictions for SC regimens were based on PK simulations using individual post-hoc estimates from pooled data (N=343) from MK-3475A-C18 (Arms 1 to 3) and in SC arm in MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. Plotted model predictions are simulated at daily time points.
Abbreviations: Q3W = every 3 weeks; Q6W = every 6 weeks.
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]

Figure 10. Comparison of model predicted with observed Ctrough



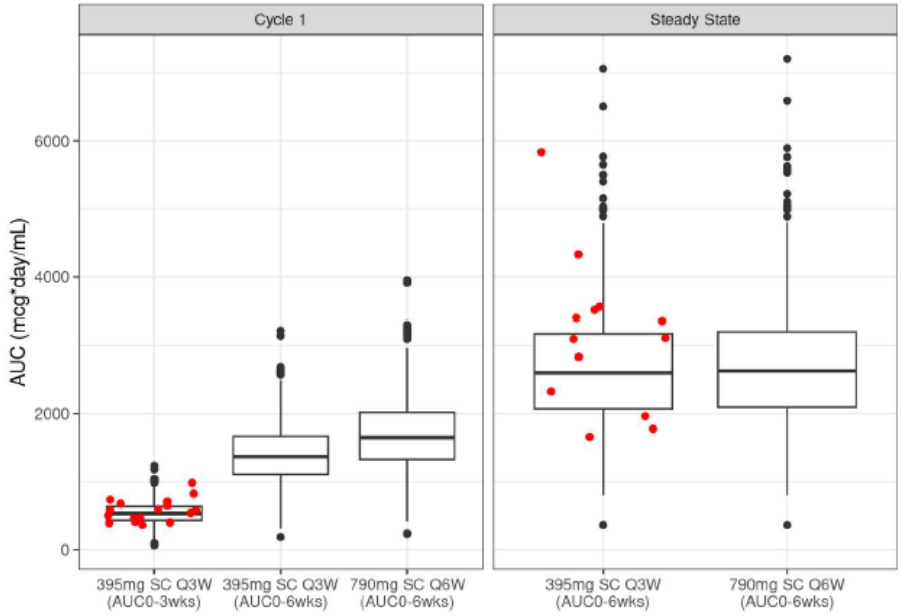
Note: Red dots (Cycle 1 – N=32; Cycle 6 – N=21) are the observed PK exposure parameters at 395 mg Q3W SC from MK-3475A-C18 Arm 4. Model-predictions for SC regimens were based on PK simulations using individual post-hoc estimates from pooled data from MK-3475A-C18 (Arms 1 to 3) and in SC arm in MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. C_{trough} in Cycle 1 was at day 21 for observed and model-predicted 395 mg Q3W SC and at day 42 for model predicted 790 mg Q6W SC. C_{trough} at steady-state was at day 126 for observed Q3W SC and model-predicted Q3W SC and Q6W SC. Percentiles of the predicted PK exposure distribution among 343 subjects at 395 mg Q3W SC and 790 mg Q6W SC given as MK-3475A are represented by the line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.
Abbreviations: C_{trough} = trough concentration; Q3W = every 3 weeks; Q6W = every 6 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]
Observed Data Source: [PC18V01MK3475A: adam-adnmpkpm]

Figure 11. Comparison of model predicted with observed Cmax



Note: Orange dots (Cycle 1 – N=44; Cycle 6 – N=26) are the observed PK exposure parameters at 395 mg Q3W SC from MK-3475A-C18 Arm 4. Model-predictions for SC regimens were based on PK simulations using individual post-hoc estimates from pooled data from MK-3475A-C18 (Arms 1 to 3) and in SC arm in MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. C_{max} was during 0-3 weeks for observed and model-predicted 395 mg Q3W SC and during 0-6 weeks for model predicted 790 mg Q6W SC. Percentiles of the predicted PK exposure distribution among 343 subjects at 395 mg Q3W SC and 790 mg Q6W SC given as MK-3475A are represented by the line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.
Abbreviations: C_{max} = peak concentration; Q3W = every 3 weeks; Q6W = every 6 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]
Observed Data Source: [PC18V01MK3475A: adam-adnmpkpm]

Figure 12. Comparison of model predicted with observed AUC



Note: Orange dots (Cycle 1 – N=17; Cycle 6 – N=13) are the observed PK exposure parameters at 395 mg Q3W SC from MK-3475A-C18 Arm 4. Model-predictions for SC regimens were based on PK simulations using individual post-hoc estimates from pooled data from MK-3475A-C18 (Arms 1 to 3) and in SC arm in MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. AUC is 0-3 weeks for observed and model-predicted 395 mg Q3W SC and 0-6 weeks for model predicted 395 mg Q3W SC and 790 mg Q6W SC. Observed $AUC_{0\text{-}6wks}$ at steady-state for Q3W SC is estimated by multiplying the observed $AUC_{0\text{-}3wks}$ at steady-state by 2. Percentiles of the predicted PK exposure distribution among 343 subjects at 395 mg Q3W SC and 790 mg Q6W SC given as MK-3475A are represented by the line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.
Abbreviations: $AUC_{0\text{-}3wks}$ = area under the concentration-time curve for 0 to 3 weeks; $AUC_{0\text{-}6wks}$ = area under the concentration-time curve for 0 to 6 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]
Observed Data Source: [PC18V01MK3475A: adam-adnmpkpm]

Table 13. PK exposure

PK Exposure			Model-predicted 395 mg Q3W SC[b]	Observed 395 mg Q3W SC in C18 Arm 4[a]	Model-predicted 790 mg Q6W SC[b]	Observed 790 mg Q6W SC in D77[c]
Early Cycle (weeks 1-6)						
C_{trough} (µg/ml)	GM (%CV)	Day 21	18.84 (39.5%)	23.59 (34.9%)	18.84 (55.5%)	22.71 (56.9%)
	GM (%CV)	Day 42	28.76 (42.8%)	-		
C_{max} (µg/ml)	GM (%CV)	Cycle 1	31.45 (41.8%)	33.03 (39.6%)	63.1 (41.9%)	66.61 (47.7%)
$AUC_{0\text{-}6wks}$ (µg·day/ml)	GM (%CV)	1317 (38.9%)		559.2 (28.8%)[d]	1597 (39.2%)	1497 (52.4%)
Steady-state (weeks 13-18)						
C_{trough} (µg/ml)	GM (%CV)	Day 126	47.76 (47.4%)	53.15 (49.6%)	33.6 (57.7%)	39.55 (91.1%)
C_{max} (µg/ml)	GM (%CV)	Cycle 3 or 6	72.54 (42%)	76.34 (41.5%)	90.1 (41.6%)	103.3 (40.9%)
$AUC_{0\text{-}6wks}$ (µg·day/ml)	GM (%CV)	2486 (42.3%)		2961 (36.9%)[e]	2506 (42.8%)	2836 (40.8%)

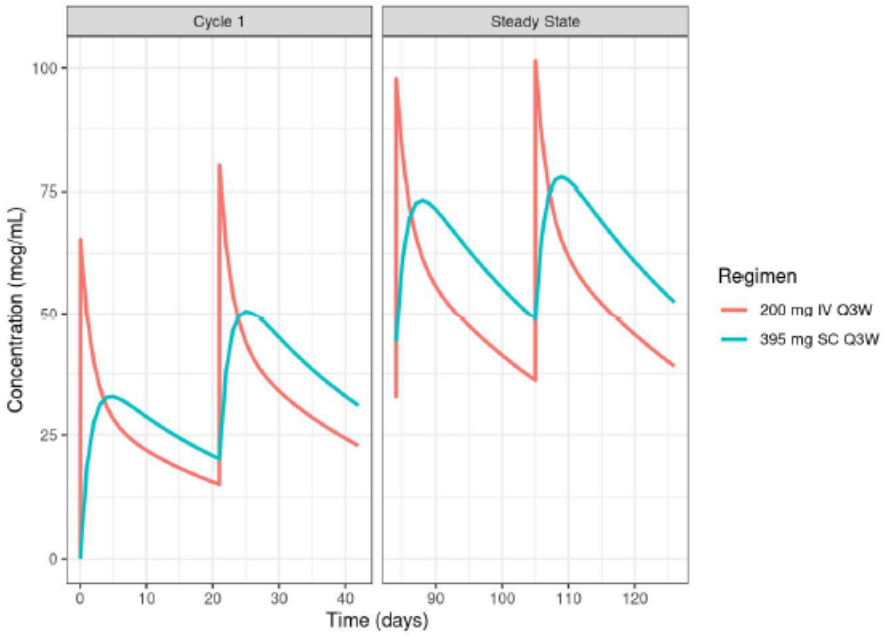
[a] C_{trough} from 32 and 21 subjects, C_{max} from 44 and 26 subjects, and AUC from 17 and 13 subjects in MK-3475A-C18 Arm 4 for Cycle 1 and steady-state, respectively
[b] C_{trough}, C_{max} and AUC from 343 subjects from MK-3475A-C18 Arms 1 to 3 and MK-3475A-D77 SC arm for Cycle 1 and at steady-state
[c] C_{trough} from 167 and 81 subjects, C_{max} from 239 and 92 subjects, and AUC from 196 and 135 subjects in SC arm in MK-3475A-D77 for Cycle 1 and steady-state, respectively, based on PP population sets for observed endpoints
[d] AUC is 0-3 weeks for observed MK-3475A-C18 Arm 4 and 0-6 weeks for model predicted 395 mg Q3W SC and observed and model-predicted 790 mg Q6W SC
[e] Observed $AUC_{0\text{-}6wks}$ at steady-state for Q3W SC is estimated by multiplying the observed $AUC_{0\text{-}3wks}$ at steady-state by 2
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]; Observed Data Source: [PC18V01MK3475A: adam-adnmpkpm], [08QL4V: analysis-adnmpkpm]

Table 14. Comparison of observed with model predicted PK exposure

PK Exposure		Model-Predicted Q3W vs. Model-Predicted Q6W	Observed Q3W vs. Observed Q6W
Early Cycle (weeks 1-6)			
% difference in GM of C_{trough}	Day 21 for Q3W vs. Day 42 for Q6W	0	4
	Day 42	53	-
% difference in GM of C_{max}	Cycle 1	-50	-50
% difference in GM of $AUC_{0\text{-}6wks}$[a]		-18	-
Steady-state (weeks 13-18)			
% difference in GM of C_{trough}	Day 126	42	34
% difference in GM of C_{max}	Cycle 3 or 6	-19	-26
% difference in GM of $AUC_{0\text{-}6wks}$[b]		-1	4

[a]AUC is 0-6 weeks for model predicted 395 mg Q3W SC and 790 mg Q6W SC.
[b]Observed $AUC_{0\text{-}6wks}$ at steady-state for Q3W SC is estimated by multiplying the observed $AUC_{0\text{-}3wks}$ at steady-state by 2
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]
Observed Data Source: [PC18V01MK3475A: adam-adnmpkpm], [08QL4V: analysis-adnmpkpm]

Figure 13. Model predicted mean PK profiles



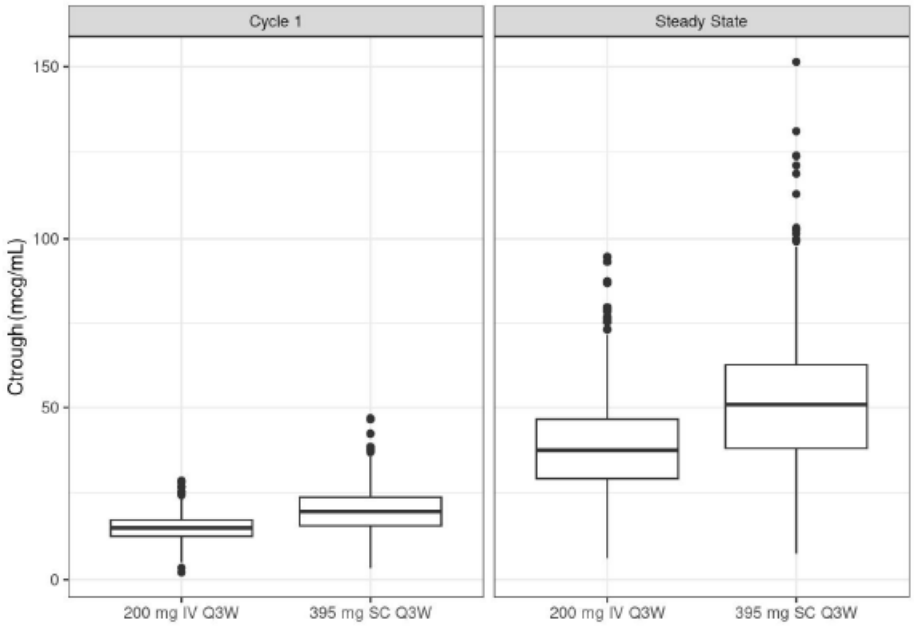
Note: Model-predictions for SC regimen were based on PK simulations using individual post-hoc estimates from pooled data from MK-3475A-C18 (Arms 1 to 3) and in SC subjects in MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. Model-predictions for IV regimen were based on PK simulations using individual post-hoc estimates from pooled data from MK-3475A-C18 (Arms 1 to 3) and MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3: 08QL4V]. Plotted model predictions are simulated at daily time points as well as at the end of the infusion if applicable.
Abbreviations: Q3W = every 3 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]

Table 15. PK exposure for model predicted SC and IV regimens

PK Exposure, GM (95% CI)	395 mg SC Q3W N=343[a]	200 mg IV Q3W N=469[b]	% Difference in GM
Cycle 1			
C_{trough} (µg/ml)	18.84 (18.09-19.61)	14.31 (13.92-14.7)	32
C_{max} (µg/ml)	31.45 (30.14-32.81)	63.97 (62.85-65.11)	-51
$AUC_{0\text{-}3wks}$ (µg·day/ml)	511 (491-531.9)	533.6 (523.3-544.1)	-4
Steady-state (Cycle 6)			
C_{trough} (µg/ml)	47.76 (45.54-50.1)	36.32 (35.04-37.65)	32
C_{max} (µg/ml)	72.54 (69.52-75.7)	98.84 (96.84-100.9)	-27
$AUC_{0\text{-}3wks}$ (µg·day/ml)	1282 (1227-1339)	1130 (1099-1162)	13

[a]: Simulations were performed for all subjects in MK-3475A-C18 (Arms 1 to 3, N=96) and in the SC arm in MK-3475A (N=247).
[b]: Simulations were performed for all subjects in MK-3475A-C18 (Arms 1 to 3, N=96) and in the IV and SC arm in MK-3475A (N=373).
Abbreviations: C_{trough} = trough concentration; C_{max} = peak concentration; $AUC_{0\text{-}3wks}$ = area under the concentration-time curve for 0 to 3 weeks; Q3W = every 3 weeks

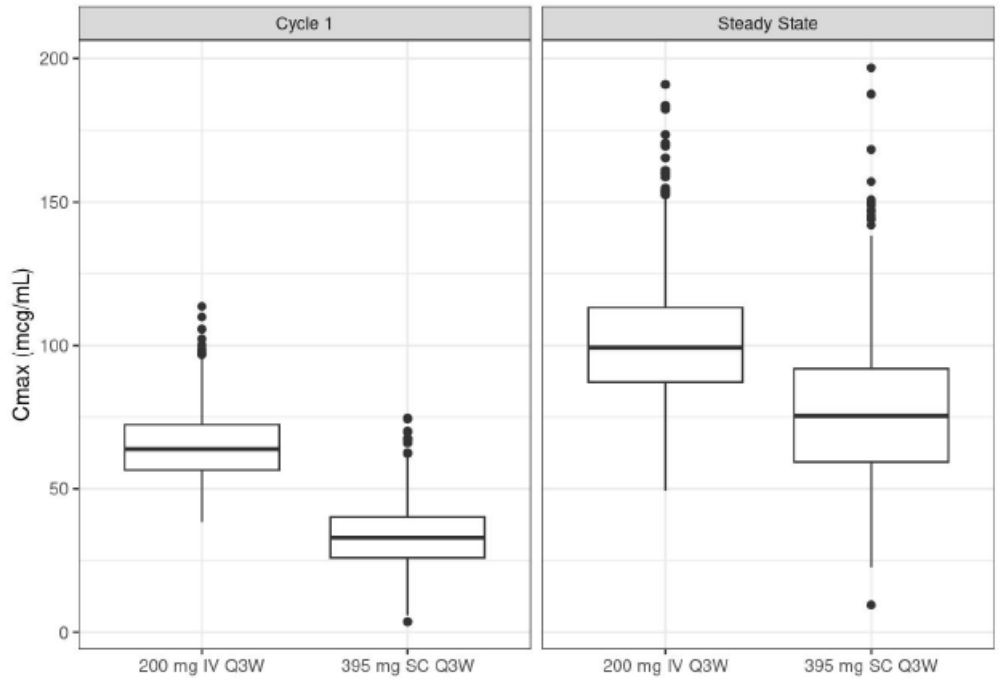
Figure 14. Comparison of model predicted Ctrough



Note: Percentiles of the predicted PK exposure distribution among 343 participants at 395 mg Q3W SC given as MK-3475A and among 469 participants at pembrolizumab 200 mg Q3W IV are represented by the line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.
Abbreviations: C_{trough} = trough concentration; Q3W = every 3 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]

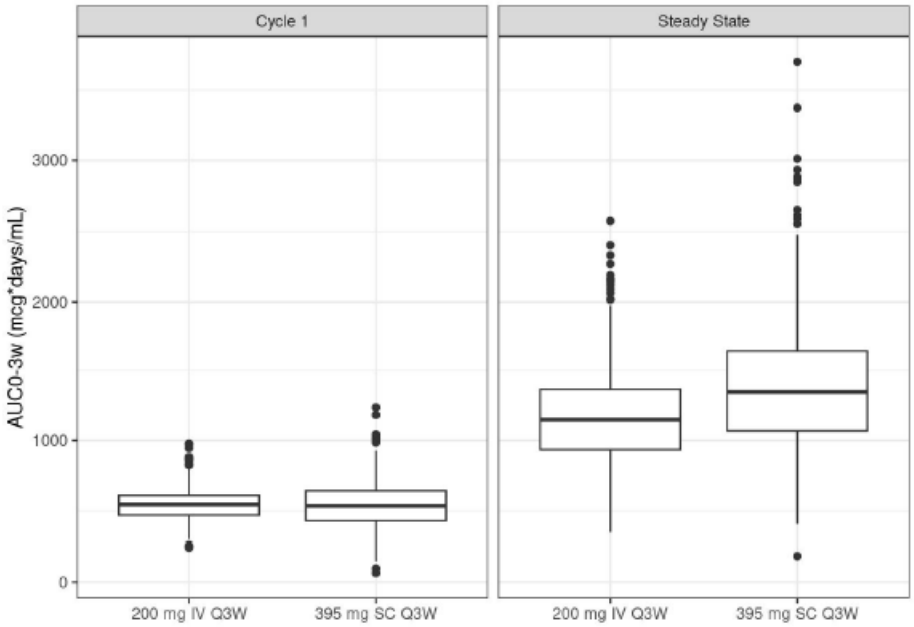
Figure 15. Comparison of model predicted Cmax

Figure 11 Comparison of Model-Predicted C_{max} for 395 mg Q3W SC as MK-3475A and Pembrolizumab 200 mg Q3W IV in Cycle 1 and at Steady-State



Note: Percentiles of the predicted PK exposure distribution among 343 participants at 395 mg Q3W SC given as MK-3475A and among 469 participants at pembrolizumab 200 mg Q3W IV are represented by the line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.
Abbreviations: C_{max} = peak concentration; Q3W = every 3 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]

Figure 16. Comparison of model predicted AUC0-3wks



Note: Percentiles of the predicted PK exposure distribution among 343 participants at 395 mg Q3W SC given as MK-3475A and among 469 participants at pembrolizumab 200 mg Q3W IV are represented by the line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.
Abbreviations: $AUC_{0\text{-}3wks}$ = area under the concentration-time curve for 0 to 3 weeks; Q3W = every 3 weeks
Simulated Data Source: [Ref. 5.3.5.3: 08QL4V]

6.2.5. Overall discussion and conclusions on clinical pharmacology

6.2.5.0. Discussion

To support the use of a SC formulation of pembrolizumab co-formulated with MK-5180 (berahyaluronidase alfa) as an alternative route of administration to pembrolizumab IV (Keytruda) for all indications in adults, the MAH conducted a pivotal phase 3 study, MK-3475A-D77, and two main supportive PK phase 1 studies: MK-3475A-C18 and ALT-BB4-01.

Moreover, two additional studies were included in the submitted dossier and were part of an earlier development program begun to evaluate the use of pembrolizumab SC administered without the berahyaluronidase alpha: KEYNOTE-555 and KEYNOTE-A86.

Non-compartmental (NCA) and modelled approaches were used to determine/estimate PK parameter parameters along studies used in support of this Application.

Bioanalytical methods. A bioanalytical method was previously developed and validated according to EMA guidelines. The analytical method was considered suitable to support clinical PK assessments of MK-3475 in the current submission. In the clinical studies (MK-3475A-C18 and MK-3475A-D77), the performance of the pembrolizumab concentration assay, including Incurred Sample Repeat (ISR) analysis, were considered acceptable.

ECL-based immunoassays were developed and validated in accordance with regulatory guidance to support the assessment of MK-5180 human plasma concentrations in clinical studies.

In general, the principles applied for method validation were in line with the approach required by the guidelines at the time of development (Guideline on bioanalytical method validation EMA EMEA/CHMP/EWP/192217/2009 Rev 1 Corr 2 – July 2011 for method showed in report S21111 and ICH Harmonised Guideline – Bioanalytical Method Validation and Study Sample Analysis M10 May 2022 for method showed in report 08MSKL and addendum 1-2).

The calibration range and limits of quantitation, intra- and inter-assay precision and accuracy, analyte stability, hook effect and dilution linearity were evaluated and calculated. Validation results showed that ECL-based assays were sufficiently accurate and precise to reliably allow the determination of MK-5180 in human plasma samples for PK studies.

The long-term stability of the MK-5180 has been updated for up to 377 days at -25 °C and -80 °C.

Although not all samples in the study MK-3475A-C18 were analyzed within the stability period assessed in the Addendum, data provided demonstrated acceptable accuracy and precision to support PK results in pivotal study MK-3475A-D77 (pembrolizumab 790 mg Q6W) and in arm 4 of clinical study MK-3475A-C18 (pembrolizumab 395 mg Q3W).

ISR assessment was not performed in clinical studies as the site of action of MK-5180 is in the tissue of the SC rather than in the systemic circulation. ECL-based immunoassays for the detection of pembrolizumab ADA and pembrolizumab NAb in human serum were previously developed and validated at PPD and WuXi according to EMA guidelines.

To detect and characterize anti-pembrolizumab antibodies, a multi-tiered analysis strategy was used. The performance of the ADA and NAb assays of pembrolizumab in clinical studies was provided. The data obtained support the validation results and the suitability of the method for the assessment of the immunogenicity of pembrolizumab.

For the assessment of the immunogenicity of MK-5180, ECL-based assays were developed and validated for the detection of anti-MK-5180 antibodies at PPD (report: 08GQZM) and at the Keyfron Bio site (report: 08Q69I). According to the guideline on the evaluation of immunogenicity of therapeutic proteins - EMA guidelines 2017, the assays were successfully validated for selectivity, drug tolerance, screening cut point, confirmation cut point, titre cut point, sensitivity and sample stability.

In the clinical studies, performance of MK-5180 ADA methods was evaluated showing acceptable results.

Evaluation and qualification of models.

First-order absorption rate constant (ka) and bioavailability (F) for SC were informed only by the Phase 1 data. The updated population PK model seems able enough to simultaneously describe pembrolizumab PK after IV or SC administrations. Indeed, precision (standard error) of parameter estimates are within 20% and plots of conditional weighted residuals versus population predictions and versus time after first dose shows that data are evenly distributed about zero suggesting no structural bias as a function of drug concentration or time with only lower concentrations not uniformly distributed around the line of identity. Goodness of Fit Plots of the Combined IV SC population PK Model show that Observations vs Population and Individual Predictions are evenly distributed about the line of identity, indicating no major bias in the population component of the model and also indicating that the model is appropriate for most individuals. From this model, the

estimated BA of pembrolizumab SC without berahyaluronidase alfa is similar (66%; 95% CI: 58% to 74 %) to that estimated with berahyaluronidase alfa.

A subsequent model (**report 08NTM7**) using serum concentrations from 81 subjects from Study C18 Arm 1 and 2 was developed to characterize the pharmacokinetic (PK) profile of pembrolizumab after subcutaneous (SC) administration of MK-3475A, and to estimate the bioavailability (F) at two distinct SC formulation strengths (130 mg/mL and 165 mg/mL).

This model was a combined intravenous (IV) and SC PK model of pembrolizumab in which all IV-related parameters (fixed effects, random effects, and covariate effects) were fixed from the reference PK model based on historical IV data while a first-order absorption process was implemented to describe the SC absorption kinetics of pembrolizumab.

Precision of parameter estimates are within 6%. Plots of conditional weighted residuals versus population predictions and versus time after first dose shows that data are evenly distributed about zero suggesting no structural bias as a function of drug concentration or time. Goodness of Fit Plots of the combined IV SC population PK Model show that Observations vs Population and Individual Predictions are evenly distributed about the line of identity, indicating no major bias in the population component of the model and also indicating that the model is appropriate for most individuals.

The estimated bioavailability of pembrolizumab following SC administration of MK-3475A using this model **was 57%** (range: 38% to 75%).

An additional popPK model (**report 08PH8G**) was developed including PK observations from 140 subjects from all four arms (1 to 4) in Study MK-3475A-C18 with the aim to further characterize and estimate the bioavailability of SC pembrolizumab for the two formulation strengths evaluated in Phase 1 Study MK-347A-C18 (Arm1:165 mg/mL and Arm2: 130 mg/mL) as well as to derive model-based individual exposure estimates of Cycle 1 Ctrough, Cycle 1 Cmax. Cycle 1 AUC0-6wks for Arms 1, 2, and 3 and Cycle 1 and Cycle 6 Ctrough, Cmax and AUC0-3wks for Arm 4. All fixed effect parameters were estimated with good precision, with RSE below 6%. Inter-individual variability (IIV) for Ka and F were 43.7 and 22.4%, respectively and random effects shrinkage for estimates parameters was acceptable (9% for Ka and 14% for F). Observed concentrations versus population (PRED) and individual (IPRED) model predictions, Population (CWRES) and individual (IWRES) conditional weighted residuals versus time and model predictions shows no major bias. Also ETA Histograms, Q-Q Plots, and Correlation Plots for the Final Combined SC and IV Pop PK Model (Run sc037) are unbiased. The pcVPC plots suggested that the model was adequate enough to predict the observed pembrolizumab concentrations following both IV and SC administrations that were generally captured throughout the simulated profile with only a trend for slight underprediction for median (50th percentile) and low (5th percentile) concentration. The estimated bioavailability of pembrolizumab following SC administration of MK-3475A using this model **was 61.1%** (CV%: 22.4%) and absorption rate was 0.301day-1 (43.7%). The median observed Tmax in Cycle 1 across all arms was estimated to be 4 days (range: 1 to 35 days).

The final combined IV and SC population PK model (**report 08QL4V**) was based on serum concentration data collected from the pivotal phase 3 study MK-3475A-D77 and from the phase 1b study MK-3475A-C18, with the PK data cutoff of 12-JUL-2024 for study D77 and 24-JUN-2024 for study C18.

The final modelling dataset included a total of 6116 PK observations from 469 patients including 377 patients from the phase 3 study D77 and 96 patients from the phase 1b study C18.

The main objectives of this analysis were to estimate PK parameters of the absorption phase for pembrolizumab following SC injection of MK-3475; to evaluate baseline patient characteristics

potentially influencing the SC absorption of pembrolizumab and to derive model-based individual exposure estimates representing primary and secondary endpoints of the non-inferiority Phase 3 study D77.

During model development different model structures were explored to adequately characterize the absorption phase of the PK profile of pembrolizumab given SC as MK-3475A. The absorption phase PK parameters i.e. first-order absorption rate constant (Ka) and bioavailability (F) for SC administration were estimated from the SC data collected, while all model parameters describing systemic PK (including fixed effects, random effects, and covariate effects) were fixed from the reference IV PK model based on historical IV data.

Finally, for the combined IV and SC model, the absorption phase for SC administration was characterized by first order absorption rate constant (Ka) and bioavailability (F) parameters. Distribution and elimination phases were described by a two-compartment model with time-dependent clearance and a fixed effect of body weight, as established historically in the reference pembrolizumab PK model

The adequacy of the structural model was assessed by different model diagnostics.

Covariate exploration for the SC absorption phase was performed in this analysis. Covariates of interests were graphically evaluated for their potential effects on absorption parameters (F or Ka) prior to the formal covariate analysis.

No trend was observed with these continuous or categorical covariates, except for sex on Ka. The effects of age, body weight, sex, tumor type, race (Asian vs. non-Asian) and injection site for SC administration, were of particular interest and formally tested in the covariate analysis.

After forward inclusion and backward elimination, sex on Ka was identified as a covariate in the combined SC and IV population PK model, with 19.2% lower Ka in female subjects which was not deemed clinically meaningful, indeed, the inclusion of sex on Ka was accompanied by a decrease in BSV on Ka of 1.11%, and so finally, no clinically meaningful covariate on Ka and F was found.

The **final estimated SC bioavailability** for pembrolizumab **was 59.9%** (95% CI: 58% to 62%, %CV: 14%), Ka was 0.32 /day (95% CI: 0.30/day to 0.34/day, %CV: 47%).

The estimates of the final model show that absorption parameters F and Ka were estimated with high precision with RSE <4%. Inter-individual variability (IIV) for Ka and F were 47% and 14%, respectively and random effects shrinkage for estimates parameters using D77 and C18 data was overall acceptable (23.3% for Ka and 32.9% for F).

Distributions of Random Effects from the Final Population PK Model show that BSV terms appear to be normally distributed and unbiased.

Model fit, evaluated with GoF plots, individual plots, and ETA distribution plots, was generally unbiased with some exceptions. In particular, diagnostic plots of observed pembrolizumab concentrations versus population model predicted concentrations show that data are evenly distributed about the line of identity, however a trend of overprediction at higher concentration can be seen.

Conditional weighted residuals (CWRES) vs. time after dose (TAD) indicate that data are randomly scattered around zero, with a slight deviation from the line of identity starting from day 50, probably due to a lowering in the number of samples after 50 days of treatment. The plot of CWRES versus population predictions shows that data are evenly distributed about zero, with only

a slight deviation at higher concentration but overall indicating no major bias in the residual error model and also Q-Q plots suggest a normal distribution of data.

The pcVPCs graphs for the final combined SC and IV PK model suggest that the model describe reasonably well the median observed data, with a slight underprediction mainly evident for low and medium concentrations (5 and 50% percentiles) that it is not an issue considering that PK parameters representing PEs were used to establish non-inferiority and their eventual underestimation is not a problem. Overall, the updated/expanded model seems to adequately describe the shape of observed IV and SC serum concentration, indeed, the model well centred the absorption phase of the SC route.

Absorption. The PK profile of MK-5180 (berahyaluronidase alfa) has been evaluated in study in ALT-BB4-01 (Part II) as secondary endpoint (the primary endpoint of that study was safety and tolerability and was evaluated in Part I of the study). Overall results from these studies showed that although few subjects had pre-dose concentration, no subjects with only post-dose samples containing MK-5180 concentrations above the LLOQ were observed, suggesting a negligible absorption of MK-5180 in humans.

The concentration of MK-5180 was also evaluated in Study C18 and D77, in which pembrolizumab is co-formulated with berahyaluronidase.

Even in these studies, no subjects with only post-dose samples containing MK-5180 concentrations above the LLOQ were observed; whereas, 2 out of 140 subjects in study C18 and 3 out of 222 subjects in study D77 showed concentration of berahyaluronidase above the LLOQ pre- and post-dose, whichcould be attributable to pre-existing matrix interference. Based on data provided in study ALT-BB4-01, D77 and C18, the absorption of berahyaluronidase is negligible also due to the fast degradation limiting the persistence in systemic circulation.

Bioavailability. The BA of pembrolizumab co-formulated with MK-5180 has been evaluated at different steps during the SC formulation's development. In the PopPK 05MV7X, including data from Keynote-555 (without berahyaluronidase) Cohort A, the BA of MK-3475 was estimated to be 66%. The BA of MK-3475A (with berahyaluronidase) was estimated within the PopPK 08NTM7 including interim data from Arms 1 and 2 of Study C18 and within the PopPK 08PH8G including all Arms of Study C18; the BA was estimated to be 57% and 61.1%, respectively.

The BA values from the various models are aligned with that estimated with the final model 08QL4V including all available SC data (60%; CV%: 14%) and similar with the BA observed for other monoclonal antibodies after SC administration (Zhao et al, 52-80%; Davis et al, 2024, 50-85%). Moreover, as expected the BA of MK-3475A is similar to MK-3475 SC (without berahyaluronidase) (66%).

No meaningful difference in bioavailability or absorption rate was found between the 130 mg/mL and 165 mg/mL MK-3475A SC formulation strengths.

The bioavailability for pembrolizumab SC without berahyaluronidase alfa was also evaluated in Study Keynote-555. As expected, the BA of pembrolizumab SC without berahyaluronidase alfa is similar (66%; 95% CI: 58% to 74 %) to that estimated with berahyaluronidase. alfa

Immunological events. The development of ADA against pembrolizumab and MK-5180 and the effect on PK have been analysed in the pivotal study D77, in C18 and in ALT-BB4-01 (only MK-5180). Moreover, for study D77 the effect of ADA on efficacy and safety has been also investigated. Overall, the immunogenicity profile is similar between SC and IV arms and in line with the known immunogenicity profile of pembrolizumab IV. No evidence of an effect of ADA on

PK is observed with comparable exposure in patients ADA positive and ADA negative and it is in line with that observed in patients treated with MK-3475 IV, while due to the high variability and the low number of ADA positive participants, no clear conclusion can be drawn regarding the effect of ADA on efficacy and safety.

Overall, the incidence of pembrolizumab ADA in study D77 (1.4%) and C18 (0.8%) are similar and within that observed for pembrolizumab IV. Regarding MK-5180, the incidence of ADA is 1.5% and 1.6% in D77 and C18, respectively; no ADA positive participants had measurable PK concentrations at the same time point but this may be attributable to the rapid clearance of berahyaluronidase.

The wording regarding "immunogenicity" reported in section 4.8 of the SmPC, based on numbers from the evaluable subjects, suggests that in patients treated with pembro SC or IV every 6 weeks, with a median duration of treatment on subcutaneous pembrolizumab exceeding 6 months (range: 1 day to 12.5 months), 1.4% (3/211) of patients developed treatmentemergent ADA and 0.5% (1/211) developed neutralising antibodies. In IV arm, 0.9% (1/114) of patients developed treatment-emergent ADA and 0% (0/114) developed neutralising antibodies. There was no evidence of an altered pharmacokinetic or safety profile with antipembrolizumab binding or neutralising antibody development. The pembrolizumab immunogenicity profile of SC pembro was consistent with the known immunogenicity profile of intravenous pembrolizumab.

Dose justification. PK exposure-matching principles were used to bridge the proposed pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A dosing regimens to the currently approved pembrolizumab IV dosing regimens (200 mg Q3W and 400 mg Q6W), making PK exposure comparison between MK-3475A and pembrolizumab IV based on data from MK-3475A-D77 and MK-3475A-C18 studies.

Data showed that pembrolizumab 790 mg Q6W SC administered as MK-3475A led to consistent PK exposure profiles with pembrolizumab 400 mg Q6W IV.

Model-predicted PK exposures at 395 mg Q3W SC were consistent with 790 mg Q6W SC with both regimens given as MK-3475A, and this is also supported by observed data from Phase 1 MK-3475A-C18 Arm 4 and Phase 3 MK-3475A-D77 studies that are consistent with model prediction, confirming that 395 mg Q3W SC dosing regimen is expected to have similar efficacy and safety profile to the 790 mg Q6W SC dosing regimen.

PK exposures for 395 mg Q3W SC as MK-3475A were also consistent with those at the approved 200 mg Q3W IV dosing regimen.

Taking into account comments reported here above, the justification provided by the MAH for the proposed posology seems reasonable. Indeed, proposed SC doses provided exposures comparable with that reached after IV administration and although Ctrough and AUC at the proposed 790 mg Q6W SC and 395 mg Q3W SC dosing regimens for MK-3475A are higher if compared to the approved pembrolizumab IV regimens, this is not a concern, considering that PK exposures for pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC are within the 5-fold range of exposures from 2 mg/kg Q3W to 10 mg/kg Q2W of pembrolizumab IV where flat exposure-response relationships for efficacy and safety have been previously established. Range of Cmax remains below that of IV administration.

Overall exposures after the two different routes of administration are comparable, and the selected dose acceptable.

Moreover, based on these considerations, the proposed text in SmPC section 4.2 for the recommended SC posology as 395 mg every 3 weeks administered over 1 minute or 790 mg every

6 weeks administered over 2 minutes, as well as the instruction in SmPC and PL on switching to the SC or IV at the next schedule dose for patients receiving IV or SC, respectively, are considered acceptable.

6.2.5.1. Conclusions

The PK profile of pembrolizumab co-formulated with berayaluronidase alfa(MK-3475A) as well as the PK profile of berahyaluronidase alfa itself (MK-5180) have been sufficiently characterized.

6.3. Clinical efficacy

6.3.1. Dose response study(ies)

Dose-response studies have not been performed. See Clinical Pharmacology for dose selection.

6.3.2. Main study

6.3.2.0. MK-3475A-D77

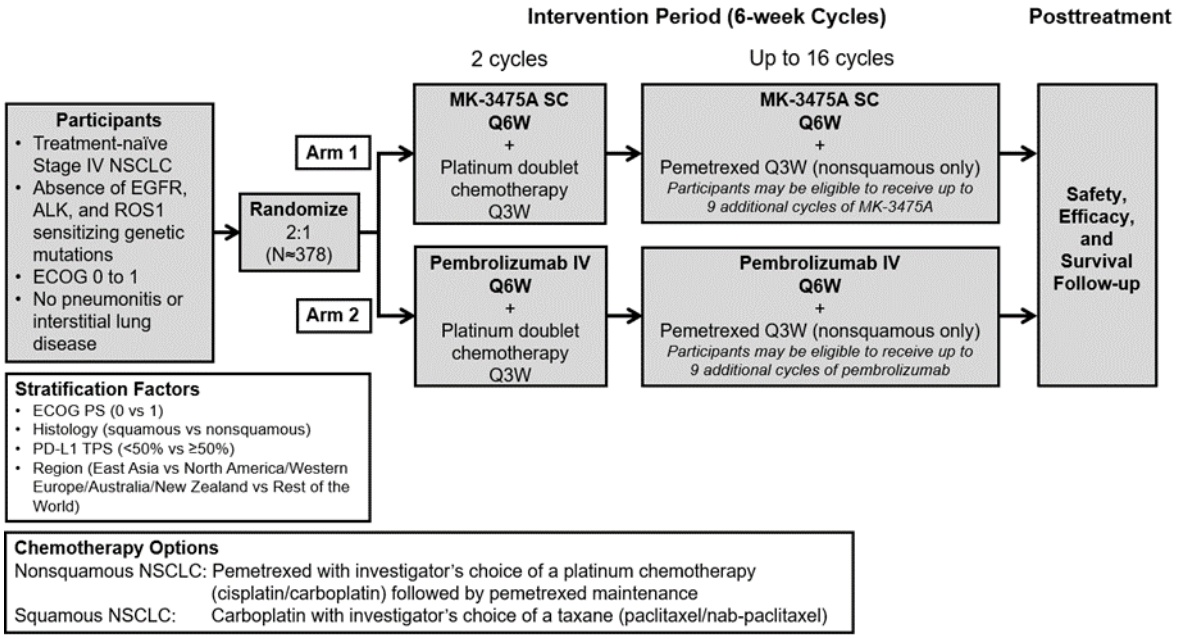
6.3.2.0.1. Study title

A Phase 3 Randomized, Open-label Clinical Study to Evaluate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab Coformulated With Hyaluronidase (MK-3475A) Versus Intravenous Pembrolizumab, Administered With Chemotherapy, in the First-line Treatment of Participants With Metastatic Non-small Cell Lung Cancer

6.3.2.0.2. Study design

MK-3475A-D77 is a Phase 3 randomized (2:1), open-label clinical trial evaluating the PK, efficacy, and safety of MK-3475A administered SC, in combination with histology-based platinum doublet chemotherapy versus pembrolizumab IV in combination with histology-based platinum doublet chemotherapy, in participants in need of treatment for 1L metastatic NSCLC without EGFR/ALK/ROS1 driver mutations, and regardless PD-L1 expression.

Figure 17 Study schema



ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; IV=intravenous; NSCLC=non–small cell lung cancer; PD-L1=programmed cell death ligand 1; PS=performance status; Q3W=every 3 weeks; Q6W=every 6 weeks; ROS1=c-ros oncogene 1; SC=subcutaneous; TPS=tumor proportion score; vs=versus

6.3.2.0.2.1. Treatment

Arm 1: MK-3475A SC (790 mg SC Q6W) + chemotherapy

Arm 2: pembrolizumab IV (400 mg IV Q6W) + chemotherapy.

Chemotherapy in both treatment arm was chosen based on NSCLC histology:

- squamous NSCLC: 4 infusions of carboplatin (AUC6 mg/mL/min IV Q3W) in combination with a taxane [paclitaxel (200 mg/m² IV Q3W)/nab-paclitaxel (100 mg/m² Weekly)]
- non-squamous NSCLC: 4 infusions of pemetrexed (500 mg/m² IV Q3W) with a platinum [cisplatin (75 mg/m² IV Q3W)/carboplatin (AUC5 mg/mL/min Q3W IV) followed by pemetrexed maintenance.

The initial treatment of pembrolizumab continued until RECIST 1.1-defined PD as determined by the investigator, unacceptable toxicity, or a maximum of 18 cycles (approximately 2 years). Participants were not permitted to crossover to the other study intervention arm. A second course of pembrolizumab could be reinitiated or subsequent BICR-verified progressive disease by RECIST 1.1 for all participants who have completed the first course achieving SD, PR, or CR.

Tumor assessment: at screening within 28 days prior to randomization, then at 6, 12 and 18 weeks from the date of randomization, then every 9 weeks or more frequently if clinically indicated until week 45, then every 12 weeks.

6.3.2.0.2.2. Randomisation

Randomization was 2:1, stratified by:

- ECOG performance status (0 vs 1)
- histology (squamous vs non-squamous)
- PD-L1 TPS (<50% vs ≥50%; PD-L1 non-evaluable were included with the TPS <50% group)
- region (East Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World).

6.3.2.0.2.3. Blinding

Open-label study.

6.3.2.0.2.4. Patient population

Key inclusion criteria:

1. Histologically or cytologically confirmed diagnosis of squamous or non-squamous NSCLC (Stage IV: M1a, M1b, M1c, AJCC Staging Manual version 8).
2. In participants with non-squamous NSCLC, confirmation that EGFR-, ALK-, or ROS1- directed therapy is not indicated as primary therapy (documentation of absence of tumor activating *EGFR* mutations [e.g., DEL19 or L858R] AND absence of *ALK* and *ROS1* gene rearrangements).
3. Measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology.
4. At least 18 years of age at the time of providing informed consent.
5. An ECOG performance status of 0 to 1.
6. A life expectancy of at least 3 months.
7. Archival tumor tissue sample or newly obtained core, incisional, or excisional biopsy of a tumor lesion not previously irradiated for determination of PD-L1 status before randomization.
8. Adequate organ function.

Key exclusion criteria:

1. Diagnosis of small cell lung cancer or, for mixed tumors, presence of small cell elements.
2. Received prior systemic anticancer therapy for metastatic NSCLC.
3. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
4. Received prior radiotherapy within 2 weeks of start of study intervention or has radiation-related toxicity requiring corticosteroids.
5. Received radiation therapy to the lung that is >30 Gray within 6 months of start of study intervention.
6. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy
7. Known additional malignancy that is progressing or has required active treatment within the past 3 years.
8. Known active CNS metastases and/or carcinomatous meningitis.

9. Active autoimmune disease that has required systemic treatment in past 2 years.
10. History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

6.3.2.0.3. Objectives and estimands

6.3.2.0.3.1. Primary objectives

Table 16 Primary objectives and endpoints

Primary Objectives	Primary Endpoints
-Objective: To compare MK-3475A SC to pembrolizumab IV with respect to Cycle 1 AUC - Hypothesis (H1): MK-3475A SC is noninferior to pembrolizumab IV with respect to the geometric mean Cycle 1 AUC of pembrolizumab	- Cycle 1 $AUC_{0\text{-}6wks}$
- Objective: To compare MK-3475A SC to pembrolizumab IV with respect to steady-state (Cycle 3) C_{trough} - Hypothesis (H2): MK-3475A SC is noninferior to pembrolizumab IV with respect to the geometric mean steady-state (Cycle 3) C_{trough} of pembrolizumab	- Steady-state (Cycle 3) C_{trough} The primary analysis will be performed on the model-based values of C_{trough}

The study was to have met its success criterion if MK-3475A was noninferior to pembrolizumab IV with respect to one or the other endpoint (dual primary endpoints).

Both endpoints were model-based.

6.3.2.0.3.2. Estimand for the primary objective

The Applicant has not defined estimands.

6.3.2.0.3.3. Statistical methods for estimation and sensitivity analysis on primary endpoints

Overview and study hypothesis

The study aimed to show the non-inferiority of pembrolizumab administered subcutaneously (SC) vs. intravenously (IV), administered in combination with histology-based platinum doublet chemotherapy, in participants with treatment-naïve metastatic NSCLC.

For both PK endpoints, the noninferiority margin with respect to the AUC and Ctrough GMR of MK-3475A SC versus pembrolizumab IV was specified to be 0.8. The rationale for the 0.8 noninferiority margin was stated to be based on the standard lower bound recommended in regulatory guidance documents for demonstration of bioequivalence for PK bridging (Food and Drug Administration 2014). An upper bound for the bioequivalence interval was not applied due to the established wide therapeutic window of pembrolizumab.

Analysis populations

The primary PK endpoint analysis was planned to be performed on the per-protocol set, while the ORR efficacy analysis was planned to be performed on ITT. The PP population for the primary PK endpoint of Cycle 1 AUC0-6 wks consists of the subset of participants in the global study who received the Cycle 1 dose, with at least 1 valid postdose PK sample in Cycle 1 and for whom a model-based assessment of AUC0-6 wks can be made. The PP population for model-based Cycle 3 Ctrough consists of the subset of participants in the global study who received the Cycle 1 dose, with at least 1 valid postdose sample and for whom a model-based assessment of Cycle 3 Ctrough can be made. The primary analysis for the primary PK endpoint of Cycle 3 Ctrough was performed on the model-based Cycle 3 Ctrough. An additional sensitivity analysis of this endpoint was performed using observed Cycle 3 Ctrough.

Statistical Methods for Key Immunogenicity/Pharmacokinetic Analyses

The hypothesis testing for noninferiority and the CIs for GMR was planned to be based on Welch's t-test statistics (which does not rely on the assumption of equal variances for SC and IV) with the log-transformed AUC and Ctrough. For Cycle 3 Ctrough, the primary analysis was planned to be based on Cycle 3 model-based Ctrough. A sensitivity analysis was planned to be performed for Cycle 3 observed Ctrough. Computation of the CIs of GMR was planned to be calculated using Welch's t-test statistics with the log-transformed AUC and Ctrough.

Planned subgroup analyses

Subgroup analyses were not planned to be performed for AUC0-6 wks and Ctrough given that historical data from Keytruda development program has consistently shown that there is no clinically relevant impact of covariates on PK. To determine descriptively whether the treatment effect is consistent across various subgroups, the between-group difference in ORR (with a nominal 95% CI) was planned to be estimated and plotted within each category of the following classification variables: Age category, Sex, Race, Smoking status, ECOG, Histology, Geographic region, PD-L1 expression.

Sample size determination

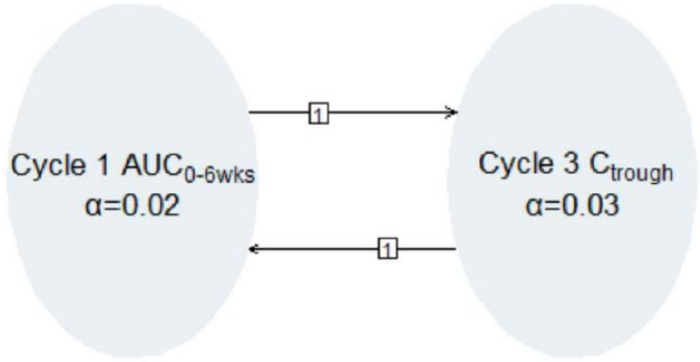
According to the last protocol version, the planned sample size is approximately 378 participants (189 in the SC arm, 126 in the IV arm). For the primary endpoint of Cycle 1 AUC0-6 wks, based on 318 participants with evaluable Cycle 1 AUC0-6 wks, the study was planned to have approximately >99.9% power to reject the null hypothesis (AUC GMR ≤0.8) under a true AUC GMR = 1.07 at the initially assigned 0.02 (1-sided) significance level. For the primary endpoint of Cycle 3 Ctrough, based on 240 participants with evaluable Cycle 3 Ctrough data, the study was planned to have approximately 99.8% power to reject the null hypothesis (Ctrough GMR ≤0.8) under a true Cycle 3 Ctrough GMR = 1.29 at the initially assigned 0.03 (1-sided) significance level. ORR is a secondary endpoint for the study. Although ORR was not planned to be formally tested for non-inferiority, based on the overall sample size of 378 participants in the global study, the study was planned to have approximately 89% power to reject the null hypothesis, ie, log(ORR ratio of Arm 1 versus Arm 2) ≤50% of -log(ORR ratio of pembrolizumab IV in combination with chemotherapy versus chemotherapy), under a true ORR of 51.1% for both arms at an overall α level of 0.025 (1 sided) using the synthesis method for noninferiority [U.S. Food and Drug Administration 2016].

The sample size was updated in General Amendment 3; initially, a lower sample size (339 participants, of which 226 in the SC arm and 113 in the IV arm) had been planned. The amended sample size was formally justified via updated standard deviations for Ctrough and amendments in the assumptions for ORR.

Overall alpha and multiplicity

The overall Type I error over the primary endpoints was planned to be strongly controlled at 0.05 (1-sided), with 0.02 initially allocated to Cycle 1 AUC0-6 wks and 0.03 to Cycle 3 Ctrough. By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], if 1 hypothesis is rejected, the alpha will be shifted to the other hypothesis.

Figure 18 Multiplicity strategy



$AUC_{0\text{-}6\ wks}$ = area under the curve from 0-6 weeks; C_{trough} = trough concentration.

Interim analyses

As per most recent protocol version, no IAs for pharmacokinetics analysis were planned in this study. Only one final analysis (FA) was planned to be performed when a minimum of 27 weeks follow-up after last participant randomized. However, two interim analyses for efficacy (PK) were planned in the initial protocol and were removed in the second general amendment due to rapid enrolment.

6.3.2.0.3.4. Secondary objectives

Table 17 Secondary objectives and endpoints

Secondary Objectives	Secondary Endpoints
- To evaluate pembrolizumab exposure for MK-3475A SC relative to pembrolizumab IV Q6W	- Cycle 1: C_{max} and C_{trough} - Steady state (Cycle 3): $AUC_{0\text{-}6wks}$ and C_{max}
- To evaluate the development of circulating anti-pembrolizumab antibodies for MK-3475A SC and pembrolizumab IV	- Anti-pembrolizumab antibodies
- To evaluate pembrolizumab C_{trough} for MK-3475A SC relative to pembrolizumab IV Q3W	- Cycle 1: Model-based C_{trough} - Steady state: Model-based C_{trough}
- To evaluate MK-3475A SC and pembrolizumab IV with respect to ORR per RECIST 1.1 as assessed by BICR	- Objective response: CR or PR
- To evaluate MK-3475A SC and pembrolizumab IV with respect to PFS per RECIST 1.1 as assessed by BICR	- PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

- To evaluate MK-3475A SC and pembrolizumab IV with respect to OS	- OS: The time from randomization to death due to any cause
- To evaluate MK-3475A SC and pembrolizumab IV with respect to DOR per RECIST 1.1 as assessed by BICR	- DOR: The time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first
- To evaluate the safety and tolerability of MK-3475A SC and pembrolizumab IV	- AE - Discontinuation of study intervention due to AEs
- To evaluate the change from baseline in global health status/QoL for MK-3475A SC and pembrolizumab IV	- Change in score from baseline at a predefined time point evaluated by EORTC QLQ-C30 in the following items: - Global health status/QoL (Items 29 and 30) - Physical functioning (Items 1 to 5) - Role functioning (Items 6 and 7)

6.3.2.0.3.5. Estimand for the secondary objectives

The Applicant has not defined estimands.

6.3.2.0.3.6. Statistical methods for estimation and sensitivity analysis on the secondary endpoints

Statistical Methods for Efficacy Analyses

Efficacy analyses were planned as descriptive only, although nominal p-values were reported. The stratification factors used for randomization was planned to be applied to all stratified analyses.

Table 18 Analysis Strategy for Key Efficacy Variables

Endpoint/ Variable	Statistical Method	Analysis Population	Missing Data Approach
ORR per RECIST 1.1 by BICR	Estimation: stratified Miettinen and Nurminen method, stratified CMH method	ITT	Participants with missing data are considered nonresponders
PFS per RECIST 1.1 by BICR	Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 2
OS	Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored at participant's last known alive date
BICR = blinded independent central review; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.			

Censoring rules for the primary and sensitivity analysis

Table 2 Censoring Rules for Primary and Sensitivity Analysis of PFS

Situation	Primary Analysis	Sensitivity Analysis
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	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 anticancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	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
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment

PD = progressive disease; PFS = progression-free survival

6.3.2.0.3.7. Tertiary objectives

Table 19 Tertiary/Exploratory Objectives and endpoints

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
- To evaluate health status using the EQ-5D-5L for MK-3475A SC and pembrolizumab IV	- Change from baseline at a predefined time point evaluated by EQ-5D-5L VAS score - Health utilities assessed using EQ-5D-5L

6.3.2.0.3.8. Estimand for the tertiary objectives

The Applicant has not defined estimands.

6.3.2.0.4. Results

6.3.2.0.4.1. Participant flow and numbers analysed

This study was conducted at 110 centers in 16 countries. The first participant first visit was on 14-FEB-2023, the last patient was randomized on 5-JAN-2024. The data cut-off was on 12-JUL-2024, the database lock was on 09-SEP-2024.

Table 20 Summary of Follow-up Duration (ITT Population)

Follow-up duration (months)[a]	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)	Total (N=377)
Median (Range)	8.7 (0.2, 13.5)	8.4 (0.4, 16.4)	8.6 (0.2, 16.4)
Mean (SD)	8.2 (3.0)	8.3 (2.8)	8.2 (2.9)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 12JUL2024

A total of 640 patients were screened. Of those, 263 were not randomized due to screen failure, the most frequently reported reasons were not meeting the inclusion criterion for participants with non-squamous histology to have confirmation that EGFR-, ALK-, or ROS-1 directed therapy was not indicated as primary therapy (27%), known active CNS metastases and/or carcinomatous meningitis (18.6%), and an ECOG performance status not of 0 to 1 (12.9%).

A total of 377 participants with metastatic NSCLC were randomly assigned in a 2:1 ratio in the study (MK-3475A + chemo: 251; pembrolizumab IV + chemo: 126)

Figure 19: Participant flow

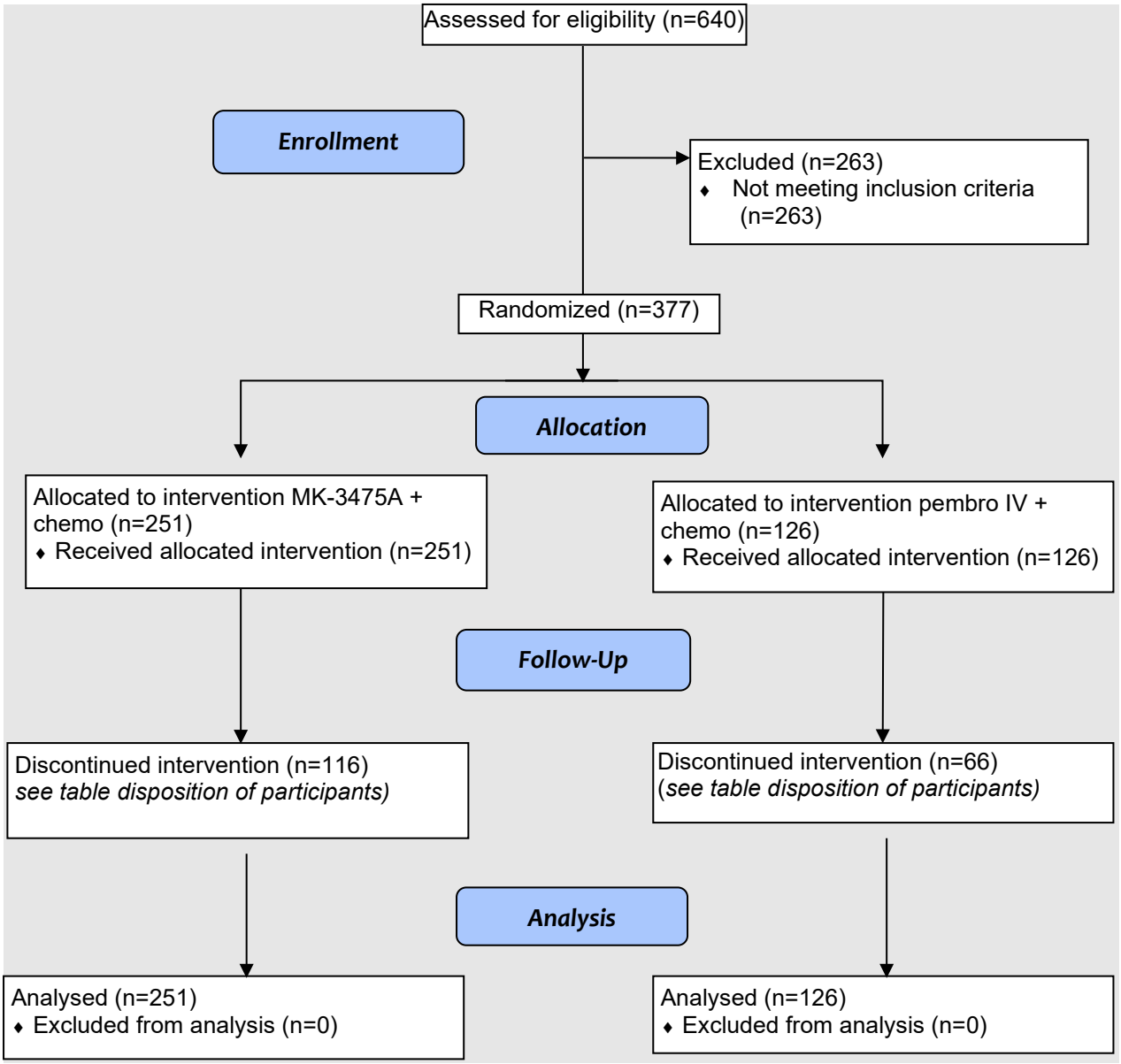


Table 21 Disposition of Participants (ITT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
Status for Study Treatment in Trial				
Started	251		126	
Discontinued	116	(46.2)	66	(52.4)
Adverse Event	36	(14.3)	16	(12.7)
Clinical Progression	10	(4.0)	3	(2.4)
Lost To Follow-Up	0	(0.0)	2	(1.6)
Non-Compliance With Protocol	0	(0.0)	1	(0.8)
Physician Decision	1	(0.4)	0	(0.0)
Progressive Disease	61	(24.3)	41	(32.5)
Withdrawal By Subject	8	(3.2)	3	(2.4)
Participants Ongoing	135	(53.8)	60	(47.6)

Status for Trial				
Discontinued	63	(25.1)	38	(30.2)
Death	57	(22.7)	37	(29.4)
Lost To Follow-Up	1	(0.4)	0	(0.0)
Withdrawal By Subject	5	(2.0)	1	(0.8)
Participants Ongoing	188	(74.9)	88	(69.8)

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: 12JUL2024

Table 22 Study population

	MK-3475A + chemo	pembro IV + chemo	Total
Number of Participants Screened			640
Number of Participants Randomized (Planned Treatment) (ITT)	251	126	377
Number of Participants Received Treatment (Actual Treatment) (APaT)	251	126	377
Number of Participants Randomized and Did not Receive Treatment	0	0	0
Number of Deaths (ITT)	61	37	98
Number of Participants Excluded from Per Protocol population for PK analysis[a]	4	0	4
Number of Participants in Per Protocol population for Cycle 1 AUC	245	126	371
Number of Participants in Per Protocol population for Cycle 3 model-based Ctrough	202	101	303

[a] These participants were excluded from the Per Protocol populations for Cycle 1 AUC and Cycle 3 Ctrough due to clinically important protocol deviations.
Database Cutoff Date: 12JUL2024.

6.3.2.0.4.2. Deviations from study plan

Table 23 Protocol amendments

Document	Date of Issue	Main changes and rationale
Amendment 3	06-FEB-2024	-To add G-CSF as primary prophylaxis during the first 4 platinum-doublet infusions in both arms. Rationale: This change was made as a result of new data from the study identified through medical monitoring, as detailed in the Dear Investigator Letter dated 21-DEC-2023. -Number of participants was updated. Boundaries and characteristics of analyses for Cycle 1 AUC0-6wks and Cycle 3 Ctrough were updated. Rationale: The faster screening rate and lower than anticipated screen failure rates resulted in over enrollment of participants. - Sample size and power for PK endpoints were updated. The assumptions in ORR non-inferiority test were updated. Rationale: see above. Further, the prevalences of histology and PD-L1 status assumed in the ORR noninferiority test are different in the current study compared to the historical data. -PK and ADA sample collection was updated.

		Rationale: Updates made to characterize chemotherapy PK and MK-5180 PK adequately.
Amendment 2	19-OCT-2023	-To update the assumptions and timing of the analyses in the SAP. Interim analyses 1 and 2 were removed. The timing for the interim safety analysis was updated. Rationale: The statistical analysis strategy has been updated. This change accounts for rapid enrollment in the study. The timing of final analysis is updated to be performed when a minimum of 27 weeks follow-up is achieved after last participant has been randomized to allow for the sufficient follow up for efficacy data. The futility analysis is not needed given internal data from earlier studies.
Amendment 1	10-Apr-2023	-To incorporate revisions based on health authority feedback. Rationale: added study duration to more clearly define the end of study; Added sample collections for MK-5180 PK and ADA to evaluate any systemic concentrations of MK-5180 or MK-5180 ADA after SC administration of MK-3475A.
Original Protocol	20-OCT-2022	Not applicable

6.3.2.0.4.3. Baseline data

Table 24 Participants Characteristics (ITT Population)

	MK-3475A + chemo		pembro IV + chemo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	251		126		377	
Sex						
Male	182	(72.5)	86	(68.3)	268	(71.1)
Female	69	(27.5)	40	(31.7)	109	(28.9)
Age (Years)						
< 65	119	(47.4)	57	(45.2)	176	(46.7)
>= 65	132	(52.6)	69	(54.8)	201	(53.3)
Mean	64.7		64.8		64.8	
SD	9.6		8.5		9.2	
Median	65.0		66.0		65.0	
Range	39 to 87		37 to 83		37 to 87	
Race						
American Indian Or Alaska Native	2	(0.8)	4	(3.2)	6	(1.6)
Asian	74	(29.5)	36	(28.6)	110	(29.2)
Black Or African American	5	(2.0)	5	(4.0)	10	(2.7)
Multiple	12	(4.8)	3	(2.4)	15	(4.0)
American Indian Or Alaska Native, White	8	(3.2)	1	(0.8)	9	(2.4)

Black Or African American, White	4	(1.6)	2	(1.6)	6	(1.6)
White	158	(62.9)	78	(61.9)	236	(62.6)
Ethnicity						
Hispanic Or Latino	74	(29.5)	41	(32.5)	115	(30.5)
Not Hispanic Or Latino	177	(70.5)	85	(67.5)	262	(69.5)
Geographic Region						
East Asia	73	(29.1)	36	(28.6)	109	(28.9)
North America/Western Europe/Australia/New Zealand	11	(4.4)	7	(5.6)	18	(4.8)
Rest of the World	167	(66.5)	83	(65.9)	250	(66.3)
PD-L1 Status						
TPS < 50%	181	(72.1)	91	(72.2)	272	(72.1)
TPS >= 50%	48	(19.1)	25	(19.8)	73	(19.4)
Unknown	22	(8.8)	10	(7.9)	32	(8.5)
PD-L1 Status						
TPS < 1%	101	(40.2)	57	(45.2)	158	(41.9)
TPS >= 1%	128	(51.0)	59	(46.8)	187	(49.6)
Unknown	22	(8.8)	10	(7.9)	32	(8.5)
PD-L1 Status						
TPS < 1%	101	(40.2)	57	(45.2)	158	(41.9)
TPS 1-49%	80	(31.9)	34	(27.0)	114	(30.2)
TPS >= 50%	48	(19.1)	25	(19.8)	73	(19.4)
Unknown	22	(8.8)	10	(7.9)	32	(8.5)
ECOG						
0	89	(35.5)	42	(33.3)	131	(34.7)
1	162	(64.5)	84	(66.7)	246	(65.3)
Histology						
Non-Squamous	167	(66.5)	83	(65.9)	250	(66.3)
Squamous	84	(33.5)	43	(34.1)	127	(33.7)
Metastatic Stage						
M1a	97	(38.6)	51	(40.5)	148	(39.3)
M1b	44	(17.5)	13	(10.3)	57	(15.1)
M1c	110	(43.8)	62	(49.2)	172	(45.6)
Overall Stage						
IVA	141	(56.2)	64	(50.8)	205	(54.4)
IVB	110	(43.8)	62	(49.2)	172	(45.6)
Brain Metastasis Status at Baseline						
Yes	19	(7.6)	14	(11.1)	33	(8.8)
No	232	(92.4)	112	(88.9)	344	(91.2)
Liver Metastasis Status at Baseline						
Yes	46	(18.3)	15	(11.9)	61	(16.2)
No	205	(81.7)	111	(88.1)	316	(83.8)
Smoking Status						
Never Smoker	38	(15.1)	23	(18.3)	61	(16.2)
Former Smoker	142	(56.6)	62	(49.2)	204	(54.1)
Current Smoker	71	(28.3)	41	(32.5)	112	(29.7)
Prior Adjuvant/Neo-adjuvant Therapy						

Yes	5	(2.0)	6	(4.8)	11	(2.9)
No	246	(98.0)	120	(95.2)	366	(97.1)
Prior Radiation						
Yes	37	(14.7)	24	(19.0)	61	(16.2)
No	214	(85.3)	102	(81.0)	316	(83.8)
Prior Thoracic Radiation						
Yes	10	(4.0)	8	(6.3)	18	(4.8)
No	241	(96.0)	118	(93.7)	359	(95.2)
SD=Standard deviation. Database Cutoff Date: 12JUL2024.						

6.3.2.0.4.4. Outcomes and estimation

The results of the protocol-specified final analysis are reported below.

Primary endpoints

NI was demonstrated for both dual primary endpoints.

Table 25 Analysis of Cycle 1 $AUC_{0\text{-}6wks}$ (Per Protocol Population)

Analysis of Cycle 1 $AUC_{0\text{-}6weeks}$
(Per Protocol Population)

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. pembro IV + chemo	
					GMR (96% CI)	p-value [b]
MK-3475A + chemo	245	1711.63 (234.65,3945.72)	1633.24 (1555.23,1715.15)	40.41	1.14 (1.06,1.22)	<0.00001
pembro IV + chemo	126	1450.73 (562.53,2858.42)	1437.58 (1373.68,1504.46)	26.23	---	---
[a] Number of Subjects with evaluable PK data. [b] The one-sided p-value non-inferiority boundary is 0.02. Database Cutoff Date: 12JUL2024.						

Source: [PD77V01MK3475A: adam-adsl; adpppm]

Table 26 Analysis of Cycle 3 model-based C_{trough} (Per Protocol Population)

Analysis of Cycle 3 Model-Based C_{trough}
(Per Protocol Population)

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. pembro IV + chemo	
					GMR (94% CI)	p-value [b]
MK-3475A + chemo	202	40.07 (10.89,120.82)	39.23 (37.04,41.55)	43.29	1.67 (1.52,1.84)	<0.00001
pembro IV + chemo	101	23.85 (4.82,53.75)	23.49 (21.61,25.54)	44.23	---	---
[a] Number of Subjects with evaluable PK data. [b] The one-sided p-value non-inferiority boundary is 0.03. Database Cutoff Date: 12JUL2024.						

Source: [PD77V01MK3475A: adam-adsl; adpppm]

A prespecified sensitivity analysis of observed steady-state (Cycle 3) Ctrough, and a sensitivity analysis of observed $AUC_{0\text{-}6weeks}$ (Cycle 1) were conducted to evaluate the robustness of the above primary results.

Table 27 Analysis of Cycle 3 Observed $C_{through}$ (Per Protocol Population)

Analysis of Cycle 3 Observed C_{trough}
(Per Protocol Population)

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. pembro IV + chemo	
					GMR (94% CI)	p-value [b]
MK-3475A + chemo	81	43.40 (0.17,136.00)	39.55 (33.31,46.97)	91.11	1.49 (1.21,1.84)	<0.00001
pembro IV + chemo	33	27.20 (7.42,54.10)	26.49 (23.00,30.51)	41.44	---	---

[a] Number of Subjects with evaluable PK data.
[b] The one-sided p-value non-inferiority boundary is 0.03.
Database Cutoff Date: 12JUL2024.

Table 28 Analysis of Cycle 1 Observed $AUC_{0\text{-}6weeks}$

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. pembro IV + chemo GMR (96% CI)
MK-3475A + chemo	149	1707.57 (262.39,4020.58)	1634.63 (1530.22,1746.15)	42.52	1.15 (1.05,1.27)
pembro IV + chemo	90	1397.82 (743.60,3268.84)	1417.59 (1335.12,1505.16)	29.21	---

[a] Number of Subjects with evaluable PK data.
Database Cutoff Date: 12JUL2024.

Secondary endpoints - PK

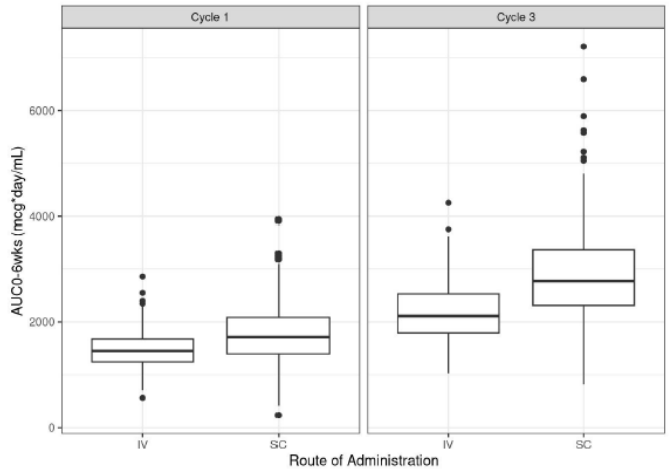
Table 29 Summary Statistics of Secondary PK Endpoints in MK-3475A-D77

PK Exposure	Statistic	790 mg Q6W SC	400 mg Q6W IV	Difference in GM (%) compared to 400 mg Q6W IV
Cycle 1 C_{trough} (µg/mL)	**Model-based**			
	N Mean (SD) Median (range) GM (CV%)	245 21.55 (9.46) 20.82 (3.432-57.21) 19.36 (52.2)	126 13.49 (5.54) 12.68 (1.259-31.77) 12.26 (50.8)	57.91
	Observed			
	N Mean (SD) Median (range) GM (CV%)	167 25.75 (12.78) 25.3 (3.39-82.5) 22.71 (56.9)	97 15.66 (10.81) 13.7 (2.37-97.9) 13.55 (57.2)	67.6
Cycle 1 C_{max} (µg/mL)	**Model-based**			
	N Mean (SD) Median (range) GM (CV%)	245 70.02 (25.34) 68.63 (7.41-149.2) 64.88 (44)	126 132.5 (28.02) 127.2 (77.29-227.3) 129.7 (20.8)	-49.98
	Observed			
	N Mean (SD) Median (range) GM (CV%)	239 72.82 (29.13) 70 (8.14-204) 66.61 (47.7)	123 138.9 (57.3) 126 (68.4-498) 131.4 (32)	-49.31
Steady-state (Cycle 3) C_{max} (µg/mL)	**Model-based**			
	N Mean (SD) Median (range) GM (CV%)	202 105 (35.19) 100 (24.18-228.3) 98.96 (36.8)	101 151.4 (33.32) 145.7 (86.36-272.7) 148 (21.6)	-33.14
	Observed			
	N Mean (SD) Median (range) GM (CV%)	92 110.6 (39.1) 109 (21-238) 103.3 (40.9)	47 153.8 (42.06) 153 (69.5-275) 148.2 (28.4)	-30.3
Steady-state (Cycle 3) AUC_{0-6wks} (µg·day/mL)	**Model-based**			
	N Mean (SD) Median (range) GM (CV%)	202 2962 (1013) 2772 (822.1-7209) 2798 (35.5)	101 2200 (601.6) 2112 (1029-4256) 2122 (27.8)	31.86

N represents the number of subjects meeting per protocol criteria for the corresponding endpoint.
Abbreviations: SC: subcutaneous; IV: intravenous; GM: geometric mean; SD=standard deviation; CV: coefficient of variation

Figure 20 Comparison of Model-based pembrolizumab Cycle 1 and Steady-state (Cycle 3) AUC 0-6wks after the administration of pembrolizumab 790 mg Q6W SC as MK-3475A and pembrolizumab 400 mg Q6W IV in study MK-3475A-D77

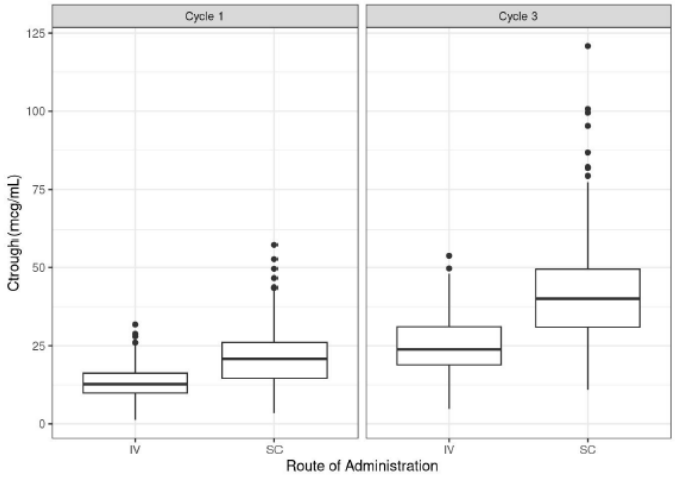
Figure 4 **Comparison of Model-based Pembrolizumab Cycle 1 and Steady-state (Cycle 3) $AUC_{0\text{-}6wks}$ After the Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in Study MK-3475A-D77**



Note: Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 400 mg Q6W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

Figure 21 Comparison of Model-based pembrolizumab Cycle 1 and Steady-state (Cycle 3) Ctrough after the administration of pembrolizumab 790 mg Q6W SC as MK-3475A and pembrolizumab 400 mg Q6W IV in study MK-3475A-D77

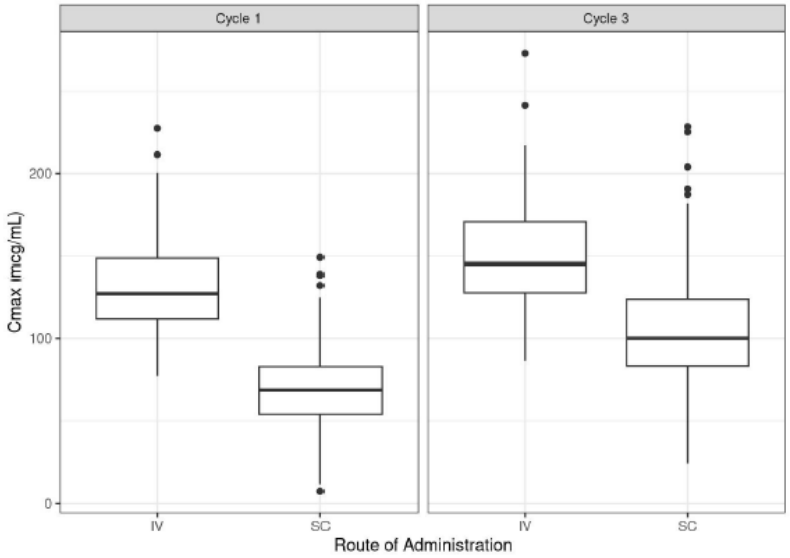
Figure 5 **Comparison of Model-based Pembrolizumab Cycle 1 and Steady-state (Cycle 3) C_{trough} After the Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in Study MK-3475A-D77**



Note: Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 400 mg Q6W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

Figure 22 Comparison of Model-based pembrolizumab Cycle 1 and Steady-state (Cycle 3) Cmax after the administration of pembrolizumab 790 mg Q6W SC as MK-3475A and pembrolizumab 400 mg Q6W IV in study MK-3475A-D77

Figure 6 Comparison of Model-based Pembrolizumab Cycle 1 and Steady-state (Cycle 3) C_{max} After the Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in Study MK-3475A-D77



Note: Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 400 mg Q6W IV are represented by the middle line (50th) and box (25th–75th). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

Table 30 Summary Statistics of Model-based Individual Exposures Estimates of Secondary Endpoints Following Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 200 mg Q3W IV

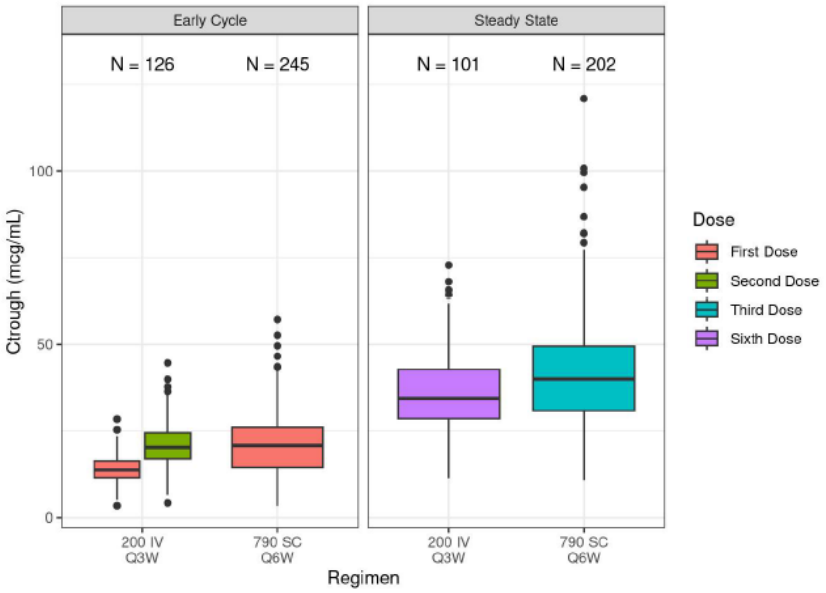
PK Exposure	Statistics	790 mg Q6W SC	200 mg Q3W IV	Difference in GM (%) compared to 200 mg IV Q3W
Early cycle, weeks 1-6		N=245	N=126	
C_{trough} (µg/ml)	Cycle 1 Mean (SD) Median (Range) GM (%CV)	21.55 (9.456) 20.82 (3.432-57.21) 19.36 (52.2)	14.1 (4.076) 13.81 (3.476-28.46) 13.49 (31.6)	43.51
	Cycle 2 (only for Q3W) Mean (SD) Median (Range) GM (%CV)		21.15 (6.781) 20.28 (4.247-44.7) 20.02 (35.8)	-3.3
Steady-state[a]		N=202	N=101	
C_{trough} (µg/ml)	Mean (SD) Median (Range) GM (%CV)	42.62 (17.78) 40.07 (10.89-120.8) 39.23 (43.3)	36.47 (12.06) 34.4 (11.41-72.85) 34.51 (35.2)	13.68

[a] Steady-state is at Cycle 3 for 790 mg Q6W SC and Cycle 6 for 200 mg Q3W IV

Abbreviations: SC=subcutaneous; IV=intravenous; GM=geometric mean; SD=standard deviation; CV=coefficient of variation.

Figure 23 Comparison of Model-based Cycle 1 and Steady-state Ctrough at pembrolizumab 790 mg Q6W SC as MK-3475A and pembrolizumab 200 mg Q3W IV

Figure 9 Comparison of Model-based Cycle 1 and steady-state C_{trough} at Pembrolizumab 790 mg Q6W SC as MK-3475A with Pembrolizumab 200 mg Q3W IV



Note: Early Cycle is at Cycle 1 for 790 mg Q6W SC and at Cycle 1 and 2 for 200 mg Q3W IV. Steady-state is at Cycle 3 for 790 mg Q6W SC and at Cycle 6 for 200 mg Q3W IV
Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 200 mg Q3W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

Secondary endpoints - Efficacy

ORR

Table 31 Analysis of Objective Response (Confirmed) Based on BICR per RECIST 1.1 (Sensitivity Analysis With Cochran-Mantel-Haenszel Method) (ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	ORR ratio vs. Pembro IV + chemo	
				Estimate (95% CI)[a]	p-Value[b]
MK-3475A + chemo	251	114	45.4 (39.1,51.8)	1.08 (0.85,1.37)	0.52045
pembro IV + chemo	126	53	42.1 (33.3,51.2)		

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded independent central review.

[a] Based on Mantel-Haenszel estimate of the common ORR ratio. Strata are defined by stratification factors: ECOG (0 vs. 1), Histology (squamous vs. nonsquamous), PD-L1 status (TPS <50% vs. >=50%), and geographic region (East Asia vs. North America/Western Europe vs. Rest of the World) with small strata collapsed as Pre-specified in the sSAP.

[b] One-sided nominal p-value using the stratified Cochran-Mantel-Haenszel test.

Database Cutoff Date: 12JUL2024

PFS

Table 32 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)

	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)
Number of Events (%)	135 (53.8)	66 (52.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.1 (6.3, 8.3)	7.8 (6.2, 9.7)
[Q1, Q3]	[4.1, 11.7]	[4.2,]
Person-months	1487.1	744.4
Event Rate / 100 Person-months	9.1	8.9
vs pembro IV + chemo		
Hazard Ratio (95% CI)[b]	1.05 (0.78, 1.43)	
PFS Rate at month 3 (%) (95% CI)	80.3 (74.8, 84.7)	82.9 (75.0, 88.5)
PFS Rate at month 6 (%) (95% CI)	64.7 (58.4, 70.3)	65.0 (55.7, 72.8)
PFS Rate at month 9 (%) (95% CI)	38.3 (30.6, 45.8)	42.8 (32.4, 52.8)
PFS Rate at month 12 (%) (95% CI)	24.8 (11.0, 41.4)	29.0 (17.4, 41.7)

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

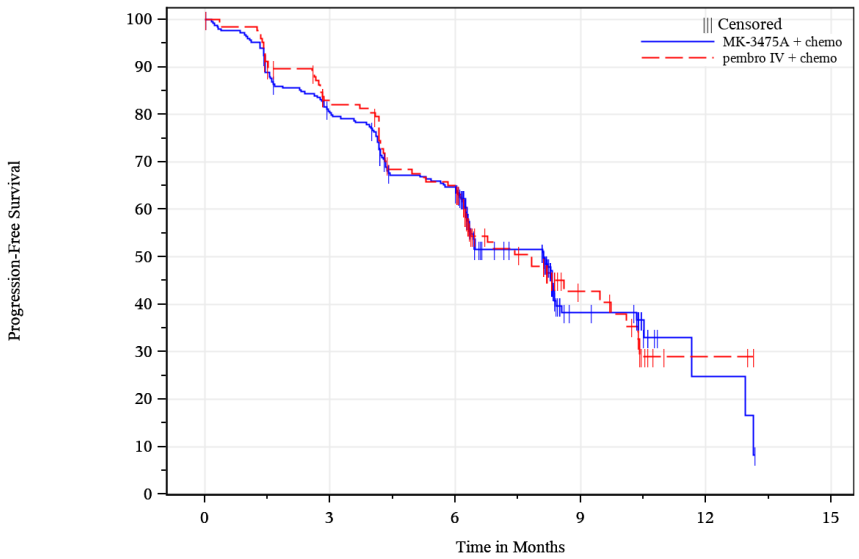
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status (0 vs. 1), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World).

NR = Not reached.

BICR = Blinded independent central review.

Database Cutoff Date: 12JUL2024

Figure 24 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)



Database Cutoff Date: 12JUL2024.

OS

Table 33 Analysis of Overall Survival (ITT Population)

	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)
Number of Events (%)	61 (24.3)	37 (29.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[9.3,]	[7.8,]
Person-months	2035.6	1037.8
Event Rate / 100 Person-months	3.0	3.6
vs pembro IV + chemo		
Hazard Ratio (95% CI)[b]	0.81 (0.53, 1.22)	
OS Rate at month 3 (%) (95% CI)	91.6 (87.5, 94.5)	95.2 (89.7, 97.8)
OS Rate at month 6 (%) (95% CI)	82.4 (77.1, 86.6)	84.1 (76.5, 89.4)
OS Rate at month 9 (%) (95% CI)	76.8 (70.7, 81.7)	72.7 (63.4, 80.0)
OS Rate at month 12 (%) (95% CI)	68.5 (58.3, 76.7)	63.2 (51.4, 72.9)

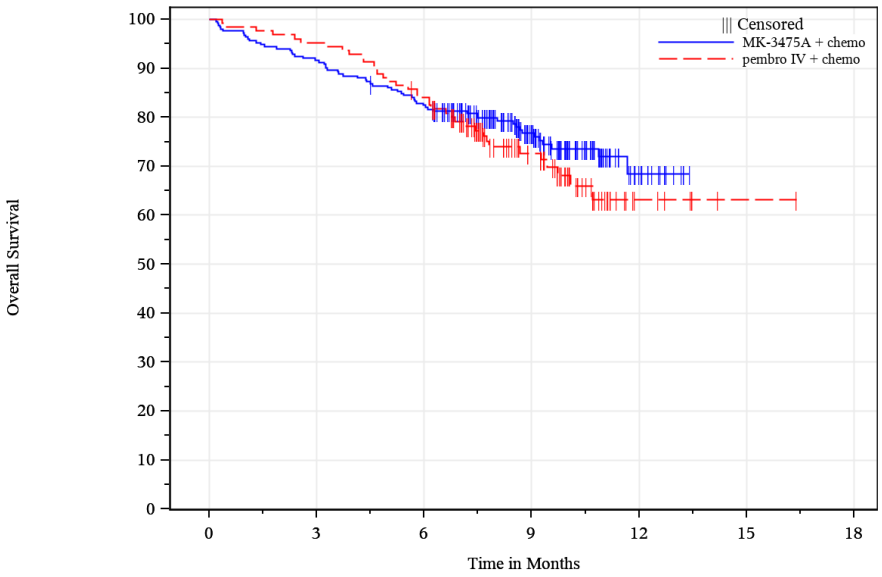
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status (0 vs. 1), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World).

NR = Not reached.

Database Cutoff Date: 12JUL2024

Figure 25 Kaplan-Meier Plot of Overall Survival (ITT Population)



At Risk

MK-3475A + chemo	251	230	206	110	15	0	0
pembro IV + chemo	126	120	105	53	7	1	0

Database Cutoff Date: 12JUL2024.

Updated OS data

Updated OS data with additional 4 months of follow-up have been provided during the procedure.

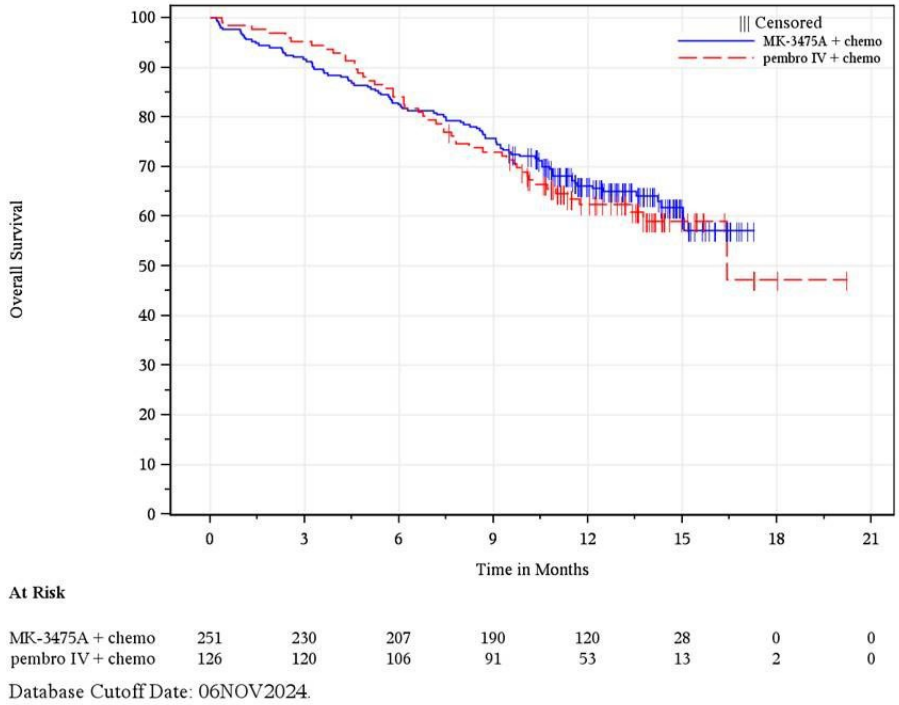
Table 34 Analysis of Overall Survival (ITT Population) - UPDATED

	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)
Number of Events (%)	90 (35.9)	49 (38.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (15.0, NR)	16.4 (13.8, NR)
[Q1, Q3]	[9.1,]	[7.8,]
Person-months	2706.5	1348.1
Event Rate / 100 Person-months	3.3	3.6
vs pembro IV + chemo		
Hazard Ratio (95% CI)[b]	0.86 (0.61, 1.23)	
OS Rate at month 3 (%) (95% CI)	91.6 (87.5, 94.5)	95.2 (89.7, 97.8)
OS Rate at month 6 (%) (95% CI)	82.5 (77.2, 86.6)	84.1 (76.5, 89.5)
OS Rate at month 9 (%) (95% CI)	75.7 (69.9, 80.5)	73.0 (64.3, 79.9)
OS Rate at month 12 (%) (95% CI)	66.2 (59.8, 71.8)	62.4 (53.1, 70.4)

[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 ECOG performance status (0 vs. 1), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World).
NR = Not reached.
Database Cutoff Date: 06NOV2024

Figure 26 Kaplan-Meier Plot of Overall Survival (ITT Population) – UPDATED



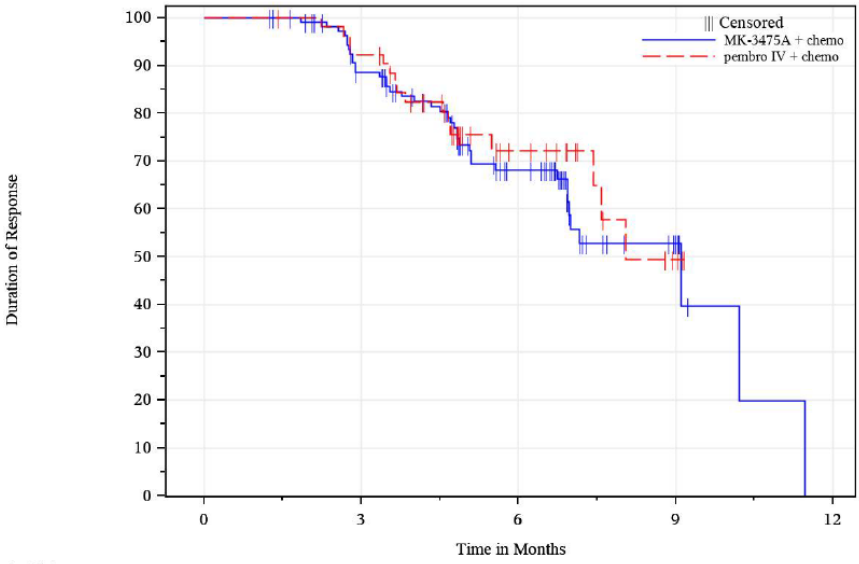
DOR

Table 35 Summary of Time to Response and Duration of Response Based on BICR per RECIST 1.1 in Participants with Confirmed Response (ITT Population)

	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)
Number of participants with response[a]	114	53
Time to Response (months)		
Mean (SD)	2.3 (1.6)	2.1 (0.9)
Median (Range)	1.5 (1.0 to 8.8)	1.5 (1.3 to 4.9)
Response Duration[b] (months)		
Median (95% CI)	9.1 (6.9, NR)	8.0 (7.4, NR)
Range	1.2+ to 11.5	1.4+ to 9.2+
Number (%[b]) of Participants with Extended Response Duration		
≥3 months	91 (88.6)	48 (92.3)
≥6 months	46 (68.1)	17 (72.1)
≥9 months	10 (52.8)	3 (49.5)

[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.
NR = Not Reached.
Database Cutoff Date: 12JUL2024

Figure 27 Kaplan-Meier Plot of Duration of Response Based on BICR per RECIST 1.1 (In Participants with a Confirmed Response) (ITT Population)



Database Cutoff Date: 12JUL2024.

Patient-reported Outcomes

Participants in the MK-3475A + chemo group maintained a similar HRQoL compared with those in the pembrolizumab IV + chemo group.

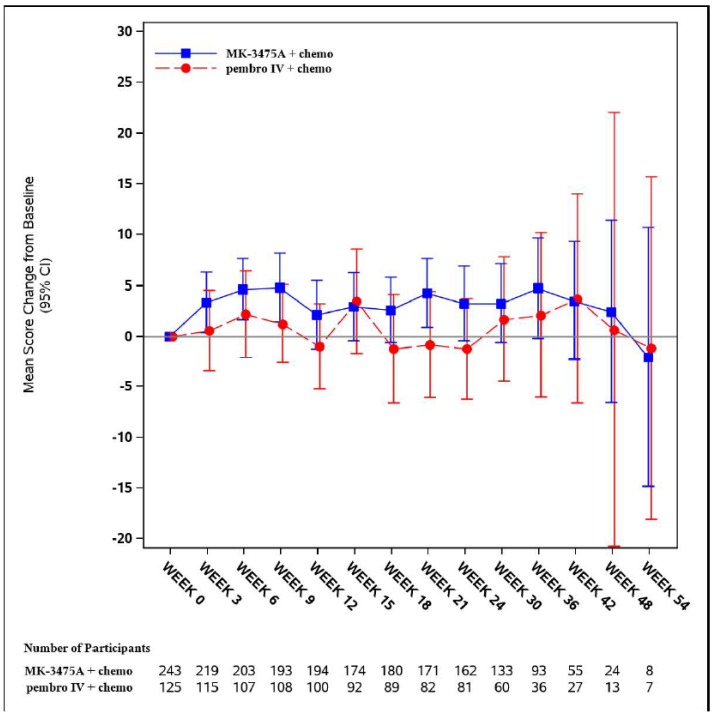
Table 36 Analysis of Change from Baseline to Week 24 in EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population)

Treatment	Baseline		Week 24		Change from Baseline to Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-3475A + chemo	243	66.63 (21.18)	167	71.96 (17.29)	250	2.12 (-0.87, 5.11)
pembro IV + chemo	125	68.87 (20.55)	82	69.82 (17.84)	126	-1.67 (-5.60, 2.26)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
MK-3475A + chemo vs. pembro IV + chemo	3.79 (-0.61, 8.19)	0.0908

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by ECOG (0 vs. 1), Histology (squamous vs. nonsquamous), PD-L1 status (TPS <50% vs. >=50%), and geographic region (East Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World) as pre-specified in the sSAP.
P-value is two-sided.
For baseline and Week 24, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 12JUL2024

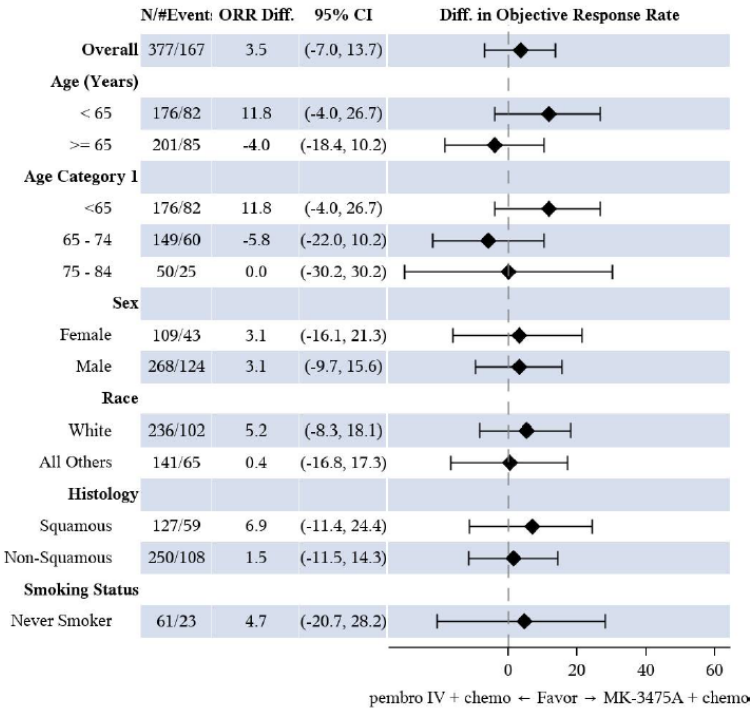
Figure 28 Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (PRO FAS Population)

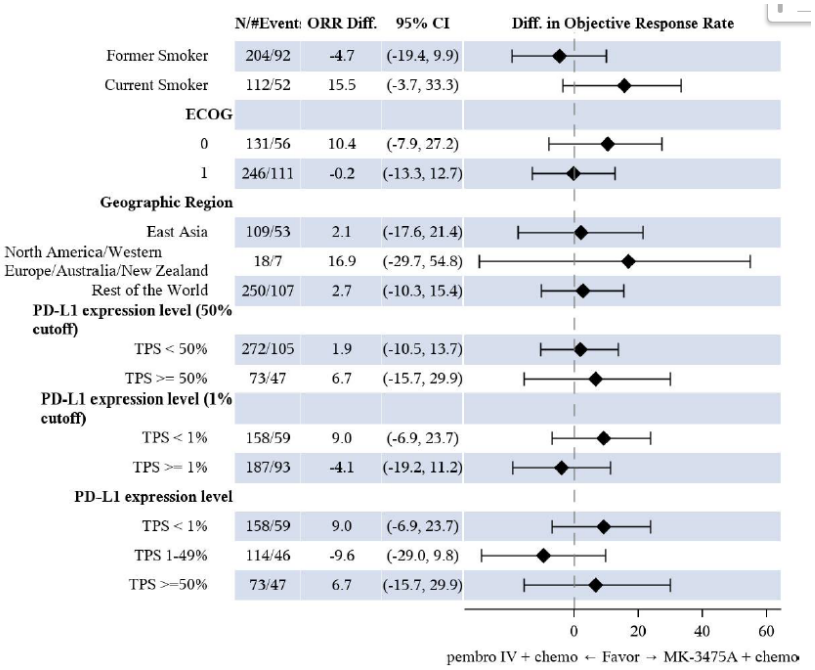


Database Cutoff Date: 12JUL2024

6.3.2.0.4.5. Pre-defined subgroup analyses

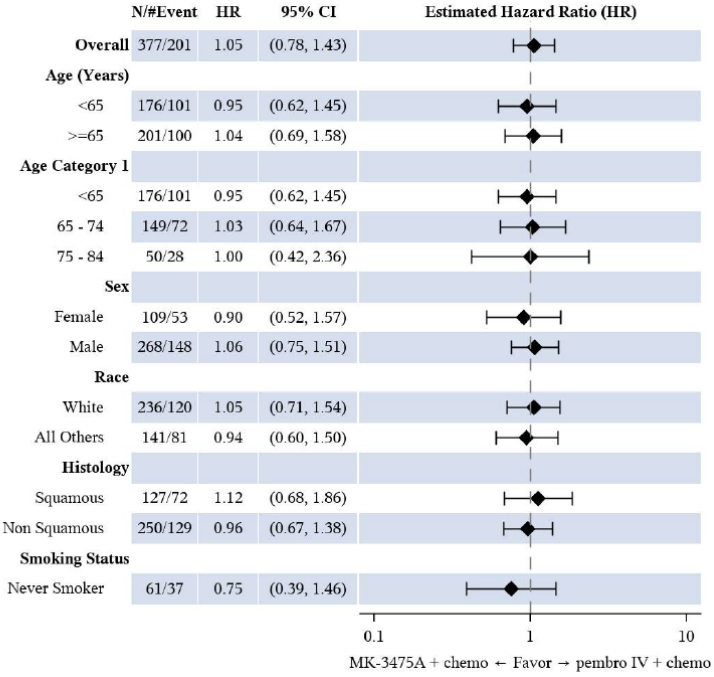
Figure 29 Forest Plot of Difference in Objective Response Rate (Confirmed) by Subgroup Factors Based on BICR per RECIST 1.1 (ITT Population)

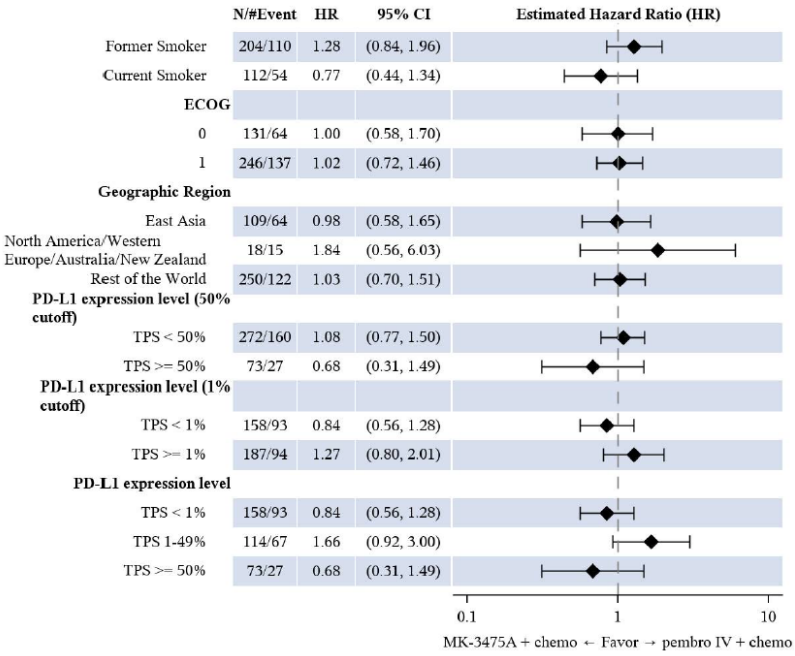




Analysis in the overall population is based on the stratified Miettinen & Nurminen method; analysis in the subgroups is based on the unstratified Miettinen & Nurminen method.
If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed in for this category of the subgroup variable.
Exception: North America/Western Europe/Australia/New Zealand subgroup category is displayed.
Database Cutoff Date: 12JUL2024.

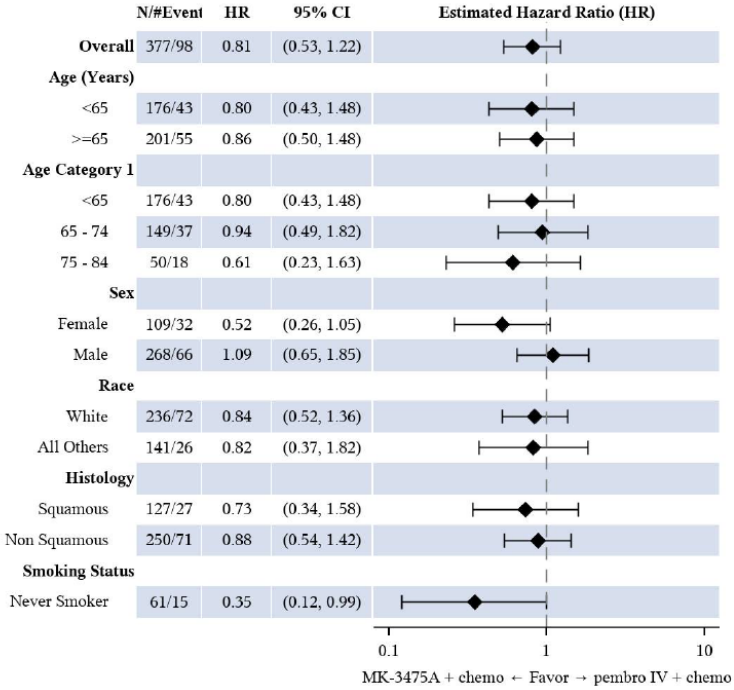
Figure 30 Forest Plot of PFS Hazard Ratio by Subgroup Factors (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)

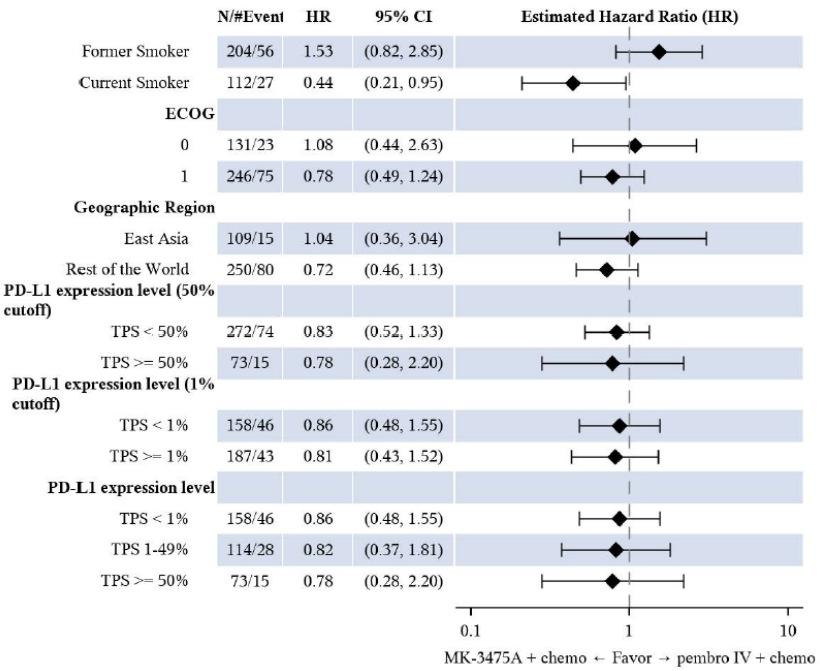




For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed in for this category of the subgroup variable.
Exception: North America/Western Europe/Australia/New Zealand subgroup category is displayed.
Database Cutoff Date: 12JUL2024.

Figure 31 Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population)





For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed in for this category of the subgroup variable.
Database Cutoff Date: 12JUL2024.

6.3.3. Clinical studies in special populations

Table 37: Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	None	None
Hepatic impairment** patients (Subjects number /total number)	None	None
Paediatric patients <18 years (Subjects number /total number)	None	None
Older patients; Age 65-74 (Subjects number /total number)	Pembro SC: 92/251 Pembro IV: 57/126	42/140
Age 75-84 (Subjects number /total number)	Pembro SC: 38/251 Pembro IV: 12/126	21/140
Age 85+ (Subjects number /total number)	Pembro SC: 2/251 Pembro IV: 0/126	2/140

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

Note: controlled trials include MK3475A-D77; non-controlled trials include MK3475A-C18

6.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

6.3.5. Supportive study(ies)

None submitted for efficacy.

6.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

6.3.7. Overall discussion and conclusions on clinical efficacy

6.3.7.0. Discussion

The MAH applied for an extension application for Keytruda (MK-3475A = pembrolizumab co-formulated with berahyaluronidase alfa, a variant of human hyaluronidase as permeation enhancer) administered as subcutaneous injection. Keytruda is currently authorised as IV formulation and indicated for a large number of solid tumors both as monotherapy and in combination with other agents. The proposed indication for the SC formulation is covering all the indications approved for IV in adults only.

The pivotal study supporting this application is the Phase 3 randomized open-label trial MK-3475A-D77 evaluating the PK, efficacy, and safety of MK-3475A SC or pembrolizumab IV in combination with histology-based platinum doublet chemotherapy, in adult patients with treatment-naïve metastatic NSCLC without EGFR, ALK or ROS1 genomic tumour aberrations.

Design and conduct of clinical study

MK-3475A-D77 was designed to demonstrate Non-Inferiority in PK parameters of pembrolizumab exposure of the SC compared to the IV formulation. The clinical efficacy comparison between the two treatment arms is to be considered descriptive only. Indeed, ORR, PFS, OS and DOR as secondary endpoints were not formally statistically tested. Such approach was considered generally acceptable by the CHMP at the time of the Scientific Advice, and it is also consistent with the recent CHMP opinions on SC formulations of other anti-PD(L)1 MoAb.

The patient population as defined by inclusion/exclusion criteria, as well as the backbone platinum-based chemotherapy administered based on tumor histology adhere to the currently approved pembrolizumab indications in 1L NSCLC and to the pivotal studies (KEYNOTE-189 and KEYNOTE-407) on which those approvals were based. Pembrolizumab was administered in MK-3475A-D77 study every 6 weeks in both treatment arms. The use of pembrolizumab 400 mg Q6W IV in the control arm is considered acceptable, being one of the approved dosing regimens for Keytruda IV.

The methods and frequency of PK/ADA sampling as well as tumor assessments in MK-3475A-D77 are considered appropriate.

The 2:1, open-label design as well as the stratification factors are considered appropriate in the setting. Several changes to key statistical aspects were implemented in protocol amendments (removal of interim analyses, unplanned updates to the sample size), mostly due to a more rapid than expected enrolment in the trial. Several methodological clarifications were provided, both regarding the analysis plan and the amendments, and the approach was eventually considered suitable to support the trial conclusion (i.e., that the new subcutaneous administration is not worse than the IV administration). This conclusion was further corroborated by supplemental analyses and several graphical representations of the data, which showed clear and consistent results.

With regard to the **PK assessment**, dual primary endpoints in study MK-3475A-D77 were model-based Cycle 1 AUC0-6wks and steady-state (Cycle 3) Ctrough, and secondary endpoints were model-based Cycle 1 Ctrough and Cmax, and steady-state (Cycle 3) AUC0-6wks and Cmax. Moreover, observed steady-state (Cycle 3) Ctrough was also assessed in a sensitivity analysis to ensure valid model-based assessment and additional observed data for secondary endpoints (Cycle 1 Ctrough and Cmax, and steady-state (Cycle 3) Cmax and AUC0-6wks) were evaluated and reported.

Overall, the PK parameters chosen as dual primary endpoints to demonstrate NI are acceptable and in line with similar applications. The MAH justified the choice for model-derived, rather than observed, parameters for the primary endpoints, because, considering that steady-state (Cycle 3) Ctrough was one of the dual primary endpoints, high attrition was expected for an observed primary endpoint due to higher drop-out rates by the end of Cycle 3 compared to early treatment cycles, as well as dose interruption/delays and missing PK sample, which would significantly impact the available sample size for an observed Ctrough endpoint. Overall, this justification is followed. It is of importance that observed data-based primary endpoint steady-state (Cycle 3) Ctrough has been also evaluated as pre-specified sensitivity analysis; additionally, a sensitivity analysis for observed Cycle 1 AUC0-6wks was submitted per CHMP request. Both analyses showed consistency between model-based and observed data-based assessments, thus suggesting that the final combined SC and IV model is robust enough to well estimate PK parameters.

Although the NI approach is acceptable, the rationale provided for the chosen NI margin for PK primary endpoints (based on FDA 2014 guidance for bioequivalence) was considered unclear. However, very good consistency of efficacy data up to month 9 (the last available time-point with complete data) is observed, which mitigates the concerns about the PK margins. Therefore, although the justification is methodologically insufficient, the conclusion of the trial still holds (also due to the strong efficacy data provided).

With regard to **clinical efficacy assessment**, the secondary efficacy endpoints evaluated in MK-3475A-D77 study were ORR, PFS and DOR, all by RECIST 1.1 per BICR, and OS. Those are standard efficacy endpoints in clinical trials in oncology, and are considered appropriate in this setting. The assessment by BICR is also appropriate giving the open-label design. PRO assessed by EORTC QLQ-C30 questionnaire were also included as secondary endpoint.

Efficacy data and additional analyses

A total of 377 patients were randomized 2:1 to pembrolizumab SC arm (251) or pembrolizumab IV arm (126), all received at least one cycle of treatment, and all were included in the ITT analysis for efficacy as well as in the APaT population analysed for safety. PK analyses were conducted using the Per Protocol (PP) population, consisting in the subset of participants who met the criteria to ensure that the data were adequate for assessment of PK endpoints.

Baseline characteristics were overall balanced between treatment arms. Patients were mostly male (71%) with median age of 65 years (range 37-87). About 63% were White, while 29% of patients were enrolled in Asia. About 45% of patients have distant/extrathoracic metastases (M1c-Stage IVB). 16% were never smokers. The baseline characteristics appear broadly consistent with the population enrolled in the 1L NSCLC Keytruda pivotal studies KEYNOTE-189 and KEYNOTE-407, apart from a lower proportion of participants with PD-L1 TPS≥50% (19.4% vs 26-34% in prior pembrolizumab studies). As the number of TPS≥50% tumors was balanced between treatment arm (indeed, PD-L1 TPS 50% was one of the stratification factors) this is not impacting the comparison between pembrolizumab SC and IV in MK-3475A-D77 study.

The MAH submitted the results of the final analysis, of MK-3475A-D77, with median survival follow-up 8.6 months.

PK results: PK results showed that pembrolizumab exposures after MK-3475A administration were within range of the exposures after pembrolizumab IV administration, demonstrating NI of the new SC formulation respect to the reference IV formulation. Although Ctrough and AUC trend to be higher after SC vs IV administration, the SC dose was conservatively selected by the MAH to be higher, to account for variability and ensure range of exposures in subjects did not fall below IV to preserve efficacy. On the other hand, Cmax ranges trend to be lower, remaining below that obtained after IV administration. These data are acceptable, considering the known PK profile of pembrolizumab. Given the 5-fold margin at the upper end of exposures (up to 10 mg/kg Q2W IV), higher Ctrough and AUC with SC do not represent a safety concern since all PK exposures are within those obtained after administration of 10 mg/kg Q2W IV. Indeed, PK primary endpoints were reached and pembrolizumab 790 mg Q6W administered SC resulted in PK exposures (Cycle 1 AUC0-6wks and steady-state [Cycle 3] Ctrough) that are noninferior to pembrolizumab 400 mg IV Q6W in patients with treatment-naïve metastatic NSCLC, being the GMR of these model-based PK parameters, well above the NI margin (0.8). This is further confirmed by sensitivity analysis, showing that the GMR of observed steady-state (Cycle 3) Ctrough after SC administration versus observed steady-state (Cycle 3) Ctrough after IV administration is above the predefined NI margin.

Regarding secondary PK endpoints, for which analyses are descriptive only, results showed that pembrolizumab exposures after MK-3475A 790 mg SC administration were within range of the exposures after pembrolizumab 400 mg IV administration. Although for the 790 mg Q6W SC dosage and for both model-based as well as for observed secondary PK endpoints, differences in GM% respect to 400 mg Q6W IV seems higher, also in this case AUC and Ctrough are higher after SC administration (in favour of NI), while Cmax is lower (in favour of safety).

Observed and predicted values are largely aligned, supporting the reliability of the model. Indeed, observed values are higher than model-based values, showing the same trend that VPC showing that the model trend to underpredict observed exposures that, as already explained, is not an issue considering that the study is evaluating the non-inferiority of SC vs IV.

Efficacy results: ORR results in the pembrolizumab SC + chemo vs pembrolizumab IV + chemo arms were highly overlapping [45.4% (95%CI 39.1,51.8) vs 42.1% (95%CI 33.3,51.2)], with same median time to response (1.5 months), similar median response duration (9.1 vs 8 months) as well as proportion of patients with extended response duration over 6 months (68% vs 72%).

PFS assessed per BICR by RECIST 1.1 was also comparable between the two arms, with respect to number of PFS events (53.8% vs 52.4%) and median PFS (8.1 vs 7.8 months), for an HR of 1.05 (95% CI: 0.78, 1.43). KM curves are mostly overlapping except marginally in favour of pembrolizumab IV+chemo arm up to month 4. Consistent results are shown in a PFS sensitivity analysis conducted according to EMA censoring rule (HR 1.04, 95%CI 0.77-1.40).

ORR and PFS results appear also overall consistent with the findings from KEYNOTE-189 and KEYNOTE-407.

In MK-3475A-D77, OS was also similar between treatment arms: HR of 0.81 (95%CI 0.53, 1.22), medians not reached. Few more OS events occurred in the pembrolizumab IV+chemo arm (24.3% vs 29.4%), however KM curves showed a slight advantage for the pembrolizumab+IV arm during the first 6 months. Afterwards curves are apparently crossing, but those are no more interpretable due to censoring. The percentages of deaths and reasons for death within 6 months appear

however overall similar between the treatment arms. An update up to 9 months OS data was provided: while the curves are definitely crossing, they are not diverging, and confidence intervals of the two survival curves are overlapping. Moreover, a supplemental analysis allowing for the crossing of the curves (restricted mean survival time at 3, 6 and 9 months as well as with premature data at 12 and 15 months) provided additional support that the subcutaneous administration is not worse, in terms of overall survival, than the intravenous administration.

PRO assessment suggested that, overall, the global health status/QoL score remained stable and was generally consistent between IV and SC treatment arms at Week 24, and no relevant differences in PRO seem evident.

ORR, PFS and OS results were overall consistent across main subgroups analyses, with no specific trends noted in one or more subgroups across all endpoints. However, the interpretation is limited by the descriptive value of efficacy results in the ITT population, and also by the small sample size in subgroups especially in the control arm (2:1 randomization).

6.3.7.1. Conclusions on the clinical efficacy

MK-3475A-D77 demonstrated non-inferiority in PK parameters model-based Cycle 1 AUC0-6wks and steady-state (Cycle 3) Ctrough of the MK-3475A SC vs pembrolizumab IV. Clinical activity of MK-3475A was generally consistent with pembrolizumab IV infusion in combination with chemotherapy in 1L non oncogene-addicted metastatic NSCLC based on descriptive efficacy endpoints ORR, DoR, PFS and OS.

6.4. Clinical safety

Please refer to Table 5: Tabular overview of main clinical studies

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

6.4.1. Safety data collection

The safety data from participants treated with MK-3475A (pembrolizumab and berahyaluronidase alfa SC) in combination with platinum doublet chemotherapy in MK-3475A-D77 (hereafter: **D77 MK-3475A + chemo dataset, N=251**) are compared to participants treated with pembrolizumab IV in

combination with platinum doublet chemotherapy in MK-3475A-D77 (hereafter: **D77 pembro IV + chemo dataset, N=126**), and then with pooled safety data from studies of pembrolizumab IV plus chemotherapy (hereafter: **pooled pembro IV + chemo dataset, N=5711**). AEs in the MK-3475A-D77 study were coded using MedDRA (Version 27.0) and toxicity was graded according to NCI CTCAE Version 5.0.

To enable a comparison of the safety profile of the MK-3475A + chemo group observed in MK-3475A-D77 with the established safety profile of pembrolizumab, especially with respect to immune mediated AEs (AEOSI), the pembrolizumab monotherapy RSD (hereafter: **pembro RSD, N=7631**) has been included.

In addition, summaries of safety results from the MK-3475A-C18, MK-3475A-F11, and ALT-BB4-01 were included to support the overall MK-3475A safety profile.

All the safety analyses were conducted using the APaT population, which included all randomized/allocated participants who received at least 1 dose of study treatment, analyzed in the treatment arm according to the study drug that they actually received.

6.4.2. Patient exposure

Safety analyses were conducted using the APaT population, which included all randomized/allocated participants who received at least 1 dose of study treatment, analyzed in the treatment arm according to the study drug that they actually received.

Table 38 Summary of Drug Exposure (APaT Population)

	D77 MK-3475A + Chemotherapy (N=251)	D77 Pembrolizumab IV + Chemotherapy Control (N=126)	Pooled Pembrolizumab + Chemotherapy SD (N=5711)	Pembrolizumab Monotherapy RSD (N=7631)
Duration on Therapy (days)				
n	251	126	5706	7631
Mean (SD)	194.07 (101.40)	188.79 (103.23)	306.63 (236.34)	239.08 (210.22)
Median	209.00	189.00	246.00	176.00
Range	1.00 to 401.00	1.00 to 483.00	1.00 to 1,732.00	1.00 to 1,157.00
Number of Cycle				
n	251	126	5706	7631
Mean (SD)	5.19 (2.41)	5.06 (2.45)	12.56 (10.11)	12.31 (10.10)
Median	5.00	5.00	10.00	9.00
Range	1.00 to 10.00	1.00 to 12.00	1.00 to 70.00	1.00 to 59.00

Duration on therapy (days) is calculated as (last dose date - first dose date + 1).
D77 is at Q6W dosing regimen, while other studies are at Q3W dosing regimen.
Database cutoff date for KN-D77: 12JUL2024.
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 Exposure by Duration (APaT Population)

	D77 MK-3475A + Chemotherapy (N=251)			D77 Pembrolizumab IV + Chemotherapy Control (N=126)			Pooled Pembrolizumab + Chemotherapy SD (N=5711)			Pembrolizumab Monotherapy RSD (N=7631)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure (months)												
> 0	251	(100.0)	133.4	126	(100.0)	65.1	5,706	(99.9)	4,790.3	7,631	(100.0)	4,995.0

≥ 1	227	(90.4)	132.7	119	(94.4)	64.9	5,315	(93.1)	4,776.5	6,637	(87.0)	4,962.4
≥ 3	203	(80.9)	128.8	99	(78.6)	61.5	4,629	(81.1)	4,659.2	5,023	(65.8)	4,693.1
≥ 6	146	(58.2)	106.3	68	(54.0)	49.5	3,459	(60.6)	4,218.5	3,781	(49.5)	4,240.0
≥ 12	8	(3.2)	8.3	7	(5.6)	7.7	2,108	(36.9)	3,252.7	1,673	(21.9)	2,558.8
≥ 18	0	(0.0)	0.0	0	(0.0)	0.0	875	(15.3)	1,758.4	783	(10.3)	1,497.5
≥ 24	0	(0.0)	0.0	0	(0.0)	0.0	376	(6.6)	866.2	186	(2.4)	394.9

Each participant is counted once on each applicable duration category row.
Duration of exposure (months) is calculated as (last dose date - first dose date + 1) / 30.4367.
Database cutoff date for KN-D77: 12JUL2024.
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 40 Patient exposure (cut off)

Open studies		Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data	
MK-3475A-C18	Arm 1/2/3	96	96	96	None applicable***	
	Arm 4	45	44	44	≥ 6 months	19
					≥ 12 months	0
MK-3475A-D77		377	377	377	≥ 6 months	214
					≥ 12 months	15

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
*** C18 Arm 1 and 2 was designed with MK-3475A treatment only in cycle 1 and 3 and Arm 3 was designed with MK-3475A treatment only in cycle 1.

6.4.3. Adverse events

Table 41 Adverse Event Summary (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	249	(99.2)	123	(97.6)	5,663	(99.2)	7,375	(96.6)
with no adverse event	2	(0.8)	3	(2.4)	48	(0.8)	256	(3.4)
with drug-related[a] adverse events	226	(90.0)	121	(96.0)	5,495	(96.2)	5,462	(71.6)
with toxicity grade 3-5 adverse events	151	(60.2)	82	(65.1)	4,422	(77.4)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	118	(47.0)	60	(47.6)	3,681	(64.5)	1,208	(15.8)
with serious adverse events	98	(39.0)	51	(40.5)	2,567	(44.9)	2,742	(35.9)
with serious drug-related adverse events	53	(21.1)	25	(19.8)	1,470	(25.7)	840	(11.0)
who died	26	(10.4)	12	(9.5)	313	(5.5)	346	(4.5)
who died due to a drug-related adverse event	9	(3.6)	3	(2.4)	75	(1.3)	42	(0.6)
discontinued any drug due to an adverse event	62	(24.7)	30	(23.8)	1,641	(28.7)	1,066	(14.0)
discontinued MK-3475A/pembrolizumab	39	(15.5)	21	(16.7)	911	(16.0)	1,066	(14.0)
discontinued any chemotherapy	57	(22.7)	24	(19.0)	1,247	(21.8)	0	(0.0)
discontinued any drug due to a drug-related adverse event	44	(17.5)	19	(15.1)	1,345	(23.6)	639	(8.4)
discontinued MK-3475A/pembrolizumab	21	(8.4)	11	(8.7)	642	(11.2)	639	(8.4)

discontinued any chemotherapy	38	(15.1)	15	(11.9)	1,019	(17.8)	0	(0.0)
discontinued any drug due to a serious adverse event	41	(16.3)	21	(16.7)	786	(13.8)	714	(9.4)
discontinued MK-3475A/pembrolizumab	33	(13.1)	19	(15.1)	649	(11.4)	714	(9.4)
discontinued any chemotherapy	35	(13.9)	16	(12.7)	532	(9.3)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	23	(9.2)	10	(7.9)	528	(9.2)	347	(4.5)
discontinued MK-3475A/pembrolizumab	16	(6.4)	9	(7.1)	415	(7.3)	347	(4.5)
discontinued any chemotherapy	17	(6.8)	7	(5.6)	335	(5.9)	0	(0.0)

[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.

For KN-D77, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-D77: 12JUL2024.

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 42 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]							
	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
Number of participants exposed	251		126		5,711		7,631	
Total exposure[b] in person-months	1764.71		871.48		60030.16		66570.95	
Total events (rate)								
adverse events	2,798	(158.55)	1,478	(169.60)	110,459	(184.01)	76,878	(115.48)
drug-related[c] adverse events	1,696	(96.11)	831	(95.35)	67,755	(112.87)	24,542	(36.87)
toxicity grade 3-5 adverse events	422	(23.91)	200	(22.95)	15,915	(26.51)	7,463	(11.21)
toxicity grade 3-5 drug-related adverse events	290	(16.43)	131	(15.03)	11,063	(18.43)	1,770	(2.66)
serious adverse events	158	(8.95)	85	(9.75)	4,996	(8.32)	4,801	(7.21)
serious drug-related adverse events	76	(4.31)	40	(4.59)	2,320	(3.86)	1,093	(1.64)
adverse events leading to death	26	(1.47)	12	(1.38)	321	(0.53)	353	(0.53)
drug-related adverse events leading to death	9	(0.51)	3	(0.34)	76	(0.13)	42	(0.06)
adverse events resulting in drug discontinuation	70	(3.97)	31	(3.56)	2,045	(3.41)	1,165	(1.75)
drug-related adverse events resulting in drug discontinuation	47	(2.66)	20	(2.29)	1,672	(2.79)	703	(1.06)
serious adverse events resulting in drug discontinuation	42	(2.38)	21	(2.41)	885	(1.47)	753	(1.13)
serious drug-related adverse events resulting in drug discontinuation	23	(1.30)	10	(1.15)	596	(0.99)	363	(0.55)

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

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

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

For KN-D77, grades are based on NCI CTCAE version 5.0.

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

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

For KN001 and KN054, a new AE episode was recorded when there was any AE change in grade, relationship, or seriousness. If the episode date ranges were continuous, then these records were counted as one AE episode.

Database cutoff date for KN-D77: 12JUL2024.

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 43 Participants With Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥10% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	249	(99.2)	123	(97.6)	5,663	(99.2)	7,375	(96.6)
with no adverse events	2	(0.8)	3	(2.4)	48	(0.8)	256	(3.4)
Anaemia	147	(58.6)	89	(70.6)	3,036	(53.2)	982	(12.9)
Neutropenia	109	(43.4)	41	(32.5)	1,440	(25.2)	82	(1.1)
Leukopenia	75	(29.9)	33	(26.2)	581	(10.2)	52	(0.7)
Thrombocytopenia	74	(29.5)	35	(27.8)	789	(13.8)	117	(1.5)
Nausea	63	(25.1)	31	(24.6)	3,007	(52.7)	1,534	(20.1)
Aspartate aminotransferase increased	47	(18.7)	18	(14.3)	989	(17.3)	538	(7.1)
Alanine aminotransferase increased	44	(17.5)	18	(14.3)	1,005	(17.6)	572	(7.5)
Fatigue	41	(16.3)	18	(14.3)	1,884	(33.0)	2,368	(31.0)
Diarrhoea	37	(14.7)	17	(13.5)	2,020	(35.4)	1,678	(22.0)
Pneumonia	36	(14.3)	17	(13.5)	396	(6.9)	487	(6.4)
Constipation	35	(13.9)	23	(18.3)	1,789	(31.3)	1,179	(15.5)
Hypothyroidism	35	(13.9)	15	(11.9)	786	(13.8)	937	(12.3)
Hypoalbuminaemia	30	(12.0)	17	(13.5)	448	(7.8)	209	(2.7)
Pruritus	29	(11.6)	16	(12.7)	722	(12.6)	1,435	(18.8)
Decreased appetite	28	(11.2)	27	(21.4)	1,547	(27.1)	1,312	(17.2)
Hyperglycaemia	28	(11.2)	14	(11.1)	361	(6.3)	360	(4.7)
Lymphocyte count decreased	25	(10.0)	9	(7.1)	309	(5.4)	130	(1.7)
Rash	25	(10.0)	12	(9.5)	943	(16.5)	1,175	(15.4)
Asthenia	24	(9.6)	16	(12.7)	1,061	(18.6)	880	(11.5)
Vomiting	23	(9.2)	8	(6.3)	1,623	(28.4)	945	(12.4)
Alopecia	22	(8.8)	13	(10.3)	1,231	(21.6)	118	(1.5)
Hypokalaemia	22	(8.8)	12	(9.5)	698	(12.2)	324	(4.2)
Weight decreased	22	(8.8)	10	(7.9)	755	(13.2)	628	(8.2)
Cough	20	(8.0)	11	(8.7)	860	(15.1)	1,392	(18.2)
Pyrexia	20	(8.0)	14	(11.1)	1,044	(18.3)	934	(12.2)
Arthralgia	19	(7.6)	15	(11.9)	859	(15.0)	1,449	(19.0)
Blood alkaline phosphatase increased	18	(7.2)	13	(10.3)	368	(6.4)	322	(4.2)
Hyponatraemia	17	(6.8)	13	(10.3)	468	(8.2)	387	(5.1)
Oedema peripheral	15	(6.0)	10	(7.9)	574	(10.1)	630	(8.3)
Back pain	14	(5.6)	12	(9.5)	572	(10.0)	847	(11.1)
Insomnia	13	(5.2)	10	(7.9)	607	(10.6)	528	(6.9)
Neuropathy peripheral	12	(4.8)	7	(5.6)	739	(12.9)	146	(1.9)
Dyspnoea	11	(4.4)	10	(7.9)	623	(10.9)	1,130	(14.8)
Headache	11	(4.4)	6	(4.8)	786	(13.8)	946	(12.4)
Peripheral sensory neuropathy	7	(2.8)	2	(1.6)	671	(11.7)	83	(1.1)
Abdominal pain	6	(2.4)	3	(2.4)	686	(12.0)	671	(8.8)
Hypomagnesaemia	5	(2.0)	4	(3.2)	573	(10.0)	184	(2.4)
Stomatitis	5	(2.0)	4	(3.2)	625	(10.9)	201	(2.6)
Neutrophil count decreased	0	(0.0)	0	(0.0)	1,581	(27.7)	53	(0.7)
Platelet count decreased	0	(0.0)	0	(0.0)	1,086	(19.0)	95	(1.2)
White blood cell count decreased	0	(0.0)	0	(0.0)	1,055	(18.5)	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 KN-D77: 12JUL2024.

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 44 Participants With Adverse Events of Neutropenia and Neutrophil Count Decreased by System Organ Class and Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	109	(43.4)	41	(32.5)	2,942	(51.5)	131	(1.7)
with no adverse events	142	(56.6)	85	(67.5)	2,769	(48.5)	7,500	(98.3)
Blood and lymphatic system disorders	**109**	**(43.4)**	**41**	**(32.5)**	**1,440**	**(25.2)**	**82**	**(1.1)**
Neutropenia	109	(43.4)	41	(32.5)	1,440	(25.2)	82	(1.1)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**1,581**	**(27.7)**	**53**	**(0.7)**
Neutrophil count decreased	0	(0.0)	0	(0.0)	1,581	(27.7)	53	(0.7)

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

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 KN-D77: 12JUL2024.

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 45 Participants With Adverse Events by Maximum Toxicity Grade (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	249	(99.2)	123	(97.6)	5,663	(99.2)	7,375	(96.6)
Grade 1	14	(5.6)	2	(1.6)	128	(2.2)	1,028	(13.5)
Grade 2	84	(33.5)	39	(31.0)	1,113	(19.5)	2,833	(37.1)
Grade 3	95	(37.8)	58	(46.0)	2,997	(52.5)	2,731	(35.8)
Grade 4	30	(12.0)	12	(9.5)	1,112	(19.5)	438	(5.7)
Grade 5	26	(10.4)	12	(9.5)	313	(5.5)	345	(4.5)
with no adverse events	2	(0.8)	3	(2.4)	48	(0.8)	256	(3.4)

Table 46 Participants With Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	151	(60.2)	82	(65.1)	4,422	(77.4)	3,514	(46.0)
with no adverse events	100	(39.8)	44	(34.9)	1,289	(22.6)	4,117	(54.0)
Neutropenia	56	(22.3)	23	(18.3)	870	(15.2)	21	(0.3)
Anaemia	47	(18.7)	30	(23.8)	1,070	(18.7)	275	(3.6)
Pneumonia	27	(10.8)	13	(10.3)	216	(3.8)	270	(3.5)
Thrombocytopenia	27	(10.8)	7	(5.6)	239	(4.2)	23	(0.3)
Neutrophil count decreased	0	(0.0)	0	(0.0)	973	(17.0)	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.

For KN-D77, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-D77: 12JUL2024.
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 47 Participants With Grade 3-5 Adverse Events of Neutropenia and Neutrophil Count Decreased by System Organ Class and Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	56	(22.3)	23	(18.3)	1,818	(31.8)	31	(0.4)
with no adverse events	195	(77.7)	103	(81.7)	3,893	(68.2)	7,600	(99.6)
Blood and lymphatic system disorders	**56**	**(22.3)**	**23**	**(18.3)**	**870**	**(15.2)**	**21**	**(0.3)**
Neutropenia	56	(22.3)	23	(18.3)	870	(15.2)	21	(0.3)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**973**	**(17.0)**	**10**	**(0.1)**
Neutrophil count decreased	0	(0.0)	0	(0.0)	973	(17.0)	10	(0.1)

Every participant is counted a single time for each applicable row and column.
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 KN-D77: 12JUL2024.
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 (Sorted by Decreasing Incidence) (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	226	(90.0)	121	(96.0)
with no adverse events	25	(10.0)	5	(4.0)
Anaemia	131	(52.2)	81	(64.3)
Neutropenia	105	(41.8)	39	(31.0)
Thrombocytopenia	71	(28.3)	34	(27.0)
Leukopenia	70	(27.9)	32	(25.4)
Nausea	56	(22.3)	27	(21.4)
Aspartate aminotransferase increased	33	(13.1)	12	(9.5)
Fatigue	33	(13.1)	15	(11.9)
Hypothyroidism	31	(12.4)	14	(11.1)
Alanine aminotransferase increased	29	(11.6)	13	(10.3)
Pruritus	26	(10.4)	10	(7.9)
Alopecia	21	(8.4)	13	(10.3)
Decreased appetite	17	(6.8)	20	(15.9)

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.
Database Cutoff Date: 12JUL2024.

Table 49 Participants With Grade 3-5 Drug-Related Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	118	(47.0)	60	(47.6)	3,681	(64.5)	1,208	(15.8)
with no adverse events	133	(53.0)	66	(52.4)	2,030	(35.5)	6,423	(84.2)
Neutropenia	54	(21.5)	22	(17.5)	844	(14.8)	13	(0.2)
Anaemia	42	(16.7)	27	(21.4)	861	(15.1)	33	(0.4)
Thrombocytopenia	25	(10.0)	6	(4.8)	217	(3.8)	11	(0.1)
Neutrophil count decreased	0	(0.0)	0	(0.0)	935	(16.4)	6	(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.
For KN-D77, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-D77: 12JUL2024.
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.

6.4.3.0. Adverse drug reactions

Injection-Site Reactions

MK-3475A-D77

Table 50 Participants With Injection-Site Reactions Adverse Events by Maximum Toxicity Grade (Incidence > 0%) (APaT Population)

	MK-3475A + chemo	
	n	(%)
Participants in population	251	
with one or more adverse events	6	(2.4)
Grade 1	6	(2.4)
with no adverse events	245	(97.6)
Injection site erythema	1	(0.4)
Grade 1	1	(0.4)
Injection site haemorrhage	1	(0.4)
Grade 1	1	(0.4)
Injection site induration	1	(0.4)
Grade 1	1	(0.4)
Injection site pain	1	(0.4)
Grade 1	1	(0.4)
Injection site reaction	2	(0.8)
Grade 1	2	(0.8)

Every participant is counted a single time for each applicable specific adverse event.
Only the highest reported grade of a given adverse event is counted for the individual participant.
Grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Database Cutoff Date: 12JUL2024.

Table 51 Summary of Injection-site Reaction Events (APaT Population)

	MK-3475A + chemo
Participants in population	251
Participants with Injection-site Reactions (%)	6 (2.4)
Number of Events	
1	5
2	1
3	0
>=4	0
Number of Doses before the First Event	
Mean (SD)	1.8 (1.3)
Median	1.0
Range	1 to 4
Time to Onset of First Injection-site Reaction from most recent dose administration (days)	
Mean (SD)	1.8 (0.4)
Median	2.0
Range	1 to 2
Time to Onset of First Injection-site Reaction from initial dose administration (days)	
Mean (SD)	36.5 (55.3)
Median	2.0
Range	1 to 126
Duration of First Event (days)[a]	
Median	5.5
Range	2 to 20

(%) = Number of participants with Injection-site Reactions / Number of participants in population.
[a] From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the Participant died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
SD = Standard Deviation.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Database Cutoff Date: 12JUL2024

MK-3475A-C18

Local injection-site reactions were observed with MK-3475A. AEs were reported for 7/46 (15.2%) participants in Arm 1, 5/44 (11.4%) in Arm 2, 1/6 (16.7%) in Arm 3, and 9/44 (20.5%) in Arm 4. All these events were non-serious, mostly mild (Grade 1) except Grade 2 events in one patient. No injection-site reactions resulted in discontinuation of study drug. The most common (>4% incidence) injection site events were injection site erythema, injection site pruritus, and injection site swelling.

MK-3475A-F11

Injection site AEs were reported in 11.1% (7/63) participants who received MK-3475A SC during Crossover Period 1 and 7.5% (4/53) participants who received MK-3475A SC during Crossover Period 2. All events were Grade 1 except one Grade 2. No events were serious, all were considered related, and none led to treatment discontinuation. The injection site AEs included injection site pain, injection site reaction, injection site erythema, injection site rash, and injection site pruritus.

ALT-BB4-01

Local injection-site reactions were reported in 26.09% of participants receiving ALT-BB4 in Part II-A, and in 16.90% of participants receiving ALT-BB4 in Part II-B. No injection-site reactions were reported in the Part II-B control group. It was noted that AEs occurred after a period of time rather than immediately following IP administration. All injection-site reactions were non-serious.

Table 52 Adverse Reactions in Patients Treated With Pembrolizumab in Combination With Chemotherapy (Approved in the Current EUPI Plus New Population Under Review) (APaT Population)

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.7% (450)	247
Blood and lymphatic system disorders			
Very common	Anaemia	50.5% (3378)	1174
Very common	Neutropenia	21.9% (1464)	885
Very common	Thrombocytopenia	12.0% (805)	242
Common	Febrile Neutropenia	4.9% (326)	315
Common	Leukopenia	8.8% (588)	235
Common	Lymphopenia	3.0% (200)	91
Uncommon	Haemolytic Anaemia[a]	0.1% (8)	7
Uncommon	Eosinophilia	0.7% (47)	4
Rare	Immune Thrombocytopenia	0.04% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	6.8% (453)	77
Rare	Sarcoidosis	0.03% (2)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	14.1% (945)	18
Common	Adrenal Insufficiency[d]	1.1% (75)	31
Common	Hyperthyroidism[e]	5.8% (391)	8
Common	Thyroiditis[f]	1.1% (74)	7
Uncommon	Hypophysitis[g]	0.7% (45)	24
Rare	Hypoparathyroidism	0.04% (3)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.9% (799)	241
Very common	Decreased Appetite	25.8% (1728)	125
Common	Hyponatraemia	8.5% (570)	216
Common	Hypocalcaemia	4.7% (313)	51
Uncommon	Type 1 Diabetes Mellitus[h]	0.3% (20)	19
Psychiatric disorders			
Very common	Insomnia	11.1% (746)	10

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Nervous system disorders			
Very common	Neuropathy Peripheral	12.9% (867)	57
Very common	Headache	13.5% (904)	20
Common	Dizziness	9.7% (651)	17
Common	Dysgeusia	8.9% (599)	3
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Epilepsy	0.1% (7)	3
Uncommon	Lethargy	0.97% (65)	2
Rare	Myasthenic Syndrome[j]	0.07% (5)	5
Rare	Guillain-Barre Syndrome[k]	0.06% (4)	4

Rare	Myelitis	0.01% (1)	1
Rare	Optic Neuritis	0.01% (1)	1
Rare	Meningitis (Aseptic)	0.01% (1)	1
Eye disorders			
Common	Dry Eye	2.9% (191)	1
Uncommon	Uveitis[l]	0.2% (13)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	3.9% (264)	61
Uncommon	Myocarditis[n]	0.2% (12)	10
Uncommon	Pericardial Effusion	0.4% (27)	10
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.8% (458)	182
Uncommon	Vasculitis[o]	0.5% (35)	6
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.9% (799)	86
Very common	Cough	14.8% (991)	5
Common	Pneumonitis[p]	3.9% (264)	95
Gastrointestinal disorders			
Very common	Diarrhoea	34.7% (2320)	253

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Very common	Nausea	50.9% (3406)	201
Very common	Vomiting	27.2% (1821)	189
Very common	Abdominal Pain[q]	18.2% (1219)	82
Very common	Constipation	31.9% (2138)	24
Common	Colitis[r]	2.6% (177)	87
Common	Gastritis[s]	2.0% (133)	9
Common	Dry Mouth	5.4% (360)	6
Uncommon	Pancreatitis[t]	0.5% (32)	23
Uncommon	Gastrointestinal Ulceration[u]	0.4% (26)	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]	1.1% (73)	54
Rare	Cholangitis Sclerosing[w]	0.03% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Rash[x]	20.0% (1336)	7
Very common	Alopecia	21.9% (1463)	6
Very common	Pruritus[y]	14.0% (935)	6
Common	Severe Skin Reactions[z]	2.5% (167)	136
Common	Erythema	3.3% (219)	5
Common	Dermatitis	1.7% (115)	5
Common	Dry Skin	5.1% (341)	2
Common	Dermatitis Acneiform	2.0% (137)	2
Common	Eczema	1.2% (78)	2
Uncommon	Psoriasis	0.6% (41)	5

Uncommon	Lichenoid Keratosis[aa]	0.1% (8)	1
Uncommon	Vitiligo[bb]	0.5% (35)	0
Uncommon	Papule	0.2% (11)	0
Rare	Stevens-Johnson Syndrome	0.04% (3)	3

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Rare	Erythema Nodosum	0.07% (5)	0
Rare	Hair Colour Changes	0.01% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[cc]	12.9% (865)	43
Very common	Arthralgia	15.4% (1031)	42
Common	Myositis[dd]	8.6% (576)	25
Common	Pain In Extremity	7.0% (469)	13
Common	Arthritis[ee]	1.6% (104)	9
Uncommon	Tenosynovitis[ff]	0.3% (21)	1
Rare	Sjogren's Syndrome	0.03% (2)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (216)	109
Uncommon	Nephritis[gg]	0.7% (45)	26
Uncommon	Cystitis Noninfective	0.3% (18)	0
General disorders and administration site conditions			
Very common	Fatigue	35.5% (2374)	279
Very common	Asthenia	16.7% (1116)	167
Very common	Pyrexia	17.5% (1173)	49
Very common	Oedema[hh]	13.3% (889)	27
Common	Influenza Like Illness	2.6% (177)	2
Common	Chills	2.9% (197)	0
Investigations			
Very common	Alanine Aminotransferase Increased	16.7% (1120)	192
Very common	Aspartate Aminotransferase Increased	16.2% (1085)	159
Common	Blood Bilirubin Increased	4.6% (305)	52
Common	Blood Alkaline Phosphatase Increased	6.5% (437)	49
Common	Blood Creatinine Increased	9.6% (645)	35
Common	Hypercalcaemia	1.7% (117)	25

		Combination Therapy (N=6695)	
		All AEs % (n)	Gr 3-5 AEs n
Uncommon	Amylase Increased	0.6% (42)	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, Primary 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 (Autoimmune Pancreatitis, Pancreatitis, Pancreatitis Acute)
u. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)
v. Hepatitis (Autoimmune Hepatitis, Drug-Induced Liver Injury, Hepatitis, Hepatitis Acute, 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, Exfoliative Rash, Pemphigoid, Pruritus, Rash, Rash Erythematous, Rash Maculo-Papular, Rash Pruritic, Rash Pustular, Skin Necrosis, 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, Glomerulonephritis Acute, 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 HNSCC (KN689: 25JUL2024)
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.

The list of ADR reported in the SmPC for pembrolizumab SC is the same as for the IV formulation, with the addition of "injection site reaction" with frequency "common".

6.4.4. Adverse event of special interest, serious adverse events and deaths, other significant events

Serious Adverse Events

Table 53 Participants With Serious Adverse Events Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)

Participants in population	251		126		5,711		7,631	
with one or more adverse events	98	(39.0)	51	(40.5)	2,567	(44.9)	2,742	(35.9)
with no adverse events	153	(61.0)	75	(59.5)	3,144	(55.1)	4,889	(64.1)
Pneumonia	25	(10.0)	13	(10.3)	223	(3.9)	272	(3.6)
Febrile neutropenia	10	(4.0)	2	(1.6)	236	(4.1)	8	(0.1)
Thrombocytopenia	10	(4.0)	3	(2.4)	47	(0.8)	10	(0.1)
Neutropenia	7	(2.8)	2	(1.6)	51	(0.9)	3	(0.0)
Death	4	(1.6)	1	(0.8)	38	(0.7)	49	(0.6)
Anaemia	3	(1.2)	6	(4.8)	134	(2.3)	65	(0.9)
Diarrhoea	3	(1.2)	0	(0.0)	113	(2.0)	70	(0.9)
Pneumonia bacterial	3	(1.2)	0	(0.0)	6	(0.1)	7	(0.1)
Pneumonitis	3	(1.2)	0	(0.0)	84	(1.5)	136	(1.8)
Respiratory failure	3	(1.2)	1	(0.8)	14	(0.2)	30	(0.4)
Nausea	2	(0.8)	1	(0.8)	55	(1.0)	30	(0.4)
Pulmonary embolism	2	(0.8)	3	(2.4)	90	(1.6)	78	(1.0)
Acute kidney injury	1	(0.4)	1	(0.8)	85	(1.5)	65	(0.9)
Adrenal insufficiency	1	(0.4)	2	(1.6)	24	(0.4)	30	(0.4)
Fatigue	1	(0.4)	2	(1.6)	27	(0.5)	22	(0.3)
Pyrexia	1	(0.4)	1	(0.8)	140	(2.5)	79	(1.0)
Sepsis	1	(0.4)	0	(0.0)	75	(1.3)	56	(0.7)
Septic shock	1	(0.4)	2	(1.6)	21	(0.4)	14	(0.2)
Aspartate aminotransferase increased	0	(0.0)	2	(1.6)	27	(0.5)	17	(0.2)
Cerebrovascular accident	0	(0.0)	2	(1.6)	26	(0.5)	20	(0.3)
Colitis	0	(0.0)	1	(0.8)	56	(1.0)	71	(0.9)
Dehydration	0	(0.0)	2	(1.6)	34	(0.6)	44	(0.6)
Dyspnoea	0	(0.0)	1	(0.8)	24	(0.4)	91	(1.2)
Oedema peripheral	0	(0.0)	2	(1.6)	4	(0.1)	6	(0.1)
Pleural effusion	0	(0.0)	1	(0.8)	45	(0.8)	88	(1.2)
Urinary tract infection	0	(0.0)	0	(0.0)	62	(1.1)	67	(0.9)
Vomiting	0	(0.0)	1	(0.8)	80	(1.4)	32	(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.

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 KN-D77: 12JUL2024.

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 54 Participants With Drug-Related Serious Adverse Events Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	53	(21.1)	25	(19.8)	1,470	(25.7)	840	(11.0)
with no adverse events	198	(78.9)	101	(80.2)	4,241	(74.3)	6,791	(89.0)
Thrombocytopenia	10	(4.0)	3	(2.4)	45	(0.8)	6	(0.1)
Febrile neutropenia	9	(3.6)	2	(1.6)	226	(4.0)	0	(0.0)
Neutropenia	7	(2.8)	2	(1.6)	47	(0.8)	1	(0.0)
Pneumonia	5	(2.0)	2	(1.6)	57	(1.0)	19	(0.2)
Anaemia	3	(1.2)	5	(4.0)	100	(1.8)	6	(0.1)
Pneumonitis	3	(1.2)	0	(0.0)	76	(1.3)	129	(1.7)
Adrenal insufficiency	1	(0.4)	2	(1.6)	23	(0.4)	25	(0.3)
Diarrhoea	1	(0.4)	0	(0.0)	95	(1.7)	44	(0.6)
Pyrexia	1	(0.4)	0	(0.0)	65	(1.1)	22	(0.3)
Septic shock	1	(0.4)	2	(1.6)	12	(0.2)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	2	(1.6)	23	(0.4)	13	(0.2)
Fatigue	0	(0.0)	2	(1.6)	20	(0.4)	7	(0.1)
Vomiting	0	(0.0)	1	(0.8)	60	(1.1)	9	(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.
Serious adverse events up to 90 days of last dose are included.
Database cutoff date for KN-D77: 12JUL2024.
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.

Deaths due to Adverse Events

Table 55 Participants With Adverse Events Resulting in Death Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups of D77 study) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	26	(10.4)	12	(9.5)	313	(5.5)	346	(4.5)
with no adverse events	225	(89.6)	114	(90.5)	5,398	(94.5)	7,285	(95.5)
Pneumonia	7	(2.8)	4	(3.2)	34	(0.6)	40	(0.5)
Death	4	(1.6)	1	(0.8)	38	(0.7)	49	(0.6)
Febrile neutropenia	3	(1.2)	0	(0.0)	1	(0.0)	1	(0.0)
Respiratory failure	3	(1.2)	1	(0.8)	9	(0.2)	17	(0.2)
COVID-19 pneumonia	1	(0.4)	0	(0.0)	2	(0.0)	1	(0.0)
Epilepsy	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenic colitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenic sepsis	1	(0.4)	0	(0.0)	1	(0.0)	1	(0.0)
Parotitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(0.4)	0	(0.0)	9	(0.2)	8	(0.1)
Pneumothorax	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary embolism	1	(0.4)	2	(1.6)	12	(0.2)	10	(0.1)
Septic shock	1	(0.4)	2	(1.6)	12	(0.2)	11	(0.1)
Femoral neck fracture	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.8)	6	(0.1)	6	(0.1)

Table 56 Participants With Drug-Related Adverse Events Resulting in Death Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups of D77 study) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	9	(3.6)	3	(2.4)	75	(1.3)	42	(0.6)
with no adverse events	242	(96.4)	123	(97.6)	5,636	(98.7)	7,589	(99.4)
Febrile neutropenia	3	(1.2)	0	(0.0)	1	(0.0)	0	(0.0)
Neutropenic colitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenic sepsis	1	(0.4)	0	(0.0)	1	(0.0)	0	(0.0)
Parotitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(0.4)	0	(0.0)	4	(0.1)	4	(0.1)
Pneumonitis	1	(0.4)	0	(0.0)	8	(0.1)	8	(0.1)
Septic shock	1	(0.4)	2	(1.6)	7	(0.1)	0	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.8)	2	(0.0)	0	(0.0)

Adverse Events of Special Interest (AEOSI)

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

Table 57 Adverse Event Summary for AEOSI (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	78	(31.1)	33	(26.2)	1,900	(33.3)	2,095	(27.5)
with no adverse event	173	(68.9)	93	(73.8)	3,811	(66.7)	5,536	(72.5)
with drug-related[a] adverse events	66	(26.3)	31	(24.6)	1,676	(29.3)	1,815	(23.8)
with toxicity grade 3-5 adverse events	16	(6.4)	7	(5.6)	543	(9.5)	543	(7.1)
with toxicity grade 3-5 drug-related adverse events	15	(6.0)	7	(5.6)	491	(8.6)	475	(6.2)
with serious adverse events	14	(5.6)	6	(4.8)	433	(7.6)	527	(6.9)
with serious drug-related adverse events	13	(5.2)	6	(4.8)	391	(6.8)	462	(6.1)
who died	1	(0.4)	0	(0.0)	17	(0.3)	13	(0.2)
who died due to a drug-related adverse event	1	(0.4)	0	(0.0)	15	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	11	(4.4)	4	(3.2)	363	(6.4)	363	(4.8)
discontinued MK-3475A/pembrolizumab	9	(3.6)	4	(3.2)	284	(5.0)	363	(4.8)
discontinued any chemotherapy	6	(2.4)	2	(1.6)	190	(3.3)	0	(0.0)
discontinued any drug due to a drug-related adverse event	11	(4.4)	4	(3.2)	354	(6.2)	356	(4.7)
discontinued MK-3475A/pembrolizumab	9	(3.6)	4	(3.2)	277	(4.9)	356	(4.7)
discontinued any chemotherapy	6	(2.4)	2	(1.6)	184	(3.2)	0	(0.0)
discontinued any drug due to a serious adverse event	7	(2.8)	3	(2.4)	234	(4.1)	231	(3.0)
discontinued MK-3475A/pembrolizumab	7	(2.8)	3	(2.4)	213	(3.7)	231	(3.0)

discontinued any chemotherapy	3	(1.2)	2	(1.6)	114	(2.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	7	(2.8)	3	(2.4)	226	(4.0)	229	(3.0)
discontinued MK-3475A/pembrolizumab	7	(2.8)	3	(2.4)	207	(3.6)	229	(3.0)
discontinued any chemotherapy	3	(1.2)	2	(1.6)	109	(1.9)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
For KN-D77, grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database cutoff date for KN-D77: 12JUL2024.
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 Participants With Adverse Events of Special Interest by AEOSI Category and Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	78	(31.1)	33	(26.2)	1,900	(33.3)	2,095	(27.5)
with no adverse events	173	(68.9)	93	(73.8)	3,811	(66.7)	5,536	(72.5)
Adrenal Insufficiency	**5**	**(2.0)**	**3**	**(2.4)**	**62**	**(1.1)**	**74**	**(1.0)**
Arthritis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**5**	**(0.1)**
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**0**	**(0.0)**
Colitis	**3**	**(1.2)**	**3**	**(2.4)**	**155**	**(2.7)**	**159**	**(2.1)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**5**	**(0.1)**
Exocrine Pancreatic Insufficiency	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**
Gastritis	**7**	**(2.8)**	**1**	**(0.8)**	**125**	**(2.2)**	**57**	**(0.7)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**6**	**(0.1)**
Haemolytic Anaemia	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**2**	**(0.0)**
Hepatitis	**1**	**(0.4)**	**0**	**(0.0)**	**65**	**(1.1)**	**80**	**(1.0)**
Hyperthyroidism	**20**	**(8.0)**	**6**	**(4.8)**	**330**	**(5.8)**	**398**	**(5.2)**
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**1**	**(0.0)**
Hypophysitis	**0**	**(0.0)**	**1**	**(0.8)**	**40**	**(0.7)**	**52**	**(0.7)**
Hypothyroidism	**35**	**(13.9)**	**15**	**(11.9)**	**787**	**(13.8)**	**939**	**(12.3)**
Infusion Reactions	**8**	**(3.2)**	**3**	**(2.4)**	**368**	**(6.4)**	**165**	**(2.2)**
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**8**	**(0.1)**
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myocarditis	**0**	**(0.0)**	**0**	**(0.0)**	**10**	**(0.2)**	**9**	**(0.1)**
Myositis	**1**	**(0.4)**	**0**	**(0.0)**	**18**	**(0.3)**	**34**	**(0.4)**
Nephritis	**0**	**(0.0)**	**2**	**(1.6)**	**38**	**(0.7)**	**37**	**(0.5)**
Optic Neuritis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Pancreatitis	**0**	**(0.0)**	**0**	**(0.0)**	**24**	**(0.4)**	**28**	**(0.4)**
Pericarditis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**11**	**(0.1)**
Pneumonitis	**13**	**(5.2)**	**1**	**(0.8)**	**228**	**(4.0)**	**324**	**(4.2)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**20**	**(0.3)**
Severe Skin Reactions	**4**	**(1.6)**	**3**	**(2.4)**	**140**	**(2.5)**	**130**	**(1.7)**
Thyroiditis	**1**	**(0.4)**	**1**	**(0.8)**	**72**	**(1.3)**	**74**	**(1.0)**

Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**7**	**(0.1)**	**25**	**(0.3)**
Vasculitis	**0**	**(0.0)**	**0**	**(0.0)**	**32**	**(0.6)**	**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 KN-D77: 12JUL2024.

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 59 Participants With Adverse Events of Special Interest by Maximum Toxicity Grade in MK-3475A-D77 (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	78	(31.1)	33	(26.2)
Grade 1	20	(8.0)	11	(8.7)
Grade 2	42	(16.7)	15	(11.9)
Grade 3	13	(5.2)	7	(5.6)
Grade 4	2	(0.8)	0	(0.0)
Grade 5	1	(0.4)	0	(0.0)
with no adverse events	173	(68.9)	93	(73.8)

Table 60 Time to Onset and Duration of AEOSI in MK-3475A-D77 (APaT Population)

	MK-3475A + chemo	pembro IV + chemo
Participants in population	**251**	**126**
Participants with AEOSI (%)	78 (31.1)	33 (26.2)
Time to Onset of First AEOSI (days)[a]		
Mean (SD)	95.1 (70.9)	99.0 (56.9)
Median	85.0	91.0
Range	1 to 307	21 to 230
Total number of episodes of AEOSI	108	39
Average number of episodes of AEOSI per participant	1.4	1.2
Episode Durations (days)[b]		
Median	159.0	267.0
Range	1 to 286+	1 to 305+

Table 61 Summary of Outcome for Participants With AEOSI in MK-3475A-D77 (APaT Population)

	Outcome	MK-3475A + chemo	pembro IV + chemo
		n (%)	n (%)
Participants in population		251	126
With one or more AEOSI	**Overall**	**78 (31.1)**	**33 (26.2)**
	Fatal	1 (1.3)	0 (0.0)
	Not Resolved	33 (42.3)	14 (42.4)
	Resolving	17 (21.8)	7 (21.2)
	Unknown	1 (1.3)	0 (0.0)
	Sequelae	0 (0.0)	0 (0.0)
	Resolved	26 (33.3)	12 (36.4)

Table 62 Summary of Concomitant Corticosteroid Use for AEOSI in MK-3475A-D77 (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
Participants with one or more events	78		33	
Treated with systemic corticosteroid	25	(32.1)	13	(39.4)
High starting dose	19	(24.4)	8	(24.2)
Low starting dose	6	(7.7)	5	(15.2)
Not treated with systemic corticosteroid	53	(67.9)	20	(60.6)

6.4.5. Discontinuation due to adverse events

Table 63 Participants With Adverse Events Resulting in Any Treatment Discontinuation in MK-3475A-D77 (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	62	(24.7)	30	(23.8)
with no adverse events	189	(75.3)	96	(76.2)
Blood and lymphatic system disorders	**17**	**(6.8)**	**6**	**(4.8)**
Anaemia	5	(2.0)	4	(3.2)
Febrile neutropenia	4	(1.6)	0	(0.0)
Neutropenia	4	(1.6)	0	(0.0)
Thrombocytopenia	5	(2.0)	2	(1.6)
Cardiac disorders	**1**	**(0.4)**	**0**	**(0.0)**
Cardiac failure	1	(0.4)	0	(0.0)
Ear and labyrinth disorders	**1**	**(0.4)**	**0**	**(0.0)**
Deafness	1	(0.4)	0	(0.0)
Endocrine disorders	**1**	**(0.4)**	**1**	**(0.8)**
Hyperthyroidism	1	(0.4)	0	(0.0)
Immune-mediated hypophysitis	0	(0.0)	1	(0.8)
Gastrointestinal disorders	**5**	**(2.0)**	**4**	**(3.2)**
Colitis	0	(0.0)	1	(0.8)
Diarrhoea	0	(0.0)	1	(0.8)
Enterocolitis	1	(0.4)	0	(0.0)
Immune-mediated enterocolitis	0	(0.0)	1	(0.8)
Intestinal obstruction	1	(0.4)	0	(0.0)
Intestinal perforation	0	(0.0)	1	(0.8)
Nausea	1	(0.4)	0	(0.0)
Neutropenic colitis	1	(0.4)	0	(0.0)
Stomatitis	1	(0.4)	0	(0.0)
General disorders and administration site conditions	**5**	**(2.0)**	**3**	**(2.4)**
Death	4	(1.6)	1	(0.8)
Fatigue	0	(0.0)	1	(0.8)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.8)
Oedema peripheral	1	(0.4)	0	(0.0)

Infections and infestations	**16**	**(6.4)**	**6**	**(4.8)**
Abdominal infection	1	(0.4)	0	(0.0)
COVID-19	1	(0.4)	0	(0.0)
Lung abscess	1	(0.4)	0	(0.0)
Neutropenic sepsis	1	(0.4)	0	(0.0)
Parotitis	1	(0.4)	0	(0.0)
Pneumonia	8	(3.2)	4	(3.2)
Pneumonia bacterial	1	(0.4)	0	(0.0)
Septic shock	1	(0.4)	2	(1.6)
Viral infection	1	(0.4)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.4)**	**1**	**(0.8)**
Femoral neck fracture	0	(0.0)	1	(0.8)
Infusion related reaction	1	(0.4)	0	(0.0)
Investigations	**6**	**(2.4)**	**4**	**(3.2)**
Alanine aminotransferase increased	4	(1.6)	0	(0.0)
Aspartate aminotransferase increased	1	(0.4)	2	(1.6)
Blood creatinine increased	1	(0.4)	0	(0.0)
Creatinine renal clearance decreased	0	(0.0)	1	(0.8)
Gamma-glutamyltransferase increased	1	(0.4)	0	(0.0)
Myocardial necrosis marker increased	0	(0.0)	1	(0.8)
Nervous system disorders	**1**	**(0.4)**	**1**	**(0.8)**
Cerebrovascular accident	0	(0.0)	1	(0.8)
Epilepsy	1	(0.4)	0	(0.0)
Renal and urinary disorders	**1**	**(0.4)**	**2**	**(1.6)**
Acute kidney injury	0	(0.0)	1	(0.8)
Nephritis	0	(0.0)	1	(0.8)
Renal impairment	1	(0.4)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**10**	**(4.0)**	**3**	**(2.4)**
Immune-mediated lung disease	1	(0.4)	0	(0.0)
Interstitial lung disease	1	(0.4)	0	(0.0)
Pneumonitis	4	(1.6)	0	(0.0)
Pneumothorax	1	(0.4)	0	(0.0)
Pulmonary embolism	1	(0.4)	2	(1.6)
Respiratory failure	2	(0.8)	1	(0.8)
Skin and subcutaneous tissue disorders	**2**	**(0.8)**	**0**	**(0.0)**
Dermatitis exfoliative	1	(0.4)	0	(0.0)
Rash	1	(0.4)	0	(0.0)
Vascular disorders	**1**	**(0.4)**	**0**	**(0.0)**
Arterial thrombosis	1	(0.4)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
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: 12JUL2024.

6.4.6. Safety in special populations

Table 64 Adverse Event Summary by Age Category (< 65, >= 65 Years) (APaT Population)

	D77 MK-3475A + Chemotherapy				D77 Pembrolizumab IV + Chemotherapy Control				Pooled Pembrolizumab + Chemotherapy SD				Pembrolizumab Monotherapy RSD			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	119		132		57		69		3,823		1,888		4,524		3,107	
with one or more AE	119	(100.0)	130	(98.5)	54	(94.7)	69	(100.0)	3,788	(99.1)	1,875	(99.3)	4,364	(96.5)	3,011	(96.9)
with no AE	0	(0.0)	2	(1.5)	3	(5.3)	0	(0.0)	35	(0.9)	13	(0.7)	160	(3.5)	96	(3.1)
with drug-related[a] AE	106	(89.1)	120	(90.9)	54	(94.7)	67	(97.1)	3,673	(96.1)	1,822	(96.5)	3,231	(71.4)	2,231	(71.8)
with toxicity grade 3-5 AE	63	(52.9)	88	(66.7)	35	(61.4)	47	(68.1)	2,928	(76.6)	1,494	(79.1)	1,917	(42.4)	1,597	(51.4)
with toxicity grade 3-5 drug-related AE	49	(41.2)	69	(52.3)	26	(45.6)	34	(49.3)	2,440	(63.8)	1,241	(65.7)	629	(13.9)	579	(18.6)
with non-serious AE	119	(100.0)	127	(96.2)	54	(94.7)	69	(100.0)	3,763	(98.4)	1,859	(98.5)	4,282	(94.7)	2,940	(94.6)
with serious AE	45	(37.8)	53	(40.2)	17	(29.8)	34	(49.3)	1,567	(41.0)	1,000	(53.0)	1,457	(32.2)	1,285	(41.4)

with serious drug-related AE	25	(21.0)	28	(21.2)	9	(15.8)	16	(23.2)	917	(24.0)	553	(29.3)	451	(10.0)	389	(12.5)
who died	8	(6.7)	18	(13.6)	2	(3.5)	10	(14.5)	140	(3.7)	173	(9.2)	158	(3.5)	188	(6.1)
who died due to a drug-related AE	3	(2.5)	6	(4.5)	0	(0.0)	3	(4.3)	32	(0.8)	43	(2.3)	21	(0.5)	21	(0.7)
discontinued drug due to an AE	22	(18.5)	40	(30.3)	9	(15.8)	21	(30.4)	986	(25.8)	655	(34.7)	554	(12.2)	512	(16.5)
discontinued drug due to a drug-related AE	16	(13.4)	28	(21.2)	7	(12.3)	12	(17.4)	842	(22.0)	503	(26.6)	333	(7.4)	306	(9.8)
discontinued drug due to a serious AE	15	(12.6)	26	(19.7)	5	(8.8)	16	(23.2)	428	(11.2)	358	(19.0)	366	(8.1)	348	(11.2)
discontinued drug due to a serious drug-related AE	9	(7.6)	14	(10.6)	3	(5.3)	7	(10.1)	312	(8.2)	216	(11.4)	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.

For KN-D77, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-D77: 12JUL2024.

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 65 Adverse Events Summary by Age Category (APaT Population)

	Age (Years)															
	MK-3475A + chemo								Pembro IV + chemo							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	119		92		38		2		57		57		12		0	
with one or more adverse events	119	(100.0)	91	(98.9)	37	(97.4)	2	(100.0)	54	(94.7)	57	(100.0)	12	(100.0)	0	(0.0)
who died	8	(6.7)	9	(9.8)	9	(23.7)	0	(0.0)	2	(3.5)	6	(10.5)	4	(33.3)	0	(0.0)
with serious adverse events	45	(37.8)	34	(37.0)	18	(47.4)	1	(50.0)	17	(29.8)	26	(45.6)	8	(66.7)	0	(0.0)
-Fatal	8	(6.7)	9	(9.8)	9	(23.7)	0	(0.0)	2	(3.5)	6	(10.5)	4	(33.3)	0	(0.0)
-Hospitalization/prolong existing hospitalization	44	(37.0)	30	(32.6)	18	(47.4)	1	(50.0)	17	(29.8)	25	(43.9)	8	(66.7)	0	(0.0)
-Life-threatening	7	(5.9)	4	(4.3)	1	(2.6)	0	(0.0)	2	(3.5)	2	(3.5)	1	(8.3)	0	(0.0)
-Disability/incapacity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
-Other important medical event	1	(0.8)	1	(1.1)	2	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	22	(18.5)	23	(25.0)	17	(44.7)	0	(0.0)	9	(15.8)	15	(26.3)	6	(50.0)	0	(0.0)
Psychiatric disorders[a]	8	(6.7)	10	(10.9)	4	(10.5)	0	(0.0)	8	(14.0)	7	(12.3)	3	(25.0)	0	(0.0)
Nervous system disorders[a]	28	(23.5)	27	(29.3)	12	(31.6)	1	(50.0)	19	(33.3)	14	(24.6)	4	(33.3)	0	(0.0)
Accidents and injuries[b]	5	(4.2)	2	(2.2)	3	(7.9)	1	(50.0)	2	(3.5)	1	(1.8)	1	(8.3)	0	(0.0)
Cardiac disorders[a]	3	(2.5)	7	(7.6)	2	(5.3)	0	(0.0)	3	(5.3)	5	(8.8)	0	(0.0)	0	(0.0)
Vascular disorders[a]	11	(9.2)	10	(10.9)	5	(13.2)	0	(0.0)	6	(10.5)	9	(15.8)	2	(16.7)	0	(0.0)
Cerebrovascular disorders[c]	1	(0.8)	3	(3.3)	0	(0.0)	0	(0.0)	1	(1.8)	2	(3.5)	0	(0.0)	0	(0.0)
Infections and infestations[a]	55	(46.2)	38	(41.3)	16	(42.1)	1	(50.0)	22	(38.6)	32	(56.1)	6	(50.0)	0	(0.0)
Anticholinergic syndrome[d]	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Quality of life decreased[d]	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[e]	8	(6.7)	9	(9.8)	3	(7.9)	1	(50.0)	7	(12.3)	3	(5.3)	0	(0.0)	0	(0.0)

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

MedDRA PTs 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment. SAEs were followed 90 days after last dose of study treatment.

[a] Based on the respective system organ class.

[b] Includes preferred terms listed for 'Accidents and injuries (SMQ)'.

[c] Includes preferred terms listed for 'Ischaemic central nervous system vascular conditions (SMQ)', 'Haemorrhagic central nervous system vascular conditions (SMQ)', 'Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ)', 'Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)'.

[d] Based on the respective preferred term.

[e] Includes preferred terms 'Orthostatic hypotension', 'Fall', 'Loss of consciousness', 'Amnesia', 'Syncope', 'Dizziness', and all preferred terms associated with high level term 'Coordination and balance disturbances', and all preferred terms associated with high level group term 'Fractures'.

Database Cutoff Date: 12JUL2024

Table 66 Adverse Event Summary by Gender (Male, Female) (APaT Population)

	D77 MK-3475A + Chemotherapy				D77 Pembrolizumab IV + Chemotherapy Control				Pooled Pembrolizumab + Chemotherapy SD				Pembrolizumab Monotherapy RSD			
	Male		Female		Male		Female		Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	182		69		86		40		2,405		3,306		4,889		2,742	
with one or more adverse events	181	(99.5)	68	(98.6)	83	(96.5)	40	(100.0)	2,387	(99.3)	3,276	(99.1)	4,711	(96.4)	2,664	(97.2)
with no adverse event	1	(0.5)	1	(1.4)	3	(3.5)	0	(0.0)	18	(0.7)	30	(0.9)	178	(3.6)	78	(2.8)
with drug-related[a] adverse events	161	(88.5)	65	(94.2)	83	(96.5)	38	(95.0)	2,297	(95.5)	3,198	(96.7)	3,457	(70.7)	2,005	(73.1)
with toxicity grade 3-5 adverse events	110	(60.4)	41	(59.4)	56	(65.1)	26	(65.0)	1,814	(75.4)	2,608	(78.9)	2,265	(46.3)	1,249	(45.6)
with toxicity grade 3-5 drug-related adverse events	88	(48.4)	30	(43.5)	41	(47.7)	19	(47.5)	1,423	(59.2)	2,258	(68.3)	814	(16.6)	394	(14.4)
with non-serious adverse events	178	(97.8)	68	(98.6)	83	(96.5)	40	(100.0)	2,364	(98.3)	3,258	(98.5)	4,618	(94.5)	2,604	(95.0)
with serious adverse events	77	(42.3)	21	(30.4)	34	(39.5)	17	(42.5)	1,185	(49.3)	1,382	(41.8)	1,797	(36.8)	945	(34.5)
with serious drug-related adverse events	42	(23.1)	11	(15.9)	17	(19.8)	8	(20.0)	622	(25.9)	848	(25.7)	566	(11.6)	274	(10.0)
who died	19	(10.4)	7	(10.1)	7	(8.1)	5	(12.5)	188	(7.8)	125	(3.8)	240	(4.9)	106	(3.9)
who died due to a drug-related adverse event	5	(2.7)	4	(5.8)	3	(3.5)	0	(0.0)	49	(2.0)	26	(0.8)	27	(0.6)	15	(0.5)
discontinued drug due to an adverse event	48	(26.4)	14	(20.3)	15	(17.4)	15	(37.5)	733	(30.5)	908	(27.5)	695	(14.2)	371	(13.5)
discontinued drug due to a drug-related adverse event	32	(17.6)	12	(17.4)	11	(12.8)	8	(20.0)	585	(24.3)	760	(23.0)	418	(8.5)	221	(8.1)
discontinued drug due to a serious adverse event	33	(18.1)	8	(11.6)	10	(11.6)	11	(27.5)	372	(15.5)	414	(12.5)	473	(9.7)	241	(8.8)
discontinued drug due to a serious drug-related adverse event	17	(9.3)	6	(8.7)	6	(7.0)	4	(10.0)	228	(9.5)	300	(9.1)	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.

For KN-D77, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-D77: 12JUL2024.

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 67 Adverse Event Summary by ECOG Status Category (0, 1) (APaT Population)

	D77 MK-3475A + Chemotherapy				D77 Pembrolizumab IV + Chemotherapy Control				Pooled Pembrolizumab + Chemotherapy SD				Pembrolizumab Monotherapy RSD			
	[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	89		162		42		84		3,085		2,619		4,016		3,440	
with one or more adverse events	89	(100.0)	160	(98.8)	40	(95.2)	83	(98.8)	3,062	(99.3)	2,594	(99.0)	3,883	(96.7)	3,324	(96.6)
with no adverse event	0	(0.0)	2	(1.2)	2	(4.8)	1	(1.2)	23	(0.7)	25	(1.0)	133	(3.3)	116	(3.4)
with drug-related[a] adverse events	84	(94.4)	142	(87.7)	40	(95.2)	81	(96.4)	2,982	(96.7)	2,507	(95.7)	3,072	(76.5)	2,295	(66.7)
with toxicity grade 3-5 adverse events	57	(64.0)	94	(58.0)	23	(54.8)	59	(70.2)	2,372	(76.9)	2,043	(78.0)	1,540	(38.3)	1,866	(54.2)
with toxicity grade 3-5 drug-related adverse events	44	(49.4)	74	(45.7)	19	(45.2)	41	(48.8)	2,023	(65.6)	1,654	(63.2)	623	(15.5)	555	(16.1)
with non-serious adverse events	89	(100.0)	157	(96.9)	40	(95.2)	83	(98.8)	3,045	(98.7)	2,570	(98.1)	3,845	(95.7)	3,214	(93.4)
with serious adverse events	31	(34.8)	67	(41.4)	14	(33.3)	37	(44.0)	1,286	(41.7)	1,274	(48.6)	1,157	(28.8)	1,491	(43.3)
with serious drug-related adverse events	15	(16.9)	38	(23.5)	7	(16.7)	18	(21.4)	767	(24.9)	700	(26.7)	442	(11.0)	381	(11.1)
who died	6	(6.7)	20	(12.3)	2	(4.8)	10	(11.9)	110	(3.6)	202	(7.7)	93	(2.3)	237	(6.9)
who died due to a drug-related adverse event	1	(1.1)	8	(4.9)	1	(2.4)	2	(2.4)	34	(1.1)	41	(1.6)	13	(0.3)	29	(0.8)
discontinued drug due to an adverse event	23	(25.8)	39	(24.1)	9	(21.4)	21	(25.0)	887	(28.8)	753	(28.8)	515	(12.8)	522	(15.2)
discontinued drug due to a drug-related adverse event	17	(19.1)	27	(16.7)	6	(14.3)	13	(15.5)	771	(25.0)	574	(21.9)	379	(9.4)	247	(7.2)
discontinued drug due to a serious adverse event	12	(13.5)	29	(17.9)	5	(11.9)	16	(19.0)	383	(12.4)	402	(15.3)	296	(7.4)	397	(11.5)

discontinued drug due to a serious drug-related adverse event	6	(6.7)	17	(10.5)	2	(4.8)	8	(9.5)	291	(9.4)	237	(9.0)	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.
For KN-D77, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-D77: 12JUL2024.
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 68 Adverse Event Summary by Region (East Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World) (APaT Population)

	D77 MK-3475A + Chemotherapy						D77 Pembrolizumab IV + Chemotherapy Control						Pooled Pembrolizumab + Chemotherapy SD						Pembrolizumab Monotherapy RSD					
	East Asia		North America/Western Europe/Australia/New Zealand		Rest of the World		East Asia		North America/Western Europe/Australia/New Zealand		Rest of the World		East Asia		North America/Western Europe/Australia/New Zealand		Rest of the World		East Asia		North America/Western Europe/Australia/New Zealand		Rest of the World	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	73		11		167		36		7		83		1,525		2,208		1,978		683		5,105		1,843	
with one or more adverse events	73	(100.0)	11	(100.0)	165	(98.8)	36	(100.0)	7	(100.0)	80	(96.4)	1,516	(99.4)	2,192	(99.3)	1,955	(98.8)	653	(95.6)	4,964	(97.2)	1,758	(95.4)
with no adverse event	0	(0.0)	0	(0.0)	2	(1.2)	0	(0.0)	0	(0.0)	3	(3.6)	9	(0.6)	16	(0.7)	23	(1.2)	30	(4.4)	141	(2.8)	85	(4.6)
with drug-related[a] adverse events	67	(91.8)	10	(90.9)	149	(89.2)	34	(94.4)	7	(100.0)	80	(96.4)	1,487	(97.5)	2,124	(96.2)	1,884	(95.2)	456	(66.8)	3,773	(73.9)	1,233	(66.9)
with toxicity grade 3-5 adverse events	44	(60.3)	6	(54.5)	101	(60.5)	27	(75.0)	5	(71.4)	50	(60.2)	1,186	(77.8)	1,734	(78.5)	1,502	(75.9)	308	(45.1)	2,369	(46.4)	837	(45.4)
with toxicity grade 3-5 drug-related adverse events	37	(50.7)	4	(36.4)	77	(46.1)	22	(61.1)	2	(28.6)	36	(43.4)	1,053	(69.0)	1,417	(64.2)	1,211	(61.2)	121	(17.7)	787	(15.4)	300	(16.3)
with non-serious adverse events	73	(100.0)	10	(90.9)	163	(97.6)	36	(100.0)	7	(100.0)	80	(96.4)	1,513	(99.2)	2,178	(98.6)	1,931	(97.6)	637	(93.3)	4,879	(95.6)	1,706	(92.6)
with serious adverse events	29	(39.7)	6	(54.5)	63	(37.7)	20	(55.6)	3	(42.9)	28	(33.7)	651	(42.7)	1,110	(50.3)	806	(40.7)	248	(36.3)	1,846	(36.2)	648	(35.2)
with serious drug-related adverse events	17	(23.3)	3	(27.3)	33	(19.8)	13	(36.1)	0	(0.0)	12	(14.5)	381	(25.0)	643	(29.1)	446	(22.5)	106	(15.5)	525	(10.3)	209	(11.3)
who died	5	(6.8)	1	(9.1)	20	(12.0)	0	(0.0)	0	(0.0)	12	(14.5)	58	(3.8)	101	(4.6)	154	(7.8)	28	(4.1)	188	(3.7)	130	(7.1)
who died due to a drug-related adverse event	1	(1.4)	1	(9.1)	7	(4.2)	0	(0.0)	0	(0.0)	3	(3.6)	12	(0.8)	26	(1.2)	37	(1.9)	2	(0.3)	18	(0.4)	22	(1.2)
discontinued drug due to an adverse event	15	(20.5)	4	(36.4)	43	(25.7)	4	(11.1)	0	(0.0)	26	(31.3)	389	(25.5)	719	(32.6)	533	(26.9)	95	(13.9)	680	(13.3)	291	(15.8)
discontinued drug due to a drug-related adverse event	11	(15.1)	4	(36.4)	29	(17.4)	4	(11.1)	0	(0.0)	15	(18.1)	334	(21.9)	607	(27.5)	404	(20.4)	66	(9.7)	407	(8.0)	166	(9.0)
discontinued drug due to a serious adverse event	10	(13.7)	3	(27.3)	28	(16.8)	3	(8.3)	0	(0.0)	18	(21.7)	170	(11.1)	345	(15.6)	271	(13.7)	70	(10.2)	438	(8.6)	206	(11.2)
discontinued drug due to a serious drug-related adverse event	6	(8.2)	3	(27.3)	14	(8.4)	3	(8.3)	0	(0.0)	7	(8.4)	119	(7.8)	252	(11.4)	157	(7.9)	45	(6.6)	210	(4.1)	92	(5.0)

[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.
Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
For KN-D77, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-D77: 12JUL2024.
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.

6.4.7. Immunological events

See Clinical Pharmacology section 6313.1.3.1

6.4.8. Safety related to drug-drug interactions and other interactions

No formal DDI studies were conducted with MK-3475A (SC).

6.4.9. Vital signs and laboratory findings

The frequency, severity, and types of laboratory abnormalities reported in the D77 MK-3475A + chemo dataset were generally consistent with the D77 pembro IV + chemo dataset, pooled pembro IV + chemo dataset, and the pembro RSD. The majority were CTCAE Grade 1 to 2 toxicity.

A clinically relevant laboratory finding (defined as Grade 3 to 4 events) of neutrophil count decreased was higher in the D77 MK-3475A + chemo dataset (27.8%) compared with the D77 pembro IV + chemo dataset (19.2%). In the MK-3475A-D77 study, the laboratory data on "neutrophil count decreased" was consistent with the reported AE results of neutropenia. Neutrophil count decreased was lower in the D77 MK-3475A + chemo dataset compared with the pooled pembro IV + chemo dataset (58.4% vs 71.2%), including Grade 3 to 4 events (27.8% vs 39.4%).

No participants met the predetermined laboratory criteria for potential DILI (ALT or AST ≥3 × ULN, bilirubin ≥2 × ULN, and alkaline phosphatase <2 × ULN).

6.4.10. Post marketing experience

Not applicable for the SC formulation.

6.4.11. Overall discussion and conclusions on clinical safety

6.4.11.0. Discussion

6.4.11.0.1. Overall assessment of available safety data

The safety data from participants treated with MK-3475A (pembrolizumab and berahyaluronidase alfa SC) in combination with platinum doublet chemotherapy in the pivotal study MK-3475A-D77 (n=251) have been compared to participants treated with pembrolizumab IV in combination with platinum doublet chemotherapy in MK-3475A-D77 (n=126), and then with pooled safety data from studies of pembrolizumab IV plus chemotherapy (n=5711). To contextualize the safety data and enable a comparison with the established safety profile of pembrolizumab, the pembrolizumab monotherapy RSD (n=7631) has been also included.

Safety results from the MK-3475A-C18, MK-3475A-F11, and ALT-BB4-01 studies have been also provided as supportive.

Participants' characteristics were well balanced between the two treatment arms of the pivotal D77 study. When compared to the pembrolizumab combo pooled dataset and with the pembrolizumab mono RSD, some differences are observed in sex, age and ECOG (generally older and more with ECOG 1 in D77), and overall less Asiatic patients in the pembrolizumab mono RSD as compared to the other 3 datasets. Indeed, the trials included in the pooled datasets have been performed in multiple tumor types and disease settings (early and advanced/metastatic).

The median **duration of therapy** in the D77 study was slightly longer in the SC arm (209 vs 189 days), but with same median number of cycles (5). Very few patients in D77 had extended duration of exposure ≥12 months, contrary to the pembrolizumab combo dataset, where median duration exposure was longer (246 days), likely attributable to the short follow-up of D77 study.

AE summary: Overall, in D77 study the incidence of AE was similar between the SC and IV arm. There was a similar incidence of overall AEs, drug-related AEs, Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, SAEs, drug-related SAEs, deaths, and discontinuation of any drug due to an AE between the two arms of the pivotal study.

In comparison with the pooled pembrolizumab+chemo dataset, no relevant differences in the overall incidence of AEs are noted with D77 study, especially after adjustment for exposure. Higher incidence, also when exposure-adjusted, of AEs and drug-related AEs leading to death is observed in both arms of D77 as compared to the pooled pembrolizumab combo arm.

In comparison with the pembrolizumab monotherapy RSD, while the overall incidence of AEs was similar to both D77 arms, the incidence of drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, drug-related SAEs, AEs leading to death, and discontinuations due to AEs and drug-related AEs were higher in the D77 MK-3475A + chemo dataset compared with the pembrolizumab RSD. This is expected, as in both arms of D77 study pembrolizumab was given with chemotherapy, vs pembrolizumab given as monotherapy in the RSD.

Adverse Events: in both treatment arms of the pivotal study D77, the most common AEs are related to **myelotoxicity**, mainly anemia (58.6% vs 70.6% in SC vs IV arm, respectively), followed by neutropenia (43.4% vs 32.5%), leukopenia (29.9% vs 26.2%) and thrombocytopenia (29.5% vs 27.8%). Myelotoxicity is expected as it is a common side effect of the chemotherapy regimens associated with pembrolizumab, and indeed myelotoxicity was observed at far lower incidence in the pembrolizumab monotherapy RSD.

However, the incidence (also after adjustment for exposure) of myelotoxicity in D77 study exceed what was reported in the pooled pembrolizumab + chemo dataset (anemia 53.2%, neutropenia 25.2%, leukopenia 10.2%, thrombocytopenia 13.8%). An additional analysis combining the PTs of "neutropenia" and "neutrophil count decreased", confirmed the higher incidence of neutropenia in the SC vs the IV arm (43.4% vs 32.5%) but showed lower incidence as compared to the pembrolizumab combo reference dataset (51.5%). The overall cumulative incidence of **neutropenia** was higher in the pembrolizumab SC vs the IV arm (all grade 43.4% vs 32.5%; G3-5 22.3% vs 18.3%), also in exposure-adjusted event rates (13.49 vs 10.67). Prophylaxis with colony stimulating factors (CSF) for treatment-induced neutropenia, initially permitted at the investigator discretion, became mandatory with protocol Amendment 3 during the 4 cycles of platinum-based chemo-immunotherapy, due to an imbalance in the frequency of neutropenia including fatal and early fatal AEs observed during the conduction of the study. The incidence of **febrile neutropenia** (G3-5) at the final analysis was 5.2% vs 1.6% in the pembrolizumab SC vs IV arm. Further, in the pembrolizumab SC arm, among the AEs leading to death that were considered by the investigator to be related to study drug (9 in total) there were 3 cases of febrile neutropenia, one case of neutropenic colitis, and one of neutropenic sepsis. When the pembrolizumab SC + chemo arm is compared to the larger reference safety dataset of pembro IV combo, such risks are however similar or even slightly reduced: all grade chemotherapy-related neutropenia 43.4% vs 51.5%, Grade 3-5 chemotherapy-related neutropenia 22.3% vs 31.8%, febrile neutropenia: 5.2% vs 5.2%, infection 43.8% vs 50.6%, serious infection 17.9% vs 14.2%. It is acknowledged that the limited number of patients in the control arm (n=126, due to the 2:1 randomization ratio) may results in higher variability and may limit adequate evaluation of the differences seen between treatment arms in neutropenia and related AEs. Further, neutropenia was not observed in studies where the pembrolizumab SC formulation was administered alone. In conclusion, this is overall reassuring.

With the exception of neutropenia and febrile neutropenia as discussed above, the incidence of the most common AEs was overall similar in the SC and IV arms of D77 study.

Grade 3-5 Adverse Events and SAE: neutropenia, anaemia and thrombocytopenia were the most common G3-5 AEs in both treatment arms of D77 study, together with **Pneumonia**, occurring at a similar rate in both treatment arms (10.8% vs 10.3%), but quite higher than in the pooled pembrolizumab combo dataset (3.8%). Pneumonia was also the most common SAE in both arms,

occurring more commonly than in the pembrolizumab combo dataset. This finding may be likely be explained by the fact that pneumonia is a known infectious complication in patients with underlying NSCLC, which was the tumor treated in D77 study. Most events of pneumonia were indeed not considered drug-related by the investigator.

After Pneumonia, the most common SAE were febrile neutropenia and neutropenia, both occurring at higher frequency in the SC arm vs the IV arm of D77, although the rate of febrile neutropenia of the SC arm is similar to pembrolizumab + chemo dataset (see above). On the contrary, anemia was more common in the IV arm.

Deaths due to AE: the incidence of death due to AE was similar in the SC and IV arm of D77 study (10.4% vs 9.5%), but higher than both pembrolizumab + chemotherapy RSD (5.5%) and the pembrolizumab monotherapy RSD (4.5%). Such difference is also observed when AE rate leading to death is adjusted for exposure. The reference safety datasets comprised safety data from participants enrolled in studies conducted across multiple cancer types in various settings, including early-stage disease. Indeed, when considering studies in the same setting of D77 (i.e. KEYNOTE-189 and KEYNOTE-407), the rate of AEs leading to death is more similar to D77, and higher than the RSDs (6.7% and 8.3%). Overall, no concern is raised.

Deaths due to treatment-related AEs in the pembrolizumab SC arm of D77 study included 3 cases of febrile neutropenia, and 1 case each of neutropenic colitis, neutropenic sepsis, parotitis, pneumonia, pneumonitis, and septic shock. Pneumonitis is a known immune mediated AE of pembrolizumab already included in the SmPC. The remaining 8 AEs leading to death, which were due to febrile neutropenia and associated infections, occurred during the first cycles of treatment when platinum doublets were administered with pembrolizumab, and were considered related to chemotherapy.

In the pembrolizumab IV arm there were 2 cases of septic shock (considered related to chemotherapy) and one case of multiple organ dysfunction syndrome (considered related to both pembrolizumab and carboplatin).

AEOSI: AEOSI includes immune-mediated events and infusion-related reactions known to be causally associated with pembrolizumab. In study D77, the overall incidence of AEOSI was similar in the pembrolizumab SC + chemo arm and in the pembrolizumab IV + chemo arm, and it was also similar to the pembrolizumab + chemo RSD and the pembrolizumab monotherapy RSD. The exposure-adjusted event rates of AE also remained similar in all datasets. In MK-3475A-D77 study, no differences are noted in terms of severity/grade of AEOSI, time to onset of first AEOSI, resolution of AEOSI, and overall use of corticosteroids, between the SC and IV arm.

The most commonly reported AEOSI in the D77 MK-3475A + chemo dataset was hypothyroidism (13.9%). The incidence of **hypothyroidism** was similar to the pembrolizumab IV arm as well as to the combo and mono reference datasets.

Among AEOSI categories, all presented similar incidences between the pembrolizumab SC and the pembrolizumab IV arm of the pivotal study, with the exception of higher incidence in the SC arm for **Pneumonitis** (5.2% vs 0.8%), **Gastritis** (2.8% vs 0.8%) and **Hyperthyroidism** (8% vs 4.8%). The incidence of Pneumonitis and Gastritis in the SC arm resulted however similar to both pembrolizumab combo and pembrolizumab mono RSD, thus not raising concern. Although hypothyroidism was more frequent in the pembrolizumab SC arm also in comparison to the pembrolizumab combo RSD and the pembrolizumab mono RSD, the characteristics of hyperthyroidism were similar in terms of grade (mostly Grade 1 or 2), median time to onset, median duration and resolution, thus no concern is raised.

In conclusion, it is agreed with the MAH that the frequency, severity, and types of AEOSI observed in the D77 MK-3475A + chemo dataset were consistent with the established safety profile of pembrolizumab. No indication-specific immune-mediated AEs unique to pembrolizumab SC were identified in D77 study.

Adverse drug reactions: as expected, as an additional adverse reaction compared to pembrolizumab IV, pembrolizumab SC injection can cause **injection-site reactions**.

In the pivotal study MK-3475A-D77, injection-site reactions in the D77 MK-3475A + chemo arm were low in frequency (2.4%, 6 patients) and all cases were Grade 1 in severity. Injection site erythema, haemorrhage, induration, and pain were each reported in 1 (0.4%) participant each while the general PT "injection site reaction" was reported in 2 (0.8%) participants. None resulted in discontinuation of study drug. The median time to onset of the first injection-site reaction was 2 days (range 1-126) from the initial dose administration, and the median duration of the first injection-site reaction was 5.5 days (range 2-20).

The incidence of local site reactions was apparently higher in both supportive studies MK-3475A-C18 (11.4%, 15.2%, 16.7% and 20.5%) and MK-3475A-F11 (7.5% and 11.1%) as compared to the pivotal trial (2.4%). The MAH stated that the methodology used for data collection differs among the various studies, besides having different dosing regimens and volumes administered. Reassuringly however, the supportive studies MK-3475A-C18 and MK-3475A-F11 confirmed the finding of the pivotal trial that the injection site reactions are usually mild (Grade 1) and do not lead to discontinuation of pembrolizumab SC. Study ALT-BB4-01 showed that the permeation enhancer berahyaluronidase alfa can also cause local injection-site reaction by itself.

Treatment discontinuation: treatment discontinuation of any drug due to AE was similar in the pembrolizumab SC + chemo arm and in the pembrolizumab IV + chemo arm of D77 study (24.7% vs 23.8%), and also in the pembrolizumab combo RSD (28.7%). Same is observed for treatment discontinuation of any drug due to drug-related AE, SAE and drug-related SAE. Further, the rate of discontinuation of pembrolizumab or any chemotherapy was similar in the three datasets. Pneumonia was the most common AE leading to discontinuation of any study drug in the D77 MK-3475A + chemo dataset, followed by Anemia and Thrombocytopenia. No relevant differences are observed in the type and incidence of AEs leading to discontinuation of study drug in the D77 MK-3475A + chemo group as compared to the D77 pembrolizumab IV + chemo group and in the pembrolizumab combo RSD.

The number of participants with AEs resulting in any treatment interruption was also similar between the three combo datasets.

Safety in special populations: Safety data by **age** (<65 vs ≥65 years) showed slightly worse toxicity of the pembrolizumab SC + chemo combo of D77 in older patients. Similar trends are however also observed in the pembrolizumab IV + chemo D77 arm, as well as in the pembrolizumab combo and pembrolizumab mono RSDs. In patients ≥65 years, no relevant differences are noted between the pembrolizumab SC and IV arm in D77 study. Tendency to higher frequency of AEs is generally seen also when participants are analysed by <65, 65-74, 75-84, ≥85 years in all datasets. As there were only 2 participants ≥85 years of age and 38 participants who were 75-84 years of age, results in these age groups should be interpreted with caution.

Safety by **gender** showed that the AE profile based in the D77 MK-3475A + chemo dataset was generally similar between male and female, and generally consistent with the D77 pembro IV + chemo dataset, the pooled pembro IV + chemo dataset, and the pembro RSD.

Safety by **region** also revealed that the overall AE profile in the D77 MK-3475A + chemo group was generally comparable between participants in East Asia, North America/Western Europe/Australia/New Zealand, and Rest of World, although the limited number of patients from Europe/Australia/New Zealand (n=11) should be noted.

Safety by **ECOG/PS** showed slight increase in number of SAE and deaths in the D77 MK-3475A + chemo dataset in ECOG 1 vs ECOG 0, however the incidences of AEs were generally consistent with the D77 pembro IV + chemo dataset, the pooled pembro IV + chemo dataset, thus no concern is raised.

Laboratory findings: the laboratory abnormalities reported in D77 study appear overall similar between the two treatment arms and consistent with the pembro combo dataset. No concerns are raised over the data provided.

6.4.11.0.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 6.4.3.1 above.

In the SmPC of the subcutaneous formulation, the list of ADR corresponds to the one for the IV formulation, specifying that the safety profile of pembrolizumab SC + chemo in the pivotal study was overall consistent with the known safety profile of the intravenous pembrolizumab + chemotherapy. As expected, injection site reactions (only Grade 1) is an additional adverse reaction for the SC formulation, which has been described in section 4.8 of the SmPC. This is acceptable.

6.4.11.1. Conclusions on clinical safety

The safety profile of MK-3475A SC in combination with chemotherapy observed in the pivotal study MK-3475A-D77 is as expected for pembrolizumab IV in combination with chemotherapy in participants with NSCLC, and more generally consistent with the safety profiles of pembrolizumab monotherapy and chemotherapy. The frequency, severity, and types of AEOSI observed in the D77 MK-3475A + chemo dataset were consistent with the established safety profile of pembrolizumab, and no indication-specific immune-mediated AEs unique to pembrolizumab SC were identified in D77 study. Compared to pembrolizumab IV, pembrolizumab SC injections cause injection-site reactions as an additional adverse reaction, which has been included in the SmPC. Local injection-site reactions of MK-3475A were however low in frequency and mild in severity. No new safety concerns for pembrolizumab were identified when administered as subcutaneous injection.

7. Risk management plan

7.1. Safety specification

7.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 69: Summary of safety concerns in the proposed RMP

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

7.1.2. Discussion on proposed safety specification

Based on the assessment of the clinical safety of pembrolizumab SC in the context of MK-3475A-D77 study, no new data have emerged on the safety profile of pembrolizumab, therefore the summary of safety concern for pembrolizumab is still considered valid.

7.2. Pharmacovigilance plan

7.2.1. Proposed pharmacovigilance plan.

Table 70: Planned additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab. The applicant did not propose any additional pharmacovigilance activities.

7.2.2. Discussion on the Pharmacovigilance Plan

No changes to section of pharmacovigilance plan are proposed, which is accepted. Routine pharmacovigilance is sufficient to monitor and characterise the risks of the product.

7.3. Plans for post-authorisation efficacy studies

Table 71: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204) (on-going)	To compare overall survival (OS), progression free survival (PFS) and objective response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.	Long term efficacy and safety	Final study report	4Q 2025
Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group (KN054): (on-going)	To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared to placebo in high-risk patients with complete resection of Stage IIIA (> 1 mm metastasis), IIIB and IIIC melanoma. To prospectively assess whether in the subgroup of patients with PD-L1- positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo (primary endpoints); distant metastasis free survival (DMFS) and overall survival (OS) in all-subjects and subjects with PD-L1-positive tumors (secondary endpoints for final study report)	Long term efficacy and safety	Final Study Report	4Q 2027
A Phase II study of pembrolizumab (MK-3475) in previously treated participants with advanced solid tumors (KN158) (on-going)	To evaluate the antitumor activity of pembrolizumab in participants with MSI-H/dMMR gastric, biliary or small intestine cancer	Additional efficacy	Clinical Study Report	1Q 2025
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma (KN716) (on-going)	To compare RFS, DMFS and OS between pembrolizumab and placebo in patients with resected Stage IIB or IIC cutaneous melanoma	Long term efficacy and safety	Clinical Study Report	4Q 2028
A randomized, Phase 3 trial with pembrolizumab versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (KN091) (on-going)	To compare OS between pembrolizumab and placebo in patients with early stage NSCLC after resection and completion of standard adjuvant therapy To assess data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab	Long term efficacy and safety	Final Study Report	3Q2026

No new post-authorisation studies are proposed specifically for this line extension for the new subcutaneous pembrolizumab formulation.

7.4. Risk minimisation measures

The MAH submitted an updated RMP version 46.0 with this application.

The (main) proposed RMP changes with the current procedure were the following:

Addition of a new formulation for pembrolizumab subcutaneous route of administration.

Addition of study MK-3475A-D77 in Modules SIII, SVII, and SVIII; no changes to the risk profile in Modules SIII, SVII, and SVIII.

PAES study KEYNOTE-716 (additional biomarker data from the ongoing resected Stage II melanoma adjuvant) is removed from the RMP. This concerns data submitted related to a separate variation (EMEA/H/C/003820/ANX).

No update to the summary of the safety concerns was proposed.

7.4.1. Proposed risk minimisation measures

The applicant did not propose any additional risk minimisation measures, beyond the already in place patient card for the risk of immune mediated adverse reactions.

Table 72: Additional risk minimisation measures

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).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

7.5. RMP Summary and RMP Annexes overall conclusion

The RMP, including Part VI and the RMP Annexes are acceptable.

7.6. PRAC Outcome

PRAC endorsed the PRAC Rapporteur's assessment of the RMP and its conclusions, without further additions.

7.7. Overall conclusion on the Risk Management Plan

☒ The CHMP and PRAC consider that the risk management plan version 46.0 is acceptable.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

8. Pharmacovigilance

8.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

8.2. Periodic Safety Update Reports submission requirements

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.

9. Product information

9.1. Summary of Product Characteristics (SmPC)

9.1.1. SmPC section 4.1 justification

For Keytruda solution for injection, section 4.1 includes all the therapeutic indications already approved for Keytruda IV in adults, i.e. excluding pediatric indications.

Based on historical PK data for pembrolizumab, no PK differences have been noted among different tumor types. Therefore, the PK data obtained in the target NSCLC population of the pivotal study MK-3475A-D77 are expected to be applicable to all tumor types for which an indication has been granted for the IV formulation. Establishing PK NI and comparable efficacy and safety in NSCLC to bridge to other approved pembrolizumab indicationsis considered acceptable, and in line with to the recent EU approvals of the subcutaneous formulations of other anti-PD(L)1 drugs.

9.1.2. SmPC section 4.2 justification

In section 4.2 of the SmPC of all formulations of Keytruda, switching from IV to SC, or from SC to IV, at their next scheduled dose, is allowed.

Based on the results of PK exposure matching used to bridge the proposed pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A dosing regimens to the currently approved pembrolizumab IV dosing regimens (200 mg Q3W and 400 mg Q6W), the proposal is considered acceptable.

9.1.3. SmPC section 4.8 justification

In the SmPC of Keytruda SC formulation solution for injection, an additional paragraph "Subcutaneous formulation" has been included in section 4.8 to inform that the safety profile of pembrolizumab SC + chemo in the pivotal study was overall consistent with the known safety profile of the intravenous pembrolizumab + chemotherapy, with the addition and the description of injection site reactions as additional adverse reaction for the SC formulation. Injection-site reactions have been reflected in the PI accordingly. Based on the assessment of the safety data provided, this is acceptable.

9.1.4. SmPC section 5.1 justification

The pivotal MK-3475A-D77 study has been described in section 5.1 of the SmPC for Keytruda SC formulation.

9.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

10. Benefit-risk assessment

10.1. Therapeutic context

Disease or condition, therapeutic indication, available therapies and unmet medical need

The Applicant is requesting the use of the SC formulation to all the currently approved indications for Keytruda IV in adults, meaning that the two currently approved paediatric indications in melanoma (12-18 years) and Hodgkin lymphoma (3-18 years) are not covered by this line extension and are not included among the therapeutic indications of the new SC formulation.

Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 6.3.2 of this document.

The pivotal study is the Phase 3 randomized 2:1 open-label multicenter trial **MK-3475A-D77** evaluating the PK, efficacy, and safety of MK-3475A SC or pembrolizumab IV in combination with histology-based platinum doublet chemotherapy, in adult patients with treatment-naïve metastatic NSCLC without EGFR, ALK or ROS1 genomic tumour aberrations. The study was designed to demonstrate Non-Inferiority in PK parameters of pembrolizumab exposure of the SC compared to the IV formulation, based on the dual primary endpoints model-based Cycle 1 AUC0-6wks and steady-state (Cycle 3) Ctrough. The clinical efficacy comparison between the two treatment arms is to be considered descriptive only: ORR, PFS, OS and DOR were secondary endpoints and were not formally tested. The final analysis of the pivotal study has been submitted.

10.2. Favourable effects

- PK results showed that pembrolizumab exposures after MK-3475A administration were within range of the exposures after pembrolizumab IV administration, demonstrating NI of the SC formulation respect to the reference IV formulation in the two primary endpoints model-based Cycle 1 $AUC_{0\text{-}6wks}$ (GMR 1.14, 96%CI 1.06, 1.22) and model-based steady-state (Cycle 3) C_{trough} (GMR 1.67, 94%CI 1.52, 1.84). A prespecified sensitivity analysis based on observed data for steady-state (Cycle 3) C_{trough} as well as a sensitivity analysis of observed Cycle 1 $AUC_{0\text{-}6wks}$ were both consistent with model-based primary results.
- PK exposure for pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC are within the 5-fold range of exposure from 2 mg/kg Q3W to 10 mg/kg Q2W of pembrolizumab IV where flat exposure-response relationship for efficacy and safety have been previously established. Range of Cmax remains below that of IV administration.
- ORR results were similar in the pembrolizumab SC + chemotherapy and pembrolizumab IV + chemotherapy arms: 45.4% (95%CI 39.1, 51.8) vs 42.1% (95%CI 33.3, 51.2). Median DOR was also comparable (9.1 vs 8 months).
- PFS assessed per BICR by RECIST 1.1 was similar between the SC and IV arms with respect to number of PFS events (53.8% vs 52.4%) and median PFS (8.1 vs 7.8 months), with an HR of 1.05 (95% CI: 0.78, 1.43). KM curves were almost overlapping.
- OS was overall comparable between treatment arms: HR of 0.81 (95%CI 0.53, 1.22), medians NR in either arm, few less OS events in the pembrolizumab SC + chemo arm (24.3% vs 29.4%). Although a small but visible crossing of the OS curves around 6 months was observed, no

differences beyond 9 months are expected based on updated OS analyses due to the specific variation.

- Acknowledging the descriptive nature and the small sample size of some subgroups especially in the control arm, the efficacy results seem overall consistent across main subgroups analysed.

10.2.1. Uncertainties and limitations about favourable effects

None.

10.3. Unfavourable effects

- Safety has been evaluated in n=251 patients receiving pembrolizumab SC + platinum-based chemotherapy and n=126 patients receiving pembrolizumab IV + platinum-based chemotherapy in the two arms of the pivotal study MK-3475A-D77 in 1L NSCLC. Safety was contextualised with the established pembrolizumab IV safety profile from the pooled pembrolizumab + chemotherapy reference dataset (n=5.711) and the pooled pembrolizumab monotherapy reference dataset (n=7.631).
- The exposure was similar in the SC and IV arms of MK-3475A-D77: median duration of therapy 209 vs 189 days, median number of cycles 5 in both arms. <5% of patients have long exposure ≥12 months due to the still limited follow-up of the study.
- Overall, the incidence of AE was similar between the SC and IV arms of the pivotal trial, in terms of overall AEs, drug-related AEs, Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, SAEs, drug-related SAEs, deaths, and discontinuation of any drug due to an AE.
- The most common AEs in MK-3475A-D77 study were related to myelotoxicity, i.e. anemia (58.6% vs 70.6%), neutropenia (43.4% vs 32.5%), leukopenia (29.9% vs 26.2%) and thrombocytopenia (29.5% vs 27.8%), which was expected as known AEs of co-administered chemotherapy. Apart from myelotoxicity, the incidence of the most common AEs was overall similar in the SC and IV arms. The rate of neutropenia, febrile neutropenia and infections was however similar between the pembro SC+chemo arm of D77 and the pembro IV+chemo reference safety dataset.
- Injection-site reaction was the additional adverse reaction of the SC formulation as compared to IV. Injections-site reactions in the D77 MK-3475A + chemo arm were low in frequency (2.4%, 6 patients), all Grade 1 in severity, and did not lead to discontinuation of pembrolizumab. Injection-site reactions occurred at higher frequency in the supportive studies, as the safety data collection was apparently different, however confirmed that reactions are usually mild and does not lead to pembrolizumab discontinuation. The permeation enhancer berahyaluronidase alfa can cause local injection-site reaction by itself.
- The overall incidence of AEOSI overall was similar in the pembrolizumab SC + chemo arm and in the pembrolizumab IV + chemo arm of D77 study, and also similar to both reference safety datasets pembrolizumab + chemo RSD and pembrolizumab monotherapy RSD. The frequency, severity, and types of AEOSI observed in the pembrolizumab SC arm were consistent with the established safety profile of pembrolizumab, with no indication-specific immune-mediated AEs unique to pembrolizumab SC formulation identified.
- Trend toward worse toxicity with higher age range was observed in the pembrolizumab SC + chemo arm of D77, which is however consisted with the IV arm as well as with the combo and mono reference datasets.

10.3.1. Uncertainties and limitations about unfavourable effects

None.

10.4. Effects Table

Table 73: Effects Table for Keytruda SC formulation (data cut-off: 12 July 2024).

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
	MK-3475A SC + chemo	pembro IV + chemo	Difference		
Model-based Cycle 1 AUC0-6wks GM (µg*day/mL)	1711.36	1450.73	GMR 1.14 (96%CI 1.06, 1.22)	**SoE:** PE, NI was met **Unc:** none	Study MK-3475A-D77
Model-based steady-state (Cycle 3) Ctrough GM (µg/mL)	40.07	23.85	GMR 1.67 (94%CI 1.52, 1.84)	**SoE:** PE, NI was met **Unc:** none	
ORR	45.4% (39.1,51.8)	42.1% (33.3,51.2)	Ratio: 1.08 (95%CI 0.85,1.37)	**SoE:** similar ORR SC vs IV **Unc:** descriptive SE	
Unfavourable Effects					
G3-5 AE	60.2%	65.1%		**SoE:** similar safety profile between SC and IV arm. **Unc:** none	
SAE	39%	40.5%		**SoE:** similar safety profile between SC and IV arm. **Unc:** none	
Deaths due to AE	10.4%	9.5%		**SoE:** similar safety profile between SC and IV arm. **Unc:** none	
Discontinuation of any drug due to AE	24.7%	23.8%		**SoE:** similar safety profile between SC and IV arm. **Unc:** none	
AEOSI	31.1%	26.6%		**SoE:** similar safety profile between SC and IV arm. No new AESOI identified **Unc:** none	
Injection site reactions	2.4%	-		**SoE:** additional ADR of the SC formulation **Unc:** none	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; SC: subcutaneous; IV: intravenous; NI: Non-Inferiority; AUC: Area Under the Curve; wks: weeks; C: concentration; ORR: overall response rate; PFS: progression free survival; OS: overall survival; PE: primary endpoint; SE: secondary endpoint; HR: hazard ratio; CI: confidence interval; NR: not reached; GM: geometric mean; GMR: geometric mean ration; AE: adverse event; SAE: serious adverse event; AEOSI: adverse event of special interest.

10.5. Benefit-risk assessment and discussion

10.5.1. Importance of favourable and unfavourable effects

The line extension to add a new formulation for pembrolizumab (MK-3475A) to be administered subcutaneously is based on a single pivotal trial (phase 3 RCT MK-3475A-D77), supported by phase 1/2 data for PK and safety. Pembrolizumab SC is co-formulated with berahyaluronidase alfa, a novel variant of human hyaluronidase used as permeation enhancer. The new formulation would be an alternative to the IV infusion, to be administered SC in 1-2 minutes in the abdomen or thigh by a healthcare professional.

Pembrolizumab exposures after MK-3475A administration were within range of the exposures after pembrolizumab IV administration, demonstrating Non-Inferiority of the new SC formulation compared to the reference IV formulation in study MK-3475A-D77. In the population enrolled in the pivotal study, consisting of 1L NSCLC adult patients with no EGFR/ALK/ROS1 alteration, an approved indication of Keytruda, pembrolizumab SC vs pembrolizumab IV associated with histology selected backbone platinum-based chemotherapy, showed similar efficacy results. ORR and DoR, as well as PFS per RECIST 1.1 by BICR and OS results, were similar between the two treatment arms. While a small but visible crossing of the OS curves around 6 months was observed, no differences beyond 9 months are expected based on updated OS analyses. Clinical efficacy endpoints were not statistically tested. A similar approach, i.e. demonstration of PK NI and descriptive similar efficacy, is consistent with recently approved SC formulations of other anti-PD(L)1 MoAbs.

The safety profile of pembrolizumab SC + chemotherapy was overall similar to the pembrolizumab IV + chemotherapy arm of the pivotal study, and in general consistent with the known toxicity of pembrolizumab monotherapy and chemotherapy. In particular, no immune-related AEs unique to pembrolizumab SC were identified. Compared to the IV formulation, the SC injection can cause in addition local injection-site reactions, which however have been shown to be generally low in frequency and mild in severity, none leading to discontinuation of pembrolizumab.

10.5.2. Balance of benefits and risks

Non-inferiority of the two formulations was concluded, with a consistent safety profile. The benefit-risk balance for the new pembrolizumab SC formulation, as an alternative to the IV formulation for all adult indications for which Keytruda is already approved, is considered positive.

10.6. Benefit-risk conclusions

The B/R for Keytruda new pharmaceutical form, solution for injection, associated with two new strengths (790 mg and 395 mg) and subcutaneous formulation is positive.