Official Protocol Title:	Pembrolizumab Coformulated With Hyaluronidase (MK3475A) Versus Intravenous Pembrolizumab, Administered With Chemotherapy, in the First-line Treatment of Participants With Metastatic Non-small Cell Lung Cancer
NCT number:	NCT05722015
Document Date:	06-FEB-2024

TITLE PAGE

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Protocol 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

Protocol Number: D77-03

Compound Number: MK-3475A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	05722015
EU CT	2022-501506-36
EudraCT	Not Applicable
jRCT	2031230049
WHO	Not Applicable
UTN	Not Applicable
IND	CCI [redacted]

Approval Date: 06 February 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	06-FEB-2024	To add G-CSF as primary prophylaxis during the first 4 platinum-doublet infusions in both arms.
Amendment 2	19-OCT-2023	To update the assumptions and timing of the analyses in the SAP.
Amendment 1	10-Apr-2023	To incorporate revisions based on health authority feedback.
Original Protocol	20-OCT-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

To add G-CSF as primary prophylaxis during the first 4 platinum-doublet infusions in both arms.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.1, Overall Design	Text was added that G-CSF will be received as primary prophylaxis during the first 4 platinum-doublet infusions in both arms.	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis	Number of participants was updated.	The faster screening rate and lower than anticipated screen failure rates resulted in over enrollment of participants.
Section 1.1, Synopsis	Intervention Groups and Duration Table was updated to include G-CSF administration.	Refer to Section 4.1 rationale.
Section 1.2, Schema	Sample size was updated.	Refer to Section 1.1 rationale.
Section 1.3.1, SoA-Screening to Cycle 2	A row was added to Table 1 to require that G-CSF will be administered in both arms. Also, a note was added to refer to Section 6.5.1.2.1 for G-CSF related information.	Refer to Section 4.1 rationale

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.3, SoA-PK and ADA Sample Collection	PK and ADA sample collection tables were updated CCI [redacted] CCI [redacted] update the timepoints for the MK-5180 PK.	Changes were made to characterize CCI [redacted] PK and MK-5180 PK
Section 2.2.6, Information on Other Study-related Therapy	Text was added to refer to Section 6.5.1.2.1 for G-CSF related information.	Refer to Section 4.1 rationale.
Section 6.1., Study Interventions Administered	Filgrastim and pegylated filgrastim (G-CSF) were added to the study interventions table.	Refer to Section 4.1 rationale.
Section 6.5.1.2.1, Colony Stimulating Factors	Text was added to clarify the timing and considerations for G-CSF administration	Refer to Section 4.1 rationale.
Section 8.1.8.4, Chemotherapy Administration	Text was added to refer to Section 6.5.1.2.1 for G-CSF related information.	Refer to Section 4.1 rationale.
CCI [redacted]		
Section 9.1, Statistical Analysis Plan Summary	Sample size and power for PK endpoints were updated.	Refer to Section 1.1 rationale. The prevalences of histology and PDL1 status assumed in the ORR noninferiority test are different in the current study compared to the historical data.
Section 9.7.1, Pharmacokinetics Interim Analysis	Evaluable participants for PK endpoints were updated.	Refer to Section 1.1 rationale.
Section 9.8.1, Cycle 1 $AUC_{0\text{-}6wks}$	Boundaries and characteristics of analyses for Cycle 1 $AUC_{0\text{-}6wks}$ were updated.	Refer to Section 1.1 rationale.
Section 9.8.2, Cycle 3 C_{trough}	Boundaries and characteristics of analyses for Cycle 3 C_{trough} were updated.	Refer to Section 1.1 rationale.
Section 9.9, Sample Size and Power Calculations	To update the sample size and the assumptions in ORR noninferiority test	Refer to Section 9.1 rationale.
Section 10.8, Appendix 8: Synthesis Method for ORR Noninferiority	The assumptions in ORR noninferiority test were updated.	Refer to Section 9.1 rationale.
Throughout the document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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

Short Title: MK-3475A SC vs pembrolizumab IV, administered with chemotherapy, in treatment-naïve metastatic NSCLC

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with treatment-naïve metastatic NSCLC.

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}
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 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 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 timepoint 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)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	First line treatment of participants with metastatic Non-small cell lung cancer
Population	Adult participants with treatment-naïve metastatic non-small cell lung cancer
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. Extension Study in Japan: The Sponsor estimates that the study will require approximately 1 additional year (beyond the global study's last participant last study related contact) from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study related contact.

Number of Participants:

Approximately 378 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1 (nonsquamous and squamous NSCLC)	MK-3475A	165 mg/mL	790 mg	SC	Day 1 of each cycle (Q6W) for 18 cycles; participants may be eligible for Second Course (9 additional cycles)	Test Product
Arm 1 (nonsquamous NSCLC)	Pemetrexed	Per Approved Product Label	500 mg/m²	IV Infusion	Days 1 and 22 of each cycle (Q3W)	Background Treatment
Arm 1 (nonsquamous NSCLC)	Cisplatin	Per Approved Product Label	75 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment
Arm 1 (nonsquamous and squamous NSCLC)	Carboplatin	Per Approved Product Label	AUC 5 for nonsquamous; AUC 6 for squamous	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment
Arm 1 (squamous NSCLC)	Paclitaxel	Per Approved Product Label	200 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment
Arm 1 (squamous NSCLC)	Nab-paclitaxel	Per Approved Product Label	100 mg/m²	IV Infusion	Days 1, 8, 15, 22, 29, and 36 of Cycles 1 and 2	Background Treatment
Arm 2 (nonsquamous and squamous NSCLC)	Pembrolizumab	25 mg/mL	400 mg	IV Infusion	Day 1 of each cycle (Q6W) for 18 cycles; participants may be eligible for Second Course (9 additional cycles)	Comparator
Arm 2 (nonsquamous NSCLC)	Pemetrexed	Per Approved Product Label	500 mg/m²	IV Infusion	Days 1 and 22 of each cycle (Q3W)	Background Treatment
Arm 2 (nonsquamous NSCLC)	Cisplatin	Per Approved Product Label	75 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment
Arm 2 (nonsquamous and squamous NSCLC)	Carboplatin	Per Approved Product Label	AUC 5 for nonsquamous; AUC 6 for squamous	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 2 (squamous NSCLC)	Paclitaxel	Per Approved Product Label	200 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment
Arm 2 (squamous NSCLC)	Nab-paclitaxel	Per Approved Product Label	100 mg/m²	IV Infusion	Days 1, 8, 15, 22, 29, and 36 of Cycles 1 and 2	Background Treatment
Arm 1 and Arm 2 (nonsquamous and squamous NSCLC)	Filgastrim	Per Approved Product Label	Per Approved Product Label	IV Infusion	Days 2 and D23 of cycles 1 and 2.	Background Treatment
Arm 1 and Arm 2 (nonsquamous and squamous NSCLC)	Pegylated Filgastrim	Per Approved Product Label	Per Approved Product Label	IV Infusion	Days 2 and D23 of cycles 1 and 2 (not to be used with Nab-Paclitaxel),	Background Treatment

AUC=area under the curve; IV=intravenous; Q3W=every 3 weeks; Q6W=every 6 weeks; SC=subcutaneous.
For commercially available supplies, the unit dose strength or formulation may vary, depending on market availability. Different formulations are still permitted as indicated.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: pembrolizumab (KEYTRUDA®, MK-3475 or SCH 900475).

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study for approximately 5 years from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening period of up to 28 days, each participant will be receiving assigned study intervention until one of the conditions for study discontinuation is met. After the end of treatment each participant will be followed for 4 years. Participants who complete study intervention after receiving 18 administrations of MK-3475A (Arm 1) or pembrolizumab (Arm 2) and may be eligible for up to 9 additional administrations of MK-3475A or pembrolizumab (approximately 1 year) upon experiencing disease progression. Participants are only eligible to receive additional administrations of the study intervention to which they were originally assigned. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Executive Oversight Committee	Yes
External Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

STUDY ACCEPTS HEALTHY PARTICIPANTS:

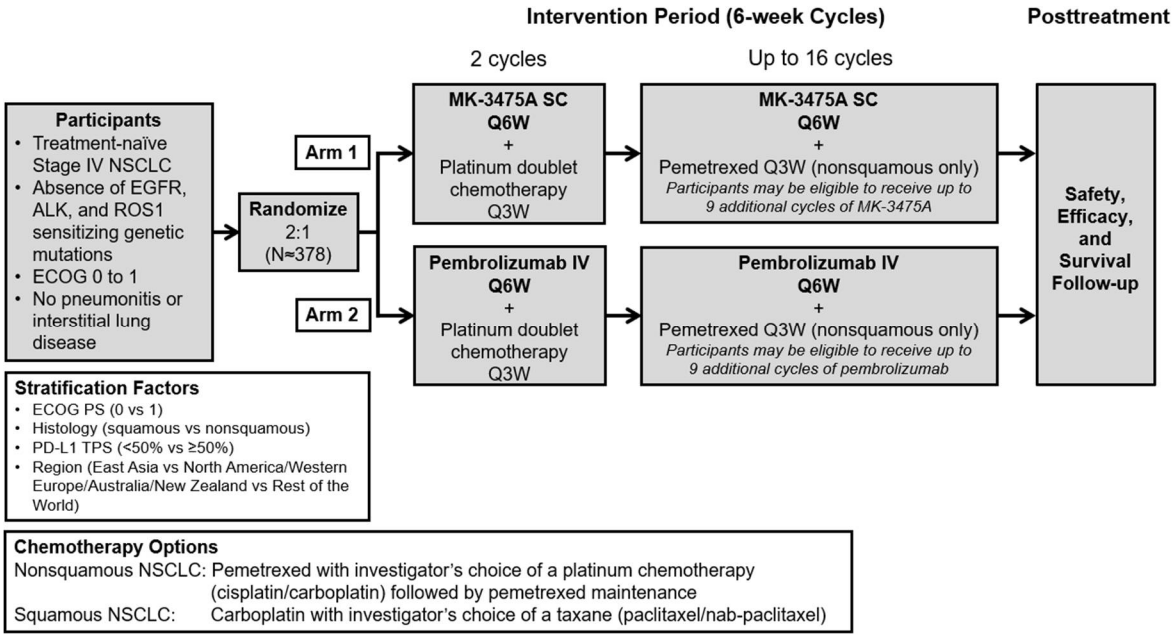
No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 MK-3475A-D77 Study Design



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.

1.3 Schedule of Activities

The SoA is organized as follows:

- Screening to posttreatment (Table 1 and Table 2)
- PK and ADA sample collection (Table 3, Table 4, Table 5 and Table 6)
- Second course retreatment (Table 7)

Details of each procedure outlined in the SoA are provided in Section 8. Unless otherwise indicated, procedures should be performed before study intervention administration. Refer to Appendix 7 for country-specific requirements.

1.3.1 Screening to Cycle 2

Table 1 Screening to Cycle 2

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Administrative Procedures																						
Informed Consent	X																					If the investigator plans to treat beyond disease progression, additional consent is required.
Informed Consent for FBR	X																					This is optional for the participant.
Inclusion/Exclusion Criteria	X																					
Participant Identification Card	X	X																				Add the randomization number at the time of randomization.
Demographics and Medical History	X																					
Tobacco Use Assessment	X																					See Section 8.1.4.1 for definitions of cigarette use.
NSCLC History	X																					
Prior/Concomitant Medication Review	X	X	X				X					X					X					C1D2 is for participants in Arm 1 only.

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Prior/Concomitant Medication Review (Nab-paclitaxel)					X	X				X	X				X	X				X	X	Additional procedures only for participants receiving nab-paclitaxel.
Enrollment Support Consultation Form	X																					Form must be reviewed by Sponsor prior to randomization.
Intervention Randomization		X																				Randomization can occur up to 3 days before C1D1 (start of study intervention)
Vital Status		←																			→	Participants may be contacted for vital status at any time during the study.
Study Intervention Administration																						
MK-3475A SC (Arm 1) **OR** Pembrolizumab IV (Arm 2)		X										X										
Pemetrexed (Nonsquamous)		X					X					X					X					
Cisplatin **OR** Carboplatin (Nonsquamous)		X					X					X					X					
Carboplatin (Squamous)		X					X					X					X					
Paclitaxel (Squamous) **OR**		X					X					X					X					If receiving paclitaxel

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Nab-paclitaxel (Squamous)		X			X	X	X			X	X	X			X	X	X			X	X	If receiving nab-paclitaxel
G-CSF			X					X					X					X				Refer to Section 6.5.1.2.1 for details.
Efficacy Assessments																						Scans should follow calendar days from randomization and should not be adjusted for delays in cycle starts.
Tumor Scan (Chest, Abdomen, and Pelvis)	X	X See note																				Postbaseline scans should be performed at Week 6 (+7 days), Week 12 (±7 days), Week 18 (±7 days), Q9W (±7 days) until Week 45, and then Q12W (±7 days) thereafter until one of the conditions for stopping tumor scans is met.

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Brain Scan	X																					All participants are required to have brain scans at screening. For participants with treated brain metastases at baseline, on-study brain scans will be acquired at Week 6 (+7 days) and then if clinically indicated and to confirm a CR. For participants without brain metastases at baseline, on-study brain scans should be acquired if clinically indicated.

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Bone Scan	X																					Bone scans are required at screening for participants with a history of bone metastases or signs/symptoms suggestive of bone metastases. On-study bone scans should be performed if clinically indicated or to confirm CR when bone metastases existed at baseline.
Patient -reported Outcomes																						
EORTC QLQ-C30		X					X					X					X					Administer in the following order: EORTC QLQ-C30 first, then EQ-5D-5L.
EQ-5D-5L		X					X					X					X					
Safety Assessments																						
Full Physical Examination	X																					
Height	X																					
Weight	X	X					X					X					X					
Directed Physical Examination		X					X					X					X					

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Directed Injection-site Physical Examination (Arm 1)			X																			In addition to the directed injection-site physical examination, participants should report any injection-site AE that occurs at any time during the study. Any potential injection-site AE should be investigated further by the site.
Vital Signs	X	X	X				X					X					X					Temperature, heart rate, respiratory rate, blood pressure. C1D2 is for participants in Arm 1 only.
Vital Signs (Nab-paclitaxel)					X	X				X	X				X	X				X	X	Additional procedures only for participants receiving nab-paclitaxel.
ANC and Platelet Count (Nab-paclitaxel)					X	X				X	X				X	X				X	X	
12-lead ECG	X																					
HIV, Hepatitis B, Hepatitis C Testing	X																					Only perform if required by the local health authority.

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Hematology and Chemistry	X	X					X					X					X					Collect screening samples within 10 days before the start of study intervention. Collect on-treatment samples and review results within 72 hours before Day 1 and Day 22 of each cycle. If screening collection is done within 72 hours before C1D1, do not need to repeat for C1D1.
CrCl	X	X					X					X					X					
CBC (Arms 1 and 2)				X					X					X					X			For Arm 1 Only: For D4 of each cycle, CBCs may be collected between Days 4 to 7.
Urinalysis	X																					Collect screening samples within 10 days before the start of study intervention.
PT or INR and aPTT/PTT	X																					

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Thyroid Function Tests (Total T3 or Free T3, T4 or FT4, TSH)	X											X										Tests must be completed and reviewed within 10 days before start of study intervention. C2D1: Collect samples within 72 hours before study intervention administration; participants may be dosed while results are pending. Total T4 and T3 preferred over FT4 and FT3.
Pregnancy Testing (Urine or Serum)	X	X					X					X					X					POCBP require a negative pregnancy test before the start of study intervention (within 24 hours for urine or within 72 hours for serum). If screening collection is done within 72 hours before C1D1, do not need to repeat for C1D1.

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
ECOG Performance Status	X	X					X					X					X					Evaluate within 7 days before randomization.
AE/SAE Review	←																				→	Report AEs occurring within 30 days after last dose of study intervention. Report SAEs within 90 days after the last dose of study intervention, or 30 days after last dose of study intervention if the participant initiates new anticancer therapy, whichever occurs first.
Pharmacokinetics																						
Anti-pembrolizumab Antibody (ADA/Nab)	See Table 3, Table 4, Table 5 and Table 6 for details																					
Pembrolizumab PK																						

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Biomarkers																						
Archival or Newly Obtained Tissue Collection	X																					Tissue must be submitted to the central laboratory for determination of PD-L1 status before randomization. Tissue will also be used for EGFR, ALK, and ROS1 testing before randomization if this testing was not already completed locally (not required for predominantly squamous histology).
Blood for Genetic Analysis		X																				Collect predose samples from randomized participants only. See Section 8.8.1.

Study Period:	**Screening**	**Intervention (6-Week Cycles)**																				**Notes**
Cycle:	**Screening**	**1**										**2**										
Cycle Day:	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	**1**	**2**	**4**	**8**	**15**	**22**	**23**	**26**	**29**	**36**	
Schedule Window:				**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	**±1**		**±1**	**±1**	**±1**	**±1**		**±3**	**±1**	**±1**	
Blood for ctDNA Analysis		X										X										Collect predose samples on C1D1 and C2D1.

ADA=antidrug antibodies; AE=adverse event; ALK=anaplastic lymphoma kinase; ANC=Absolute neutrophil count; aPTT=activated partial thromboplastin time; C=cycle; CBC=complete blood count; CR=complete response; CrCl=creatinine clearance; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC/Discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30; EQ-5D-5L=EuroQol 5-dimension, 5-level Questionnaire; FBR=future biomedical research; FT4=free thyroxine; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; IV=intravenous; NAB=neutralizing antibody; NSCLC=non-small cell lung cancer; PD L1=programmed cell death ligand 1; PK=pharmacokinetics; POCBP=participant/participants of childbearing potential; PT=prothrombin time; PTT=partial thromboplastin time; QXW=every X weeks; ROS=c-ros oncogene 1; SAE=serious adverse event; SC=subcutaneous; T3=triiodothyronine; TSH= thyroid-stimulating hormone.

1.3.2 Cycle 3 to Posttreatment

Table 2 Cycle 3 to Posttreatment

Study Period:	**Intervention (6-Week Cycles)**							**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**3**			**4 to 18**		**19+**		**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**2**	**22**	**1**	**22**	**1**	**22**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**					
Administrative Procedures												
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X			C3D2 is for participants in Arm 1 only.
Subsequent Antineoplastic Therapy Status								X	X	X	X	
Vital Status	◄										►	Participants may be contacted for vital status at any time during the study.
Study Intervention Administration												
MK-3475A SC (Arm 1) **OR** Pembrolizumab IV (Arm 2)	X			X								
Pemetrexed (Nonsquamous)	X		X	X	X	X	X					Pemetrexed maintenance continues until one of the conditions for discontinuation of study intervention is met.
Efficacy Assessments												Scans should follow calendar days from randomization and should not be adjusted for delays in cycle starts.
Tumor Scan (Chest, Abdomen, and Pelvis)	X See note							X		X		Postbaseline scans should be performed at Week 6 (+7 days), Week 12 (±7 days), Week 18 (±7 days), Q9W (±7 days) until Week 45, and then Q12W (±7 days) thereafter until one of the conditions for stopping tumor scans is met. If a scan was obtained within 4 weeks before treatment DC, a scan at DC is not required.

Study Period:	**Intervention (6-Week Cycles)**							**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**3**			**4 to 18**		**19+**		**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**2**	**22**	**1**	**22**	**1**	**22**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**					
Brain Scan												For participants with brain metastases at baseline, on-study brain scans will be acquired at Week 6 (+7 days) and then if clinically indicated and to confirm a CR. For participants without brain metastases at baseline, on-study brain scans should be acquired if clinically indicated.
Bone Scan												On-study bone scans should be performed if clinically indicated or to confirm CR when bone metastases existed at baseline.
Patient-reported Outcomes												
EORTC QLQ-C30	X		X	X See note				X	X			Administer on D1 and D22 of cycles 3 and 4, and D1 of Cycles 5 to 9. In Years 2 and 3, administer PROs every 2 cycles (C10D1, C12D1, etc.) until discontinuation. From Cycle 27 (after Year 3), PROs will not be collected for participants receiving study intervention until the discontinuation visit. Administer in the following order: EORTC QLQ-C30 first, then EQ-5D-5L.
EQ-5D-5L	X		X	X See note				X	X			
Safety Assessments												
Full Physical Examination								X				
Weight	X		X	X	X	X	X	X	X			
Directed Physical Examination	X		X	X	X	X	X		X			

Study Period:	**Intervention (6-Week Cycles)**							**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**3**			**4 to 18**		**19+**		**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**2**	**22**	**1**	**22**	**1**	**22**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**					
Directed Injection-site Physical Examination (Arm 1)	X	X										On C3D1, examination of the injection site should be performed as part of the directed physical examination. In addition to the directed injection-site physical examination, participants should report any injection-site AE that occurs at any time during the study. Any potential injection-site AE should be investigated further by the site.
Vital Signs	X	X	X	X	X	X	X	X	X			Temperature, heart rate, respiratory rate, blood pressure. C3D2 is for participants in Arm 1 only.
Hematology and Chemistry	X		X	X	X	X	X	X	X			Collect on-treatment samples and review results within 72 hours before Day 1 and Day 22 of each cycle.
CrCl	X		X	X	X	X	X	X	X			
Urinalysis									X			
Thyroid Function Tests (Total T3 or Free T3, T4 or FT4, TSH)	X			X				X	X			Collect samples within 72 hours before study intervention administration; participants may be dosed while results are pending. Total T4 and T3 preferred over FT4 and FT3.
Pregnancy Testing (Urine or Serum)	X		X	X	X	X	X	X	X			Pregnancy testing should be conducted at the end of relevant systemic exposure (see Section 8.3.5).
ECOG Performance Status	X		X	X	X	X	X	X	X	X		

Study Period:	**Intervention (6-Week Cycles)**							**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**3**			**4 to 18**		**19+**		**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**2**	**22**	**1**	**22**	**1**	**22**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**					
AE/SAE Review	◄———						———►		X	X		Report AEs occurring within 30 days after last dose of study intervention. Report SAEs within 90 days after the last dose of study intervention, or 30 days after last dose of study intervention if the participant initiates new anticancer therapy, whichever occurs first.
Pharmacokinetics												
Anti-pembrolizumab Antibody (ADA/Nab)	See Table 3, Table 4, Table 5 and Table 6 for details											
Pembrolizumab PK												
Biomarkers												
Blood for ctDNA Analysis				X See note				X				Collect predose samples on C4D1, C7D1, and EOT.

ADA=antidrug antibodies; AE=adverse event; C=cycle; CR=complete response; CrCl=creatinine clearance; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC/Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30; EQ-5D-5L=EuroQol 5-dimension, 5-level Questionnaire; FBR=future biomedical research; FT4=free thyroxine; IV=intravenous; NAB=neutralizing antibody; PK=pharmacokinetics; QXW=every X weeks; SAE=serious adverse event; SC=subcutaneous; T3=triiodothyronine; T4=thyroxine; TSH= thyroid-stimulating hormone.

1.3.3 PK and ADA Sample Collection

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Study Period	Intervention (6-week cycles)													Notes
	Predose	End of infusion	Postdose											
Cycle	**1**													
Cycle Day	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**15**	**29**	**42**	
Schedule Window										**±1**	**±2**	**±3**	**±1**	CCI [redacted]
Serum for Anti-pembrolizumab Antibody (ADA/Nab)	X												X	
Arm 1 (SC): Serum for Pembrolizumab PK	X			X	X	X	X	X	X	X	X	X	X	
Arm 2 (IV): Serum for Pembrolizumab PK	X	X				X					X	X	X	
Arm 1 (SC): Serum for Anti-MK-5180 Antibody (ADA)	X												X	
Arm 1 (SC): Plasma for MK-5180 PK	X		X CCI [redacted]	X									X	
ADA=antidrug antibodies; C=cycle; D=day; IV=intravenous; Nab=neutralizing antibody; PK=pharmacokinetics; QXW=every X weeks; SC=subcutaneous.														


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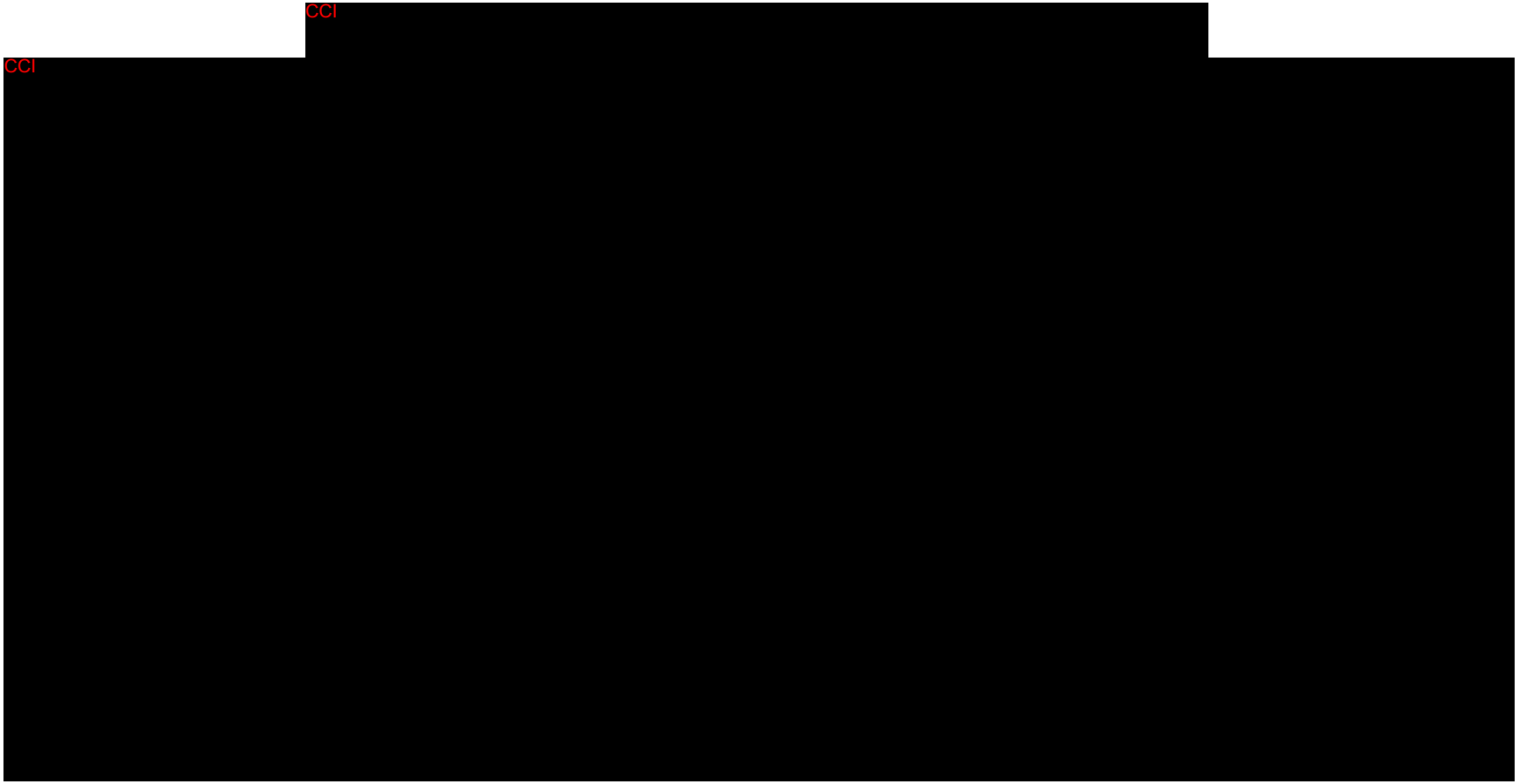
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Study Intervention	**Intervention (6-week Cycles)**										**Notes**
Cycle	**3**							**6 to 18**			
Cycle Day:	**Predose**	**End of Infusion**	**Postdose**					**Predose**	**Postdose**		
	1	**1**	**1**	**2**	**4**	**10**	**42**	**1**	**1**	**2**	
Schedule Window					**±2**	**±2**	**±1**	**±3**			
Serum for Anti-pembrolizumab Antibody (ADA/Nab)	X						X	X CCI			CCI
Arm 1 (SC): Serum for Pembrolizumab PK	X				X	X	X	X CCI			
Arm 2 (IV): Serum for Pembrolizumab PK	X	X			X		X	X CCI			
Arm 1 (SC): Serum for Anti-MK-5180 Antibody (ADA)	X										
Arm 1 (SC): Plasma for MK-5180 PK	X		X CCI	X				X CCI	X CCI	X	

ADA=antidrug antibodies; C=cycle; D=day; IV=intravenous; Nab= neutralizing antibodies; PK=pharmacokinetics; QXW=every X weeks; SC=subcutaneous

1.3.4 Second Course Retreatment

Table 7 Second Course Retreatment

Study Period:	**Intervention (6-Week Cycles)**			**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**1**	**2**	**3 to 9**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**1**	**1**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±3**	**±3**	**±3**					
Administrative Procedures								
Eligibility Criteria	X							
Concomitant Medication Review	X	X	X	X	X			
Subsequent Antineoplastic Therapy Status				X	X	X	X	
Vital Status	◄					►	X	Participants may be contacted for vital status at any time during the study.
Study Intervention Administration								
MK-3475A SC (Arm 1) **OR** Pembrolizumab IV (Arm 2)	X	X	X					Participants are to receive MK-3475A SC or pembrolizumab IV based on the Arm to which they were initially randomized.
Efficacy Assessments								Scans should follow calendar days and should not be adjusted for delays in cycle starts.
Tumor Scan (Chest, Abdomen, and Pelvis)	X See note			X		X		Second Course baseline images are to be captured within 28 days before Second Course C1D1. Scans should be performed Q12W (±7 days) from Second Course C1D1 (Weeks 12, 24, 36, and 48). If a scan was obtained within 4 weeks before treatment DC, a scan at DC is not required.
Brain Scan	X							For participants with brain metastases at baseline or before entering Second Course, perform baseline brain scans within 28 days before Second Course C1. Brain scans during Second Course to be performed as clinically indicated.
Safety Assessments								
Full Physical Examination	X			X				
Weight	X	X	X	X	X			

Study Period:	**Intervention (6-Week Cycles)**			**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**1**	**2**	**3 to 9**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**1**	**1**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±3**	**±3**	**±3**					
Directed Physical Examination		X	X		X			Participants in Arm 1 should report any injection-site AE that occurs at any time during the study. Any potential injection-site AE should be investigated further by the site.
Vital Signs	X	X	X	X	X			Temperature, heart rate, respiratory rate, blood pressure.
12-lead ECG	X							
Hematology and Chemistry	X	X	X	X	X			Collect baseline samples within 10 days before Second Course C1. After Second Course C1, samples to be collected and results reviewed within 72 hours before administration of study intervention in each cycle.
CrCl	X	X	X	X	X			
Urinalysis	X				X			Collect baseline samples within 10 days before Second Course C1.
PT or INR and aPTT/PTT	X							
Thyroid Function Tests (Total T3 or Free T3, FT4, TSH)	X	X	X	X	X			Tests must be completed and reviewed within 10 days before Second Course C1. For Second Course C2 and on, collect samples within 72 hours before study intervention administration; participants may be dosed while results are pending.
Pregnancy Testing (Urine or Serum)	X	X	X	X	X			POCBP require a negative pregnancy test before the start of study intervention (within 24 hours for urine or within 72 hours for serum) before Second Course C1. At home pregnancy testing should be conducted midcycle (Day 22 ±3 days of each treatment cycle) during the intervention period. Pregnancy testing should be conducted at the end of relevant systemic exposure (see Section 8.3.5).

Study Period:	**Intervention (6-Week Cycles)**			**End-of-Treatment**	**Posttreatment**			**Notes**
Cycle:	**1**	**2**	**3 to 9**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	**1**	**1**	**1**	**At time of discon**	**30 days after last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	If DC visit occurs ≥30 days from the last dose of study intervention, a Safety Follow-up is not required.
Schedule Window:	**±3**	**±3**	**±3**					
ECOG Performance Status	X	X	X	X	X	X		Perform within 7 days before Second Course C1. To be assessed before dosing at each cycle.
AE/SAE Review	◄———		———►		X	X		Report AEs occurring within 30 days after last dose of study intervention. Report SAEs within 90 days after the last dose of study intervention, or 30 days after last dose of study intervention if the participant initiates new anticancer therapy, whichever occurs first.

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; DC/Discon=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FT4=free thyroxine; IV=intravenous; POCBP=participant/participants of childbearing potential; PT=prothrombin time; PTT=partial thromboplastin time; QXW=every X weeks; SAE=serious adverse event; SC=subcutaneous; T3=triiodothyronine; TSH= thyroid-stimulating hormone.

2 INTRODUCTION

This is a Phase 3 study evaluating the noninferiority of PK exposure between MK-3475A SC and pembrolizumab IV, both administered in combination with platinum doublet chemotherapy, in participants with treatment-naïve metastatic NSCLC.

2.1 Study Rationale

KEYTRUDA® (MK-3475, pembrolizumab) is approved globally for the treatment of patients across multiple indications. The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W administered by IV infusion. SC formulations of pembrolizumab are being developed to provide an alternative route of administration with the potential for increased accessibility. Benefits of SC administration include time savings for patients and providers, convenience, reduced administration costs, ease of administration, and reduced health care resource burden. SC administration will also reduce patient chair time, making it feasible for infusion centers to treat more patients.

MK-3475A is a coformulation of pembrolizumab with MK-5180, a novel hyaluronidase that increases the volume of SC pembrolizumab delivery and enhances its dispersion. This study will evaluate the noninferiority of PK exposure between MK-3475A SC and pembrolizumab IV, both administered Q6W. MK-3475A or pembrolizumab will be administered in combination with platinum doublet chemotherapy in participants with treatment-naïve metastatic NSCLC.

2.2 Background

2.2.1 Subcutaneous Formulation

There is a strong patient preference for therapeutics to be administered by SC injection over IV infusion. In an open-label, randomized study of the preference for SC or IV administration of trastuzumab, 91.5% of participants preferred SC administration (95% CI: 87.2 to 94.7; $p<0.0001$) [Pivot, X., et al 2013]. The 2 most common reasons for this preference were because SC administration saved time and resulted in less pain or discomfort. Healthcare professionals also preferred SC administration of trastuzumab; of 103 healthcare professionals, 73.8% preferred SC, 1.9% preferred IV, and 24.3% had no preference [Pivot, X., et al 2013]. Similar results were reported from a study evaluating the preference for SC or IV administration of rituximab [Rummel, M., et al 2017].

An SC formulation of pembrolizumab has been developed to provide an alternative route of administration with the potential for increased accessibility. Clinical data from Cohort A of Study KEYNOTE-555 CCI [redacted] CCI which is consistent with the bioavailability reported for other SC administered mAbs (range: 50% to 85%). Clearance was the same for SC and IV formulations and no positive ADA were observed. Preliminary safety data from the first 3 cycles of treatment revealed no new safety signals. Injection-site data gathered from participant questionnaires as well as reported drug-

related skin and SC tissue disorder AEs indicate a low frequency of primarily mild pruritus, rash, or redness.

Phase 3 study KEYNOTE-A86 is evaluating noninferiority of PK exposure between pembrolizumab SC and IV administration. Participants with treatment-naïve metastatic NSCLC are randomly assigned in a 2:1 ratio to study intervention Arm A (pembrolizumab SC Q3W with chemotherapy) or Arm B (pembrolizumab IV Q3W with chemotherapy). The dual primary endpoints of Cycle 1 $AUC_{0\text{-}3wks}$ and Cycle 6 C_{trough} enable characterization of pembrolizumab exposure.

Both KEYNOTE-555 and KEYNOTE-A86 are evaluating SC pembrolizumab as a single entity for Q3W dosing. One constraint of SC administration without a hyaluronidase is the skin's resistance to bulk fluid flow that limits drug delivery and dispersion and makes Q6W dosing infeasible for SC pembrolizumab as a single entity. MK-3475A, a coformulation of pembrolizumab with a novel hyaluronidase (MK-5180), is being developed to increase the volume of SC pembrolizumab delivery and enhance its dispersion. Hyaluronidase products have been used clinically for more than 70 years to facilitate the distribution of coadministered drugs by temporarily breaking down local connective tissue [Wohlrab, J., et al 2014]. The Q6W dosing regimen of MK-3475A SC is being evaluated in Phase 1 study MK-3475A-C18 and this Phase 3 study, MK-3475A-D77.

MK-3475A-C18 is a FIH, Phase 1 study to evaluate the PK, safety, and tolerability of MK-3475A administered by SC injection to participants with unresectable, advanced melanoma, metastatic NSCLC, or advanced or metastatic RCC. A primary objective of MK-3475A-C18 is to establish the bioavailability of pembrolizumab when administered subcutaneously at a solution strength of 165 mg/mL or 130 mg/mL, coformulated with MK-5180, as MK-3475A. The 2 solution strengths of MK-3475A have different viscosities, so pembrolizumab bioavailability will be assessed at each solution strength in 2 study arms. These data inform a PK model used to conduct simulations and select an optimal SC Q6W dose of pembrolizumab in MK-3475A. The selected pembrolizumab SC dose will have exposures comparable to the approved 400 mg Q6W dose of pembrolizumab IV (see Section 4.3.1).

Pembrolizumab serum concentration data available from 81 participants collected during Cycle 1 (ie, Weeks 1 to 6; MK-3475A SC administration) and Cycle 2 (ie, Weeks 7 to 12; pembrolizumab IV administration) across both study arms of MK-3475A-C18, along with extensive historical pembrolizumab IV PK data, were used to characterize the PK of SC pembrolizumab given as MK-3475A using population PK modeling. The analysis showed that pembrolizumab combined with hyaluronidase when administered SC as MK-3475A had an estimated bioavailability of 57% (range: 38% to 75%). Median time to achieve maximum pembrolizumab serum concentration was estimated to be 4 days (range: 2 to 35 days). The 2 SC solution strengths of pembrolizumab (165 mg/mL and 130 mg/mL) had similar absorption PK when administered as MK-3475A. As of 22-JUN-2022, ADA were observed in 1 of 83 participants (<2%). A preliminary review of systemic safety data from MK-3475A-C18 revealed no new safety signals. All local injection-site reactions were nonserious, mostly mild (Grade 1), and effectively managed.

2.2.2 Non-small Cell Lung Cancer

The global incidence of lung cancer was 2.2 million cases in 2020, resulting in an estimated 1.8 million deaths, representing the second most frequently diagnosed cancer and the leading cause of cancer death in 2020 [Sung, H., et al 2021]. NSCLC represents approximately 85% of all lung cancers [National Cancer Institute 2020]. Of patients with NSCLC, tumor histology is approximately 46% adenocarcinoma, 16% squamous, and most of the remainder "not otherwise specified" [Sulpher, J. A., et al 2013], though histology varies somewhat by geographic region. At the time of diagnosis, approximately 80% of patients in the US with lung cancer have locally advanced or metastatic disease that is not amenable to surgical resection, and the 5-year relative survival for patients with metastatic lung cancer is only approximately 7% [National Cancer Institute 2022].

The therapeutic landscape in metastatic NSCLC was dramatically changed with approvals of immunotherapy agents, particularly immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway (pembrolizumab, nivolumab, and atezolizumab) for both treatment-naïve and previously treated disease, irrespective of histology. KEYNOTE-024 and KEYNOTE-042 established pembrolizumab monotherapy as first-line therapy for participants with metastatic NSCLC whose tumors express PD-L1 with a TPS ≥50% (EU) or TPS ≥1% (in US and other countries), respectively, with no *EGFR* or *ALK* genomic tumor aberrations [Reck, M., et al 2021] [Mok, T. S. K., et al 2019].

Following this, the positive results from KEYNOTE-189 and KEYNOTE-407 led to the approval of pembrolizumab in combination with pemetrexed and platinum chemotherapy for first-line treatment of patients with metastatic nonsquamous NSCLC whose tumors have no *EGFR* or *ALK* genomic tumor aberrations, and pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for first-line treatment of patients with metastatic squamous NSCLC, regardless of PD-L1 status [Rodriguez-Abreu, D., et al 2021] [Gandhi, L., et al 2018] [Paz-Ares, L., et al 2018]. Other options for treatment in first-line NSCLC for patients without actionable genomic alteration include other immune checkpoint inhibitor regimens such as nivolumab and ipilimumab ± chemotherapy and atezolizumab ± chemotherapy (with or without bevacizumab).

2.2.3 Pharmaceutical and Therapeutic Background

MK-3475A is a SC drug product of pembrolizumab and 2000 U/mL MK-5180 (recombinant human hyaluronidase) being developed to enhance the permeation of SC pembrolizumab.

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV or SC immunotherapy for multiple malignancies.

Hyaluronan (also known as hyaluronic acid) is key to creating the skin resistance that limits SC dispersion and absorption of drugs [Frost, G. I. 2007]. Hyaluronidases increase tissue permeability by degrading glycosaminoglycan hyaluronan [Wohlrab, J., et al 2014]. When

administered SC, hyaluronidase results in a temporary breakdown of local connective tissue, increasing the dispersion and absorption of drugs and fluids. After injection, hyaluronic acid is regenerated and the barrier is restored within 48 hours.

There are ovine, bovine, and human recombinant hyaluronidase drug products that have received regulatory approval as adjuvants or permeation enhancers to increase the dispersion and absorption of drugs injected SC. Several IV administered oncology products have introduced hyaluronidase into formulations with mAbs to allow SC injection. Products such as trastuzumab (Genentech), rituximab (Roche), daratumumab (Janssen), and pertuzumab/trastuzumab (Genentech) have been approved in the EU and US as formulations with hyaluronidase. These products, trastuzumab and hyaluronidase (Genentech), rituximab and hyaluronidase (Genentech), daratumumab and hyaluronidase (Janssen), and pertuzumab, trastuzumab, and hyaluronidase (Genentech), use from 10,000 U to 30,000 U of hyaluronidase injected SC over 2 to 8 minutes. The SC images of these drug products have been approved for some of the same indications as their respective IV images.

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Refer to the respective IBs for additional background information about MK-3475A and pembrolizumab.

2.2.4 Preclinical and Clinical Studies

The nonclinical development program for MK-3475A relies on previously conducted studies in support of pembrolizumab, supplemented with studies related to MK-5180 or the SC drug product, MK-3475A.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

2.2.5 Ongoing Clinical Studies

Refer to the respective IBs for a summary of ongoing clinical studies for MK-3475A and pembrolizumab.

2.2.6 Information on Other Study-related Therapy

Pemetrexed, carboplatin, cisplatin, paclitaxel and/or nab-paclitaxel are standard of care therapies for the treatment of patients with NSCLC. Refer to the product labels for additional information.

Refer to Section 6.5.1.2.1 or information on G-CSF.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

MK-3475A may provide important benefits such as improved patient convenience and compliance with therapy. This product may also provide an alternative SC dosage form of pembrolizumab that could facilitate the delivery of a larger volume of drug and result in less discomfort to the patient and increased tolerability of the injection. It is expected that pembrolizumab delivered by SC administration will maintain a favorable benefit-risk profile comparable to that of IV administration.

In NSCLC, the safety profile of pembrolizumab in combination with chemotherapy is generally consistent with the known safety profile of pembrolizumab monotherapy and the combination regimens administered. Further, the combination of pembrolizumab and platinum doublet chemotherapy is approved for the first-line treatment of patients with metastatic NSCLC [Rodriguez-Abreu, D., et al 2021] [Gandhi, L., et al 2018] [Paz-Ares, L., et al 2018].

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with treatment-naïve metastatic NSCLC.

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}
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 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 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 timepoint 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)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

This study will have met its success criterion if MK-3475A SC is noninferior to pembrolizumab IV at Q6W dosing regimens with respect to Cycle 1 AUC or steady-state (Cycle 3) C_{trough}.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multisite, open-label study of MK-3475A SC and platinum doublet chemotherapy versus pembrolizumab IV and platinum doublet chemotherapy in participants with treatment-naïve metastatic NSCLC. Participants must have newly diagnosed, untreated Stage IV NSCLC, and ECOG PS of 0 to 1.

After a screening period of up to 28 days, participants will be randomly assigned in a 2:1 ratio to Arm 1 or Arm 2. One cycle is 6 weeks.

- Arm 1: MK-3475A SC Q6W for up to 18 cycles in combination with platinum doublet chemotherapy.

- Arm 2: Pembrolizumab IV Q6W for up to 18 cycles in combination with platinum doublet chemotherapy.

- Platinum doublet chemotherapy.

    - Nonsquamous NSCLC: Up to 4 infusions of pemetrexed Q3W with investigator's choice of a platinum chemotherapy (cisplatin Q3W or carboplatin Q3W), followed by pemetrexed maintenance until one of the conditions for discontinuation of study intervention is met.
    - Squamous NSCLC: Up to 4 infusions of carboplatin Q3W with investigator's choice of a taxane (paclitaxel Q3W or nab-paclitaxel [Days 1, 8, 15, 22, 29, and 36 of Cycles 1 and 2]).

Randomization will be stratified by ECOG performance status, histology, PD-L1 TPS, and region. Each participant will receive study intervention until one of the conditions for discontinuation of study intervention is met (Section 7.1).

The dual primary objectives of the study are to compare Cycle 1 $AUC_{0\text{-}6wks}$ and steady-state (Cycle 3) C_{trough} for MK-3475A SC vs pembrolizumab IV at Q6W dosing regimens. Noninferiority will be evaluated with the noninferiority margin of 0.8. Tumor response will be evaluated per an adjustment to RECIST 1.1 (Section 8.2.1). Safety assessments are detailed in Section 8. AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in NCI CTCAE Version 5.0.

Participants are not permitted to crossover to the other study intervention arm.

Participants who complete study intervention after receiving 18 cycles of MK-3475A or pembrolizumab may be eligible for up to 9 additional cycles of MK-3475A (if on Arm 1) or pembrolizumab (if on Arm 2) (approximately 1 year) upon experiencing BICR-verified disease progression (Section 6.1.2).

After the end-of-treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. Participants who discontinue for reasons other than centrally-verified radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met (Section 8.2.1.3). All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

After enrollment of the global study has completed, participants in Japan will continue to be enrolled and randomized in a 2:1 ratio in Arms 1 and 2 until the sample size for the Japanese participants reaches approximately 39. The extension study will be identical to the global study (eg, open-label, with identical inclusion and exclusion criteria, and study procedures), with the exception of an additional sSAP for participants enrolled in Japan. Details of the analysis will be provided in the separate Japan-specific sSAP document.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Pembrolizumab IV in combination with platinum doublet chemotherapy is indicated for the first-line treatment of patients with metastatic NSCLC. MK-3475A SC is a coformulation of pembrolizumab with MK-5180 that is being developed to provide an alternative route of administration with potential benefits for patients. This study will primarily compare pembrolizumab exposures between MK-3475A SC (Arm 1) and pembrolizumab IV (Arm 2) over Q6W dosing regimens, both in combination with chemotherapy, in participants with treatment-naïve metastatic NSCLC.

Additional descriptive comparisons of pembrolizumab C_{trough} between MK-3475A and pembrolizumab 200 mg IV Q3W will also be made using model-based exposures. Note that there is no arm in the study with the pembrolizumab 200 mg IV Q3W regimen; the C_{trough} exposure outcomes for this dosing regimen will be only based on a PK model.

Randomization will be stratified by the following 4 factors, which all have the potential to influence efficacy outcomes, to ensure an approximately equal allocation of participants across the 2 arms.

1. ECOG performance status (0 vs 1): ECOG performance status affects survival and is a known prognostic factor in NSCLC [Dall'Olio, F. G., et al 2020].
2. Histology (squamous vs nonsquamous): CCI [redacted] CCI

3. PD-L1 TPS (<50% vs ≥50%): Tumor expression of PD-L1 is associated with clinical benefit from pembrolizumab in participants with NSCLC. Exploratory analyses from KEYNOTE-042, KEYNOTE-189, and KEYNOTE-407 show trends in improved efficacy outcomes with increased PD-L1 TPS expression (PD-L1 TPS ≥50%) [Mok, T. S. K., et al 2019a] [Gandhi, L., et al 2018] [Paz-Ares, L., et al 2018a].

4. Stratification by geographic region (East Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World) is to ensure an approximately equal allocation of participants from these regions across the treatment arms.

4.2.1 Rationale for Endpoints

4.2.1.1 Pharmacokinetic Endpoints

The dual primary endpoints of Cycle 1 $AUC_{0\text{-}6wks}$ and steady-state (Cycle 3) C_{trough} will be used to compare pembrolizumab exposures between MK-3475A SC and pembrolizumab IV Q6W.

Cycle 1 $AUC_{0\text{-}6wks}$ is the most conservative PK value to ensure noninferiority of SC exposure relative to IV. Any differences in exposure between SC and IV administrations of pembrolizumab should reduce after multiple dosing due to accumulation. Therefore, demonstrating noninferiority of SC AUC exposure at Cycle 1 will imply noninferiority at steady-state as well. The higher AUC exposure at steady-state following SC dosing is not expected to exceed the established clinical safety margin for pembrolizumab (ie, exposure at 10 mg/kg Q2W IV).

Steady-state (Cycle 3) C_{trough} is the concentration at the end of the 6-week dosing interval after the third dose, which is steady state for pembrolizumab. Because the pharmacological activity of mAbs is mediated through direct interaction with a specific target, target saturation can be used as a surrogate for maximal pharmacologic and therapeutic activity. Pembrolizumab exposures at the approved IV doses are expected to maintain PD-1 target saturation throughout the dosing interval and thereby efficacy. Therefore, C_{trough} for the approved IV dose of 400 mg Q6W can be considered a threshold above which target saturation and efficacy will be maintained. Demonstration of noninferiority of pembrolizumab steady-state (Cycle 3) C_{trough} for MK-3475A SC would enable the inference that efficacy similar to pembrolizumab IV dosing will be maintained.

The secondary PK endpoints will enable further characterization of pembrolizumab exposure:

- For comparison with pembrolizumab IV Q6W:
  - Cycle 1: C_{max} and C_{trough}
  - Steady state (Cycle 3): $AUC_{0\text{-}6wks}$ and C_{max}
- For comparison with pembrolizumab IV Q3W:
  - Model-based C_{trough} at Cycle 1 and steady state

4.2.1.2 Antidrug Antibodies

Formation of ADA can potentially confound drug exposures at therapeutic doses and prime for subsequent toxicities. The emergence of pembrolizumab ADA will be evaluated as a secondary endpoint to assess pembrolizumab immunogenicity after SC administration of MK-3475A.

4.2.1.3 Efficacy Endpoints

Secondary efficacy endpoints include OS and ORR, PFS, and DOR based on RECIST 1.1 criteria as assessed by BICR. These are commonly accepted endpoints by both regulatory authorities and the oncology community.

4.2.1.3.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

4.2.1.4 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version [5.0].

4.2.1.5 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated via the following assessment tools: EORTC QLQ-C30 and EQ-5D-5L questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.5.1 EORTC QLQ-C30

EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing HRQoL in oncology studies [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a

higher value indicates increased severity of symptoms. TTD and mean change from baseline in global health status or QoL scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

4.2.1.5.2 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.6 CCI

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Germline genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations.

Genetic (DNA) tumor analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify important tumor-specific DNA changes (eg, mutations, methylation status, microsatellite instability, etc). Key molecular changes of interest to oncology drug development may also include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (eg, colorectal cancer). Genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that might correlate to clinical response to treatment with antitumor therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Expression of individual genes may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling. Circulating tumor RNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Immunohistochemical (IHC) and/or proteomic analyses using tumor

Tumor samples from this study may undergo histopathological (eg, PD-L1 IHC), proteomic, and/or immunological analyses. These approaches could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other biomarkers

In addition to expression on the tumor tissue, tumor-derived proteins can be shed from tumor and released into the blood. Assays such as ELISA may be used to measure such proteins in serum and/or plasma. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers.

Other molecular changes of interest may include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated. Furthermore, when applicable, cell populations may be also separated by either flow cytometry or mass cytometry-based sorting. These approaches may be used to quantify cell- and/or tissue-based analytes to further elucidate mechanism of action and/or assess disease-related parameters.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

All participants will receive pembrolizumab administered with platinum doublet chemotherapy based on histology.

The use of pembrolizumab IV as an active comparator ensures that participants receive the current approved formulation in the control arm. The PK exposures of MK-3475A SC will be compared to pembrolizumab IV.

To reduce participant and site burden, the different routes of administration will not be masked; therefore, this is an unblinded, open-label study.

4.3 Justification for Dose

4.3.1 MK-3475A Subcutaneous Dose

Available PK data from the FIH, Phase 1 study of MK-3475A, 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.

PK model-based simulations indicate that a pembrolizumab SC dose of 790 mg Q6W leads to comparable exposures as the approved pembrolizumab IV dose of 400 mg Q6W. The mean PK profiles comparing 790 mg Q6W SC and 400 mg Q6W IV doses are presented in Figure 5. In principle, similar PK exposures lead to similar efficacy and safety of pembrolizumab, given that the exposure-response relationships for both efficacy and safety are well established for pembrolizumab.

Efficacy is expected to be retained with SC pembrolizumab at the dose of 790 mg Q6W based on the following:

- C_{trough} at a 790 mg Q6W SC dose is expected to be approximately 30% higher than 400 mg Q6W IV throughout the treatment duration. Moreover, the distributions of C_{trough} overlap between SC and IV at both Cycle 1 and steady state (Figure 2).

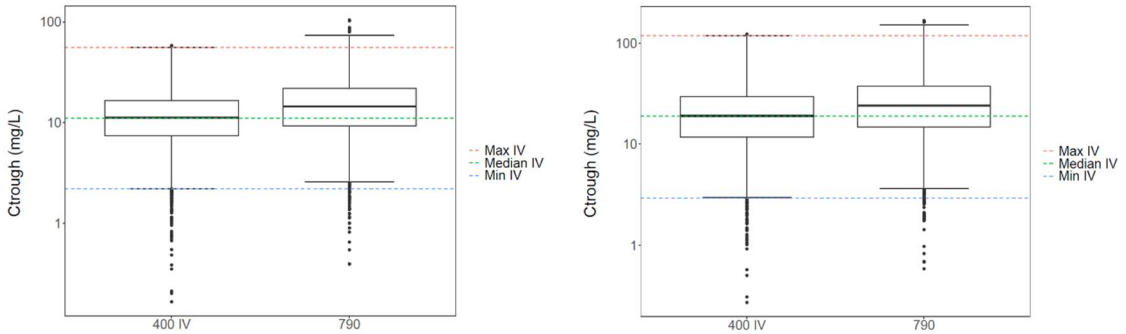
- $AUC_{0\text{-}6wks}$ exposure at a 790 mg Q6W SC dose is expected to be approximately 10% higher than 400 mg Q6W IV throughout the treatment duration. Moreover, the distributions of $AUC_{0\text{-}6wks}$ overlap between SC and IV at both Cycle 1 and steady state (Figure 3).

Safety is expected to be maintained with SC pembrolizumab at the dose of 790 mg Q6W based on the following:

- C_{max} is expected to be lower (by approximately 35% at Cycle 1 and approximately 22% at steady state) than the C_{max} achieved at 400 mg Q6W IV (Figure 4). Therefore, there is no increase in C_{max} expected throughout the duration of treatment relative to the approved dose of 400 mg Q3W IV.

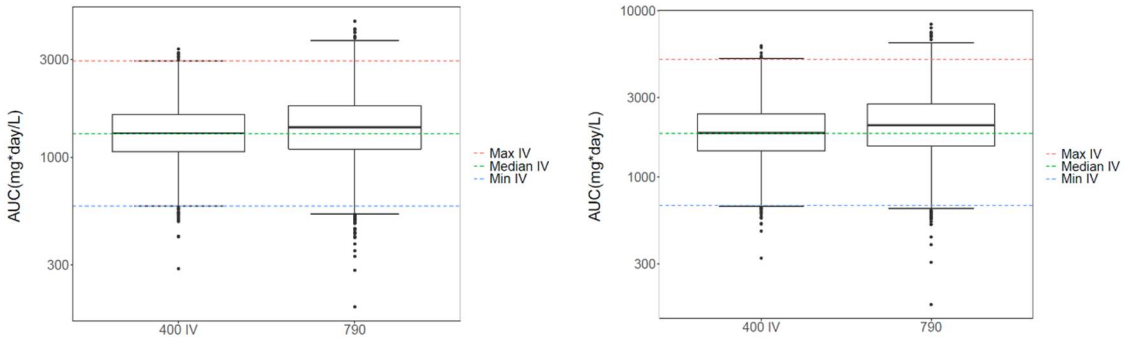
- All SC exposures (C_{max}, C_{avg}, C_{trough}) over the dosing interval of 6 weeks and throughout the duration of treatment are expected to remain below the C_{max} and initial concentrations of 400 mg Q6W IV and well below the highest dose and exposures established for clinical safety (ie, 10 mg/kg Q2W).

Figure 2 Distribution of C_{trough} at Cycle 1 and Steady State Using PK Model-based Simulations at a Dose of 790 mg Q6W SC and 400 mg Q6W IV of Pembrolizumab



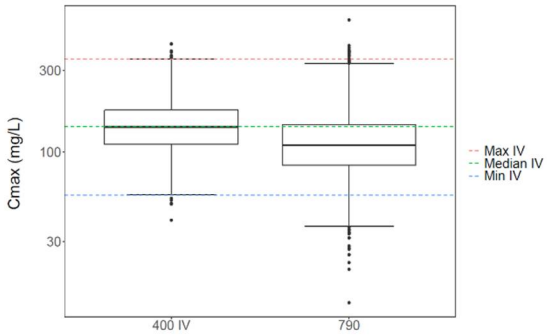
C_{trough}=trough concentration; IV=intravenous

Figure 3 Distribution of $AUC_{0\text{-}6wks}$ at Cycle 1 and Steady State Using PK Model-based Simulations at a Dose of 790 mg Q6W SC and 400 mg Q6W IV of Pembrolizumab



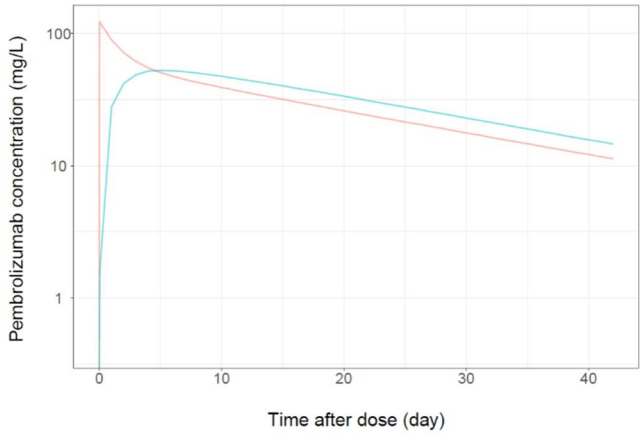
AUC=area under the curve; IV=intravenous

Figure 4 Distribution of C_{max} at Steady State Using PK Model-based Simulations at a Dose of 790 mg Q6W SC and 400 mg Q6W IV of Pembrolizumab



C_{max}=maximum concentration; IV=intravenous

Figure 5 Mean Cycle 1 PK Profile From Model-based Simulations at a Dose of 790 mg Q6W SC (Blue Line) and 400 mg Q6W IV (Red Line) of Pembrolizumab



MK-3475A also includes MK-5180 at a 2000 U/mL concentration to maintain consistency with marketed mAbs formulated with hyaluronidase. Rituximab and hyaluronidase (Genentech), trastuzumab and hyaluronidase (Genentech), and daratumumab and hyaluronidase (Janssen) all contain 2000 U/mL of hyaluronidase. The enzyme activity of MK-5180 in the dose concentration is comparable to the marketed rHuPH20 from Halozyme Therapeutics present in these other products. Limited existing clinical data also indicate no specific benefit on bioavailability by increasing the concentration of hyaluronidase. Study MK-3475A-C18 will provide data on the safety of MK-5180 being used as part of MK-3475A.

4.3.2 Pembrolizumab Intravenous Dose

The planned dose of pembrolizumab for this study is 400 mg Q6W.

The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

PK simulations demonstrating that in terms of pembrolizumab exposures:

- C_{avg} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.

- Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- E-R for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

Efficacy, safety, and PK data from KEYNOTE-555 Cohort B continue to support the consistency of the benefit-risk profile for pembrolizumab 400 mg Q6W to the 200 mg Q3W dosing, and further support the conclusion that the 400 mg Q6W dosing regimen provides comparable efficacy and safety to the Q3W regimen in all approved adult indications.

4.3.3 Chemotherapy Dose

The platinum doublet chemotherapy treatments used in this study are established regimens for metastatic NSCLC (pemetrexed and carboplatin or cisplatin [nonsquamous] or carboplatin with paclitaxel or nab-paclitaxel [squamous]).

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact, which is the LPLV for the final assessment of the study (eg, to evaluate safety and/or long-term efficacy). Therefore, the maximum follow-up will be approximately 5 years from the time the first participant provides documented informed consent (approximately 3 years after study intervention has been completed). The last participant that provides documented informed consent will be followed for approximately 4 years (or approximately 2 years after study intervention has been completed).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Refer to Appendix 7 for country-specific requirements.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Histologically or cytologically confirmed diagnosis of squamous or nonsquamous NSCLC (Stage IV: M1a, M1b, M1c, AJCC Staging Manual, version 8).

   Note: Mixed tumors will be characterized by the predominant cell type (squamous or nonsquamous); however, small cell elements are not permitted.

2. Confirmation that EGFR-, ALK-, or ROS1-directed therapy is not indicated as primary therapy (documentation of absence of tumor-activating *EGFR* mutations [eg, DEL19 or L858R] AND absence of *ALK* and *ROS1* gene rearrangements).

   Note: If participant's tumor has a predominantly squamous histology, molecular testing for *EGFR* mutation and *ALK* and *ROS1* translocations is not required.

   Note: The presence of a *KRAS* mutation in a participant's tumor is permitted.

   Note: Due to insufficient sensitivity, negative ctDNA results for *EGFR*, *ALK*, and *ROS1* cannot be used to satisfy this inclusion criterion.

3. Measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable (eligible for selection as target lesions) if progression has been shown in such lesions.

Demographics

4. An individual who is at least 18 years of age at the time of providing informed consent.

Assigned Male Sex at Birth

5. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

   - Chemotherapy: 90 days

   - MK-3475A and pembrolizumab: No contraception required for participants capable of producing sperm

- Refrains from donating sperm

  PLUS either:

- Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method, as a condom may break or leak.

  Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

  - Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Assigned Female Sex at Birth

6. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP

  OR

- Is a POCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The participant agrees not to donate eggs (ova, oocytes) to others or freeze/store during this period for the purpose of reproduction. The length of time required to continue contraception for each study intervention is as follows:

    - Chemotherapy: 180 days
    - MK-3475A: 120 days
    - Pembrolizumab: 120 days

    The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

  - Has a negative highly sensitive pregnancy test (as required by local regulations) within 24 hours (for urine test) or within 72 hours (for serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

  - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

8. Archival tumor tissue sample or newly obtained core, incisional, or excisional biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

   Note: Tumor tissue will be used to determine PD-L1 status by central testing before randomization. Tumor tissue from after diagnosis of metastatic disease is preferred.

9. An ECOG performance status of 0 to 1 assessed 7 days before randomization.

10. A life expectancy of at least 3 months.

11. Participants who have AEs due to previous anticancer therapies must have recovered to ≤Grade 1 or baseline. Participants with endocrine-related AEs who are adequately treated with hormone replacement or participants who have ≤Grade 2 neuropathy are eligible.

12. Adequate organ function as defined in the following table (Table 8). Specimens must be collected within 10 days before the start of study intervention.

Table 8 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated[b] creatinine clearance	≥60 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Diagnosis of small cell lung cancer or, for mixed tumors, presence of small cell elements.

Prior/Concomitant Therapy

2. Received prior systemic anticancer therapy for their metastatic NSCLC.

   Note: Prior treatment with chemotherapy and/or radiation as a part of neoadjuvant or adjuvant therapy or chemoradiation therapy for nonmetastatic NSCLC is allowed as long as therapy was completed at least 12 months before diagnosis of 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 (eg, CTLA-4, OX-40, CD137).

4. Received prior systemic anticancer therapy including investigational agents within 4 weeks before randomization.

5. Received prior radiotherapy within 2 weeks of start of study intervention or has radiation-related toxicity requiring corticosteroids.

   Note: Two weeks or fewer of palliative radiotherapy for non-CNS disease, with a 1-week washout, is permitted.

6. Received radiation therapy to the lung that is >30 Gray within 6 months of start of study intervention.

7. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

8. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

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

10. Known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.

11. Known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks as confirmed by repeat imaging performed during study screening, are clinically stable and have not required steroid treatment for at least 14 days before the first dose of study intervention.

12. Severe hypersensitivity (≥Grade 3) to study intervention and/or any of its excipients.

13. Active autoimmune disease that has required systemic treatment in past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.

14. History of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

    Note: Participants with lymphangitic spread of their NSCLC are not excluded.

15. Active infection requiring systemic therapy.

16. History of HIV infection. HIV testing is not required unless mandated by local health authority.

17. History of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection.

    Note: Testing for Hepatitis B or C is not required unless mandated by local health authority.

18. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

19. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

20. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

21. History of allogenic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no restrictions on caffeine, alcohol, or tobacco.

5.3.3 Activity Restrictions

There are no restrictions on activity.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 9.

Refer to Appendix 7 for country-specific requirements.

Table 9 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1 (nonsquamous and squamous NSCLC)	Experimental	MK-3475A	Biological/Vaccine	Solution	165 mg/mL	790 mg	SC	Day 1 of each cycle (Q6W) for 18 cycles; participants may be eligible for Second Course (9 additional cycles)	Test Product	IMP	Central
Arm 1 (nonsquamous NSCLC)	Experimental	Pemetrexed	Drug	Injection, Powder, Lyophilized, For Solution	Per Approved Product Label	500 mg/m²	IV Infusion	Days 1 and 22 of each cycle (Q3W)	Background Treatment	NIMP/AxMP	Local or central
Arm 1 (nonsquamous NSCLC)	Experimental	Cisplatin	Drug	Solution	Per Approved Product Label	75 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment	NIMP/AxMP	Local or central
Arm 1 (nonsquamous and squamous NSCLC)	Experimental	Carboplatin	Drug	Solution	Per Approved Product Label	AUC 5 for nonsquamous; AUC 6 for squamous	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment	NIMP/AxMP	Local or central
Arm 1 (squamous NSCLC)	Experimental	Paclitaxel	Drug	Solution	Per Approved Product Label	200 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment	NIMP/AxMP	Local or central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1 (squamous NSCLC)	Experimental	Nab-paclitaxel	Drug	Solution	Per Approved Product Label	100 mg/m²	IV Infusion	Days 1, 8, 15, 22, 29, and 36 of Cycles 1 and 2	Background Treatment	NIMP/AxMP	Local or central
Arm 2 (nonsquamous and squamous NSCLC)	Active Comparator	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	400 mg	IV Infusion	Day 1 of each cycle (Q6W) for 18 cycles; participants may be eligible for Second Course (9 additional cycles)	Comparator	IMP	Central
Arm 2 (nonsquamous NSCLC)	Active Comparator	Pemetrexed	Drug	Injection, Powder, Lyophilized, For Solution	Per Approved Product Label	500 mg/m²	IV Infusion	Days 1 and 22 of each cycle (Q3W)	Background Treatment	NIMP/AxMP	Local or central
Arm 2 (nonsquamous NSCLC)	Active Comparator	Cisplatin	Drug	Solution	Per Approved Product Label	75 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment	NIMP/AxMP	Local or central
Arm 2 (nonsquamous and squamous NSCLC)	Active Comparator	Carboplatin	Drug	Solution	Per Approved Product Label	AUC 5 for nonsquamous; AUC 6 for squamous	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment	NIMP/AxMP	Local or central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2 (squamous NSCLC)	Active Comparator	Paclitaxel	Drug	Solution	Per Approved Product Label	200 mg/m²	IV Infusion	Days 1 and 22 of Cycles 1 and 2 (Q3W)	Background Treatment	NIMP/AxMP	Local or central
Arm 2 (squamous NSCLC)	Other	Nab-paclitaxel	Other	Solution	Per Approved Product Label	100 mg/m²	IV Infusion	Days 1, 8, 15, 22, 29, and 36 of Cycles 1 and 2	Background Treatment	NIMP/AxMP	Local or central
Arm 1 and Arm 2 (nonsquamous and squamous NSCLC)	Other	Filgastrim	Other	Solution	Per Approved Product Label	Per Approved Product Label	IV Infusion	Days 2 and D23 of cycles 1 and 2.	Background Treatment	NIMP/AxMP	Local
Arm 1 and Arm 2 (nonsquamous and squamous NSCLC)	Other	Pegylated Filgastrim	Other	Solution	Per Approved Product Label	Per Approved Product Label	IV Infusion	Days 2 and D23 of cycles 1 and 2 (not to be used with Nab-Paclitaxel),	Background Treatment	NIMP/AxMP	Local

AUC=area under the concentration-time curve; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational medicinal product/auxiliary medicinal product; NSCLC=non-small cell lung cancer; Q3W=every 3 weeks; Q6W=every 6 weeks; SC=subcutaneous.

For commercially available supplies, the unit dose strength or formulation may vary, depending on market availability. Different formulations are still permitted as indicated.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 9 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Treatment

The initial treatment or first course of MK-3475A (Arm 1) or pembrolizumab (Arm 2) consists of 18 treatments. Note: The number of treatments is calculated starting with the first dose.

Participants are not permitted to crossover to the other study intervention arm.

These participants may be eligible for Second Course described in Section 6.1.2.

6.1.2 Second Course

All participants who have completed the first course (achieved SD, PR, or CR) may be eligible for up to an additional 9 cycles of MK-3475A (if on Arm 1) or pembrolizumab (if on Arm 2) if there is BICR-verified progressive disease by RECIST 1.1 after initial treatment. This retreatment is the Second Course of this study.

Participants may enter the Second Course if all of the following criteria are met:

1. The participant received MK-3475A or pembrolizumab, determined on unblinding if applicable.

2. No new anticancer treatment was administered after the last dose of study intervention

3. The participant meets all of the inclusion criteria and none of the exclusion criteria

4. The study is ongoing

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-3475A and pembrolizumab are provided in the Pharmacy Manual. Chemotherapeutic agents will be prepared and administered as per local and institutional guidelines according to the approved product labels.

The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to Arm 1 (MK-3475A SC) and Arm 2 (pembrolizumab IV), respectively.

All participants will be evaluated prior to randomization, during which an enrollment support consultation form will be completed by the Investigator and reviewed by the Sponsor.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. ECOG performance status (0 vs 1)
2. Histology (squamous vs nonsquamous)
3. PD-L1 TPS (<50% vs ≥50%; PD-L1 nonevaluable participants will be included with the TPS <50% group)
4. Region (East Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World)

A rationale for the selected stratification factors is provided in Section 4.2.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease
  - For use as premedication for chemotherapeutic agents

- Phenytoin during therapy with cisplatin/carboplatin

- For each chemotherapy agent used in the study, any medication prohibited in the approved product label

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention, all study interventions must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol

- Radiation therapy
  Note: Palliative radiation therapy to a symptomatic nontarget solitary lesion or to the brain may be allowed at the investigator's discretion and on discussion with the Sponsor.

- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

Refer to Appendix 7 for country-specific requirements.

6.5.1 Rescue Medications and Supportive Care

6.5.1.1 Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

6.5.1.2 Chemotherapy

For supportive care measures for the management of AEs that may result from treatment with chemotherapy, refer to the approved product labels for these agents.

For all agents and all administration, antiemetic therapy should follow MASCC guidelines [Roila, F., et al 2016]and should include a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and/or aprepitant as per the MASCC guidelines.

Prior to pemetrexed infusion, all participants should receive the appropriate supplementation of vitamin B12, folic acid, and dexamethasone. See Section 8.1.8.4.1.

Prior to paclitaxel infusion, all participants should be premedicated with oral or IV corticosteroids, diphenhydramine, and H2 antagonists according to the approved product label and/or standard practice. See Section 8.1.8.4.4.

In addition, all participants should receive the appropriate corticosteroid premedications as per the local approved label.

Additional predications and pre- and post-cisplatin hydration should be administered as per standard practice.

6.5.1.2.1 Colony Stimulating Factors

The use of CSFs is highly recommended as primary prophylaxis to reduce the risk of febrile neutropenia in this patient population, especially as many subjects have multiple co-morbidities and advanced disease.

- For all participants, G-CSF primary prophylaxis is required during the first 4 platinum-doublet infusions in both arms, starting on Days 2 and 23 of Cycles 1 and 2.
  - Filgrastim will be administered for 7 days for platinum/pemetrexed or platinum/paclitaxel, and 5 days for platinum/nab-paclitaxel.
  - Pegylated filgrastim will be administered once for platinum/pemetrexed or platinum/paclitaxel. It cannot be used for platinum/nab-paclitaxel.

Please note that G-CSF should not be used within 14 days before randomization and within at least 24 hours (7 days for pegylated G-CSF) before the last dose of study intervention unless absolutely necessary.

The American Society of Clinical Oncology guidelines for use of CSFs should be followed for this study [Smith, T. J., et al 2015].

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected

irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 10.

Table 10 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	**Toxicity Grade (CTCAE v5.0)**	**Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations**	**Corticosteroid and/or Other Therapies**	**Monitoring and Follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold until clinically stable or permanently discontinue [d]		
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion/Injection Reactions Related to Pembrolizumab Monotherapy, Coformulations or IO Combinations

Pembrolizumab monotherapy, coformulations or IO combinations may cause severe or life-threatening infusion/injection reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion/injection and generally resolve completely within 24 hours of completion of infusion/injection. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations or IO combinations associated infusion/injection reactions are provided in Table 11.

Table 11 Pembrolizumab Monotherapy, Coformulations or IO Combinations Infusion/Injection Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction, IV infusion/ SC administration interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 2 Requires therapy or IV infusion/ SC administration interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop IV infusion/SC injection (if not already fully administered) Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Similarly, if symptoms resolve within 1 hour of stopping the SC injection, the injection may be continued. Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion/injection of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of IV infusion or SC administration); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop IV infusion/SC injection (if not already fully administered). Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing

h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=oral; SC=subcutaneous.

Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 6 weeks or 42 days of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Chemotherapy Dose Modifications

If a participant experiences a >10% weight change from baseline, the doses of paclitaxel/nab-paclitaxel, pemetrexed, and cisplatin/carboplatin should be recalculated.

Dose modifications due to AEs will depend on the investigator's assessment of causality. If appropriate, the investigator may attribute each toxicity event to paclitaxel/nab-paclitaxel, pemetrexed, and cisplatin/carboplatin, or pembrolizumab alone, or to the combination, and use a stepwise dose modification (Table 12 through Table 14).

If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative recommended dose adjustment should be followed (ie, the dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any particular component will have that intervention discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or be further reduced, if necessary. There will be no dose escalations in this study.

Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both agents should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications. If all 3 agents are discontinued due to a toxicity, the participant must be discontinued from the study.

Study intervention-related toxicities must be resolved to baseline or Grade ≤1 (with the exception of alopecia, Grade 2 fatigue, Grade 2 peripheral neuropathy, Grade 2 anemia, endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement and creatinine clearance, for which the guidelines provided below may be followed) prior to administering the subsequent cycle. Participants must not receive the next cycle of chemotherapy if any of the following apply:

- ANC <1500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <8 g/dL
- Total bilirubin level >1.5 × ULN
- AST and ALT levels ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present

- CrCl will be based on the Cockcroft-Gault formula or another acceptable standard formula. Alternatively, CrCl can be determined from a 24-hour urine collection.
  - For participants receiving cisplatin, the scheduled dose of cisplatin may only be administered if the calculated CrCl is ≥50 mL/min.

If CrCl falls to <50 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥50 mL/min, decrease cisplatin to DL -1 (Table 12). Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the second occurrence of CrCl <50 mL/min, decrease cisplatin to DL -2 upon improvement of CrCl to ≥50 mL/min. Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.
- At the third occurrence of CrCl <50 mL/min, cisplatin should be discontinued. If in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, at the discretion of the investigator and in consultation with the Sponsor.
  - For participants receiving carboplatin, the scheduled dose of carboplatin may only be administered if the calculated CrCl is ≥40 mL/min.

If CrCl falls to <40 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥40 mL/min, decrease carboplatin to DL-1 (Table 12).

At the second occurrence of CrCl <40 mL/min, decrease carboplatin to DL -2 (Table 12) upon improvement of CrCl to ≥40 mL/min.

- At the third occurrence of CrCl <40 mL/min, carboplatin should be discontinued.

During concurrent chemotherapy treatment:

- If paclitaxel/nab-paclitaxel or pemetrexed dosing is delayed or interrupted on Day 1, the platinum agent and MK-3475A/pembrolizumab should also be delayed/interrupted. If platinum-based chemotherapy doublet is delayed or interrupted during Cycles 1 through 2, participants should be seen weekly until toxicity resolves.
- If platinum dosing is delayed or interrupted on Day 1, MK-3475A/pembrolizumab and pemetrexed/paclitaxel/nab-paclitaxel should also be delayed/interrupted. If platinum-based chemotherapy doublet is delayed or interrupted during Cycles 1 through 2, participants should be seen weekly until toxicity resolves.

- If MK-3475A/pembrolizumab dosing is delayed or interrupted, platinum-based chemotherapy can continue as scheduled. MK-3475A/pembrolizumab administration should be attempted at the next cycle of therapy.
- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 days) despite supportive treatment. If only one of the agents is thought to be causing the specified toxicity leading to a 21-day delay of administration of the next cycle, that chemotherapeutic agent can be withheld and treatment can continue with MK-3475A/pembrolizumab and the remaining chemotherapy drug. MK-3475A/pembrolizumab dosing can continue with 1 agent or as monotherapy.

The reason for the dose interruption or reduction should be captured on the appropriate eCRF.

A participant is allowed to switch from cisplatin to carboplatin if the participant develops unexpected toxicities with the use of cisplatin (including hearing loss), becomes ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the participant. This switch from cisplatin to carboplatin requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

A participant may be allowed to switch from paclitaxel to nab-paclitaxel if the participant experiences an infusion reaction to paclitaxel and the investigator considers switching to be in the best interest of the participant. This switch from paclitaxel to nab-paclitaxel requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

CTCAE v5.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 12 through Table 14. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent.

Table 12 Dose Level Modifications for Chemotherapeutic Agents

	Nonsquamous: Pemetrexed Plus Platinum-based Chemotherapy			**Squamous: Carboplatin Plus Taxane (Paclitaxel or Nab-paclitaxel)**		
	Pemetrexed	**Carboplatin**	**Cisplatin**	**Carboplatin**	**Paclitaxel**	**Nab-paclitaxel**
Dose Level 0 (starting dose)	500 mg/m^2	AUC 5 mg/mL/min	75 mg/m^2	AUC 6 mg/mL/min	200 mg/m^2	100 mg/m^2
Dose Level -1	375 mg/m^2	AUC 3.75 mg/mL/min	56 mg/m^2	AUC 4.5 mg/mL/min	150 mg/m^2	75 mg/m^2
Dose Level -2	250 mg/m^2	AUC 2.5 mg/mL/min	38 mg/m^2	AUC 3 mg/mL/min	100 mg/m^2	50 mg/m^2
Dose Level -3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

AUC=area under the curve

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 13 and Table 14. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. These data are based on Day 1 cell counts.

Table 13 Recommended Chemotherapy Dose Modifications for Hematological Toxicity

Drug-related Toxicity[a]	**Cisplatin**	**Carboplatin**	**Paclitaxel**	**Nab-paclitaxel**	**Pemetrexed**
	Dose Level (DL) from Table 12				
Neutrophils (ANC) <500/mm^3 without fever	DL -1	DL -1	DL-1	DL-1	DL-1
Febrile neutropenia (fever ≥38.5°C and ANC <1,000/mm^3)	DL -1	DL -1	DL-1	DL-1	DL-1
Platelets <50,000/mm^3 without significant bleeding or requiring blood transfusion	DL -1	DL -1	DL-1	DL-1	DL-1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring blood transfusion	DL -2	DL -2	DL-2	DL-2	DL-2
Grade 4 hemoglobin	DL -1	DL -1	DL-1	DL-1	DL-1

ANC = absolute neutrophil count; DL = dose level

Note: If toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents. Investigators may decide to use supportive measures/treatment and/or secondary prophylaxis as per institutional standards (eg, filgrastim, pegfilgrastim, transfusions) instead of dose reductions for the next dose, if considered in the best interest of the participant.

a Should the hematologic toxicity recur; the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

Table 14 Recommended Chemotherapy Dose Modifications for Nonhematological Toxicity

Drug-Related Toxicity[a]	**CTCAE Grade**	**Cisplatin**	**Carboplatin**	**Paclitaxel**	**Nab-paclitaxel**	**Pemetrexed**
		Dose Level (DL) from Table 12				
Nausea/vomiting	Grade ≥3[b]	DL -1	DL -1	DL-1	DL-1	No modification
Mucositis	Grade ≥3[b]	DL -1	DL -1	DL-1	DL-1	DL-2
Diarrhea	Grade ≥3[b]	DL -1	DL -1	DL-1	DL-1	DL-1
Peripheral neuropathy	Grade 2	DL -1[c]	No modification	DL-1	DL-1	No modification
	Grade 3	Discontinue[d]	DL -1	Discontinue	Discontinue	DL-1
	Grade 4	Discontinue	DL -1	Discontinue	Discontinue	DL-1
Total bilirubin	Grade 2	No modification	No modification	DL-2	DL-2	No modification
	Grade 3	No modification	No modification	Discontinue	Discontinue	No modification
	Grade 4	No modification	No modification	Discontinue	Discontinue	No modification
AST or ALT Elevation	Grade 3	DL -1	DL -1	Discontinue	Discontinue	DL-1
	Grade 4	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Other nonhematologic toxicity (except fatigue and transient arthralgia and myalgia)	Grade ≥3	DL -1	DL -1	DL-1	DL-1	DL-1

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events; DL = dose level.

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next dose. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents.

a Should the toxicity recur; the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

b The first occurrence of Grade ≥3 nausea/vomiting, mucositis, and diarrhea should be managed symptomatically with optimal medical therapy and improve to Grade ≤1 prior to proceeding with additional therapy. Should these events recur despite aggressive management, a dose modification can be employed once the AE improves to Grade ≤1.

c If Grade 2 neurotoxicity recurs after DL -1, drug will be given at DL -2 or switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor. If Grade 2 neurotoxicity persists after 2 dose level reductions and 21-day hold, switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

d If Grade 3 neurotoxicity occurs, cisplatin will be discontinued, and, upon improvement, a switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

6.7 Intervention After the End of the Study

Upon study completion, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab, if available.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

This section is not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.12.3 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Interruption of chemotherapy for more than 6 weeks. Participants may continue on study following Sponsor consultation.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.5 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study is outlined in the Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.4.1 Tobacco Use Assessment

Definitions for cigarette use are as follows [Land, S. R., et al 2016]:

- Current smokers: persons who report smoking ≥100 cigarettes during their lifetime and who, at the time of screening, reported smoking every day or some days within the last year.
- Former smokers: persons who report smoking ≥100 cigarettes during their lifetime and who, at the time of screening, had stopped smoking 1 year prior.
- Never smokers: persons who report smoking <100 cigarettes during their lifetime.

8.1.4.2 Non-small Cell Lung Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's NSCLC.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. In addition, new medications started during the Second Course through the Second Course Safety Follow-up Visit should be recorded.

8.1.5.3 Subsequent Antineoplastic Therapy

Details of subsequent therapies for cancer and/or details of radiation therapy and surgery for the treatment of the cancer, after discontinuation of study intervention, will be collected. Reasons for starting subsequent antineoplastic therapies, including access to other PD-1/PD-L1 inhibitors or investigational drugs will be collected.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or appropriately qualified designee according to the specifications within the Pharmacy Manual. All study interventions will be administered on an outpatient basis.

Study intervention should begin within 3 days of randomization. The investigator will select the chemotherapy regimen before randomization.

8.1.8.1 Timing of Dose Administration

Study interventions should be administered after all procedures and assessments have been completed. On applicable visits, MK-3475A or pembrolizumab will be administered before chemotherapy.

8.1.8.2 MK-3475A Administration

MK-3475A (790 mg Q6W) will be administered by SC injection in the participant's abdomen or thigh.

The Pharmacy Manual contains specific instructions on the preparation and administration of MK-3475A.

8.1.8.3 Pembrolizumab Administration

Pembrolizumab (400 mg Q6W) will be administered by IV infusion over approximately 30 minutes.

The Pharmacy Manual contains specific instructions on the preparation and administration of pembrolizumab.

8.1.8.4 Chemotherapy Administration

Unless there is a change in weight >10%, the same dose of chemotherapy can be used throughout the intervention period (provided there are no additional toxicities).

For all agents and all administration, antiemetic therapy should follow MASCC guidelines [Roila, F., et al 2016] and should include a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and/or aprepitant as per the MASCC guidelines. For details regarding G-CSF primary prophylaxis, please refer to Section 6.5.1.2.1.

8.1.8.4.1 Pemetrexed (Nonsquamous)

Pemetrexed (500 mg/m^2 Q3W) will be administered as an IV infusion over approximately 10 minutes as per local and institutional guidelines according to the approved product labels. Pemetrexed administration is to be completed at least 30 minutes before the initiation of carboplatin or cisplatin. All participants should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis as listed below (or as per local label):

- Folic acid 350 to 1000 µg po: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 pemetrexed infusions thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

- Dexamethasone prophylaxis 4 mg po bid (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during the first 4 pemetrexed infusions but not to exceed doses in MASCC guidelines [Roila, F., et al 2016].

8.1.8.4.2 Cisplatin (Nonsquamous)

Cisplatin (75 mg/m^2 Q3W) will be administered as an IV infusion over 30 to 180 minutes on Day 1 and Day 22 for two 42-day cycles as per local and institutional guidelines according to the approved product labels.

Participants are allowed to switch from cisplatin to carboplatin if the participant becomes ineligible for further cisplatin therapy according to local guidelines and the investigator considers switching to carboplatin to be in the best interest of the participant.

8.1.8.4.3 Carboplatin (Nonsquamous and Squamous)

Carboplatin (AUC 6 [mg/mL/min] squamous; AUC 5 [mg/mL/min] nonsquamous) will be administered as an IV infusion over approximately 60 minutes Q3W on Day 1 and Day 22 for two 42-day cycles as per local and institutional guidelines according to the approved product labels. The carboplatin dose should be calculated using the Calvert Formula (see below) and should not exceed 900 mg (squamous) or 750 mg (nonsquamous).

Calvert Formula (Squamous dose):

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert Formula should not exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 6 × (125 + 25)
  = 6 × 150
  = 900 mg

Calvert Formula (Nonsquamous dose):

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert Formula should not exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 5 × (125 + 25)
  = 5 × 150
  = 750 mg

CrCl must be calculated using the Cockcroft-Gault formula for estimating CrCl in mL/min based on serum creatinine:

- Male: [(140 - age (y)) × weight (kg)]/[72 × serum creatinine (mg/dL)]
- Female: [(140 - age (y)) × weight (kg)] × 0.85/[72 × serum creatinine (mg/dL)]

Alternatively, CrCl can be determined from a 24-hour urine collection.

Note: Dose may be rounded to the nearest 50 mg at the discretion of the investigator, and according to institutional standards.

Additional premedications should be administered as per standard practice.

8.1.8.4.4 Paclitaxel or Nab-paclitaxel (Squamous)

Paclitaxel or nab-paclitaxel will be administered immediately after MK-3475A or pembrolizumab and should be completely administered prior to initiating the carboplatin dose.

- Paclitaxel (200 mg/m^2 Q3W) will be administered as an IV infusion over 3 hours on Day 1 and Day 22 for two 42-day cycles as per local and institutional guidelines according to the approved product labels. All participants should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.
- Nab-paclitaxel (100 mg/m^2) will be administered as an IV infusion over 30 minutes on Day 1, 8, 15, 22, 29, and 36 for two 42-day cycles as per local and institutional guidelines according to the approved product labels.

Participants are allowed to switch from paclitaxel to nab-paclitaxel if the participant experiences an infusion reaction to paclitaxel and the investigator considers switching to be in the best interest of the participant.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and 8.12.3.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

- A newly obtained core, incisional, or excisional biopsy of a tumor lesion, which was not previously irradiated

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status in participants with NSCLC for treatment with pembrolizumab.

The PD-L1 result will be masked to the site.

8.2 Efficacy/ Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term ‘scan’ refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

If brain scans are performed, magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain x-rays acquired for correlation, should also be submitted to the iCRO.

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment include PET or PET-CT. Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

At Screening, participant eligibility will require radiographic documentation of at least 1 lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1 and as assessed by the local site investigator/radiology, prior to participant randomization.

All scheduled scans for participants will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows disease progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

The screening scans must be submitted to the iCRO for retrospective review.

Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days of randomization and can be assessed by the iCRO.

If brain scans are required to document the stability of existing metastases, the brain scan should be acquired during screening. The specific methods permitted for this study are described in the SIM.

Bone scans are required at screening for participants with a history of bone metastases and/or for those participants with indicative clinical signs/symptoms such as bone pain or elevated alkaline phosphatase levels.

Bone scan refers to imaging methods used to assess bone metastasis. The specific methods permitted for this study are described in the SIM.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 6 weeks (42 days +7 days) and at 12 weeks (84 days ±7 days) and 18 weeks (126 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 45 weeks (315 days ±7 days), participants who remain on treatment will have scans performed every 12 weeks (84 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans are to be performed until disease progression is identified by the investigator and verified by the BICR, or until any of these conditions are met:

- the start of new anticancer treatment
- pregnancy
- death

- withdrawal of consent
- the end of study

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

For participants with treated brain metastases at baseline, on-study brain scans will be acquired at Week 6 (+7 days) and then if clinically indicated and to confirm a CR. For participants without brain metastases at baseline, on-study brain scans should be acquired if clinically indicated.

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization, refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days before restarting study intervention with MK-3475A or pembrolizumab.

If disease progression has been verified by BICR for the First Course, the Second Course may be initiated. The disease progression scan may be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets scan standards.

The first scan should be performed at 12 weeks (84 days ±7 days) after restarting study intervention. Subsequent tumor scans are to be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Scans are to be performed until:

- disease progression
- the start of new anticancer treatment
- pregnancy
- withdrawal of consent
- death
- completion of Second Course
- or notification by the Sponsor, whichever occurs first.

Response assessments and progressive disease are determined by investigator assessment.

The only Second Course scan to be provided to the iCRO is the baseline scan if it is the final scan for the Initial Treatment or First Course.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Upon investigator-assessed disease progression, the indicative scan(s) is/are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
  - continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired)
  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression
  - if subsequent scan(s) indicate progression, request verification from iCRO
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

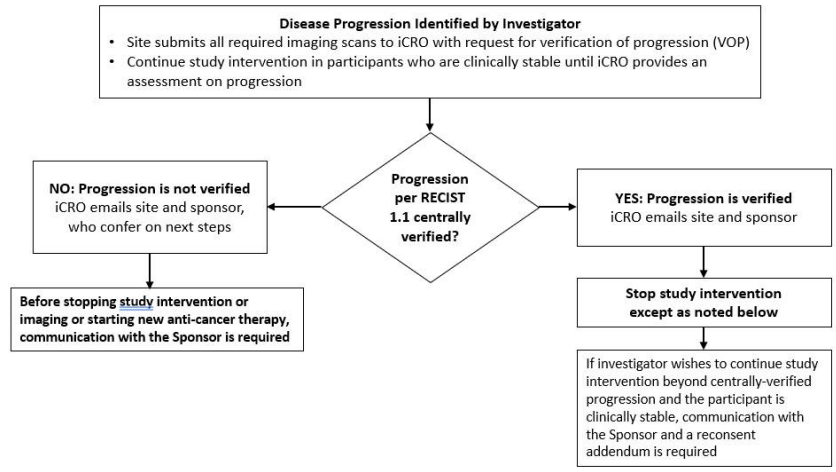
If disease progression is verified, the process continues as follows:

- investigator judgment will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

Figure 6 illustrates the study intervention decision process involving verification of disease progression for participants.

- For the purpose of this decision process, lack of clinical stability is defined as:
  - unacceptable toxicity
  - clinical signs or symptoms indicating clinically significant disease progression
  - decline in performance status
  - rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 6 Study Intervention Decision-Making Process When Progression per RECIST 1.1 is Observed by Investigator



iCRO=imaging Contract Research Organization; VOP=verification of progression

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then EQ-5D-5L. The questionnaires should be administered Day 1 and Day 22 of Cycles 1 to 4, and Day 1 for Cycles 5 to 9. In Years 2 and 3, administer questionnaires every 2 cycles (Cycle 10 Day 1, Cycle 12 Day 1, etc.) until discontinuation. From Cycle 27 (after Year 3), PROs will not be collected for participants receiving study intervention until the discontinuation visit.

If the Treatment Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the ePROs do not need to be repeated.

It is best practice and strongly recommended that ePROs are administered to randomized participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

Refer to Appendix 7 for country-specific requirements.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Participants randomized to receive MK-3475A SC (Arm 1) will also receive a directed physical examination of the injection site.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.3 Directed Injection-site Physical Examination

Participants randomized to receive MK-3475A SC (Arm 1) must receive a directed physical examination at the injection site at the timepoints detailed in Section 1.3. Any injection-site AE should be reported using standard AE/SAE reporting methods. Injection-site reaction and pain may include, but are not limited to, the following:

- Injection-site redness/erythema
- Injection-site swelling/edema
- Injection-site tenderness/pain/discomfort/irritation
- Injection-site bruising
- Injection-site infection
- Injection-site hard lump (mass, nodule)/induration
- Injection-site inflammation
- Injection-site rash
- Injection-site hematoma/hemorrhage
- Injection-site extravasation
- Injection-site dermatitis
- Injection-site discoloration/pallor
- Injection-site vesicles/ulcers

Participants in Arm 1 will be informed about the potential injection-site reactions listed above. In addition to a directed injection-site physical examination, any injection-site AE should be reported by participants at any time during the study. Any potential injection-site AE should be investigated further by the site. At all scheduled visits, including at PK sample collections, any injection-site AEs should be recorded in the AE eCRF.

8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs and weight at Screening, prior to the administration of each dose of study intervention, end-of-treatment, and during the 30-day Safety Follow-up as specified in the SoA.

- Vital signs include temperature, heart rate, respiratory rate, and blood pressure.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- Vital signs will be measured in a semisupine position after 5 minutes rest.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECG is specified in Section 1.3. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted at every protocol cycle as per SoA.
  - Pregnancy testing should be conducted midcycle (Day 22 of each treatment cycle), as per SoA, during intervention.
  - Pregnancy testing (urine and/or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
    - Chemotherapy: 180 days
    - MK-3475A: 120 days
    - Pembrolizumab: 120 days
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant’s participation in the study.

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status at Screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

The ECOG performance status closest to randomization will be used to stratify participants.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

Adverse events will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc, the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 15.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 15 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing that the fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

An overdose of MK-3475-A will be defined as ≥ 5 times the recommended dose.

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Refer to the approved label for guidance on an overdose of any chemotherapy agents.

8.6 Pharmacokinetics

Refer to Appendix 7 for country-specific requirements.

8.6.1 Blood Collection for Pembrolizumab and MK-5180 Pharmacokinetics

Sample collection, storage, and shipment instructions for serum and plasma samples will be provided in the Laboratory Manual. PK samples should be drawn according to the PK collection schedule for all participants (Section 1.3.3); however [redacted]

- Arm 1 (SC) participants
  - Cycle 1 Days 2 to 7: [redacted]
- Arm 2 (IV) participants
  - Cycle 1: [redacted]
  - Cycle 1 Days 15 and 29: [redacted]

- CCI [redacted]
- MK-5180 PK (plasma) collection for Arm 1 (SC) participants
  - CCI [redacted]

If ongoing PK sample collection for MK-5180 is deemed to be unnecessary by the Sponsor based on available data, sample collection for MK-5180 may be reduced or discontinued.

Blood samples collected may be stored and further analysis may be performed, if required.

8.6.2 Blood Collection for Antidrug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. ADA samples should be drawn according to the ADA collection schedule for all participants (Section 1.3.3). Every effort should be taken to collect samples at 30 days after end of study intervention for anti-pembrolizumab antibody. Simultaneous PK sampling is required for interpretation of ADA analysis.

If ongoing ADA sample collection for MK-5180 is deemed to be unnecessary by the Sponsor based on available data, sample collection for MK-5180 may be reduced or discontinued.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

CCI [redacted]

8.8.1 Planned Genetic Analysis Sample Collection

CCI

[redacted]

8.9 Future Biomedical Research Sample Collection

CCI

[redacted]

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days after cessation of study intervention, or 30 days after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Pharmacoeconomics

Time and resource savings have been established for SC administration of oncology drugs compared with IV administration [De Cock, E., et al 2016]. A Time & Motion observational pharmacoeconomic study will be conducted in parallel and will assess healthcare utilization parameters by collecting data on time and resource use at a selected subset of sites participating in the MK-3475A-D77 study. Details of this observational study will be described and reported in a separate protocol.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention.or sooner as indicated in the SoA.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

All participants will be evaluated prior to randomization. Investigators will review inclusion/exclusion criteria to ensure eligibility. An enrollment support consultation form will be completed by the Investigator and reviewed by Sponsor.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.12.2.1 Optional Home Health Visits for PK Sampling

A global home health vendor is available to be used for participants in both Arm 1 and Arm 2 who must have additional PK samples taken during Cycle 1 and Cycle 3. The home health visiting nurse service may be used if approved by local health authorities for PK sampling at the following PK visits: Cycle 1 Days 3, 4, 5, 6, 7, 10, 15, 29, 42 and Cycle 3 Days 4, 10, 42.

If the visiting nurse service is used for any of the visits listed above, the nurse will be instructed to immediately contact the site if the participant reports any potential AE to the nurse. In addition to this, the investigator should contact the participant by phone on the same day as the nurse visit, or as soon as possible (if the home health visit occurred on a weekend or holiday) to perform an investigator AE assessment. Refer to the nursing manual for additional details.

8.12.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Randomized participants who discontinue study intervention for reasons other than progressive disease will move into the Follow-up Phase (Section 8.12.4).

8.12.4 Posttreatment Visit

8.12.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

If a participant has a discontinuation visit ≥30 days after the last dose of study intervention, the Safety Follow-up Visit is not required.

Participants who are eligible for Second Course retreatment with MK-3475A or pembrolizumab may have up to 2 safety follow-up visits: 1 after the Initial Treatment or First Course and 1 after the Second Course.

8.12.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than BICR-verified disease progression will begin Efficacy Follow-up and should be assessed as detailed in the SoA (Section 1.3) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with MK-3475A or pembrolizumab according to the criteria in Section 6.1.2 will move from Efficacy Follow-up to Second Course when they experience BICR-verified disease progression. Details are provided in the SoA (Section 1.3) for retreatment with MK-3475A or pembrolizumab.

8.12.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.12.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of future biomedical research) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12. See Appendix 7 for country-specific information.

Study Design Overview	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
Treatment Assignment	Approximately 378 participants will be randomized in a 2:1 ratio between 2 treatment groups: (1) MK-3475A SC Q6W in combination with platinum doublet chemotherapy and (2) pembrolizumab IV Q6W in combination with platinum doublet chemotherapy. Randomization stratification factors are: 1) ECOG (0 versus 1), 2) Histology (squamous versus nonsquamous), 3) PD-L1 TPS (<50% versus ≥50%; PD-L1 nonevaluable participants will be included with the TPS <50% group), and 4) Region (East Asia versus North America/Western Europe/Australia/New Zealand versus Rest of the World). This is an open-label study.
Analysis Populations	• PK (primary): Per-protocol Set • Efficacy: ITT • Safety: APaT • PRO: PRO FAS
Primary Endpoint(s)	• Cycle 1 $AUC_{0\text{-}6\ wks}$ • Steady-state (Cycle 3) C_{trough} (the primary analysis will be performed on the model-based values of C_{trough})

Secondary Endpoints	• For descriptive comparison to pembrolizumab IV Q6W:
	  ○ Cycle 1: C_{max}, C_{trough}
	  ○ Cycle 3: $AUC_{0\text{-}6\ wks}$, C_{max}
	• For descriptive comparison to pembrolizumab IV Q3W:
	  ○ Model-based C_{trough} at Cycle 1 and steady state
	• ADA
	• ORR
	• PFS
	• OS
	• DOR
	• Safety and tolerability
	• PROs

Statistical Methods for Key Immunogenicity/ Pharmacokinetic Analyses	For both primary hypotheses of noninferiority of MK-3475A SC versus pembrolizumab IV with respect to Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough}, the noninferiority margin with respect to the AUC and C_{trough} GMR of MK-3475A SC versus pembrolizumab IV is specified to be 0.8. Computation of the CIs of GMR will be calculated using 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 C_{trough}.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen's method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	**Pharmacokinetics** There are no planned IAs for pharmacokinetics analysis in this study. One final analysis (FA) is planned to be performed when a minimum of 27 weeks follow-up after last participant randomized. This is expected about 16.2 months after first participant randomized. The purpose of FA is for noninferiority of Cycle 1 $AUC_{0\text{-}6wks}$ and Cycle 3 C_{trough}. **Safety** The study plans 1 interim safety analysis, which will be performed approximately 7 months after first participant is randomized. Details will be specified in the DMC charter.
Multiplicity	The overall Type I error over the primary endpoints is strongly controlled at 0.05 (1-sided), with 0.02 initially allocated to Cycle 1 $AUC_{0\text{-}6\ wks}$ and 0.03 to Cycle 3 C_{trough}. By using the graphical approach of Maurer and Bretz [Maurer, W., et al 2011], if 1 hypothesis is rejected, the alpha will be shifted to the other hypothesis.
Sample Size and Power	The planned sample size is approximately 378 participants. For the primary endpoint of Cycle 1 $AUC_{0\text{-}6\ wks}$, based on 318 participants with evaluable Cycle 1 $AUC_{0\text{-}6\ wks}$, the study has 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 C_{trough}, based on 240 participants with evaluable Cycle 3 C_{trough} data, the study has approximately 99.8% power to reject the null hypothesis (C_{trough} GMR ≤0.8) under a true Cycle 3 C_{trough} GMR = 1.29 at the initially assigned 0.03 (1-sided) significance level.

Japan Extension Study	Japan participants randomized during the global study phase will be included in all global study analyses (PK, efficacy and safety). Japan participants randomized during the Japan extension phase will be excluded from all global study analyses. Japan participants randomized during global and extension phases will both be included in the Japan-specific analyses. Details of the analysis regarding to the endpoints, population, analysis timing, etc will be provided in the separate Japan-specific sSAP document.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Sponsor will generate the randomized allocation schedule(s) for study intervention assignment, and the randomization will be implemented in an interactive voice response system by a study vendor.

Although the study is open-label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented.

Extension Study In Japan

For all participants in Japan, including participants randomized in the global study and the extension study, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented to the statistician(s)/programmer(s) responsible for the analysis of the Extension Study in Japan. The extent to which individuals are unblinded to the results will be limited, and blinded and unblinded members will be clearly documented.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. For the primary hypotheses of noninferiority of MK-3475A SC to pembrolizumab IV based on assessment of Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough}, the noninferiority margin for the GMR of MK-3475A SC versus pembrolizumab IV is set to be 0.8. The rationale for the 0.8 noninferiority margin is 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.

9.4 Analysis Endpoints

Pharmacokinetics, safety, and efficacy endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Pharmacokinetics Endpoints

The methodological details for assessment of model-based PK exposures ($AUC_{0\text{-}6\ wks}$ and C_{trough}) will be summarized in a separate MAP.

Primary

- Cycle 1 $AUC_{0\text{-}6\ wks}$

Cycle 1 $AUC_{0\text{-}6\ wks}$ is defined as the model-based area under curve exposure over a 6-week dosing interval in Cycle 1.

- Cycle 3 C_{trough}

Cycle 3 C_{trough} is defined as the trough concentration at the end of the dosing interval in Cycle 3, representing steady-state.

Two assessments of this endpoint will be made: model-based C_{trough}, which is the value predicted by the PK model, and observed C_{trough}, which is the measured value. The primary analysis for Cycle 3 C_{trough} will be based on the model-based value. A sensitivity analysis of this endpoint will be performed on the observed value.

Secondary

For descriptive comparison with pembrolizumab IV Q6W:

- Cycle 1 C_{trough}

Cycle 1 C_{trough} is defined as the trough concentration at the end of the dosing interval in Cycle 1. Two assessments of this endpoint will be made: observed C_{trough}, which is the measured value, and model-based C_{trough}, which is the value predicted by the PK model.

- Cycle 3 $AUC_{0\text{-}6\ wks}$

Cycle 3 $AUC_{0\text{-}6\ wks}$ is defined as the model-based area under curve exposure over a 6-week dosing interval in Cycle 3, representing steady-state.

- Cycle 1 C_{max}

Cycle 1 C_{max} is defined as the peak concentration over the dosing interval in Cycle 1. Two assessments of this endpoint will be made: observed C_{max}, which is the measured value, and model-based C_{max}, which is the value predicted by the PK model.

- Cycle 3 C_{max}

Cycle 3 C_{max} is defined as the peak concentration over the dosing interval in Cycle 3, representing steady-state. Two assessments of this endpoint will be made: observed C_{max}, which is the measured value, and model-based C_{max}, which is the value predicted by the PK model.

For descriptive comparison with pembrolizumab IV Q3W:

- Model-based Cycle 1 C_{trough}

Model-based Cycle 1 C_{trough} is defined as the value of trough concentration at the end of the dosing interval in Cycle 1, as predicted by the PK model.

- Model-based steady-state C_{trough}

Model-based steady-state C_{trough} is defined as the value of trough concentration at the end of the dosing interval at steady-state, as predicted by the PK model. This corresponds to the model-predicted C_{trough} value at Cycle 3 for MK-3475A Q6W and at Cycle 6 for pembrolizumab 200 mg IV Q3W.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, and vital signs.

9.4.3 Efficacy Endpoints

Secondary

- Objective Response Rate (ORR)

The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

- Progression-free survival (PFS)

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

- Overall Survival (OS)

OS is defined as the time from randomization to death due to any cause.

- Duration of Response (DOR)

For participants who show confirmed CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

9.4.4 Immunogenicity Endpoint

Immunogenicity (ADA incidence) will be assessed by analyzing the development of ADAs following administration of MK-3475A SC and pembrolizumab IV.

9.4.5 PRO Endpoints

Change from baseline in EORTC QLQ-C30 global health/QoL scale (Items 29 and 30) and physical functioning domain score (Items 1 through 5) and role functioning domain scores (Items 6 and 7).

Exploratory PRO endpoints as described in Section 4.2.1.5 will be evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Pharmacokinetics Analysis Populations

The PP population will be used for the analysis of PK data in this study.

PP Populations for Primary PK Endpoints

- Cycle 1 $AUC_{0\text{-}6\ wks}$

The PP population for the primary PK endpoint of Cycle 1 $AUC_{0\text{-}6\ wks}$ 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 $AUC_{0\text{-}6\ wks}$ can be made.

- Cycle 3 C_{trough}

The primary analysis for the primary PK endpoint of Cycle 3 C_{trough} will be performed on the model-based Cycle 3 C_{trough}. An additional sensitivity analysis of this endpoint will be performed using observed Cycle 3 C_{trough}.

- The PP population for model-based Cycle 3 C_{trough} 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 C_{trough} can be made.
- The PP population for the observed Cycle 3 C_{trough} consists of the subset of participants in the global study who received all 3 doses from Cycle 1 to 3 within the permissible dosing window as per the SoA and have a valid PK sample on Cycle 3 Day 42 with no documented assay or bioanalytical error and within permissible window as per the PK SoA (ie, within Days 41 to 43 of the dosing day in Cycle 3).

Any participants or data values excluded from the primary analyses for the primary PK endpoints will be identified, along with the reasons for exclusion, in the CSR.

PP Populations for Secondary PK Endpoints

For descriptive comparison with pembrolizumab IV Q6W

- Cycle 1 C_{trough}

The PP population for observed Cycle 1 C_{trough} consists of the subset of participants in the global study who received the Cycle 1 dose and have a valid PK sample on Cycle 1 Day 42 with no documented assay or bioanalytical error and within permissible window as per the PK SoA (ie, within Days 41 to 43 of the dosing day in Cycle 1).

The PP population for model-based Cycle 1 C_{trough} consists of the subset of participants in the global study who received the Cycle 1 dose, with at least 1 valid postdose sample in Cycle 1 and for whom a model-based assessment of C_{trough} can be made.

- Cycle 3 $AUC_{0\text{-}6\ wks}$

The PP population for Cycle 3 $AUC_{0\text{-}6\ wks}$ 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 $AUC_{0\text{-}6\ wks}$ can be made.

- Cycle 1 C_{max} and Cycle 3 C_{max}

The PP population for the observed Cycle 1 C_{max} consists of the subset of participants in the global study who received the Cycle 1 dose within the permissible dosing window as per the SoA, and have a valid PK sample on Cycle 1 Day 1 end-of-infusion for the IV arm or at least 1 valid PK sample on Cycle 1 Days 5 to 10 for the SC arm with no documented assay or bioanalytical error and within permissible window as per the PK SoA.

The PP population for the observed Cycle 3 C_{max} consists of the subset of participants in the global study who received all 3 doses from Cycle 1 to 3 within the permissible dosing window as per the SoA, and have a valid PK sample on Cycle 3 Day 1 end-of-infusion for the IV arm or at least 1 valid PK sample on Cycle 3 Days 5 to 10 for the SC arm with no documented assay or bioanalytical error and within permissible window as per the PK SoA.

The PP population for model-based Cycle 1 C_{max} and model-based Cycle 3 C_{max} consists of the subset of participants in the global study who received the Cycle 1 dose, with at least 1 valid postdose sample in Cycle 1 and for whom a model-based assessment of Cycle 1 C_{max} and Cycle 3 C_{max}, respectively, can be made.

For descriptive comparison with pembrolizumab IV Q3W

- Model-based Cycle 1 C_{trough} and Steady-state C_{trough}

The PP population for model-based Cycle 1 C_{trough} and model-based steady-state C_{trough} consists of the subset of participants in the global study who received the Cycle 1 dose, with at least 1 valid postdose sample in Cycle 1 and for whom a model-based assessment of Cycle 1 and steady-state C_{trough}, respectively, can be made.

Extension Study in Japan

After enrollment of the global study is completed, the study will continue to randomize participants in Japan until the sample size for participants in Japan reaches approximately 39. The participants in Japan randomized and treated in the extension study after completion of the global enrollment will not be included in the PP population for the global study. The Japan PP population for PK endpoint of Cycle 1 $AUC_{0\text{-}6\ wks}$ consists of the subset of participants in the global study and extension 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 $AUC_{0\text{-}6\ wks}$ can be made. The Japan PP population for PK endpoint of Cycle 3 C_{trough} consists of participants in the global study and extension study who received the Cycle 1 dose, with at least 1 valid postdose sample and for whom a model-based assessment of Cycle 3 C_{trough} can be made.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants in the global study who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

Extension Study in Japan

The participants in Japan randomized and treated in the Japan extension study after completion of the global enrollment will not be included in the safety analysis population for the global study. The Japan APaT population, including all participants in Japan randomized in the global study and the extension study who received at least 1 dose of study treatment, will be analyzed separately.

9.5.3 Efficacy Analysis Populations

The ITT population will serve as the population for efficacy analysis. All randomized participants in the global study will be included in this population. Participants will be included in the treatment group to which they are randomized.

Extension Study in Japan

The participants in Japan randomized in the extension study after completion of the global enrollment will not be included in the efficacy analysis population for the global study. The Japan ITT population, including all participants in Japan randomized in the global study and the extension study, will be analyzed separately.

9.5.4 PRO Analysis Populations

The PRO analyses are based on the PRO FAS population, defined as all randomized participants in the global study who have at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Pharmacokinetics results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values may be computed for efficacy analyses and other pharmacokinetics analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Pharmacokinetics Analyses

The primary objectives are to compare GMR between MK-3475A SC and pembrolizumab IV based on Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough}. These objectives will be assessed via the following noninferiority hypothesis:

$$H_0: GMR = \frac{GM_{SC}}{GM_{IV}} \leq 0.8$$

$$H_1: GMR = \frac{GM_{SC}}{GM_{IV}} > 0.8$$

The hypothesis testing for noninferiority and the CIs for GMR will 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 C_{trough}. For Cycle 3 C_{trough}, the primary analysis will be based on Cycle 3 model-based C_{trough}. A sensitivity analysis will be performed for Cycle 3 observed C_{trough}.

For each PK exposure (C_{trough}, $AUC_{0\text{-}6\ wks}$ and C_{max}, for Cycles 1 and 3) by treatment, the following descriptive statistics will be provided: N (number of participants with nonmissing data), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) – 1), where s^2 is the observed variance on the natural log-scale).

Based on PK data obtained in this study as well as historical PK data, an integrated population PK analysis will be performed to characterize the PK profile of pembrolizumab following SC and IV administrations and provide individual model-based PK exposure measures. Details are provided in the MAP.

9.6.2 Statistical Methods for Safety Analyses

The primary safety analyses will include only events that occur prior to Second Course treatment.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least 1 AE, drug-related AE, serious AE, serious drug-related AE, Grade 3 to 5 AE, a discontinuation from study treatment due to an AE, an AE that led to treatment interruption, and an AE resulting in death. Only point estimates by treatment group are provided. The number and percentage for injection-site reactions will be provided for the MK-3475A SC arm.

Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided if at least 10% of participants in any treatment group exhibit the event. The threshold of at least 10% of participants was chosen because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥2% of participants in 1 of the treatment groups) will also be summarized by point estimate and 95% CIs.

CIs for between treatment group differences will be provided using the Miettinen and Nurminen's method [Miettinen, O. and Nurminen, M. 1985]. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Table 16 summarizes the analysis strategy for safety endpoints in this study.

Table 16 Analysis Strategy for Safety Endpoints

Analysis Part	Safety Endpoint	Descriptive Statistics	95% between-group CI
Overall Safety Assessment	Specific AEs (incidence ≥10% of participants in 1 of the treatment groups)	X	X
	Specific Grade 3-5 AE (incidence ≥5% of participants in 1 of the treatment groups)	X	X
	Specific serious AE (incidence ≥2% of participants in 1 of the treatment groups)	X	X
	Any AE	X	
	Any Grade 3-5 AE	X	
	Any Serious AE	X	
	Any Drug-related AE	X	
	Any Serious and Drug-related AE	X	
	Any Grade 3-5 and Drug-related AE	X	
	Discontinuation from Study Treatment due to AE	X	
	AE that Resulted in Death	X	
	AE that Led to Treatment Interruption	X	
	Injection-site Reaction	X	
	Specific AEs, SOCs (incidence >0% of participants in any treatment group)	X	
	Change from Baseline Results (lab toxicity shift)	X	
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	

AE=adverse event; AEOSI=adverse event of special interest; CI=confidence interval; SOC=system organ class

9.6.2.2 Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated will be evaluated separately. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI.

9.6.3 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the efficacy objectives (which are secondary objectives in the study). For this study, efficacy analyses are descriptive only. No Type I error control is applied to efficacy analyses, so p-values, if provided, are nominal only and provided for descriptive purposes.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], stratified Cochran-Mantel-Haenszel method, and stratified Cox model. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

The efficacy analyses for ORR, DOR and PFS will include responses and documented progression events that occur prior to Second Course treatment.

9.6.3.1 Objective Response Rate

The stratified Miettinen and Nurminen's method will be used for comparison of the ORR between 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. Furthermore, the stratified Cochran-Mantel-Haenszel method for ORR ratio will also be used for comparison of the ORR between 2 treatment groups. The stratification factors used for randomization (see Section 6.3.2) will be applied to the stratified analysis specified above. The ratio of ORR and its 95% CI on the logarithmic scale based on the normal approximation will be reported as applicable.

9.6.3.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, an additional sensitivity analysis with different sets of censoring rules will be performed. The sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analysis are summarized in Table 17.

Table 17 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

9.6.3.3 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.3.4 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed complete response or partial response will be included in this analysis. Censoring rules for DOR are summarized in Table 18.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~ 5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 18 Censoring Rules for DOR

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

9.6.3.5 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 19.

Table 19 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 17
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.

9.6.4 Statistical Methods for Patient-Reported Outcome Analyses

This section describes the planned analyses for the PRO endpoints.

Change from Baseline

The time point for the change from baseline will be determined based on data review prior to the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the global health status/QoL, physical functioning, role functioning, dyspnea, chest pain, and cough, a constrained longitudinal data analysis model proposed by Liang and Zeger [Liang, K-Y. and Zeger, S. L. 2000]will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and stratification factors used for randomization (see Section 6.3.2) as covariates. The treatment difference in terms of LS mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and postbaseline time point.

9.6.5 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

There are no planned IAs for pharmacokinetics and efficacy endpoints for this study. The study plans 1 interim safety analysis.

An eDMC will serve as the primary reviewer of the results of the interim safety analysis of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Treatment-level results from the interim safety analysis will be provided to the eDMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim safety analysis.

Although the study is open label, analyses or summaries generated by randomized treatment assignment, or actual treatment received, will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

9.7.1 Pharmacokinetics Interim Analysis

There is no planned IAs for pharmacokinetics analysis in this study. The analysis planned, endpoints evaluated, and driver of timing are summarized in Table 20.

Table 20 Summary of Analysis Strategy

Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
Cycle 1 $AUC_{0\text{-}6\ wks}$, Cycle 3 C_{trough}	~A minimum of 27 weeks follow-up after last participant randomized	~ 16.2 months	• noninferiority of Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough}
$AUC_{0\text{-}6\ wks}$=area under the curve from 0-6 weeks; C_{trough}=trough concentration; By the timing of analysis, ~240 participants with evaluable Cycle 3 model-based C_{trough} data are expected, and ~318 participants with evaluable Cycle 1 $AUC_{0\text{-}6\ wks}$ data are expected.			

9.7.2 Safety Interim Analysis

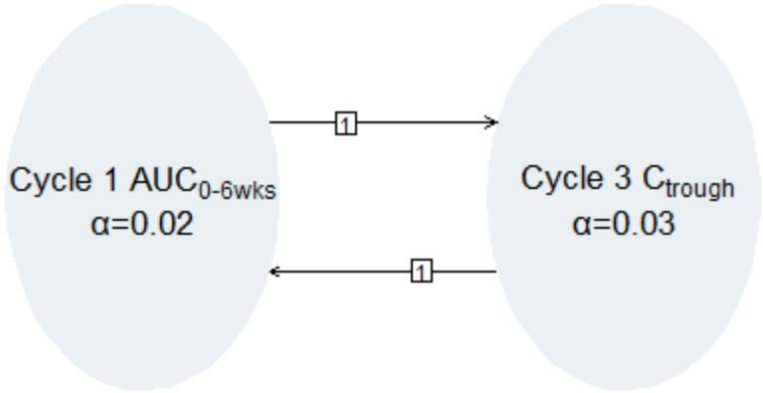
The eDMC will be responsible for periodic interim safety reviews as specified in the DMC charter. The study plans 1 interim safety analysis, which will be performed approximately 7 months since first participant is randomized. Details will be specified in the DMC charter.

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W., et al 2011] to provide strong multiplicity control for multiple hypotheses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 7 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

The Type I error rate for testing of the primary endpoints will be strongly controlled at an overall α level of 0.05 (1-sided). The initial α assigned to the hypothesis for Cycle 1 $AUC_{0\text{-}6\ wks}$ and the hypothesis for Cycle 3 C_{trough} will be 0.02 (1-sided) and 0.03 (1-sided) respectively. If the hypothesis for Cycle 1 $AUC_{0\text{-}6\ wks}$ is rejected, the corresponding alpha can be reallocated to Cycle 3 C_{trough}. If the hypothesis for Cycle 3 C_{trough} is rejected, the corresponding alpha can be reallocated to Cycle 1 $AUC_{0\text{-}6\ wks}$.

Figure 7 Multiplicity Strategy



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

9.8.1 Cycle 1 $AUC_{0\text{-}6\ wks}$

The study will test the Cycle 1 $AUC_{0\text{-}6\ wks}$ noninferiority hypothesis only once. Following the multiplicity strategy as outlined in Figure 7, the hypothesis for Cycle 1 $AUC_{0\text{-}6\ wks}$ may be tested at α=0.02 one-sided (initially allocated α) or at α=0.05 one-sided (if the hypothesis for Cycle 3 C_{trough} is rejected). Table 21 shows the boundary properties for each of these α levels for the Cycle 1 $AUC_{0\text{-}6\ wks}$ analysis.

Table 21 Boundaries and Properties for Cycle 1 AUC NI Analysis

Analysis	**Value**	**α=0.02**	**α=0.05**
n*: 318 Month: 16.2	*p* (1-sided)[a]	0.02	0.05
	Approximate GMR at bound[b]	0.87	0.85
	P(Cross) if GMR=0.8[c]	0.02	0.05
	P(Cross) if GMR=0.9[d]	0.82	0.91
	P(Cross) if GMR=1.07[e]	>0.999	>0.999

AUC=area under the curve; GMR=geometric mean ratio; NI=noninferiority; PP=per protocol
The number of participants with evaluable data and timings are estimated approximately.
*n is the number of participants with evaluable Cycle 1 $AUC_{0\text{-}6\ wks}$ in the PP population.
[a]*p* (1-sided) is the nominal α.
[b]GMR at bound is the approximate GMR required to reach a noninferiority bound.
[c]P(Cross if GMR=0.8) is the probability of crossing a bound under the null hypothesis.
[d]P(Cross if GMR=0.9) is the probability of crossing a bound when the true GMR=0.9.
[e]P(Cross if GMR=1.07) is the probability of crossing a bound when the true GMR=1.07.
Additional assumptions used for the calculation are specified in Section 9.9.

9.8.2 Cycle 3 C_{trough}

The study will test the hypothesis for Cycle 3 C_{trough} noninferiority only once. Following the multiplicity strategy as outlined in Figure 7, the Cycle 3 C_{trough} hypothesis may be tested at α=0.03 one-sided (initially allocated α) or at α=0.05 one-sided (if the hypothesis for Cycle 1 $AUC_{0\text{-}6\ wks}$ is rejected). Table 22 shows the boundary properties for each of these α levels for the Cycle 3 C_{trough} analysis.

Table 22 Boundaries and Properties for Cycle 3 C_{trough} NI Analysis

Analysis	Value	α=0.03	α=0.05
n*: 240 Month: 16.2	*p* (1-sided)[a]	0.03	0.05
	Approximate GMR at bound[b]	0.97	0.95
	P(Cross) if GMR=0.8[c]	0.03	0.05
	P(Cross) if GMR=1[d]	0.63	0.71
	P(Cross) if GMR=1.29[e]	0.998	0.999

C_{trough}=trough concentration; GMR=geometric mean ratio; NI=noninferiority; PP=per protocol.
The number of participants with evaluable data and timings are estimated approximately.
*n is the number of participants with evaluable Cycle 3 model-based C_{trough} in the PP population.
[a]*p* (1-sided) is the nominal α.
[b]GMR at bound is the approximate GMR required to reach the noninferiority bound.
[c]P(Cross if GMR=0.8) is the probability of crossing a noninferiority bound under the null hypothesis.
[d]P(Cross if GMR=1) is the probability of crossing a noninferiority bound when the true GMR=1.
[e]P(Cross if GMR=1.29) is the probability of crossing a noninferiority bound when the true GMR=1.29.
Additional assumptions used for the calculation are specified in Section 9.9.

9.8.3 Safety Analyses

The DMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the DMC can request corresponding PK and/or efficacy data. DMC review of PK data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment. However, to account for any multiplicity concerns raised by the DMC review of unplanned PK data prompted by safety concerns, a sensitivity analysis for Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough} adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

The study will randomize approximately 378 participants in a 2:1 ratio into the MK-3475A SC and pembrolizumab IV arms. Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough} are dual primary endpoints for the study, with ORR as a secondary endpoint.

For the Cycle 1 $AUC_{0\text{-}6\ wks}$ endpoint, based on a target number of 318 evaluable participants for Cycle 1 $AUC_{0\text{-}6\ wks}$, the study has approximately >99.9% power to reject the null hypothesis (Cycle 1 $AUC_{0\text{-}6\ wks}$ GMR≤0.8) when the true GMR for Cycle 1 $AUC_{0\text{-}6\ wks}$ is 1.07 at the initially allocated α=0.02 (1 sided).

For the Cycle 3 C_{trough} endpoint, based on a target number of 240 evaluable participants for model-based Cycle 3 C_{trough}, the study has approximately 99.8% power to reject the null hypothesis (Cycle 3 C_{trough} GMR ≤0.8) when the true GMR for Cycle 3 C_{trough} is 1.29 at the initially allocated α=0.03 (1 sided).

The assumptions for the above sample size and power calculations are listed below. The assumptions come from PK modeling based on historical pembrolizumab IV data/reference PK model and MK-3475A-C18 data for SC (N=81). To ensure robust SC dose selection, both mean level and stochastic simulations were performed using PK parameter estimates from the combined SC and IV PK model informed by the reference pembrolizumab IV PK dataset (including 2993 participants with melanoma or NSCLC, pooled from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024) and SC PK dataset including MK-3475A-C18 and KN-555 Cohort A data for SC.

- Log(AUC) and Log(C_{trough}) follows a normal distribution for both MK-3475A SC and pembrolizumab IV arms, thus the GMR under natural log-scale follows a normal distribution.

- Cycle 1 $AUC_{0\text{-}6\ wks}$ GMR = 1.07 and Cycle 3 C_{trough} GMR = 1.29 under the alternative hypothesis.

- The standard deviations for log($AUC_{0\text{-}6\ wks}$) at Cycle 1 are 0.313 and 0.371 for IV and SC, respectively.

- The standard deviations for log(C_{trough}) at the end of Cycle 3 are 0.741 and 0.737 for IV and SC, respectively.

- Approximately 84% participants among the ITT population will have evaluable Cycle 1 $AUC_{0\text{-}6\ wks}$ data.

- Approximately 64% participants among the ITT population will have evaluable model-based Cycle 3 C_{trough} data.

- The projected enrollment period is approximately 10 months.

ORR is a secondary endpoint for the study. Although ORR will not be formally tested for noninferiority, based on the overall sample size of 378 participants in the global study, the study can 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]. Details are provided in Appendix 8.

Based on the historical data from KEYNOTE-189 and KEYNOTE-407, the power calculation for ORR assumes the following:

- In the current study, the projected prevalence of PDL1 TPS ≥50% is 19% and PDL1 TPS<50% is 81%.
- CCI
- ORR ratio=1 (MK-3475A SC vs pembrolizumab IV) under the alternative hypothesis.
- CCI

The sample size and power calculations were performed using R.

Extension Study in Japan

After the enrollment for the global study has completed, the study will continue to randomize participants in a 2:1 ratio into the MK-3475A SC and pembrolizumab IV arms in Japan until the sample size for the Japanese participants reaches approximately 39. Participants in Japan randomized after completion of enrollment in the global study will not be included in the analysis of the global study.

9.10 Subgroup Analyses

Subgroup analysis will not be performed for $AUC_{0\text{-}6\ wks}$ and C_{trough} given that historical data from KEYTRUDA® development program has consistently shown that there is no clinically relevant impact of covariates on PK. Details about subgroup analyses for ORR will be provided in the Japan-specific sSAP.

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles in which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study

completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 23 will be performed by the local laboratory.
- All on-treatment samples will be collected before administration of study intervention.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 23 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[a] MCH[a] %Reticulocytes[a]		WBC count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN or urea[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Carbon dioxide (CO_2 or bicarbonate)[a]	Chloride	Phosphorous[a]
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Lactate dehydrogenase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase[a] by dipstick • Microscopic examination[a] (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)			
Other Screening Tests	• FSH (as needed in PONCBP only) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) as required by local health authority or institutional regulations • Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. • Thyroid function tests (T3 (or Free T3), Total T4 (or FT4), TSH) Total T4 and T3 preferred over FT4 and FT3.			

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; FT4=free thyroxine; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; RBC=red blood cell; PT=prothrombin time; PTT=partial thromboplastin time; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

Notes:
[a] Performed only if considered the local standard of care.
[b] Absolute or % acceptable per institutional standard.
[c] BUN is preferred; if not available, urea may be tested.
[d] Measured or calculated creatinine clearance. Creatinine clearance should be calculated per the Cockcroft-Gault formula.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Refer to Appendix 7 for country-specific requirements.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study).
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?

- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
    - Yes, there is a reasonable possibility of study intervention relationship:
        - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
    - No, there is not a reasonable possibility of study intervention relationship:
        - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile and capable of becoming pregnant following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

- Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[a] • IUS[b] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [b] IUS is a progestin releasing IUD.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent.

Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Argentina

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.2 China

Biomarker sample collection, testing, and analysis as described in the following sections will be dependent on approval by the Human Genetic Resources Administration of China for participants enrolled in China:

- Section 1.3: Schedule of Activities
- Section 4.2.1.6: Planned Exploratory Biomarker Research
- Section 5: Inclusion Criteria, Exclusion Criteria
- Section 8.8: Biomarkers

Future biomedical research will not be conducted in China.

Section 4.1 Overall Design

After enrollment of the global study is complete, the study may remain open to enrollment in China until the target number of participants in China has been enrolled to meet local requirements.

Section 6.1 Study Intervention(s) Administered

All study interventions will be administered on an outpatient basis. However, hospitalization is acceptable if it is standard procedure for the local site.

Section 8.6.1 Blood Collection for Pembrolizumab and MK-5180 Pharmacokinetics *and*

Section 8.6.2 Blood Collection for Antidrug Antibodies

PK and ADA sample collection for MK-5180 will not be reduced or discontinued.

Appendix 2 Clinical Laboratory Tests

Routine Urinalysis by dipstick: a urine leukocyte count by microscopy is acceptable when the leukocyte esterase by dipstick cannot be performed.

10.7.3 Czech Republic

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 6.5 Concomitant Therapy

In addition to all restrictions or concomitant medications listed in Section 6.5, specific concomitant therapies or vaccinations noted below are prohibited during the study:

- Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 90 days after the last dose of study intervention.

10.7.4 France

Section 1.3 Schedule of Activities

An audiogram will be performed at screening and at the beginning of each cycle.

Section 5.2 Exclusion Criteria

Participants with a hearing impairment.

Section 8.3 Safety Assessments

An audiogram will be performed at screening and at the beginning of each cycle. If any hearing issues arise, an additional audiogram will be performed.

10.7.5 Italy

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.6 Japan

Section 1.3 Schedule of Activities

- For the assistance to early diagnosis of pneumonitis/interstitial lung disease in study participants, the following items, such as SpO_2, CRP, KL-6, and SP-D, will be measured in this study. These items should be measured as follows:

  - SpO_2 at the timing of vital sign assessment.

  - CRP, KL-6, and SP-D at screening*, predose on Day 1 of every cycle, EOT, and the Safety Follow-up Visit (30 days after last dose).

*Should be measured at the timing of clinical laboratory tests (such as hematology/chemistry).

If pneumonitis/ILD occurs, regardless of causality with study intervention, an independent ILD evaluation committee will conduct adjudication of cases of the pneumonitis/ILD. For this purpose, relevant data, such as chest imaging (from the baseline to the recovery of pneumonitis/ILD) will be submitted to MSD K.K.

Section 9 Statistical Analysis Plan

A Japan sSAP will be prepared separately to address Japan-specific study objectives to meet the local regulatory requirements.

10.7.7 Romania

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.8 South Africa

Section 1.3 Schedule of Activities

HIV testing at screening is mandatory.

Testing for active tuberculosis is required at screening and every 6 months during treatment as mandated by local regulation.

10.7.9 United Kingdom

Section 5.1 Inclusion Criteria - Demographics

Participants assigned male sex at birth are to be advised to seek counseling on sperm storage before starting treatment with pemetrexed and/or platinum-based therapy as per respective SmPCs.

Section 6.5 Concomitant Therapy

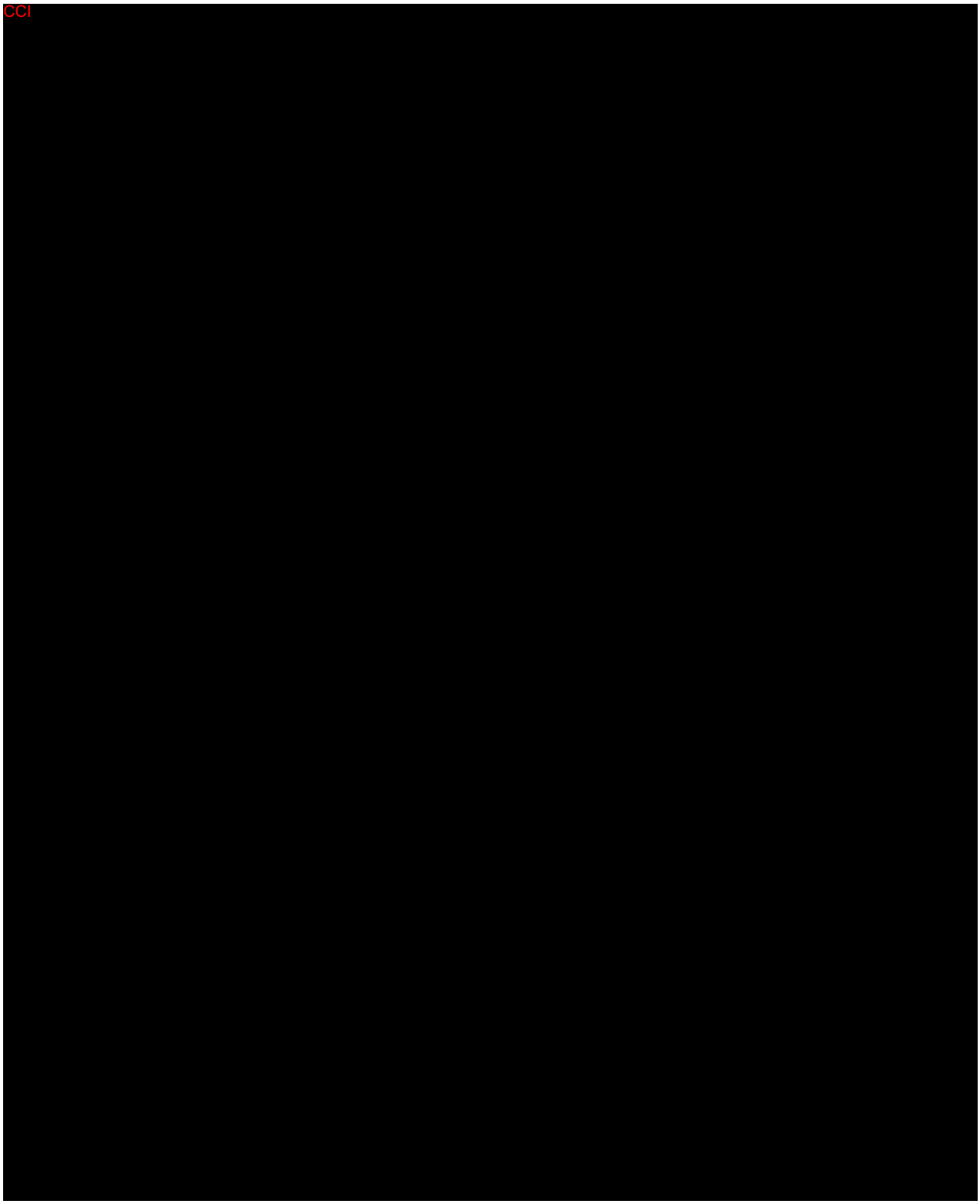
Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

10.8 CCI

CCI



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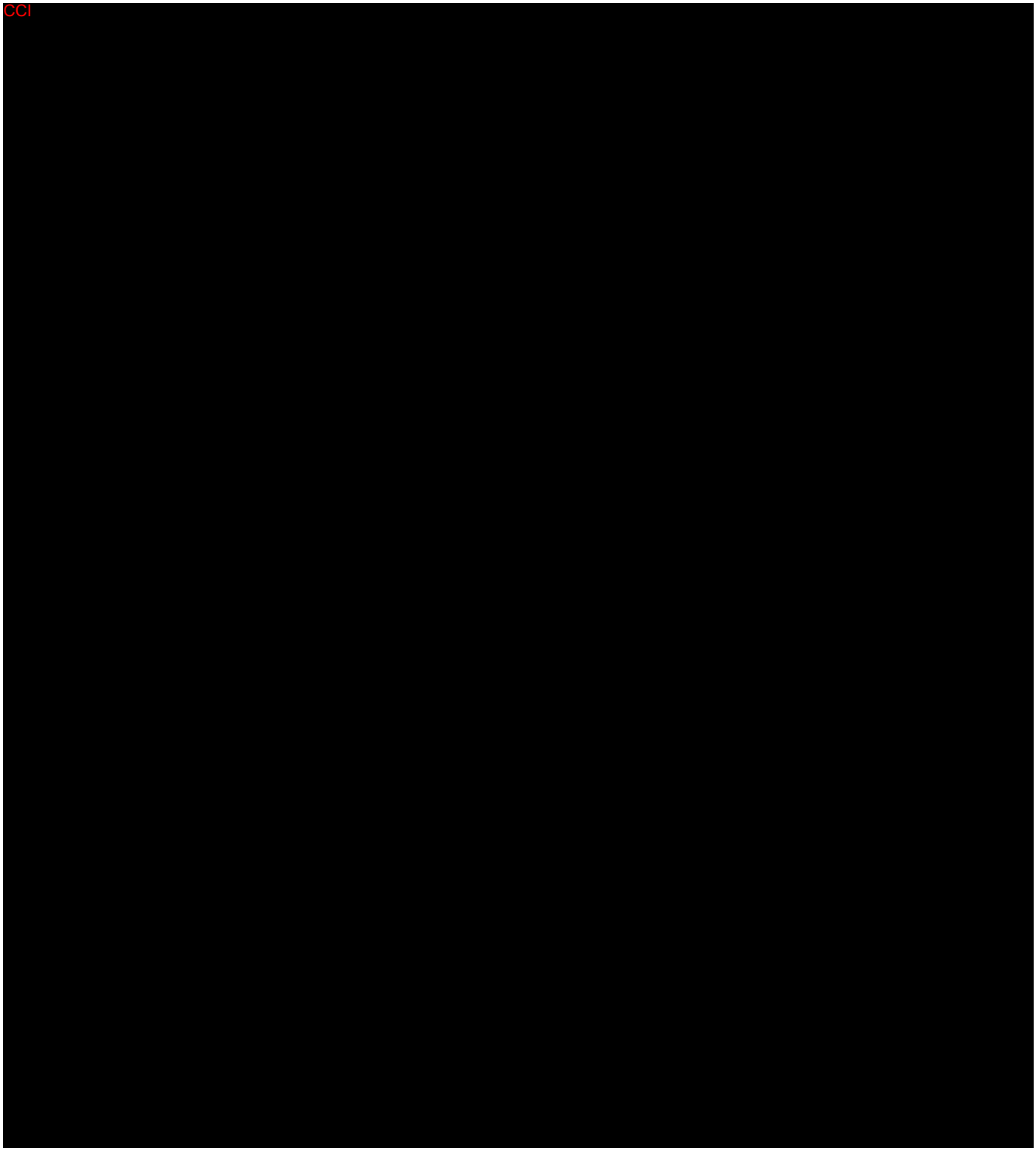

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	Activities of daily living
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-3wks	area under the curve from 0 to 3 weeks
AUC0-6wks	area under the curve from 0 to 6 weeks
BICR	blinded independent central review
bid	twice a day
C	Cycle
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
Cmax	maximum concentration
Cmin	minimum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2

Abbreviation	Expanded Term
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CRP	c-reactive protein
CSFs	Colony Stimulating Factors
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
Ctrough	trough concentration
CV	coefficient variation
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency

Abbreviation	Expanded Term
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EOT	End-of-Treatment
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQol 5-dimension, 5-level Questionnaire
E-R	exposure-response
EU	European Union
FA	final analysis
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM	geometric mean
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGRAC	Human Genetic Resources Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA(s)	interim analysis(ses)

Abbreviation	Expanded Term
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IL-10	Interleukin 10
ILD	interstitial lung disease
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IO	immune-oncology
irAE	immune-related AE
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IUD	intrauterine device
IUO	internal use only
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
KRAS	KRAS proto-oncogene
LAM	lactational amenorrhea method
LLN	lower limit of normal
LPLV	Last Patient, Last Visit
LS	least square

Abbreviation	Expanded Term
mAb	monoclonal antibody
MAP	Modeling and Simulation Analysis Plan
MASCC	Multinational Association of Supportive Care in Cancer
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
NCI	National Cancer Institute
NI	noninferiority
NSCLC	Non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
po	oral
POCBP	participant/participants of childbearing potential
PONCBP	participant/participants of nonchildbearing potential
PP	per-protocol
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks

Abbreviation	Expanded Term
Q3W	every 3 weeks
Q6W	every 6 weeks
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
rHuPH20	recombinant human hyaluronidase
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOP	Standard Operating Procedures
SP-D	surfactant protein D
SpO2	saturation of peripheral oxygen
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
t1/2	half life
T3	triiodothyronine
T4	thyroxine
TEA	Treatment Eligibility Assessment (form)
TPS	tumor proportion score
TSH	thyroid stimulating hormone
TTD	time to true deterioration

Abbreviation	Expanded Term
ULN	upper limit of normal
US	United States
VAS	Visual Analog Scale
VS	vital signs
WBC	white blood cell

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