Official Protocol Title:	A Phase 2 Study to Evaluate Patient Reported Preference for Subcutaneous Pembrolizumab Coformulated with Hyaluronidase (MK-3475A) Over Intravenous Pembrolizumab Formulation in Participants With Multiple Tumor Types (MK-3475A-F11)
NCT number:	NCT06099782
Document Date:	05-Feb-2024

TITLE PAGE

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Protocol Title: A Phase 2 Study to Evaluate Patient Reported Preference for Subcutaneous Pembrolizumab Coformulated with Hyaluronidase (MK-3475A) Over Intravenous Pembrolizumab Formulation in Participants With Multiple Tumor Types (MK-3475A-F11)

Protocol Number: F11-02

Compound Number: MK-3475A

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

Legal Registered Address:

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P.O. Box 2000
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Regulatory Agency Identifying Number(s):

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EU CT	2023-506017-22
EudraCT	Not applicable
jRCT	jRCT2051230147
WHO	Not applicable
UTN	U1111-1293-0814
IND	161465

Approval Date: 05 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 02	05-FEB-2024	To address Health Authority/Agency feedback to update country-specific requirements for France and Poland with mandatory HBV, HCV, and HIV testing at screening.
Amendment 01	05-SEP-2023	To address Health Authority/Agency request to ensure that biases deriving from the potential differences in mental and cognitive condition of participants are mitigated at enrollment and participants are competent to judge presented options.
Original Protocol	19-JUL-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

To address Health Authority/Agency feedback to update country-specific requirements for France and Poland with mandatory HBV, HCV, and HIV testing at screening.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.7.3 Country-specific Requirements: France and Section 10.7.5 Country-specific Requirements: Poland	Added country-specific requirements for HBV, HCV, and HIV testing at screening.	This change was made to address Health Authority/Agency feedback to add mandatory HBV, HCV, and HIV testing at screening to the country-specific appendices for France and Poland.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	Added NCT and jRCT numbers.	NCT and jRCT numbers became available.
Section 1.3, Schedule of Activities	Added an X to the screening column for imaging assessments.	This change was made to clarify that imaging assessments are required during the screening period.

Section Number and Name	Description of Change	Brief Rationale
Section 10.1.1 Code of Conduct for Interventional Clinical Trials	Added statement that the clinical trial will be conducted in compliance with Regulation (EU) 536/2014.	This change was made to comply with Regulation (EU) 536/2014.
Throughout 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 2 Study to Evaluate Patient Reported Preference for Subcutaneous Pembrolizumab Coformulated with Hyaluronidase (MK-3475A) Over Intravenous Pembrolizumab Formulation in Participants With Multiple Tumor Types (MK-3475A-F11)

Short Title: Patient Reported Preference for Subcutaneous MK-3475A Over Intravenous Pembrolizumab Formulation in Multiple Tumor Types

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In participants at least 18 years of age with early-stage or advanced/ metastatic solid tumors.

Primary Objective	**Primary Endpoint**
To evaluate participant preference for MK-3475A SC	Participant preference assessed by response of MK-3475A SC on PPQ question 1
Secondary Objectives	**Secondary Endpoints**
To evaluate the reasons for preference for MK-3475A SC	Participant responses to PPQ question 3
To evaluate participant satisfaction with route of administration of MK-3475A SC and pembrolizumab IV	Participant responses to the TASQ SC and TASQ IV
To evaluate participants choice of administration for the study Treatment Continuation Period	Participant choice of MK-3475A SC for the study Treatment Continuation Period
To evaluate the safety and tolerability of MK-3475A SC and pembrolizumab IV	AE Discontinuation of study intervention due to AEs

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Solid tumour
Population	Participants with early-stage or advanced/metastatic solid tumors
Study Type	Interventional
Intervention Model	Cross-Over This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 144 participants will be randomized to the study as described in Section 9.

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 A	MK-3475A	165 mg/mL	395 mg	SC	Day 1 of each cycle (Q3W) for C1-C3. On completion of C3, participant will be switched to IV infusion.	Test Product
Arm A	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (Q3W) for C4-C6. On completion of C6, participant will receive preferred IMP for up to 17 cycles (melanoma and RCC) or 35 cycles (NSCLC).	Comparator
Arm B	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (Q3W) for C1-C3. On completion of C3, participant will be switched to SC.	Comparator
Arm B	MK-3475A	165 mg/mL	395 mg	SC	Day 1 of each cycle (Q3W) for C4-C6. On completion of C6, participant will receive preferred IMP for up to 17 cycles (melanoma and RCC) or 35 cycles (NSCLC).	Test Product

C=cycle; IMP= investigational medicinal product; IV=intravenous; NSCLC= non–small cell lung cancer; Q3W=every 3 weeks; RCC=renal cell carcinoma; SC=subcutaneous.

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 1 year for adjuvant RCC and melanoma and 2 years for metastatic NSCLC from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be receiving assigned intervention for approximately 1 year for adjuvant RCC and melanoma and 2 years for metastatic NSCLC. After the end of treatment each participant will be followed for up to 90 days. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

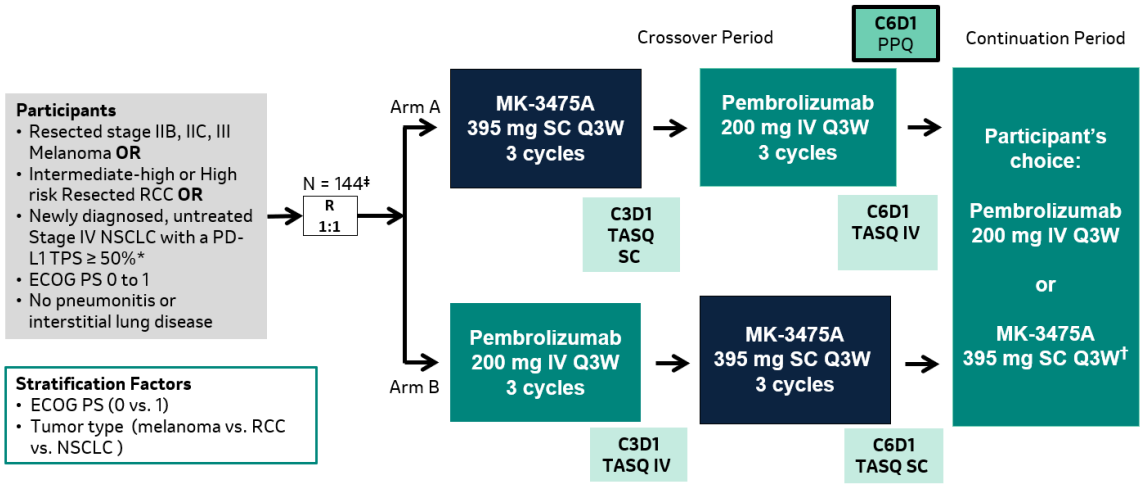
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



ALK=anaplastic lymphoma kinase; C=cycle; D=day; 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; PPQ=Patient Preference Questionnaire; PS=Performance Status; Q3W=every 3 weeks; RCC=renal cell carcinoma; ROS1=c-ros oncogene 1; SC=subcutaneous; TASQ=Therapy Administration Satisfaction Questionnaire; TPS=tumor proportion score.

*For NSCLC, the absence of EGFR, ALK, and ROS1 sensitizing genetic aberrations is required for eligibility purposes.

‡Enrollment cap will be implemented to ensure approximately 33% participants with melanoma, 33% participants with RCC, and 33% participants with metastatic NSCLC.

†Total duration of treatment: 17 cycles for adjuvant treatment of melanoma and RCC and 35 cycles for first line treatment of metastatic NSCLC.

1.3 Schedule of Activities

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.

Table 1 Study Schedule of Activities

Study Period:	**Screening Phase**	**Intervention Phase (21-Day Cycles)**							**EOT/Discon-tinuation**	**Follow-up**		**Notes**
Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35***	**At treatment discontinuation**	**30 days post last dose**	**90 days post last dose contact**	***Cycles 18-35 for NSCLC participants only.**
Cycle Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Schedule Window		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Participant Identification Card	X	X										The Participant Identification Card should be updated with the randomization number at the time of randomization.
Demographics and Medical History	X											
Tobacco Use Assessment (NSCLC participants only)	X											See Section 8.1.4.1 for definitions of cigarette use.
Prior/Concomitant Medication Review	<---------->											Prior medications: Record medications taken within 28 days before first dose and medications regularly administered at intervals greater than 28 days before first dose. Concomitant medications: Record new medications started during the study through the postintervention follow-up, as well as any changes to dose, frequency, and route that occur.
Intervention Randomization		X										Randomization can occur up to 3 days before C1D1 (start of study intervention).

Study Period:	**Screening Phase**	**Intervention Phase (21-Day Cycles)**							**EOT/Discon-tinuation**	**Follow-up**		**Notes**
Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35***	**At treatment discontinuation**	**30 days post last dose**	**90 days post last dose contact**	***Cycles 18-35 for NSCLC participants only.**
Cycle Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Schedule Window		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Vital Status		<----------						---------->				Participants may be contacted for vital status at any time during the study. Collect Vital Status at 90 days post last dose in case of SAE.
Study Intervention Administration												
MK-3475A SC **OR** Pembrolizumab IV Administration[a]		X	X	X	X	X	X	X*				*17 cycles for adjuvant RCC and melanoma; 35 cycles for metastatic NSCLC.
Imaging Assessments												
Tumor Scan	X	<----------						---------->				Perform per SoC for each tumor type.
Brain Scan	X	<----------						---------->				
Bone Scan	X	<----------						---------->				
Safety Assessments												
Full Physical Examination Including Weight and Height	X								X			Collect height at Screening only.
Directed Physical Examination		X	X	X	X	X	X	X		X		For melanoma participants: The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence.
Vital Signs	X	X	X	X	X	X	X	X	X	X		Temperature, HR, RR, BP, and weight.
Pregnancy Testing	X	X	X	X	X	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).

Study Period:	**Screening Phase**	**Intervention Phase (21-Day Cycles)**							**EOT/Discon-tinuation**	**Follow-up**		**Notes**
Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35***	**At treatment discontinuation**	**30 days post last dose**	**90 days post last dose contact**	***Cycles 18-35 for NSCLC participants only.**
Cycle Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Schedule Window		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
12-lead ECG	X											Perform at Screening and as clinically indicated thereafter.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X		Evaluate within 3 days before the planned start of study intervention.
Hematology and Chemistry	X	X	X	X	X	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 of each cycle.
Urinalysis	X											Collect screening samples within 10 days before the start of study intervention.
HBV, HCV, HIV Testing	X											Only perform if required by the local health authority or if known history of infection.
Thyroid Function Tests (TSH, T3, T4)	X		X		X		X	X		X		Screening samples to be collected within 10 days before the first dose of study intervention. Perform at Day 1 of every other cycle starting from C2 until C35 (collect sample within 72 hours prior). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and T4 are acceptable.
PT or INR and aPTT/PTT (baseline only)	X											Collect screening samples within 10 days before the start of study intervention.

Study Period:	**Screening Phase**	**Intervention Phase (21-Day Cycles)**							**EOT/Discon-tinuation**	**Follow-up**		**Notes**
Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35***	**At treatment discontinuation**	**30 days post last dose**	**90 days post last dose contact**	***Cycles 18-35 for NSCLC participants only.**
Cycle Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Schedule Window		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
AE/SAE review	X	X	X	X	X	X	X	X	X	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. Refer to Section 8.5.3 for follow-up of AE/SAE.
Questionnaires												Perform at each visit specified below, in the following order: PPQ then TASQ then HCP. Ensure the PPQ and TASQ are completed BEFORE the participant leaves the Cycle 6 clinic visit.
Patient Preference Questionnaire (PPQ)[a]							X					Administer at C6D1 after study intervention administration.
Therapy Administration Satisfaction Questionnaire-SC (TASQ SC)				X			X					Administer for Arm A at C3D1 and for Arm B at C6D1 after the SC treatment administration.
Therapy Administration Satisfaction Questionnaire-IV (TASQ IV)				X			X					Administer for Arm B at C3D1 and for Arm A at C6D1 after the IV treatment administration.
Participant Choice Questionnaire for Continuation Period							X					Administer after study intervention administration and after completion of both questionnaires (PPQ & TASQ).
Healthcare Professional Questionnaire							X					HCP to complete at C6D1 after the participant has completed study intervention and the PPQ and TASQ.

Study Period:	**Screening Phase**	**Intervention Phase (21-Day Cycles)**							**EOT/Discon-tinuation**	**Follow-up**		**Notes**
Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35***	**At treatment discontinuation**	**30 days post last dose**	**90 days post last dose contact**	***Cycles 18-35 for NSCLC participants only.**
Cycle Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Schedule Window		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Tumor Tissue for Biomarker Status												
PD-L1 Status (NSCLC participants only)	X											PD-L1 status from local laboratory before randomization. PD-L1 must be determined by using the Dako PD-L1 IHC 22C3 pharmDx diagnostic kit with TPS ≥50 positive status defined.
EGFR, ALK, ROS1 (NSCLC participants only)	X											EGFR, ALK, and ROS1 testing from local laboratory before randomization (not required for predominantly squamous histology).

AE=adverse event; ALK=anaplastic lymphoma kinase; aPTT=activated partial thromboplastin time; BP=blood pressure; C=cycle; D=day; ECG=electrocardiogram; EGFR=epidermal growth factor receptor; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HBV=hepatitis B virus; HCP=healthcare professional; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; IHC= immunohistochemistry; INR=international normalized ratio; IV=intravenous; NSCLC=non–small cell lung cancer; PD-L1=programmed cell death ligand 1; POCBP=participant/participants of childbearing potential; PPQ=Patient Preference Questionnaire; PT=prothrombin time; PTT=partial thromboplastin time; RCC=renal cell carcinoma; ROS1=c-ros oncogene 1; RR=respiratory rate; SAE=serious adverse event; SC=subcutaneous; SoC=standard of care; T3=triiodothyronine; T4= thyroxine; TASQ=Therapy Administration Satisfaction Questionnaire; TPS=tumor proportion score; TSH= thyroid-stimulating hormone.

[a] Participant must complete the Treatment Crossover Period including all 3 MK-3475A SC and 3 pembrolizumab IV cycles to complete the C6D1 PPQ.

2 INTRODUCTION

This is a Phase 2 study evaluating patient preference of MK-3475A SC over pembrolizumab IV in participants with resected Stage IIB, IIC, III melanoma, intermediate-high or high risk resected RCC, or newly diagnosed, untreated Stage IV NSCLC with a PD-L1 TPS ≥50%.

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. Specific patient preference data in support of MK-3475A may help demonstrate value to different stakeholders and contribute to the totality of evidence supporting use of MK-3475A SC.

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.

MK-5180 is a variant of rHuPH20. Studies to date have shown that MK-5180 has improved thermal and pH stability compared with rHuPH20. MK-5180 is a glycoprotein and is expressed in CHO cells (CHO-DG44-DHFR) and has the same function of enzyme-mediated hyaluronan degradation, aiding drug product dispersion and dermal layer reconstitution, as commercially available hyaluronidases on the market.

MK-3475A is a coformulation of pembrolizumab with MK-5180. This study will evaluate the patient preference between MK-3475A SC and pembrolizumab IV, both administered Q3W in participants with resected Stage IIB, IIC, III melanoma, intermediate-high or high risk resected RCC, or newly diagnosed, untreated Stage IV NSCLC with a PD-L1 TPS ≥50%.

2.2 Background

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 immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

2.2.1 Subcutaneous Formulation

A strong patient preference has been shown for oncology 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].

In a Phase 2, randomized, open-label study of preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer, 85% of participants (95% CI: 78.5-90.2%) preferred SC; 13.8% preferred IV and 1.3% had no preference. The main reasons for SC preference were reduced clinic time and comfort during administration. HCP perceptions of median patient treatment room time ranged from 33.0-50.0 min with SC and 130.0-300.0 min with IV [O'Shaughnessy, J., et al 2021].

A 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, a Phase 1 evaluation of pembrolizumab SC Q3W, show that the estimated bioavailability of pembrolizumab SC was 66% (95% CI: 58% to 74%), 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]. MK-3475A SC is being evaluated in the Phase 1 study MK-3475A-C18 and the 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. The study is to evaluate the safety, tolerability and PK profile (specifically absorption phase) of pembrolizumab when administered subcutaneously at a concentration of 165 mg/mL or 130 mg/mL, formulated with MK-5180, a recombinant human hyaluronidase dispersant. The primary purpose of this study is to establish the bioavailability of pembrolizumab when administered subcutaneously as MK-3475A for further clinical development. Due to differences in the viscosity of the 2 concentrations (165 mg/mL or 130 mg/mL) of pembrolizumab in the MK-3475A SC formulation, the bioavailability of pembrolizumab will be assessed at each concentration. The results of this study will contribute to an understanding of the PK characteristics of pembrolizumab administered SC with MK-5180 in Q3W and Q6W dosing regimens.

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 injection-site AEs were nonserious and the majority of participants (8 of 9) experienced AEs that were Grade 1. There were 2 reported Grade 2 injection-site AEs (injection-site pruritus and injection-site erythema) and they both occurred in the same participant.

MK-3475A-D77 is a Phase 3 study evaluating the noninferiority of PK exposure between MK-3475A SC and pembrolizumab IV Q6W, both administered in combination with platinum doublet chemotherapy, in participants with treatment-naïve metastatic NSCLC.

2.2.2 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.

Dye dispersion studies performed using sequential or concomitant administration showed that diffusion of Trypan Blue was highest with increasing doses of MK-5180 or when the dye was sequentially administered with minimum delay after the MK-5180 injection. Nonclinical PK studies of MK-5180 indicate negligible systemic exposure. MK-5180 was well tolerated after SC administration in 1-month repeat dose toxicity studies in rats and cynomolgus monkeys.

In light of existing nonclinical and clinical data for pembrolizumab and the lack of toxicity of MK-5180 due to its negligible systemic exposure, nonclinical evaluation MK-3475A was limited to a 1-month SC tolerability study in monkeys. MK-3475A was well tolerated with acceptable local tolerability at the SC injection sites and draining lymph nodes. The MK-3475A formulation contained 165 mg/mL pembrolizumab and 13.8 µg/mL (2000 U/mL) MK-5180, which is equivalent to the maximum concentration for pembrolizumab and is at least 1000-fold higher than the MK-5180 dose in the proposed clinical formulation. In addition, systemic exposure to pembrolizumab in monkeys administered MK-3475A is consistent with the expected systemic exposure in monkeys administered as pembrolizumab alone. The safety of MK-3475A in nonclinical studies is therefore considered comparable to the safety of pembrolizumab alone.

Refer to the respective IBs for preclinical data and a summary of ongoing clinical studies.

2.2.3 Ongoing Clinical Studies

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

2.2.4 Information on Other Study-related Therapy

Not applicable.

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 an alternative SC dosage form of pembrolizumab that could offer patients an alternate form of administration maintaining the efficacy and safety of IV pembrolizumab with shorter administration time, improved patient convenience, satisfaction, and quality of life.

Pembrolizumab delivered by SC administration is expected to maintain a favorable benefit-risk profile comparable to that of IV administration.

Due to large volume of drug given under the skin, injection reactions are expected with MK-3475A.

IV pembrolizumab is approved for the indications being evaluated in this study. The benefit of MK-3475A is expected to be similar to that of IV pembrolizumab.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In participants at least 18 years of age with early-stage or advanced/ metastatic solid tumors.

Primary Objective	**Primary Endpoint**
To evaluate participant preference for MK-3475A SC	Participant preference assessed by response of MK-3475A SC on PPQ question 1
Secondary Objectives	**Secondary Endpoints**
To evaluate the reasons for preference for MK-3475A SC	Participant responses to PPQ question 3
To evaluate participant satisfaction with route of administration of MK-3475A SC and pembrolizumab IV	Participant responses to the TASQ SC and TASQ IV
To evaluate participants choice of administration for the study Treatment Continuation Period	Participant choice of MK-3475A SC for the study Treatment Continuation Period
To evaluate the safety and tolerability of MK-3475A SC and pembrolizumab IV	AE Discontinuation of study intervention due to AEs
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate healthcare provider preference for route of treatment administration	Healthcare provider preference assessed by HCP questionnaire (HCPQ)

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, 2-arm, crossover, multisite, open-label study of MK-3475A SC and pembrolizumab IV in participants with resected Stage IIB, IIC, III melanoma, intermediate-high or high risk resected RCC, or newly diagnosed, untreated Stage IV NSCLC with a PD-L1 TPS ≥50%.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 (Table 1) of the SoA. Details of each procedure are provided in Section 8.

After a screening period of up to 28 days, participants will be randomly assigned in a 1:1 ratio to Arm A or Arm B. One cycle is 3 weeks.

- Arm A: MK-3475A SC Q3W for 3 cycles followed by pembrolizumab IV Q3W for 3 cycles
- Arm B: pembrolizumab IV Q3W for 3 cycles followed by MK-3475A SC Q3W for 3 cycles

This period of 3+3 cycles (6 total cycles) in both treatment arms constitutes the study Treatment Crossover Period. The PPQ will be administered at C6D1 after study intervention administration.

After completion of the Treatment Crossover Period as described above, participants will enter the Treatment Continuation Period. Participants may continue their preferred intervention for up to a total of 17 cycles (for adjuvant melanoma and RCC participants) or 35 cycles (for metastatic NSCLC participants) of treatment.

Randomization will be stratified by ECOG performance status and tumor type (melanoma vs RCC vs NSCLC). Each participant will receive study intervention until one of the conditions for discontinuation of study intervention is met (Section 7.1).

The primary study endpoint is participant preference assessed by response of MK-3475A SC on PPQ question 1. Refer to Section 9 for statistical analysis plan details.

After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in the SoA and Section 8.5. Participants who present with SAEs will be contacted by telephone at 90 days post last dose for SAE follow-up.

Refer to Appendix 7 for country-specific requirements.

4.2 Scientific Rationale for Study Design

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. 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 evaluate preference of MK-3475A SC or pembrolizumab IV with a crossover design using Q3W dosing in participants with selected tumor types.

This is an open-label crossover study with pembrolizumab monotherapy. The intent is to evaluate the proportion of participants that prefer SC pembrolizumab over IV pembrolizumab.

A crossover study design allows participants to experience both forms of administration and minimizes variability as each participant serves as their own control. This removes the interparticipant variability from the comparison between groups and the effect of participant-level covariates.

Randomization will be stratified by the following 2 factors, which all have the potential to influence patient preference.

1. ECOG performance status (0 vs 1): ECOG performance status would balance participants in both arms as there may be a higher dropout rate in the less stable participants.
2. Tumor type (melanoma vs RCC vs NSCLC): The oncology clinical studies to date which have outcome measures based on patient preferences have been conducted in a single tumor type [Rummel, M., et al 2017]. In addition, some of these studies included only patients with early-stage disease [Pivot, X., et al 2013] [O'Shaughnessy, J., et al 2021]. Pembrolizumab has multiple indications across tumor types and disease stages, hence it is important to evaluate patient preference on the mode of administration in multiple tumor types and in both the early-stage (adjuvant setting) and metastatic stage. Therefore, the study will plan to enroll approximately 33% each of participants to be treated in:
    - First line metastatic NSCLC harboring PD-L1≥50%
    - Adjuvant indication for intermediate-high or high risk RCC
    - Adjuvant indication of resected Stage IIB, IIC, III melanoma

The distribution of approximately 33% for each tumor type was chosen to allow for equivalence across the tumors. Further, the 33% metastatic NSCLC tumor type would include data in the same population as MK-3475A-D77 Phase 3 noninferiority study (metastatic NSCLC).

Pembrolizumab monotherapy is approved globally for early-stage RCC and melanoma in the adjuvant setting as well for advanced NSCLC with a TPS score of ≥50%. Evaluating patient preference in patients receiving pembrolizumab or MK-3475A as monotherapy regimen will allow patients to fully appreciate the value of both SC and IV modes of administration with

minimal effect of confounders, such as the addition of other IV chemotherapy drugs or orally administered agents.

The study is designed to allow SC and IV mode of administrations to be administered for 3 cycles each, every 3 weeks (total of 6 cycles) in each arm during the Treatment Crossover Period. The timing of switching the mode of administration within the arm (after 3 cycles) allows participants to experience both modes of administration, in addition to minimizing the overall duration of the study. The 3-week cycle duration allows frequent administrations of both SC and IV mode of administration, and minimizes recall bias compared with the 6-week cycle duration. Additionally, it allows most participants to complete the first 6 cycles in 18 weeks for Q3W versus 36 weeks for Q6W in the Treatment Crossover Period with minimal discontinuation rates when most participants are in stable condition.

Prior oncology studies evaluating preference for SC and IV support this decision as these have included a switch after 3 to 4 cycles. In all these studies, benefits of SC administration were reported with patients experiencing 3 to 4 cycles of each mode of administration, none less than 3 cycles have been conducted. Hence, the timing of switching the mode of administration (crossover after 3 cycles) for the IV and SC routes of administration within the proposed study would provide the necessary insights regarding patient preference and lower rates of discontinuations [Center for Drug Evaluation and Research 2019] [Center for Drug Evaluation and Research 2020] [Center for Drug Evaluation and Research 2017].

4.2.1 Description of Endpoints

4.2.1.1 Patient Preference Measures

4.2.1.1.1 PPQ

The PPQ (developed and owned by Roche Products Limited [Copyright © 2013]) is an instrument that has been developed from patient interviews and includes questions to evaluate directly from participants their preference regarding mode of administration, as well as the strength of the preference, and the reason for the preference. The PPQ has been established as a questionnaire to collect data to derive the primary endpoint to assess patient preference of mode of administration, SC or IV, in several randomized crossover clinical studies [O'Shaughnessy, J., et al 2021] [Rummel, M., et al 2017]. The questions are worded as described below:

Question 1 is “All things considered which method of administration do you prefer” with response options of IV, SC or no preference. This is data to support the primary endpoint of this study, proportions of patients who prefer IV, SC or have no preference.

Question 2 is “If you have a preference for one of the administration routes, how strong is the preference?” with response options of very strong, fairly strong, not very strong.

Question 3 asks patients “If you have a preference for one of the administration routes, what are the TWO main reasons for your preference?” with response options of feels less emotional distressing, requires less time in the clinic, lower level of injection-site pain, feels more comfortable during administration, and option for “other, please specify _____”

allowing the respondent to specify the reason. The participant responses to this question supports the secondary endpoint of proportions of the reasons for patient preference.

As this questionnaire is the primary and secondary endpoint of this study, completion of the questionnaire must be checked BEFORE the participant leaves the site at Cycle 6.

4.2.1.1.2 TASQ

The TASQ is a 12-item questionnaire that asks questions regarding different aspects of satisfaction. The TASQ instruments include questions asking the participants about satisfaction with the relevant mode of administration, experiences related to the administration (eg, pain, swelling, redness, feeling of restriction), convenience and time related questions (time for administration, time associated with the 'setting', time with the HCP), preference and if they would recommend the mode of administration to another patient. There are 2 versions of this questionnaire, a subcutaneous version (TASQ SC) and an intravenous version (IV). The questions are similar but ask about the relevant mode of administration experienced [Theodore-Oklota, C., et al 2016]. In this study, the participant will complete the appropriate version of the questionnaire based on the assignment of SC or IV at Cycle 3, after completing therapy at this visit, and complete the other version of the questionnaire when completing the other mode of administration at Cycle 6.

4.2.1.1.3 Participant Choice Questionnaire

The participant's choice of MK-3475A SC or pembrolizumab IV for the Treatment Continuation Period will be documented on the Participant Choice Questionnaire, administered at C6D1 after study intervention administration and completion of the PPQ and TASQ.

4.2.1.2 Health Care Professional Questionnaire

This is a questionnaire that asks health care professionals their preference of IV, SC, or "no preference". This will be completed one time by each HCP for each participant. The HCP is the study nurse who has administered both IV and SC study intervention to the participant.

4.2.1.3 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.

4.3 Justification for Dose

4.3.1 MK-3475A Subcutaneous Dose

The planned dose of pembrolizumab in MK-3475A for this study is 395 mg Q3W. Available PK data from the FIH, Phase 1 study of MK-3475A, Study MK-3475A-C18, was used to develop a population PK model and estimate the bioavailability of pembrolizumab when

administered SC as MK-3475A (see Section 2.2.1 for details) to enable Phase 3 dose selection and further clinical development. Study MK-3475A-C18 was amended to include an arm to evaluate the PK profile of pembrolizumab when administered Q3W as MK-3475A SC in participants with unresectable, advanced melanoma.

PK model-based simulations indicate that a pembrolizumab SC dose of either 395 mg Q3W or 790 mg Q6W leads to comparable exposures as the approved pembrolizumab IV doses. 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. Refer to the MK-3475A IB for further PK data.

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 200 mg Q3W. Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is a globally approved dose of pembrolizumab for adults across all indications.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant 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 EEA, the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The maximum follow-up period will be when study intervention has been completed (1 year for adjuvant RCC and melanoma and 2 years for metastatic NSCLC) for all evaluable participants. The last study-related contact will be the LPLV date for the final prespecified analysis.

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.

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. The participant must have a histologically- or cytologically-confirmed early stage or advanced/ metastatic solid tumor by pathology report who meet all the listed conditions of eligibility for 1 of the following indications:

- Melanoma:
  - Has surgically resected and histologically/pathologically confirmed diagnosis of Stage IIB and IIC (pathological or clinical), or III cutaneous melanoma per AJCC eighth edition guidelines (Appendix 8). Participants with BRAF-mutated melanoma are eligible to enroll.
    - A therapeutic lymph node dissection defined as an anatomically complete lymphadenectomy of the involved nodal basin for macroscopic disease (clinically, radiographically, or sonographically [if performed] detectable lymph nodes) is required (Appendix 9). SLN biopsy and CLND for microscopic disease, however, are not required.
  - Has not received any prior systemic therapy for their melanoma beyond surgical resection.
    Note: In case of an indication for post lymph node dissection radiotherapy, this must have been completed within 11 weeks after surgery and 2 weeks before treatment initiation. Radiotherapy may alter the process of wound healing. If the wound healing is not adequate, the participant is not eligible.
  - No more than 13 weeks have elapsed between final surgical resection and randomization. Treatment should start only after adequate wound healing from the surgical procedure as assessed by the investigator. If there is a delay of ≤2 weeks exceeding 13 weeks due to unforeseen circumstances, the eligibility should be discussed with the Sponsor and the decision documented. A delay of up to 1 week for screening imaging requirements will be allowed if Sponsor has allowed up to 1 week extension between surgical resection and randomization.
    Note: Final surgical resection is defined in this protocol as the final surgical

procedure required to achieve complete resection of melanoma and render the participant disease free.

- Has no evidence of metastatic disease on imaging after resection as determined by investigator assessment. All suspicious lesions amenable to biopsy should be confirmed negative for malignancy.

- **NSCLC:** Has histologically or cytologically confirmed diagnosis of squamous or nonsquamous Stage IV NSCLC with a PD-L1 TPS ≥50% determined using the Dako PD-L1 IHC 22C3 pharmDx diagnostic kit (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.
  - 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.
  - Has measurable disease as assessed by the local site investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.

- **RCC:** Has histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features. Diagnosis of RCC with clear cell component is to be made by the investigator:
  - Has intermediate-high or high risk of RCC recurrence as defined by the following pathological tumor-node-metastasis and Fuhrman grading status [Leibovich, B. C., et al 2003] [Rini, B. I., et al 2009] [Fuhrman, S. A., et al 1982]:
    a. Intermediate-high risk RCC
       - pT2, Gr 4 or sarcomatoid, N0, M0
       - pT3, Any Gr, N0, M0

    b. High risk RCC
       - pT4, Any Gr N0, M0
       - pT Any stage, Any Gr, N+, M0
  - Have undergone a partial nephroprotective or radical complete nephrectomy with negative surgical margins.
  - Must have undergone a nephrectomy ≥28 days before signing informed consent and ≤12 weeks before randomization.

- Must be tumor free as assessed by the investigator ≤28 days from randomization.

2. Have a life expectancy of at least 3 months.

Demographics

3. Is an individual of any sex/gender, from 18 years of age inclusive, at the time of providing the informed consent.

Assigned Male Sex at Birth

No measures.

Assigned Female Sex at Birth

4. 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), 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 120 days after the last dose of study intervention. 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 (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a 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 8.4.5.
  - 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

5. The participant has provided documented informed consent for the study.

Additional Categories

6. The participant can complete the questionnaires without assistance, in the opinion of the primary investigator.
7. 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.
8. HIV-infected participants must have well controlled HIV on ART, defined as:
   a. Having a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening.
   b. Having achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening.
   c. Have not had any AIDS-defining opportunistic infections within the past 12 months.
   d. Have been on a stable ART regimen, without changes in drugs or dose modification, for at least 4 weeks before randomization and agree to continue ART throughout the study.
   e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
9. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks, and have undetectable HBV viral load before randomization. Hepatitis B screening tests are not required unless:
   a. Known history of HBV infection
   b. As mandated by local health authority
10. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.
    Note: Participants must have completed curative antiviral therapy at least 4 weeks before randomization.
    Hepatitis C screening tests are not required unless:
    a. Known history of HCV infection
    b. As mandated by local health authority
11. Adequate organ function as defined in the following table Table 2. Specimens must be collected within 10 days before the start of study intervention.

Table 2 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 **OR** GFR	Measured or calculated creatinine clearance ≥30 mL/min **OR** GFR criterion ≥30 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; PTT=partial thromboplastin time; 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 participants assigned female sex at birth and F = 1 for participants assigned male sex at birth

12. An ECOG performance status of 0 to 1 assessed within 3 days before the start of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1. Diagnostic exclusions related to the tumor types evaluated:

a. NSCLC
   - Diagnosis of small cell lung cancer or, for mixed tumors, presence of small cell elements.

b. Melanoma
   - Has ocular, mucosal, or conjunctival melanoma.
     Note: resected acral cutaneous melanoma is allowed.

c. RCC
   - Has had major surgery, other than nephrectomy, within 12 weeks before randomization.
     Note: If participants received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention before starting study treatment.
   - Has received prior radiotherapy for RCC.
   - Has residual thrombus post nephrectomy in the vena renalis or vena cava.

Prior/Concomitant Therapy

2. 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).
3. Received prior systemic anticancer therapy including investigational agents within 4 weeks before randomization.
4. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
   Refer to Section 6.5 for information on COVID-19 vaccines.

NSCLC Participants

5. Received prior radiotherapy within 2 weeks of start of study intervention, or has radiation-related toxicities, requiring corticosteroids.
   Note: Two weeks or fewer of palliative radiotherapy for non-CNS disease is permitted. The last palliative radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.
6. Received prior systemic anticancer therapy for their metastatic NSCLC.
   Note: Prior treatment with neoadjuvant or adjuvant therapy for nonmetastatic NSCLC is allowed as long as therapy was completed at least 12 months before diagnosis of metastatic NSCLC.
7. Received radiation therapy to the lung that is >30 Gray within 6 months of start of study intervention.

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 medication.Note: The use of inhaled or topical steroids and systemic steroids at physiologic doses (up to 5 mg/m^2/day prednisone equivalent with maximum dose of 10 mg daily) is allowed on study.
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, melanoma in situ, 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.
    Note: Participants with a history of mucosal or uveal melanoma are excluded from this study even if diagnosis and treatment were completed >3 years ago.
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 pembrolizumab and/or any of its excipients.
13. Active autoimmune disease that has required systemic treatment in the 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.
15. Active infection requiring systemic therapy.
16. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.
17. 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.
18. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

19. History of allogeneic tissue/solid organ transplant.
20. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

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

No restrictions are required.

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 once for eligibility.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention 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 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 intervention(s) to be used in this study are outlined in Table 3.

Table 3 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 A	Experimental	MK-3475A	Biological/Vaccine	Injection, Solution	165 mg/mL	395 mg	SC	Day 1 of each cycle (Q3W) for C1-C3. On completion of C3, participant will be switched to IV infusion.	Test Product	IMP	Central
Arm A	Active Comparator	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (Q3W) for C4-C6. On completion of C6, participant will receive preferred IMP for up to 17 cycles (melanoma and RCC) or 35 cycles (NSCLC).	Comparator	IMP	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 B	Active Comparator	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (Q3W) for C1-C3. On completion of C3, participant will be switched to SC.	Comparator	IMP	Central
Arm B	Experimental	MK-3475A	Biological/Vaccine	Injection, Solution	165 mg/mL	395 mg	SC	Day 1 of each cycle (Q3W) for C4-C6. On completion of C6, participant will receive preferred IMP for up to 17 cycles (melanoma and RCC) or 35 cycles (NSCLC).	Test Product	IMP	Central

C=cycle; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; NSCLC=non–small cell lung cancer; Q3W=every 3 weeks; RCC=renal cell carcinoma; SC=subcutaneous.

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 3 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

Treatment consists of a Treatment Crossover Period (3+3 Cycles of either MK-3475A followed by pembrolizumab IV [Arm A] or pembrolizumab IV followed by MK-3475A [Arm B]) followed by preferred intervention for up to a total of 17 cycles (melanoma and RCC) or 35 cycles (NSCLC) of treatment.

Note: The number of treatments is calculated starting with the first dose.

Participants are not permitted to switch prematurely to the other study intervention during the first 6 cycles of treatment.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-3475A or pembrolizumab are provided in the Pharmacy Manual.

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 1:1 ratio to Arm A (MK-3475A SC Q3W for 3 cycles followed by pembrolizumab IV Q3W for 3 cycles) and Arm B (pembrolizumab IV Q3W for 3 cycles followed by MK-3475A SC Q3W for 3 cycles), respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. ECOG performance status (0 vs 1)
2. Tumor type (melanoma vs RCC vs NSCLC)

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.

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.

The following medications and vaccinations are prohibited during the study:

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

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention 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: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- 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 8.5.

6.5.1 Rescue Medications and Supportive Care

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.

6.6 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 4.

Table 4 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, or 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	

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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
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 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		
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 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal

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

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × 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 5.

Table 5 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
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.	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
	Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	
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

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; 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 3 weeks or 21 days of the originally scheduled dose and within 42 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.

6.7 Intervention After the End of the Study

Not applicable.

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

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.

Participants must complete the Treatment Crossover Period (see Section 4.1) including all 3 MK-3475A SC and 3 pembrolizumab IV cycles in order to complete the C6D1 PPQ. Any participant who does not complete the Treatment Crossover Period will be discontinued from study intervention.

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

- The participant requests to discontinue study intervention.
- Any prohibited concomitant therapy outlined in Section 6.5.
- 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 before 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.
- 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.

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 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, 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 will not exceed the volume mentioned 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 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 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 and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant 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 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 dated signature.

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.

8.1.2 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.

8.1.5 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 case of SAE, record medication through the 90-day Follow-up Period.

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.

8.1.7 Assignment of 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 an appropriately qualified designee according to the specifications within the pharmacy manual.

8.1.8.1 Timing of Dose Administration

Study interventions should be administered after all procedures and assessments have been completed.

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 8.5.

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

The local laboratory will use the tissue sample to ascertain PD-L1 status using the Dako PD-L1 IHC 22C3 pharmDx diagnostic kit. The Dako PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status in participants with NSCLC for treatment with pembrolizumab. EGFR, ALK, and ROS1 at the local laboratory must use tumor tissue for testing to confirm absence of sensitizing alterations.

8.2 Questionnaires

Planned time points for all questionnaires are provided in the SoA.

The PPQ and TASQ in this study will be completed by the participant on an eCOA tablet. The implementation of the electronic version will follow all necessary global confidentiality regulations, including the EMA Guideline on computerized systems and electronic data in clinical trials. Refer to the Site Manual for eCOA site level operations.

As the PPQ is the primary and secondary endpoint of this study, completion of the questionnaire must be checked BEFORE the participant leaves the site at the Cycle 6 Visit.

The participant's choice of MK-3475A SC or pembrolizumab IV for the Treatment Continuation Period will be documented on the Participant Choice Questionnaire, administered at the Cycle 6 Visit after study intervention administration and completion of the PPQ and TASQ.

8.3 Imaging Assessments

8.3.1 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.

Imaging should be performed per SoC for each tumor type. Treatment beyond disease progression is not allowed.

8.4 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.

8.4.1 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.

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

8.4.1.1 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.

8.4.1.2 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.

For melanoma participants: The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence.

8.4.1.3 Injection Site Reactions

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

Any injection-site AEs should be recorded in the AE eCRF.

8.4.2 Vital Signs

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

- VS include temperature, HR, RR, and BP.
- BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- VS will be measured in a semisupine position after 5 minutes rest.

8.4.3 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.

8.4.4 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.

8.4.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.4.5 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 as per SoA at every protocol treatment cycle during intervention.
  - Pregnancy testing (urine and/or serum) should be conducted at the end of relevant systemic exposure. The length of time required to continue pregnancy testing for each study intervention is:
    - 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.

8.4.6 Performance Assessments

8.4.6.1 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 (see Appendix 10) 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).

8.5 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.

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

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 8.5.3. 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.

8.5.1 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 8.5.5, 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 6.

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

Table 6 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting 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	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 (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
ECI (does 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
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)

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

8.5.2 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.

The PPQ designed for participant respondents that are included in the study requires the free text field to be reviewed for SAE identification and reporting by the investigator or a qualified designee. The assessment of these SAEs should follow the requirements outlined in Section 8.5.

8.5.3 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.

8.5.4 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.

8.5.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are 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 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.

Refer to Appendix 7 for country-specific requirements.

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

Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

8.5.7 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. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× 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).

8.6 Treatment of Overdose

An overdose of MK-3475A 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.

8.7 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.9 Biomarkers

Biomarker samples will not be collected in this study.

8.10 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.11 Medical Resource Utilization and Health Economics

Not applicable.

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.

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.

Participants may be rescreened one time after initially failing to meet the inclusion/exclusion criteria.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

8.12.3 Posttreatment 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.

8.12.4 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 principal statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

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

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule(s) for study treatment assignment. The algorithm for the randomized allocation of participants will be implemented in an IVRS by a study vendor.

9.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

There are no hypotheses associated with any of the objectives.

9.3 Analysis Endpoints

Participant preference and satisfaction measure endpoints and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.3.1 Participant Preference and Satisfaction Measure Endpoints

Primary

- Participant preference assessed by response of MK-3475A SC on PPQ question 1

Secondary

- Participant responses to question 3 of the patient preference questionnaire
- Participant responses to question 1 of the TASQ SC and TASQ IV
- Participants' choice of MK-3475A SC for the study treatment Continuation Period

Exploratory

- Healthcare provider preference assessed by HCP question (HCPQ)

9.3.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test results, and vital signs. Safety measurements are provided in Section 4.2.1.2 and Section 8 of the protocol.

9.4 Analysis Populations

9.4.1 Participant Preference and Satisfaction Measure Analysis Populations

The Full Analysis Set (FAS) population will be used for the analysis of participant preference and satisfaction measure primary endpoint in this study.

The FAS population will include all randomized participants who received all three doses of MK-3475A subcutaneous and all three doses of Pembrolizumab intravenous during the treatment crossover period and subsequently answered at least question 1 of the PPQ at Cycle 6 Day 1 (C6D1).

9.4.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population.

Analyses of laboratory test results and vital signs will include only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis will assess change from baseline, a baseline measurement is also required.

9.5 Statistical Methods

9.5.1 Statistical Methods for Participant Preference and Satisfaction Measure Analyses

The primary objective of this study is to evaluate participant preference for MK-3475A SC based on the participant preference rate (PPR). PPR is defined as the proportion of participants indicating an overall preference for MK-3475A SC in question 1 of the PPQ. The point estimate of PPR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]. Additionally, PPR will be descriptively summarized by treatment arm as a supportive analysis.

The secondary participant preference and satisfaction measure variables will be summarized descriptively.

Table 7 Analysis Strategy for Key participant preference and satisfaction measure Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint Analysis				
Proportion of participants who prefer MK-3475A SC with treatment preference assessed by PPQ question 1	P	Estimation: point estimate, 95% CI using exact binomial method proposed by Clopper and Pearson	FAS	Not Applicable
Key Secondary Endpoints Analysis				
Participant responses to question 3 of the patient preference questionnaire	P	Descriptive summary	FAS	Participants with missing data are considered to have no response
Participant responses to question 1 of the TASQ SC and TASQ IV	P	Descriptive summary	FAS	Participants with missing data are considered to have no response
Proportion of participants who choose MK-3475A SC for the study treatment Continuation Period	P	Descriptive summary	Participants who choose to receive a treatment in continuation period	Not Applicable

FAS=Full Analysis Set.
[a] P=Primary approach

9.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results and vital signs. Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and preferred term [PT]), and when specified by NCI CTCAE grade. For each participant, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The overall safety endpoints include the number of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE, Grade 3-5 AE, AEOSI, who discontinue from study intervention due to an AE, or with an AE resulting in death. The number and percentage for injection-site reactions will be provided for participants who receive MK-3475A SC treatment.

The safety evaluation will include a summary of the number and percentage of participants with each type of AE by treatment intervention for cycles 1-3 and cycles 4-6 in the Crossover

Period, and by treatment arm in the overall study. For overall safety endpoints, specific AEs and safety topics of special interest that meet predefined threshold rules, point estimates and 95% CIs for the differences between treatment groups (i.e., treatment interventions for cycles 1-3 in the Crossover Period, treatment interventions for cycles 4-6 in the Crossover Period and treatment arms in the overall study) in the percentages of participants with events will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985].

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test**.**

For continuous safety measures, such as change from baseline in laboratory, vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment arm.

9.6 Interim Analyses

There are no formal interim analyses planned in this study. An interim analysis may be conducted to support a future regulatory submission. The results of this interim analysis will be evaluated by a Sponsor's Executive Oversight Committee.

The final analysis (FA) is to be performed approximately 14.5 months after the first participant is enrolled. Participants will continue to be followed after the final analysis until the overall study ends.

9.7 Multiplicity

No multiplicity adjustment is planned as there are no hypotheses in this study.

9.8 Sample Size and Power Calculations

In this study, approximately 144 participants will be randomized to treatment arms A or B.

9.9 Subgroup Analyses

To determine whether the participant preference rate (PPR) is consistent across various subgroups, the estimate of PPR (with a nominal 95% CI) will be estimated and plotted within each category of the following subgroup variables:

- ECOG PS (0, 1)
- Tumor type (Melanoma, RCC, NSCLC)

For subgroups determined by the levels of a stratification factor, the derived strata based on eCRF collected information (as compared to the IRT/IVRS strata) will be used as the default. If the number of participants in a category of a subgroup variable is less than 10% of the FAS population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

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), Regulation (EU) 536/2014, the 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 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will decide on any recommendations 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 8 will be performed by the local laboratory.
- 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 8 Protocol-required Clinical 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, FT4, TSH)			

Laboratory Assessments	Parameters
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; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=international normalized ratio; 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; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC= white blood cell. 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.	

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."

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 8.5.6 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 addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.5.1.
- 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 reexposed 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; (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 REEXPOSURE 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 8.5.1 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 following menarche and capable of becoming pregnant 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, Müllerian 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 2 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 nonhormonal 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[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Nonhormonal 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.
Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner 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] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation. [c] IUS is a progestin-releasing IUD. Note: • Tubal occlusion includes tubal ligation

Refer to Appendix 7 for country-specific requirements.

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

Not applicable.

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.

Section 1.3 Schedule of Activities – Screening and Treatment Phase

Pregnancy testing must be performed at each cycle during treatment as well as at the end of study intervention.

10.7.2 Chile

8.5.5 Pregnancy and Exposure During Breastfeeding

Follow-up of all reported pregnancies and childbirth is mandatory. Additionally, follow-up of the newborns for up to 6 months of age is mandatory.

10.5.2 Contraception Requirements

Use of emergency hormonal contraception is permitted for POCBPs who have engaged in unprotected sexual activity.

10.7.3 France

Section 1.3 Schedule of Activities

Pregnancy testing must be performed prior to study intervention administration at each cycle during the treatment period, as well as before the last dose of study intervention, and 30 days after the last dose at the end of study intervention. HBV, HCV, and HIV testing at screening is mandatory.

Section 4.1 Overall Design

No efficacy analysis is planned for this open-label study. Additionally, the safety profile of pembrolizumab is well established, therefore this study will not include an external or internal DMC, however medical monitoring will be performed on a continual basis.

10.7.4 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.

10.7.5 Poland

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.8 Appendix 8: Melanoma Staging

The AJCC has designated staging by TNM classification to define melanoma.

Staging tables are adapted from the AJCC, Eighth Edition. Refer to the AJCC guidelines for more information [Gershenwald, J. E., et al 2017].

Staging tables are provided as follows:

[Table 9]	Melanoma T Category Definition
[Table 10]	Melanoma N Category Definition
[Table 11]	Melanoma M Category Definition
[Table 12]	AJCC Pathological (pTNM) Staging Groups
[Table 13]	AJCC Clinical Prognostic (cTNM) Staging Groups

Table 9 Melanoma T Category Definition

T-Stage	**T-Stage Definition (Thickness and Ulceration)**
TX	Primary tumor thickness cannot be assessed (ulceration status not applicable)
T0	No evidence of primary tumor (ulceration status not applicable)
Tis	Melanoma in situ (ulceration status not applicable)
T1	≤1.0 mm (ulceration status unknown or unspecified)
T1a	<0.8 mm without ulceration
T1b	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration
T2	>1.0-2.0 mm (ulceration status unknown or unspecified)
T2a	>1.0-2.0 mm without ulceration
T2b	>1.0-2.0 mm with ulceration
T3	>2.0-4.0 mm (ulceration status unknown or unspecified)
T3a	>2.0-4.0 mm without ulceration
T3b	>2.0-4.0 mm with ulceration
T4	>4.0 mm (ulceration status unknown or unspecified)
T4a	>4.0 mm without ulceration
T4b	>4.0 mm with ulceration
T=primary tumor.	

Table 10 Melanoma N Category Definition

N Category	Number of Tumor-Involved Regional Lymph Nodes	Presence of In-transit, Satellite, and/or Microsatellite Metastases
NX	Regional Nodes not assessed (exception: pathological N category not required for T1 melanomas, use clinical N information)	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (detected by SLN biopsy)	No
N2b	Two or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

N=regional lymph node

Table 11 Melanoma M Category Definition

M Category	**Anatomic Site**	**Lactate Dehydrogenase Level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated
CNS=central nervous system; M=distant metastasis		

Table 12 AJCC Pathological (pTNM) Staging Groups

Staging (AJCC Eighth Edition)			
0	Tis	N0	M0
IA	T1a	N0	M0
IA	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	T3b	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIB	T0	N1b, N1c	M0
IIIC	T0	N2b, N2c, N3b, N3c	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T1a/b-t2a	N1b/c or N2b	M0
IIIB	T2b/T3a	N1a-N2b	M0
IIIC	T1a-T3a	N2c or N3a/b/c	M0
IIIC	T3b/T4a	Any N≥N1	M0
IIIC	T4b	N1a-N2c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

AJCC=American Joint Committee on Cancer; M0 = No evidence of distant metastases; N0 = No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis; pTNM=AJCC Pathological; T=primary tumor.

Table 13 AJCC Clinical Prognostic (cTNM) Staging Groups

Staging (AJCC Eighth Edition)			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	T3b	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T, Tis	≥N1	M0
IV	Any T	Any N	M1

AJCC = American Joint Committee on Cancer; M0 = No evidence of distant metastases; N0 = No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis.

10.9 Appendix 9: Surgical Considerations (Melanoma)

Recommendation for Surgical Management:

a. Wide excision with a 1-2 cm clinical margin surrounding the primary lesion or biopsy scar is recommended for entry on to this protocol. If the primary melanoma is completely resected within the wide excision margin, the resection is acceptable.
b. For lesions with Breslow's thickness >2 mm, a 2 cm minimum clinical margin is recommended when anatomically feasible. On other body sites with limited tissue availability a narrower margin is acceptable to avoid excessive morbidity.
c. For subungual melanoma, interphalangeal metacarpal/metatarsal-phalangeal amputation with histologically negative margins constitutes an adequate wide excision.
d. The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular or deep fascia. Fascia may be included at the discretion of the operating surgeon.
e. The pathology report should report surgical margins and whether surgical resection margins are involved with the tumor, including close margin (eg, <1 mm between tumor and resection margin) and tumor abutting margin.

Closure of the defect (eg, primary advancement flap closure, split thickness skin graft, complex reconstruction) is at the discretion of the surgeon.

Therapeutic lymph node dissection for macroscopic disease

For this study a therapeutic axillary lymph node dissection is required for macroscopic disease (ie, clinically, radiographically, sonographically [if performed] detectable nodes).

Axillary Lymphadenectomy:

Axillary node dissection must include all involved nodes or at least 10 nodes are required for adequacy if this exceeds the number of involved nodes taken from Levels I and II and the Level III nodes. The boundaries of the dissection should include the axillary vein superiorly beginning at the thoracic outlet and coursing to the latissimus dorsi tendon. The lateral border of the dissection is the anterior edge of the latissimus dorsi muscle. The posterior boundary is the subscapular muscle. The anterior border of the resection is the pectoralis major group. The inferior boundary of the dissection should be the juncture of the latissimus dorsi and the serratus anterior muscles.

The contents within these boundaries should be completely removed with the exception of the long thoracic nerve and the thoracodorsal nerve, which should be identified during the dissection and preserved throughout. As stated, the pectoralis minor muscle may be divided or sacrificed with the specimen at the discretion of the surgeon. Care should be exercised that in the superior part of the dissection, the anterior pectoral nerve is not injured. The preferable approach to the axilla is through a horizontal incision in the line of the skin crease, 3 or 4 cm below the apex of the skin fold of the axilla.

Inguinal Lymphadenectomy:

A superficial femoral node dissection should be performed by excising all of the nodes inferior to the inguinal ligament and bounded by the medical border of the sartorius muscle in the lateral border of the adductor magnus muscle. The fatty and lymphatic tissues should be dissected carefully off the femoral vessels and nerves all the way up to the inguinal canal and for 3 cm superior to the inguinal ligament. The saphenous vein is resected to ensure complete excision of the lymph nodes. Transposition of the sartorius muscle should be considered (but is not mandatory) to cover the femoral vessels after complete lymphatic excision. Ideally, this area should be entered through a curvilinear incision staring laterally over the inguinal ligament and curving medially and inferiorly ending over the midpoint of the adductor magnus muscle. A minimum of 5 nodes must be resected for adequacy if this exceeds the detected number of involved nodes.

Deep Inguinal and External Iliac Node Dissection:

Deep inguinal and external iliac node dissection can be most easily approached by incising the abdominal wall musculature 3 or 4 cm superior to the inguinal ligament. This incision is taken down through the external oblique, internal oblique and transversus muscles, and the surgeon at that point stays extraperitoneally as in the approach to the iliac vessels for renal transplantation. With this approach, the external, internal and common iliac arteries are exposed and the lymphatics coursing among the iliac vessels are excised. A full ilioinguinal (deep) inguinal node dissection is advised in case of overt inguinal node- metastasis and when Cloquet’s node is positive.

(Modified) Radical Neck Dissection:

Classic or modified radical neck dissection must be performed for patients with melanoma of the head and neck and involved nodes. A minimum of 15 nodes must be resected for adequacy if this exceeds the detected number of involved nodes. Patients with melanoma located on the ear and anterior scalp and face require superficial parotidectomy along with a radical neck procedure. The boundaries of the radical neck dissection are inferiorly the clavicle; the mandible, the mastoid and the tail of the parotid gland superiorly; the anterior border of the trapezius muscle posteriorly and the strap muscle of the larynx anteriorly. The sternocleidomastoid muscle may be sacrificed or preserved at the surgeon's discretion. For posterior nodes, the radical neck incision must be extended posteriorly or a second incision must be made so that the suboccipital nodal group can be resected. For posterior neck dissection, surgical and pathological resection of at least 5 nodes are required for adequacy if this exceeds the detected number of involved nodes.

10.10 Appendix 10: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: adapted from[ECOG ACRIN Cancer Research Group 2016]

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
$AUC_{0\text{-}3wks}$	area under the curve from 0 to 3 weeks
BP	blood pressure
BRAF	proto-oncogene B-raf
C	cycle
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CLND	complete lymph node dissection
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
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Abbreviation	Expanded Term
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
cTNM	AJCC Clinical Prognostic
C_{trough}	trough concentration
CYP	cytochrome P450
D	day
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCOA	electronic clinical outcome assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EU CT	European Union Clinical Trials
FA	final analysis
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gr	grade

Abbreviation	Expanded Term
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCP	health care professional
HCPQ	HCP questionnaire
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
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
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
IO	Immune oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
jRCT	Japan Registry of Clinical Trials
KRAS	Kirsten rat sarcoma viral oncogene homolog
LLOQ	lower limit of quantitation

Abbreviation	Expanded Term
LPLV	Last Patient, Last Visit
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
OTC	over the counter
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PK	pharmacokinetic
POCBP	participant/participants of childbearing potential
PPQ	Patient Preference Questionnaire
PPR	participant preference rate
PSA	prostate-specific antigen
pTNM	AJCC Pathological
Q3W	every 3 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
rHuPH20	recombinant human hyaluronidase
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SLAB	supplemental laboratory test(s)
SLN	sentinel lymph node
SoA	schedule of activities

Abbreviation	Expanded Term
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TASQ	Therapy Administration Satisfaction Questionnaire
TNM	tumor, node, metastasis
TPS	tumor proportion score
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number
VS	vital signs

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