Official Protocol Title:	A Phase 1b Multi-center Clinical Study of Selumetinib (MK-5618) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Solid Tumors.
NCT number:	NCT03833427
Document Date:	28-APR-2021

Title Page

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Protocol Title: A Phase 1b Multi-center Clinical Study of Selumetinib (MK-5618) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Solid Tumors.

Protocol Number: 001-04

Compound Number: MK-5618

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	139596

Approval Date: 28 April 2021

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	28-APR-2021	This amendment was issued to update the dose modification and toxicity management guidelines for irAEs.
Amendment 03	09-JAN-2019	This is a Canada-specific amendment to address Agency feedback.
Amendment 02	20-DEC-2018	This amendment was issued to address Agency feedback.
Amendment 01	19-OCT-2018	This amendment incorporates the approved Study Design (Figure 1).
Original protocol	12-OCT-2018	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

This amendment was issued to update the dose modification and toxicity management guidelines for irAEs.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
6.6.1.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	The dose modification and toxicity management guidelines for irAEs and table were updated.	The dose modification and toxicity management guidelines for irAEs and table were updated as requested by the U.S. FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1b Multi-center Clinical Study of Selumetinib (MK-5618) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Solid Tumors.

Short Title: A Phase 1b Study of Selumetinib plus Pembrolizumab in Metastatic/Advanced Solid Tumors

Acronym:

Hypotheses, Objectives, and Endpoints:

There is no hypothesis testing in this study.

The objectives and endpoints apply to the study population of male and female participants at least 18 years of age with metastatic/advanced solid tumors. Participants receiving selumetinib in combination with pembrolizumab will be evaluated as follows:

Primary Objectives	Primary Endpoints
- To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of selumetinib when used in combination with pembrolizumab	- Dose-limiting toxicities (DLTs) - Adverse events (AEs) - Study drug discontinuations due to an AE
Secondary Objectives	Secondary Endpoints
- To evaluate the pharmacokinetics (PK) of selumetinib	- Pharmacokinetic parameters including area under the curve (AUC), minimum concentration (C_{min}) and maximum concentration (C_{max})

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Advanced Metastatic Solid Tumors
Population	Participants with advanced metastatic solid tumors
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 40 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 50 participants will be enrolled in this dose escalation study, as described in Section 9; the overall sample size will be 84 participants maximum for this dose escalation study.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>This is a multiple dose escalation study using the single agent, modified toxicity probability interval (mTPI) design and will evaluate safety, tolerability, and efficacy in the following treatment interventions:
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Level</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Regimen/ Treatment Period/ Vaccination Regimen</th><th>Use</th></tr>
<tr><td rowspan="7">Selumetinib</td><td>MK-5618</td><td>DL 1</td><td>50 mg</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>MK-5618</td><td>DL 2</td><td>75 mg</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>MK-5618</td><td>DL3</td><td>100 mg</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>MK-5618</td><td>DL4</td><td>125 mg</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>MK-5618</td><td>DL5</td><td>150 mg</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>MK-5618</td><td>DL6</td><td>200 mg</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>MK-5618</td><td>DL7 onwards</td><td>Above 200 mg (up to 300 mg)</td><td>BID</td><td>Oral</td><td>2 weeks on followed by 1 week off</td><td>Experi-mental</td></tr>
<tr><td>Pembrolizumab</td><td>MK-3475</td><td>DL1-DL7</td><td>200 mg</td><td>Once every 3 weeks</td><td>IV Infusion</td><td>Every 3 weeks (Q3W)</td><td>Experi-mental</td></tr>
<tr><td colspan="8">Abbreviations: BID = twice daily; IV = intravenous</td></tr>
</table>
Based on the emerging safety and/or efficacy signals, an alternate dose level, alternative drug administration frequency and dosing schedule(s) may be explored and an optimal dose will be selected based on totality of data (PK, PD and safety) emerging throughout the trial.</td></tr>
<tr><td>Total Number</td><td>There is 1 intervention group (selumetinib + pembrolizumab) in this dose escalation study.</td></tr>
</table>

Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study treatment until disease progression is radiographically documented, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) when clinically appropriate; unacceptable adverse event(s) (AEs); intercurrent illness that prevents further administration of treatment; investigator's decision to discontinue the participant; or administrative reasons requiring cessation of treatment; or until the participant has received 35 treatment cycles of selumetinib and pembrolizumab treatment (approximately 2 years). After the end of treatment, participants are to be followed up for safety for at least 30 days following the last study dosing and until recovery or stabilization of all related toxicities. During the first year in the study, tumor measurements will continue to be made every 9 weeks until progressive disease is observed, and each participant will be followed for survival. After 12 months on study, imaging will be performed every 12 weeks from first dose or as clinically indicated. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and when clinically appropriate, confirmed by the site per iRECIST (for participants treated with pembrolizumab), the start of a new anti-cancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. Upon identification of the preliminary RP2D of selumetinib for use in combination with pembrolizumab, additional participants with solid tumors will be enrolled in the dose expansion phase of this trial. Participants in the expansion phase of this trial will receive selumetinib in combination with pembrolizumab as dual therapy. The dose expansion phase in this study will be initiated through an amendment to this protocol.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

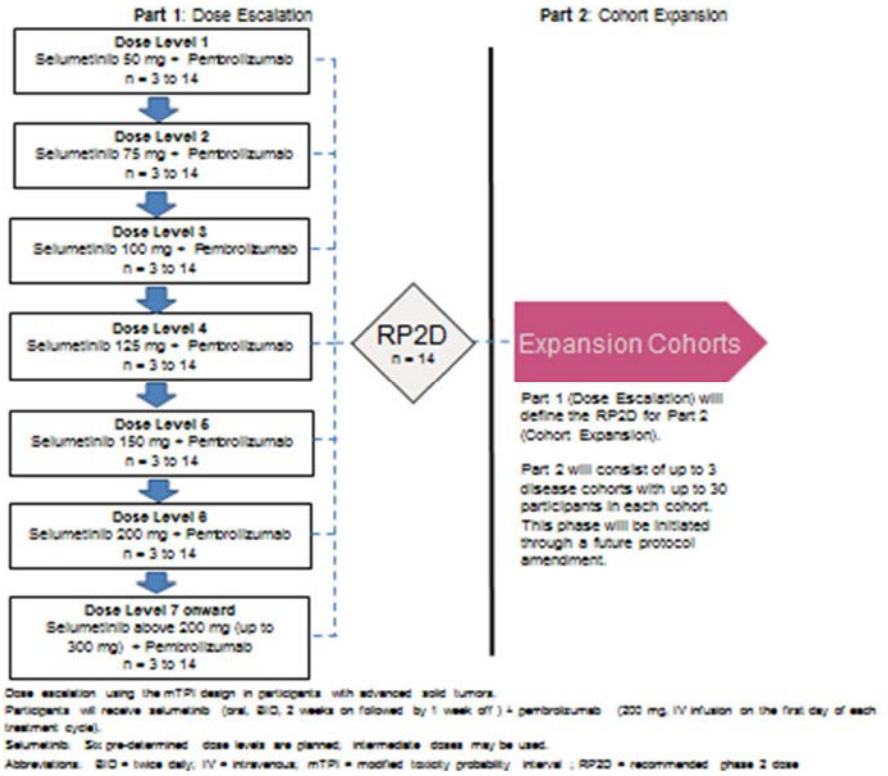

Figure 1 Study Design: Dose Escalation of Selumetinib in Combination with Pembrolizumab

1.3 Schedule of Activities (SoA)

Dose Escalation

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treatment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treatment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Administrative Procedures																
Informed Consent	X															
Informed Consent for optional on-treatment tumor biopsy	X															
Informed Consent for FBR (optional)	X															
Participant Identification Card	X	X														Card will be updated once the participant is allocated and receives a treatment number.
Inclusion/Exclusion Criteria	X															
Demographics and Medical History	X															
Cancer disease status and Prior Treatment history	X															
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treatment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treatment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Selumetinib Administration		X ◄———									———► X					Administered BID, 2 weeks on/1 week off. Administered prior to pembrolizumab infusion on days when study treatments are administered on the same day.
Pembrolizumab Administration		X	X		X	X	X		X	X	X					Administered IV, Q3W

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Efficacy Assessments																
Tumor Imaging	X	X ◄——————————►									X	X		X		Screening: must be obtained within 28 days prior to the date of Cycle 1 Day 1 (C1D1). On-study imaging: • First 12 months: Obtain Q9W (63 days ±7 days) calculated from the date of first dose. See Section 8.2. • After first 12 months: Obtain Q12W (±14 days) calculated from the date of first dose. See Section 8.2.

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Clinical Procedures/Assessments																
Review Adverse Events	X	X ◄———									———► X	X	X	X		AEs that occur after the IC form is signed but before treatment allocation must be reported if: • Event causes participant to be excluded from the study, or • Event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy or a study procedure Follow-up Visits: AEs will be collected when participant is in the clinic for tumor imaging assessment.
Full Physical Examination	X											X				
Directed Physical Examination		X	X		X	X	X		X	X	X					

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Height, Weight, and Vital Signs	X	X	X		X	X	X		X	X	X	X				Height will be measured at Visit 1 only. Vital signs: temperature, pulse, respiratory rate, and blood pressure
12-Lead Electrocardiogram	X		X		X	X	X		X	X	X	X	X			ECG will be performed in triplicate to confirm QTcF interval at screening. ECG will be performed predose, every cycle, starting at C2.
Full Ophthalmic Examination (Q8W)	X		X ◄———		———	———	———	———	———	———	———► X	X	X			Performed at screening, Cycle 2, Day 1 and then Q8W (±7 days) from C2D1 and EoT. An ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EoT (± 7 days)
Echocardiogram/ MUGA scan (Q12W)	X		X				X				X	X				Obtain scans as follows: • Screening • Treatment: C2D1 and C5D1, then Q12W • EoT

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
ECOG Performance Scale	X	X	X		X	X	X		X	X	X	X				Screening: assess within 3 days prior to the first dose of study intervention. Day 1 of treatment cycle visits: Obtain prior to administration of study intervention

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Survival Status		X ◄———									———► X	X	X	X	X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.
LOCAL Laboratory Assessments																
Pregnancy Test – Urine or Serum β-hCG, if applicable	X	X	X		X	X	X		X	X	X					Pregnancy tests may be performed if clinically warranted, or as defined by local regulations. Monthly pregnancy testing should be conducted as per local regulations where applicable.
PT/INR and aPTT	X															Testing may be more frequent if participant is receiving anticoagulant therapy.
CBC with Differential	X	X	X		X	X	X		X	X	X	X	X			
Chemistry Panel	X	X	X		X	X	X		X	X	X	X	X			

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Urinalysis	X		X			X			X		X	X	X			To be performed at screening, and every other cycle starting at C2.
T3 and T4 or FT3, FT4, TSH	X		X			X			X		X	X	X			To be performed at screening, and every other cycle starting at C2. T3 and T4 are preferred; if not available, Free T3 and T4 may be tested.
Creatine kinase																Obtain as clinically indicated.

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
CENTRAL Laboratory Assessments																
Selumetinib Pharmacokinetics		X	X	X			X	X								Samples will be collected C1D1: • Pre-dose: Collect at time 0; morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn, and • Post-dose: Hours Post-dose: Hours 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hrs (prior to PM dosing for BID regimen). Additional samples will be collected at C2D1, C2D14, C5D1 and C5D14 at time 0 pre-dose (- 10 minutes). Morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn.

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Pembrolizumab Pharmacokinetics		X	X		X		X				X					Samples will be collected: • Pre-dose Cycle 1: Collect at time 0 (pre-dose) within 24 hrs before infusion. Cycles 2, 3, 5, 8 and every 4 cycles thereafter: Collect at time 0 within 24 hrs before infusion.
Blood for Genetic Analysis		X														Collected predose.
Blood for RNA Analyses		X	X	X				X				X				Samples will be collected: • Pre-dose: C1D1, C2D1, C2D14, and C5D14 • EoT visit
Blood for Plasma Biomarker Analyses		X	X	X				X				X				Samples will be collected: • Pre-dose: C1D1, C2D1, C2D14, and C5D14 • EoT visit
Blood for Serum Biomarker Analyses		X	X	X				X				X				Samples will be collected: • Pre-dose: C1D1, C2D1, C2D14, and C5D14 • EoT visit
Blood for ctDNA		X	X	X				X				X				Samples will be collected: • Pre-dose: C1D1, C2D1, C2D14, and C5D14 • EoT visit

Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)										End of Treat-ment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Screening (Visit 1)	1	2		3	4	5		6	7	8 to 35	Discon-tinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Time point:		D1	D1	D14	D1	D1	D1	D14	D1	D1	D1	At time of Treat-ment Discon-tinuation	30 days Post-last dose	Q9W or Q12W Post-discon	Every 12 weeks Post-discon	
Scheduling Window (Days)	-28 to -1		±3	-3	±3	±3	±3	-3	±3	±3	±3		±7	±7	±14	
Tumor Tissue Collection																
Archival or Newly Obtained Tumor Tissue collection	X															
On-treatment Tumor Biopsy (Optional)			X													

Abbreviations: aPTT/PTT= activated prothrombin time/partial thromboplastin time; β-hCG=human chorionic gonadotropin; BID=twice daily; CBC=complete blood count; ctDNA=circulating tumor DNA; Discon=discontinuation; dMMR= deficient mismatch repair; DNA=deoxyribonucleic acid ; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=end of treatment; FBR=future biomedical research; FT3=free triiodothyronine; FT4=free thyroxine; IHC= immunohistochemistry; IV=intravenous; MSI/MMR= microsatellite instability/mismatch repair; MUGA= multigated acquisition; PD=progressive disease; PK= pharmacokinetic; PT/INR = prothrombin time/International Normalized Ratio; PT/PTT=prothrombin time/partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W= every 12 weeks; QTcF = Fridericia's Q-T interval corrected formula; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

2 INTRODUCTION

The mitogen-activated protein kinase (MAPK) pathway is a conserved developmental pathway that regulates organ development and tissue homeostasis by transmitting signals through a series of phosphorylation events emanating from receptor tyrosine kinases (RTKs), RAS family members, RAF family members, mitogen-activated extracellular signal-regulated kinase 1/2 (MEK1/2) (*MAP2K1/2*), and extracellular signal-regulated kinase 1/2 (ERK1/2) (*MAPK3/1*). Nuclear translocation of activated ERK1/2 then triggers the transcriptional activation of multiple target genes involved in modulating the cellular processes of differentiation, proliferation, survival, migration, and angiogenesis [McCubrey, J. A., et al 2007]. With constitutive activation of ERK1 and ERK2 found frequently in human cancer cells from a variety of tissues (eg, lung, pancreas, colon, ovary, kidney, skin, and thyroid) {050Q2N}. Amplification, overexpression, or mutations in RTKs and genetic alterations in upstream components of the MAPK pathway, including KRAS, NRAS, HRAS, CRAF, BRAF, MEK1, and MEK2, alter cell signaling in tumors {050QBQ}.

Dysregulation of MAPK pathway in the majority of melanoma and other malignancies, including colon, pancreatic, and non-small-cell lung cancer, makes MEK an attractive therapeutic target as one of the main downstream molecules of MAPK pathway {050PR2}.

Numerous potent, selective allosteric MEK inhibitors have been developed and have undergone clinical evaluation of their ability to inhibit tumor growth {050QB3, 050NYY}. However, most MEK inhibitors have demonstrated limited clinical efficacy as single-agent therapies. Only trametinib showed improved progression-free and overall survival (OS) both as a single agent and in combination with the BRAF inhibitor, dabrafenib {050QBQ}. More recently, another MEK inhibitor, cobimetinib—when used in combination with the BRAF-inhibitor, vemurafenib—was reported to improve progression-free survival among patients with BRAF V600-mutated metastatic melanoma [Ascierto, P. A., et al 2016].

Selumetinib (MK-5618) is an orally available highly selective inhibitor of both MEK1 and MEK2 with a favorable toxicity profile (see Investigator's Brochure [IB]). Preclinical data have demonstrated that MEK inhibition by selumetinib is one of the effective strategies for targeting dysregulated MAPK pathway that leads to unregulated cell proliferation and development and progression of melanoma. Clinical studies have proven the potential antitumor activity of selumetinib in a subset of melanoma patients such as *BRAF* mutant melanoma and uveal melanoma harboring *GNAQ*/*GNA11* mutations[Yeh, T. C., et al 2007].

In clinical studies, a phase I trial in pediatric patients with recurrent or refractory low-grade glioma has been reported. In this study, 25 subjects received a median of 13 cycles (range: 1 to 26). Fourteen (37%) completed all protocol treatment (26 cycles [n = 13], 13 cycles [n = 1]) with at least stable disease; 2-year progression-free survival at the RP2D was 69 ± SE (standard error) 9.8% [Banerjee, A., et al 2017]. The study showed that selumetinib had promising antitumor activity in children with low-grade glioma (LGG); in the early Phase 2 result, selumetinib was effective in treating children with recurrent/refractory LGG, including those with neurofibromatosis type 1 (NF-1)-associated LGG and pilocytic astrocytomas (PA) harboring BRAF V600E mutation or BRAF-KIAA 1549 fusion. Larger prospective studies

are necessary to determine the specific role of this agent in treating children with LGG harboring specific molecular aberrations in the future [Fangusaro, J., et al 2017]; Selumetinib also show antitumor response in adult patients as pretreatment prior to RAI therapy for patients with high risk Differentiated Thyroid Cancer (DTC) [Hong, C. M. 2017].

In the last decade, cancer immunotherapy has positively revolutionized outcomes and basic concepts of oncological treatments. Most of such breakthroughs are due to the discovery and therapeutic modulation of key immune-regulatory molecules (checkpoints) at the interface between immune effectors and tumor microenvironment [Zou, W. and Chen, L. 2008]. Monoclonal antibodies targeting co-inhibitory immune checkpoints (eg, PD-1 and CTLA-4) have demonstrated clinical activity in several malignances, including melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, head and neck squamous cell carcinoma, MSI-high colorectal carcinoma, Merkel cell carcinoma, and Hodgkin lymphoma, and have changed the practice of medical oncology [Jenkins, R. W., et al 2018], however, most patients do not respond to immunotherapy, likely because of intrinsic tumor resistance [Le, A. V. P., et al 2018]. The proposed mechanisms have included a lack of immune cell infiltration, poor antigen expression, and tumor-mediated silencing of the immune system via cytokine release. With cancer cells escaping immune recognition and elimination, cancer cells may begin to utilize additional mechanisms to create an immunosuppressive environment. This can be induced by the recruitment of immunosuppressive cells (myeloid-derived suppressor cells [MDSCs] and regulatory T cells) to create a “wound healing” environment and the generation of tolerogenic signals, such as interleukin-10 (IL-10), transforming growth factor-beta (TGF-β) and extracellular adenosine [Lindau, D., et al 2012].

2.1 Study Rationale

Emerging data suggest that combining programmed death 1 (PD1)/programmed death–ligand 1 (PD-L1) inhibitors with other agents might sensitize tumors to immunotherapy and/or provide additive efficacy [Weinstock, M. 2015] [Bever, K. M. 2017].

Preclinical studies showed that MEK inhibition (MEKi) reduces accumulation of MDSCs ($CD11b^{+}$ $MHCII^{-}$ $Ly6C^{hi}$ cells) in tumor-bearing mice [Allegrezza, M. J., et al 2016], and selumetinib, as a monotherapy, or in combination with anti-CTLA-4, decreased intratumoral $CD11b^{+}$ $Ly6G^{+}$ neutrophil or MDSCs cells in the CT26 mouse tumor model [Poon, E., et al 2017]; MEKi induces a more favorable immune infiltrate within a tumor [Ebert, P. J., et al 2016]; Braf/MEKi treatment leads to higher rates of viable melanoma cell expressing PD-1 and PD-L2, and therefore it could sensitize the tumor to a direct inhibitory effect of anti-PD-1 antibody [Sanlorenzo, M., et al 2018].

Previous clinical data supporting this hypothesis were presented at the American Society of Clinical Oncology (ASCO) meeting in 2018 [Bendell, J. C., et al 2018]. Atezolizumab (a PD-L1 inhibitor) in combination with cobimetinib (a MEKi), across all 84 colorectal cancer (CRC) patients, median OS was 9.8 months, with 6-month and 12-month landmark OS at 65 and 43 percent, respectively. In the previously described Phase 1 dose escalating trial of atezolizumab and cobimetinib and in metastatic CRC [Bendell, J. C., et al 2017], no dose-limiting toxicities were observed, and expansion occurred at atezolizumab 800 mg Q2W and

cobimetinib 60 mg (Daily for 21 days of each 28-day cycle). This dose of cobimetinib is the same as the recommended monotherapy cobimetinib dose found in the labeled prescribing information. However, according to topline findings from the Phase 3 IMblaze370 study, combination therapy with the PD-L1 inhibitor atezolizumab (Tecentriq®) and the MEKi cobimetinib (Cotellic®) failed to improve overall survival (OS) versus regorafenib (Stivarga®) in previous treated patients with locally advanced or metastatic CRC, (https://www.onclive.com/web-exclusives/atezolizumab-cobimetinib-combo-falls-short-in-phase-iii-mcrc-trial).

All these results indicate that MEKi selumetinib may combine with PD-1 antibody such as pembrolizumab for antitumor treatment. Consequently, this study is designed to assess safety, tolerability, pharmacokinetics (PK), and explore preliminary efficacy in participants with advance metastatic solid tumors.

2.2 Background

Refer to the respective IB for detailed background information on selumetinib and the MK-3475 IB/approved labeling for detailed background information on pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Selumetinib Pharmaceutical and Therapeutic Background

Selumetinib is a MEKi, under clinical evaluation in multiple indications. For more details, refer to the selumetinib IB.

2.2.1.2 Pembrolizumab Pharmaceutical and Therapeutic Background

Keytruda™ (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications, refer to the pembrolizumab IB.

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.

The objective of this study is to assess the safety and tolerability of the combination study medication.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no hypothesis testing in this study.

The objectives and endpoints apply to the study population of male and female participants at least 18 years of age with metastatic/advanced solid tumors. Participants receiving selumetinib in combination with pembrolizumab will be evaluated as follows:

Objectives	Endpoints
Primary	
• To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of selumetinib when used in combination with pembrolizumab	• Dose-limiting toxicities (DLTs) • Adverse events (AEs) • Study drug discontinuations due to an AE
Secondary	
• To evaluate the pharmacokinetics (PK) of selumetinib	• Pharmacokinetic parameters including area under the curve (AUC), minimum concentration (C_{min}) and maximum concentration (C_{max})
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1 multicenter, worldwide, open-label study of selumetinib in combination with pembrolizumab in participants with histologically or cytologically confirmed diagnosis of metastatic/advanced solid tumor.

The monotherapy RP2D dose for selumetinib is 75 mg twice-daily (BID) with continuous dosing. At the monotherapy RP2D, trough inhibition of phosphorylation of ERK as an indirect measure of MEK inhibition by selumetinib was reported to be approximately 20%, where studies in non-small cell lung cancer (NSCLC) and melanoma failed to demonstrate efficacy. For the intermitted dose schedule, it may be possible to increase the selumetinib dose beyond what was tolerated for continuous monotherapy dosing because of the observation that intermittent MEK dosing is tolerated at higher doses. The potential maximum dose of selumetinib in the escalation maybe above 200 mg (up to 300 mg) BID with intermittent dosing (14 days on/7 days off). While this dose is higher than the RP2D for continuously administered monotherapy selumetinib, preclinical and clinical observations suggest higher doses may be tolerated with intermittent dosing.

In each dose level, the modified toxicity probability interval (mTPI) design with a target DLT rate of approximately 30% will be applied to identify a potential maximum tolerated dose (MTD). Based on the emerging safety and/or efficacy signals, other dose levels may also be explored in consultation and agreement with the investigator and Sponsor. The totality of the data will be considered before deciding on the dose level(s) to carry forward to further development (ie, preliminary RP2D).

Pre-treatment tumor tissue is required to be provided prior to allocation into the study. If not available, a tumor biopsy must be obtained prior to entry in the study. Upon identification of

the preliminary RP2D of selumetinib for use in combination with pembrolizumab, additional participants with specified solid tumor types will be enrolled in the dose expansion phase of this study. The specific tumor types (cohorts) will be selected based on the totality of the data at the time of the RP2D determination. Up to 30 participants for each cohort in the expansion phase of this study will receive selumetinib in combination with pembrolizumab as dual therapy. The details for the dose expansion phase in this study will be specified in an amendment to this protocol and will include up to 3 disease cohorts.

CCI

After a screening phase of up to 28 days, each participant will receive the assigned intervention until disease progression is radiographically documented and confirmed by the site per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Participants will be monitored carefully for the development of adverse events (AEs), and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. In participants who have initial evidence of radiological progressive disease by RECIST 1.1, it will be at the discretion of the investigator whether to continue a participant on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Adverse events will be evaluated by the investigator, according to criteria outlined in the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0, to establish the safety and tolerability of MK-5618 in combination with pembrolizumab as per the primary objective of this study. The definition of DLTs and criteria for dose modification are outlined in Sections 6.6.2.2 and 6.6.1.

Participants will be treated until progressive disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with study intervention or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study. After the end of treatment, participants are to be followed up for safety for at least 30 days following the last study dosing and until recovery or stabilization of all related toxicities. Tumor measurements will continue to be made every 9 weeks until progressive disease is observed, and each participant will be followed for survival. Imaging will not be collected during Survival Follow-up.

Participants may also agree to provide an optional on-treatment biopsy for biomarker analysis as outlined in the Schedule of Activities (Section 1.3).

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

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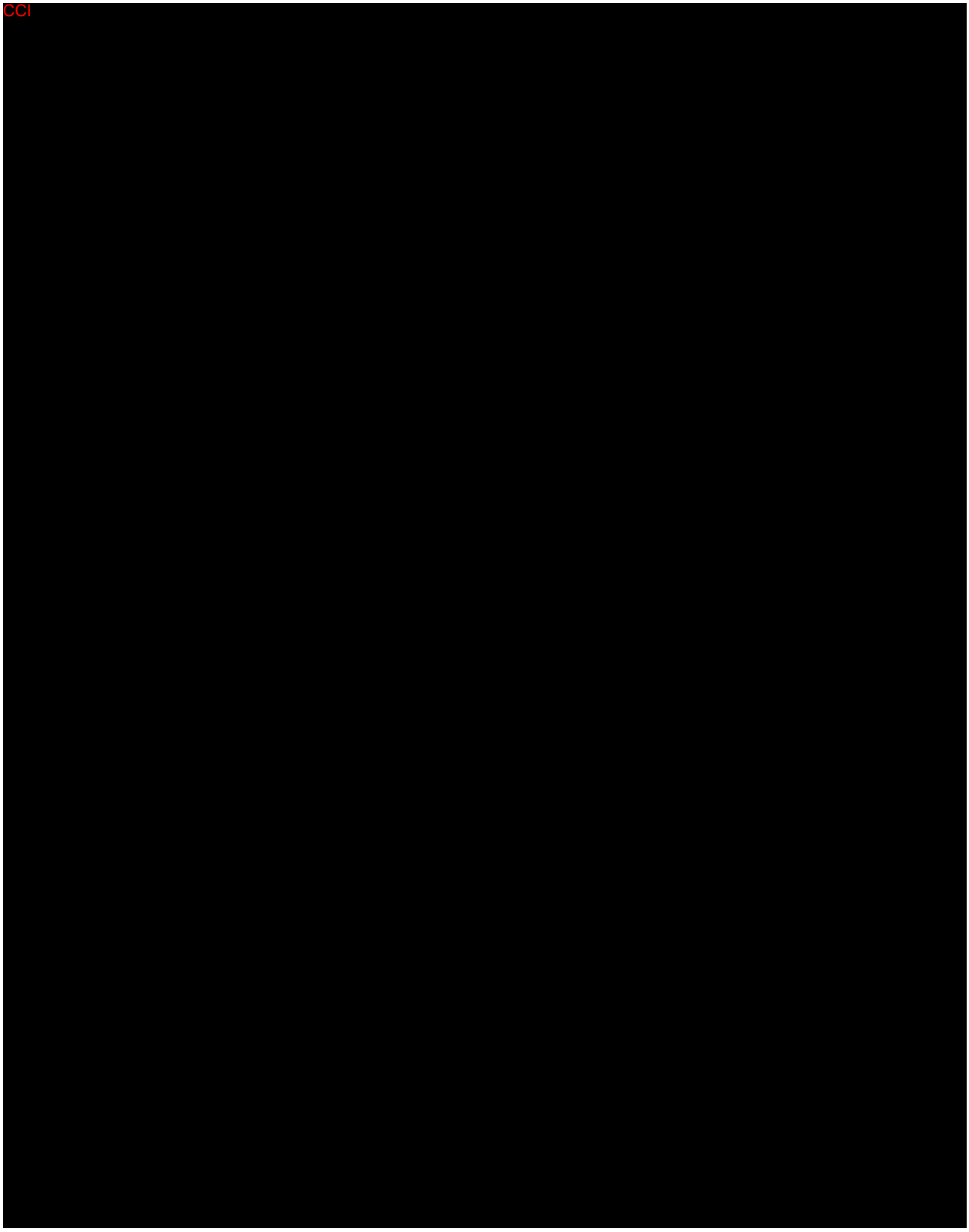

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[redacted]

4.2.1.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs and number of discontinuations of study treatment due to an AE. Safety and tolerability will be assessed by clinical review throughout the trial. The toxicities and grades experienced by participants who have received study treatment, including AEs, SAEs and events of clinical interest (ECIs) will be summarized. Other safety measures evaluated in study include laboratory tests, ECGs, echocardiogram (ECHO)/multigated acquisition (MUGA) scan, vital signs, ECG measurements, physical examinations, and eye examination.

4.2.1.3 Pharmacokinetic Endpoints

Pharmacokinetic endpoint is secondary CCI [redacted] for selumetinib CCI [redacted] CCI [redacted] Pharmacokinetic profile of selumetinib and pembrolizumab will be characterized. The PK concentrations of selumetinib (and its metabolites) CCI [redacted] CCI [redacted] will be used to derive PK parameters of the agents. Furthermore, the results of these analyses will be potentially used in conjunction with the pharmacodynamics, safety, and exploratory endpoint data to help assess future dosing strategies for selumetinib.

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[redacted]

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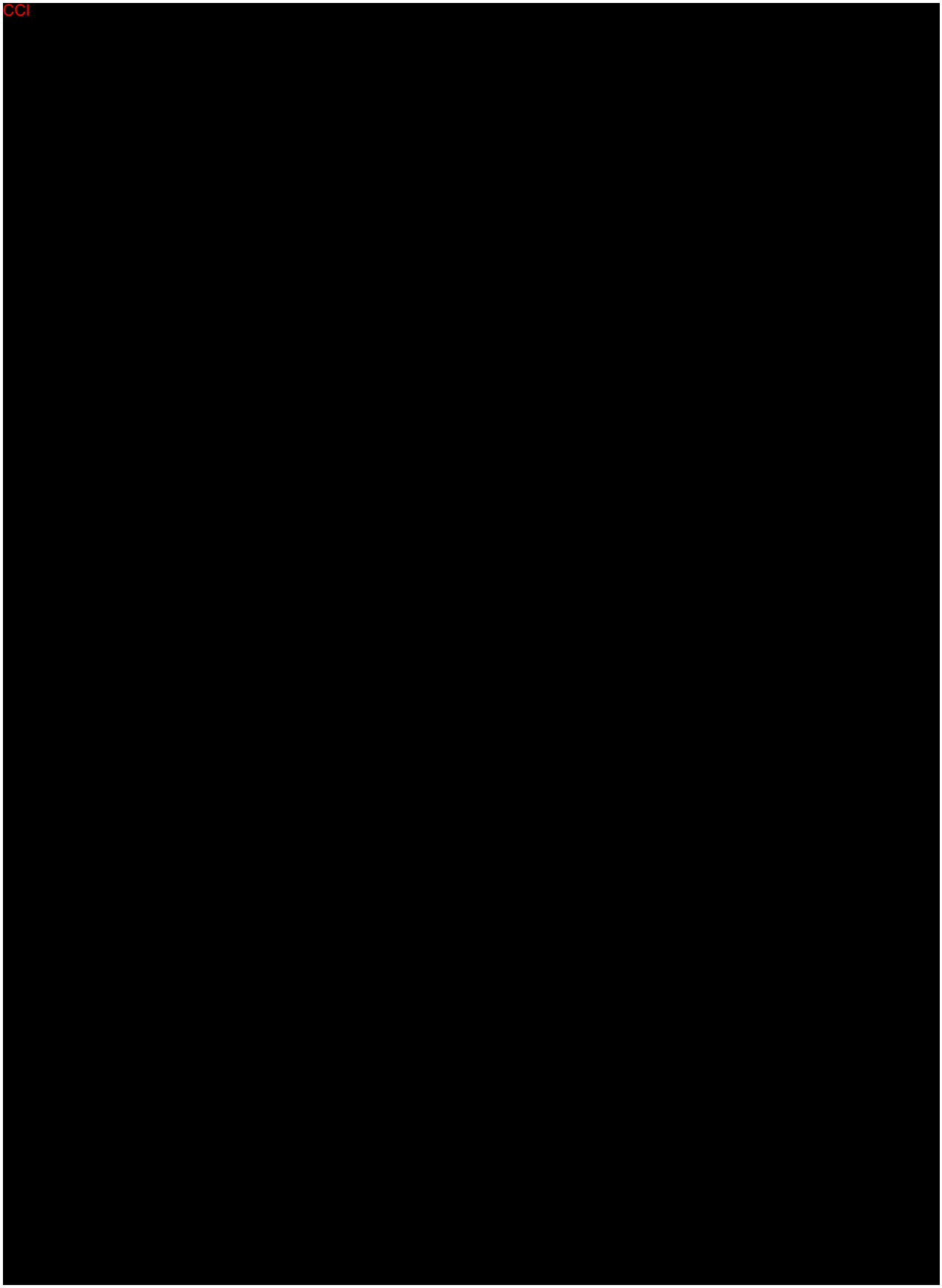

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[redacted]

4.2.1.5 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

This study does not include comparators or placebo.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of Selumetinib

The RP2D for selumetinib as monotherapy is 75 mg PO BID, administered continuously. In this study, the starting dose of selumetinib will be 50 mg oral BID dosed intermittently for the first 14 days of each 21-day cycle. The dose will be escalated, in 25-mg increments, to above 200 mg (up to 300 mg) oral BID per the mTPI rule, maintaining the intermittent schedule. Outcomes of phase II trial of selumetinib propose that enhanced inhibition of MEK

is associated with a greater clinical response, but MEK inhibition also causes dose dependent AEs. Thus, intermittent dosing might have better results than continuous administration. Preclinical studies have demonstrated that intermittent dosing may delay the development of acquired resistance [Faghfuri, E., et al 2018] [Xue, Y., et al 2017].

4.3.1.2 Rationale for Dose Interval and Escalation Increments

Doses of selumetinib will start at 50 mg BID, below the monotherapy RP2D dose for selumetinib of 75 mg BID. Dose escalation increments for selumetinib in combination with pembrolizumab will be to 75 mg (50% increase) initially, to the monotherapy RP2D for selumetinib, and then 33% or lower afterwards in increments of 25 mg.

- Starting Dose (Dose Level [DL] 1): MK-5618 50 mg (oral) twice daily (BID), 2 weeks on/1 week off + MK-3475 200 mg IV every 3 weeks (Q3W)
- Escalation Dose (DL2): MK-5618 75 mg (oral) BID, 2 weeks on/1 week off + MK-3475 200 mg IV Q3W
- Escalation Dose (DL3): MK-5618 100 mg (oral) BID, 2 weeks on/1 week off + MK-3475 200 mg IV Q3W
- Escalation Dose (DL4): MK-5618 125 mg (oral) BID, 2 weeks on/1 week off + MK-3475 200 mg IV Q3W
- Escalation Dose (DL5): MK-5618 150 mg (oral) BID, 2 weeks on/1 week off + MK-3475 200 mg IV Q3W
- Escalation Dose (DL6): MK-5618 200 mg (oral) BID, 2 weeks on/1 week off + MK-3475 200 mg IV Q3W
- Escalation Dose (DL7 onwards): MK-5618 above 200 mg (up to 300 mg; oral) BID, 2 weeks on/1 week off + MK-3475 200 mg IV Q3W

This Dose Escalation study will follow the mTPI method (Section 4.3.1.4) to identify the preliminary RP2D of selumetinib used in combination with pembrolizumab.

4.3.1.3 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). These studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a physiologically-based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.1.4 Dose Finding Using a Modified Toxicity Probability Interval Design

Dose finding will follow the mTPI design [Ji Y, Li Y, Bekele BN 2007] with a target DLT rate of 30%. Dose escalation and de-escalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of DLTs (Section 6.6.2.2) observed at the current dose level. The DLT observation period for this trial is defined as 21 days for the participant.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled within 7 to 14 days of initiating the current

dose level. In Table 1, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the trial due to unacceptable toxicity, respectively. For example, if 0 out of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated and the current dose will not be explored further. If 1 out of 3 participants at a given dose level develops a DLT, then additional participants should be enrolled at that dose level following the rules below.

When adding participants to a dose level in response to a "stay" decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 1). Secondly, to determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 1). The same principles will be applied whether 3, 4, 5, or 6 participants are initially enrolled at that dose level.

A D or DU decision at the lowest dose level will stop the trial. An E decision at the highest dose level will result in staying at that level.

Dose finding will end after 14 participants have been enrolled at any of the tested doses and the decision is to stay at the current dose. After 14 participants have been enrolled at any of the tested doses, dose finding will stop if the mTPI table indicates "S" for staying at current dose. Otherwise, up to 14 new participants may be enrolled at a lower dose if "D" or "DU" is indicated, or at a higher dose if "E" is indicated.

The pool-adjacent-violators-algorithm [Ji, Y. 2013] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to Part 2, and the escalation schedule may be adjusted based on PD, PK, and safety data emerging throughout the trial.

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 1, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%).

Table 1 Dose-finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose											
Number of Participants with at least 1 DLT	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

Abbreviations: D = De-escalate to the next lower dose; DU = The current dose is unacceptably toxic; E = Escalate to the next higher dose; S = Stay at the current dose.

Target toxicity rate = 30%

Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03 [Ji Y, Li Y, Bekele BN 2007] [Ji, Y. 2013] [Ji, Y., et al 2010]

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Early study termination will be the result of the following specified criteria:

1. Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants that negatively impact the risk:benefit ratio

2. Plans to modify or discontinue the development of the study drug

Ample notification will be provided in the event of Sponsor decision to no longer supply selumetinib or pembrolizumab.

5 STUDY POPULATION

Male/Female participants who are at least 18 years of age with advanced metastatic solid tumors will be enrolled in this study.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Have a histologically or cytologically confirmed advanced or metastatic solid tumor by pathology report and have received, or been intolerant to, all treatment known to confer clinical benefit.

2. Have measurable disease by RECIST 1.1 as assessed by local site investigator/radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

3. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.

4. Have the ability to swallow and retain oral medication and not have any clinically significant gastrointestinal abnormalities that might alter absorption.

    Examples of clinically significant gastrointestinal abnormalities: perforation, diverticulitis, duodenal resection, esophageal stenosis.

    Examples of gastric surgeries that can potentially impact absorption: lap band, Roux-en Y, sleeve.

5. Demonstrate adequate organ function as defined in Table 2.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1,500/mcL
Platelets	>100,000/mcL
Hemoglobin	>9 g/dL or >5.6 mmol/L[a]
Renal	
Serum creatinine or creatinine clearance (CrCl) (measured or calculated)[b] or Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X ULN OR >30mL/min for participant with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN or Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 X ULN
AST (SGOT) and ALT (SGPT)	<2.5 X ULN or ≤5 × ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	< 1.5 X ULN unless participant is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	< 1.5 X ULN unless participant is receiving anticoagulant therapy

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase);
AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase);
GFR = glomerular filtration rate; ULN = upper limit of normal.
[a] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).
[b] Creatinine clearance (CrCl) should be calculated per institutional standard. If no local guideline is available, CrCl should be calculated using the Cockcroft-Gault Method: CrCl = [(140-age) * weight (kg) * (0.85 for females only)] / (72 * serum creatinine).
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines.

Demographics

6. Is male or female and a minimum of 18 years of age inclusive at the time of signing the informed consent.

Male Participants

7. Agree to use a contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days after the last dose of study intervention and refrain from donating sperm during this period.

Female Participants

8. Not be pregnant (Appendix 5) or breastfeeding, and at least 1 of the following conditions applies:

   a. Not be a woman of childbearing potential (WOCBP) as defined in Appendix 5.

      OR

   b. A WOCBP must agree to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of study intervention.

Informed Consent

9. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Criteria

10. Human immunodeficiency virus (HIV) infected participants must have well controlled HIV on anti-retroviral therapy (ART), defined as:

    - Participants on ART must have a CD4+ T-cell count >350 cells/mm^3 at the time of screening

    - Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the lower limit of quantification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening

    - Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1)

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study treatment, or has not recovered to CTCAE Grade 1 or better from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related AEs). Participants receiving ongoing replacement hormone therapy for endocrine immune-related AEs will not be excluded from participation in this study.

2. Has clinically active central nervous system metastases and/or carcinomatous meningitis. Participants with previously-treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study treatment administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks prior to enrollment.

3. Has had a severe hypersensitivity reaction (≥ Grade 3) to treatment with a monoclonal antibody/component of the study treatment, and/or has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents and/or excipients used in the study.

4. Has an active infection requiring therapy.

5. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

6. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is not considered a form of systemic treatment and is allowed. Use of nonsystemic steroids is permitted.

7. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to allocation.

8. Participants with known Hepatitis B or C infections, or known to be positive for Hepatitis B antigen/Hepatitis B virus DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative Hepatitis C virus RNA results greater than the lower limits of detection of the assay.

   Note: No testing for Hepatitis B, Hepatitis C, and HIV is required unless mandated by local health authority.

9. HIV infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

10. Has undergone major surgery and has not recovered adequately from any toxicity and/or complications from the intervention prior to starting study therapy.

    Note: Surgery that required general anesthesia must be completed at least 2 weeks before first study intervention administration.

Note: Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study intervention administration and participants should be recovered.

11. Has baseline peripheral neuropathy/paresthesia Grade >1.

12. Have any medical, psychiatric, cognitive, or other condition that may compromise the participant's ability to understand the participant information, give informed consent, comply with the study protocol, or complete the study, in the opinion of the treating investigator.

13. Patients with clinically significant cardiovascular disease as defined by the following:

    a. Uncontrolled hypertension (at randomization: systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥95 mmHg, despite optimal therapy)

    b. Left ventricular ejection fraction (LVEF) <55% measured by echocardiography (or MUGA)

    c. Symptomatic heart failure (NYHA grade II to IV), prior or current cardiomyopathy, or severe valvular heart disease

    d. Uncontrolled angina (Canadian Cardiovascular Society grade II to IV despite medical therapy)

    e. Clinically significant cardiac arrhythmia and/or conduction abnormality ≤6 months prior to start of study treatment

    f. Myocardial infarction or acute coronary syndrome ≤6 months prior to start of study treatment

    g. Mean QT interval calculated according to the Frederica method (QTcF) interval: Male >450 ms; Female >470 ms

14. Have a history of thromboembolic or cerebrovascular event(s) within 6 months prior to study enrollment, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism.

15. Have neuromuscular disorder associated with an elevated creatine kinase (eg, inflammatory myopathy, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.

16. Have a history of, or current, retinal vein occlusion (RVO) or current risk factors for RVO (eg, uncontrolled glaucoma, ocular hypertension, history of hyperviscosity, or hypercoagulability syndromes).

17. Have retinal degenerative disease.

18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, make administration of the study treatments hazardous or make it difficult to monitor adverse effects such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

20. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

Prior/Concomitant Therapy

21. Has received a live-virus vaccine within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

22. Has received prior therapy with compounds targeting PD-1, PD-L1, PD-L2, an MEK inhibitor (eg, cobimetinib, trametinib), or an ERK inhibitor (eg, MK-8353, GCD-0994, ulixertinib).

Prior/Concurrent Clinical Study Experience

23. Is currently participating and receiving study treatment in a study of an investigational agent or has participated and received study treatment in a study of an investigational agent or has used an investigational device within 28 days of administration of selumetinib.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.

Pregnancy Exclusion

24. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study treatment (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

5.3 Special Consideration for Participants of Asian Ethnicity

Plasma exposure of selumetinib (C_{max} and AUC) is higher, at a population level, in subjects of Asian ethnicity by approximately 1.5- to 2-fold compared with Western subjects. However, the PKs of selumetinib show considerable variation and there is overlap in the range of exposure experienced by Asian and Western subjects (some individual Asian subjects have similar plasma levels to those in Western subjects). The higher average plasma exposure was not associated with a change in the tolerability profile of single dose selumetinib.

Patients of Asian ethnicity are not excluded from studies evaluating selumetinib. However, when considering enrolling an individual of Asian ethnicity to a selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher selumetinib plasma levels outweighs the potential benefit of treatment with selumetinib. The Patient Information and Consent form for studies of selumetinib includes information on the possibility of higher selumetinib plasma levels and occurrence of AEs in Asian subjects than in subjects who are not of Asian origin. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of Selumetinib.

Additional details are available in the selumetinib IB.

5.4 Lifestyle Considerations

5.4.1 Meals and Dietary Restrictions

Selumetinib should be taken on an empty stomach (no food or drink other than water for approximately 2 hours prior to dosing and approximately 1 hour after dosing).

5.4.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no study-specific restrictions.

5.4.3 Activity Restrictions

There are no study-specific restrictions.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (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.

5.6 Participant Replacement Strategy

In order to adequately evaluate the safety of the doses administered in this study, all participants enrolled must meet the criteria for evaluability for Cycle 1. Participants are considered nonevaluable and will be replaced if:

- They are allocated but not treated.
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related AEs.

- They receive less than 75% of the total selumetinib or pembrolizumab study treatment in Cycle 1 and did not experience a DLT.

Participants who are not evaluable will be replaced unless accrual to the cohort has stopped. Nonevaluable participants will not be counted toward the total number of participants in the cohort for DLT evaluation.

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.

Study intervention supplies provided by the Sponsor will be packaged to support enrollment. Study intervention 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	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen / Treatment Period / Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Selumetinib + Pembrolizumab	Experimental	Selumetinib (MK-5618)	Drug	Capsule	25 mg	50 mg 75 mg 100 mg 125 mg 150 mg 200 mg Above 200 mg (up to 300 mg)	Oral	BID: 2 weeks on followed by 1 week off	Experimental	IMP	Provided centrally by Sponsor
Selumetinib + Pembrolizumab	Experimental	Pembrolizumab (MK-3475)	Drug	Vial	200 mg	200 mg	IV Infusion	Q3W	Experimental	IMP	Provided centrally by Sponsor

Abbreviations: BID = twice daily; IV = intravenous; Q3W = every 3 weeks
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

This is an open-label study. Study intervention assignment will occur centrally using an interactive response technology system.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

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

Interruptions from the protocol-specified treatment for ≥12 weeks for selumetinib doses for non-drug related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention will be required.

6.5.1 Acceptable Concomitant Medication

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 except for those that are prohibited as described in Section 6.5.2. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Of note, selumetinib can be administered with caution in participants who are receiving concomitant coumarin anticoagulant medications, eg, warfarin. These participants should have their INR monitored, anticoagulant assessments conducted more frequently, and the dose of the anticoagulant therapy adjusted accordingly.

All concomitant medications received within 28 days before the first dose of study intervention and 30 days after the last dose of study intervention should be recorded. Concomitant medications administered after 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than selumetinib (MK 5618) and pembrolizumab (MK-3475).
- For agents that may affect the metabolism of selumetinib (eg, strong inhibitors and inducers of CYP2C19 or CYP3A4), caution should be taken. However, changes in exposure of selumetinib with strong inhibitors/inducers would be moderate based on clinical evidence (1.5-fold).
- Participants should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

  Note: Selumetinib capsules contain vitamin E in the form of D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E, which acts as a formulation excipient.

- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion after the DLT observation period.

- Live vaccines within 28 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Participants may receive other medications that the investigator deems to be medically necessary.

6.5.3 Supportive Care

6.5.3.1 Selumetinib Supportive Care Guidelines

Hypertension

It is recommended that additional blood pressure monitoring occur for participants who may be at risk (participants with hypertension at baseline) or those with antecedents of hypertension or those treated with antihypertensive medication. Early initiation of treatment is recommended after diagnosis, with aggressive management of emergent hypertension.

Nausea and/or vomiting

Because nausea and vomiting have been reported for selumetinib, it is recommended that participants are educated on the possibility of occurrence of these side effects prior to starting study treatment. Participant education as well as proper management of nausea and/or vomiting at the first sign is important. Clinical judgment and experience of the treating physician should guide the management plan of each participant. Participants experiencing nausea and/or vomiting CTCAE Grade ≥1 should receive antiemetics at the discretion of the treating physician (as per local guideline). It is recommended that participants be provided a prescription for antiemetics and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, metoclopramide, ondansetron, or aprepitant may be administered to participants on an "as needed" basis. Medication use should be recorded accordingly.

Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity and the guidelines provided in Section 6.6.1.

As guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from ASCO [Sepulveda, A. R., et al 2017], ESMO [Van Cutsem, E., et al 2016], and Multinational Association of Supportive Care (MASCC) can be used [Basch, E., et al 2011] [Roila, F., et al 2010].

Diarrhea

Diarrhea should be treated promptly with appropriate supportive care, including loperamide. Subjects should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in 1 day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Subjects should be also advised to drink liberal quantities of clear fluids to help prevent dehydration. Supportive care with steroids (as described in Section 6.5.3.2).

Skin Toxicity

Clinical judgment and experience of the treating physician should guide the management plan of each participant. In general, the following interventions are in addition to the rash dosing adjustment guidelines in Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations:

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with study drug or later as needed.

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back.

Topical agents include non-oily sunscreen (para-aminobenzoic acid free, SPF ≥30, ultraviolet A/ultraviolet B protection), topical steroids (preferably mometasone cream, ie, Elocon®) and topical erythromycin (ie, Eryaknen® or topical pimecrolimus).

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2 to 3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild rash (CTCAE Grade 1)

- Consider prophylactic rash treatment if not already started.

- Topical or other topical corticosteroid (ie, mometasone cream) and/or topical antibiotic (ie, erythromycin 2%) are recommended.

- The participant should be reassessed by the investigator.

Moderate rash (CTCAE Grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as: lymecycline (408 mg once daily), doxycycline (100 mg BID) or minocycline (50 to 100 mg once daily).

- Although there has been no evidence of phototoxicity or photosensitivity in participants being treated with selumetinib, doxycycline (or minocycline as second-line) should be

used with thorough ultraviolet protection (ie, avoidance of direct exposure to sunlight, use of sunscreen and sunglasses).

- Use of acitretin is not recommended.

Severe rash (CTCAE Grade 3 to 4)

CTCAE Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, ie, 0.3 to 0.5 mg/kg) [Lacouture, M. E., et al 2011].
- Use of acitretin is not recommended.

CTCAE Grade 4

- Immediately discontinue the participant from study drug and treat the participant with oral and topical medications (see recommendation CTCAE Grade 3).

Symptomatic Treatment:

It is strongly recommended that participants who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions, use cool compresses and oral antihistaminic agents
- For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®
- For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

6.5.3.2 Pembrolizumab Supportive Care Guidelines

Subjects 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 6.6.1.2, Table 6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do

not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Section 6.6.1.2, Table 6 for guidelines regarding dose modification and supportive care.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Modifications Due to Adverse Events

In previous studies of selumetinib and pembrolizumab monotherapy, overlapping toxicities have been observed for selumetinib and pembrolizumab (refer to IBs). These overlapping toxicities include pneumonitis, diarrhea/colitis, cardiac function decrease, and skin rash.

In the current study, the relationship of these AEs to selumetinib and/or pembrolizumab may be difficult to unambiguously assign. Therefore, if a participant experiences an AE related to either treatment, both selumetinib and pembrolizumab will be modified or discontinued as described in Table 4 and Table 5.

If 2 different therapies are proposed in these tables, the most conservative/effective treatment should be chosen (ie, steroid). Further, if the investigator believes the treatment emergent toxicity is unambiguously related to only one of the agents, they may continue the participant on the unrelated agent following consultation with the Sponsor**.**

6.6.1.1 Selumetinib Dose Modification Due to Adverse Events

The starting dose level for selumetinib is 50 mg BID, and a dose reduction below 50 mg BID is not allowed. Participants requiring additional reductions must discontinue selumetinib treatment.

Missed/skipped doses will not be made up (ie, the participant should not double their dose if the previous dose was missed). When a toxicity results in a dose reduction, the dose cannot be re-escalated.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. In general, doses should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate.

Table 4 provides dose adjustment recommendations for selumetinib-induced toxicities. During dose interruption the site should consult with the Sponsor regarding the discontinuation and/ or resumption of treatment.

Table 4 Dose Modification Guideline for Selumetinib

Eye disorders- Retinal Events (including serious detachment of the retina)	
Grade 1	Maintain dose level of selumetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days.
Grade 2	Interrupt selumetinib dosing and refer the participant to ophthalmologist within 1 week and obtain OCT within 10 days: • If resolved to baseline or Grade ≤1 within 10 days, resume treatment at current dose level; continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤1 within 10 days, resume treatment at 1 reduced dose level (1 level below that previously received); continue the schedule of visual assessments established per protocol. • If on retreatment Grade 2 reoccurs, permanently discontinue selumetinib.
Grade 3	Interrupt selumetinib and refer the participant to ophthalmologist within 1 week and obtain OCT: • If resolved to baseline or Grade ≤1 within 7 days, resume treatment at current dose level; continue the schedule of visual assessments schedule established per protocol. • If not resolved to baseline or Grade ≤1 within 7 days, continue to hold the selumetinib dose and repeat ophthalmic assessment in 10 days. • If resolved to baseline or Grade ≤1, resume treatment at 1 reduced dose level; continue the schedule of visual assessments established per protocol. • If remains Grade 3, permanently discontinue selumetinib. • If on retreatment Grade 3 reoccurs, permanently discontinue selumetinib.
Grade 4	Permanently discontinue selumetinib and immediately follow up with ophthalmic monitoring.

Eye disorder - RVO	
Any Grade	Permanently discontinue selumetinib.
Other eye disorders (ie, Non-retinal Events)	
Grade 1 to -2	Maintain dose level of selumetinib and increase frequency of ophthalmic monitoring to at least 14 days until stabilization or resolution.
Grade 3	Interrupt selumetinib and refer participant to ophthalmologist within 1 week: • If resolved to Grade ≤1 in ≤21 days, resume treatment at 1 reduced dose level. • If not resolved to Grade ≤1 in ≤21 days, permanently discontinue selumetinib.
Grade 4	Permanently discontinue selumetinib.
Liver-related adverse events	
Grade 1 AST or ALT (>ULN to 3 x ULN)	Maintain dose level of selumetinib.
Grade 2 AST or ALT (>3 to 5.0 x ULN) or 3 x baseline value (if liver metastasis) AND blood bilirubin ≤2.0 x ULN	Interrupt dose of selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤14 days, resume treatment at current dose level and schedule. • If resolved in >14 days, resume treatment at 1 reduced dose level. Recurrence: • Interrupt dosing of selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume treatment at 1 reduced dose level.
Grade 2 AST or ALT (>3 to 5.0 x ULN or 3 x baseline value (if liver metastasis) AND blood bilirubin >2.0 x ULN	Interrupt dose of selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤7 days, resume treatment at 1 reduced dose level. If not resolved in ≤7 days, permanently discontinue selumetinib.

Grade 3 AST or ALT (>5.0 to 8.0 x ULN) AND blood bilirubin ≤2.0 x ULN	Interrupt dose of selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤14 days, resume treatment at current dose level and schedule. • If resolved in >14 days, resume treatment at 1 reduced dose level. Recurrence: • Interrupt dosing of selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume treatment at 1 reduced dose level.
AST or ALT (>8 x ULN) AND blood bilirubin* ≤2.0 x ULN	Permanently discontinue selumetinib.
AST or ALT (>5.0 x ULN) AND blood bilirubin* >2.0 x ULN	Permanently discontinue selumetinib.
AST or ALT Grade 4 (>20.0 x ULN)	Permanently discontinue selumetinib.
Cardiac disorders	
Left ventricular systolic dysfunction Asymptomatic decrease of >10% in LVEF compared to baseline and the LVEF is below the institution's lower limit of normal	Interrupt dose of selumetinib and repeat evaluation of LVEF within 2 weeks. • If the LVEF recovers (defined as LVEF ≥50% or ≥LLN and absolute decrease ≤10% compared to baseline) ≤3 weeks, resume treatment at 1 reduced dose level after approval by the Sponsor Medical Monitor. Monitor LVEF 2 weeks after restarting on selumetinib, every 4 weeks for 12 weeks and subsequently as per protocol. • If the LVEF does not recover within 3 weeks, permanently discontinue participant from study treatment. Closely monitor LVEF until resolution (or 16 weeks).
Grade 3 to 4	Permanently discontinue participant from selumetinib. Closely monitor LVEF until resolution (or 16 weeks).
CK elevation	
Grade 1 to 2	Continue treatment on same dose level. Ensure patient is adequately hydrated. Monitor closely CK and serum creatinine levels. (If total CK ≥3 X ULN, measure isoenzymes and myoglobin in blood and urine).

Grade 3 (>5.0 to 10.0 x ULN) without renal impairment (ie, serum creatinine <1.5 x ULN or 1.5 x baseline)	If asymptomatic, maintain dose of selumetinib. Monitor closely and measure isoenzymes and myoglobin in blood and urine. If symptomatic (muscle pain/spasms or muscle weakness), interrupt dose of selumetinib until resolved to CTCAE Grade ≤1 and monitor closely, then: • If resolved in ≤21 days, then resume treatment at 1 reduced dose level. • If resolved in >21 days, permanently discontinue selumetinib.
Grade 4 (>10 x ULN) without renal impairment (ie, serum creatinine <1.5 x ULN or 1.5 x baseline)	If asymptomatic, interrupt dose of selumetinib and monitor closely. Ensure patient is adequately hydrated and monitor and measure isoenzymes and myoglobin in blood or urine, and serum creatinine. • If resolved in ≤21 days, then resume treatment at 1 reduced dose level. • If resolved in >21 days, permanently discontinue selumetinib. If symptomatic, permanently discontinue selumetinib. If symptomatic (muscle pain/spasms), permanently discontinue selumetinib.
Grade 3 or 4 with renal impairment (ie, serum creatinine ≥1.5 x ULN or 1.5 x baseline)	Interrupt selumetinib dose until resolved to Grade <1 or baseline level. Ensure patient is adequately hydrated. Monitor isoenzymes and myoglobin in blood or urine, and serum creatinine, then: • If resolved in ≤21 days, then resume treatment at 1 reduced dose level. • If resolved in >21 days, permanently discontinue selumetinib. Recurrence: • Permanently discontinue selumetinib.
Rash	
Grade 1	Treatment with selumetinib will be maintained at the current dose. Initiate prophylactic regimen if it was not already and monitor closely.
Grade 2	First occurrence: • Treatment with selumetinib will be maintained at the current dose and rash will be closely monitored. Initiate prophylactic regimen if it was not already started. • Reassess within a maximum of two weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤1. Resume treatment at the current dose level. Second occurrence: • Reassess within a maximum of 2 weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤1. Resume treatment a 1 reduced dose level. • Only one dose reduction is permitted.

Grade 3	First occurrence: • Treatment with selumetinib will be interrupted. Reassess the participant weekly. Consider referral to dermatologist and manage rash per dermatologist's recommendation. • Interrupt treatment until improvement to Grade ≤1. Resume treatment of the current dose level and schedule. Second occurrence: • Interrupt treatment until improvement to Grade ≤1. Resume treatment with selumetinib at a reduced dose level. If participant is at the lowest dose, participant will be discontinued. • Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Grade 4	Permanently discontinue selumetinib.
Diarrhea	
Uncomplicated Grade 1 to 2	Consider temporary interruption of selumetinib until resolved to Grade ≤1. Resume treatment of the current dose level and schedule.
Complicated Grade 1 to 2	Temporarily interrupt selumetinib treatment until resolved to Grade ≤1. Resume treatment at 1 reduced dose level. If participant is at the lowest dose, participant will be discontinued.
Grade 3 to 4	Temporarily interrupt selumetinib treatment until resolved to Grade ≤1. Resume treatment at 1 reduced dose level. If participant is at the lowest dose, participant will be discontinued.
Nausea/Vomiting	
Grade 1 to 2	Treatment with selumetinib will be maintained at the current dose. Promptly institute antiemetic measure.
Grade 3	Temporarily interrupt selumetinib treatment until resolved to Grade ≤1. Resume treatment at the current dose level if, in the judgment of the investigator, the toxicity is considered to be unrelated to selumetinib, or at 1 reduced dose level. Note: Interrupt dose for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue selumetinib treatment
Interstitial lung disease/pneumonitis	
Grade 1	Maintain dose level of selumetinib Monitor weekly.
Grade 2	Withhold selumetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced dose level. If not resolved within 3 weeks, permanently discontinue selumetinib.
Grade 3 to 4	Permanently discontinue selumetinib.

Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold selumetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced dose. If not improved, permanently discontinue.
Life threatening PE	Permanently discontinue selumetinib.
All other adverse events (suspected to be related)	
Grade 1 to 2	If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider study drug interruption or reduction.
Grade 3	For other AEs, interrupt study drug until resolution to Grade ≤1 or to pre-treatment/baseline level. If the event resolves within 21 days, then study drug may be resumed at 1 reduced dose level (1 level below that previously received) based upon the investigator's discretion.
Grade 4	Permanently discontinue study drug.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID= twice daily; CK=creatine kinase; CTC=Common Terminology Criteria; DVT=deep vein thrombosis; ECG=electrocardiogram; LLN= lower limit of normal; LVEF=left ventricular ejection fraction; OCT= ocular coherence tomography; PE=pulmonary embolism; RVO=retinal vein occlusion; QTc=Q-T interval QTcF=QT interval calculated according to the Fridericia method; ULN= upper limit of normal.

6.6.1.2 Pembrolizumab Dose Modification Due to Adverse Events

6.6.1.2.1 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 5.

Table 5 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 (CTCAEv4.0)	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 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 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		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 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 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic 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 [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	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		
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 [b]		
	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] 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.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.1.2.2 Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 subject 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 (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Abbreviations: po = taken by mouth/oral. 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 Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

6.6.1.2.3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

6.6.2 Dose Administration/Escalation

6.6.2.1 Dose Administration (Preparation)

Details on preparation and administration of selumetinib and pembrolizumab are provided in the appropriate Pharmacy/Procedures Manual.

6.6.2.2 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE Version 4.0 based on the investigator assessment. The DLT window of observation will be during first 21-days of treatment.

The occurrence of any of the following toxicities will be considered a DLT, if assessed by the investigator to be possibly, probably or definitely related to study drug administration, excluding toxicities clearly not related to the drug, such as disease progression, environmental factors, unrelated trauma:

1. Grade 4 non-hematologic toxicity (not laboratory).
2. Hematologic toxicity:
    - Grade 4 neutropenia >5 days
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia with clinically significant bleeding
    - Other Grade 4 hematologic toxicity lasting ≥7 days
3. Any non-hematologic AE Grade 3 severity (not laboratory) should be considered a DLT, with the following exceptions:
    - Grade 3 fatigue lasting ≤3 days
    - Grade 3 diarrhea, nausea, or vomiting lasting <72 hours in the absence of maximal medical therapy
    - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care
4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the participant, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week
    - The abnormality results in a Drug-induced Liver Injury (DILI) (see Sections 8.4.1 and 8.4.7 for criteria).

      Examples of some exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities include liver function tests, urine acid.

5. Febrile neutropenia Grade 3 or Grade 4:

    - Grade 3 is defined as absolute neutrophil count <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.

    - Grade 4 is defined as absolute neutrophil count <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

6. An elevated AST or ALT lab value that is ≥3X the upper limit of normal and an elevated total bilirubin lab value that is ≥2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is <2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
7. Any prolonged delay (>2 weeks) in initiating Cycle 2 study treatment due to a treatment-related toxicity.

8. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.

9. Missing >25% of selumetinib doses as a result of drug-related AE(s) during the first treatment cycle.

10. Grade 5 toxicity

11. Cardiac disorders

    - Absolute decrease in LVEF >10% compared with baseline and the LVEF is below the institution's lower limit of normal

    - Left ventricular systolic dysfunction Grade ≥3

    - Other cardiac disorders Grade ≥3

12. Vascular disorders

    - Hypertension CTCAE Grade ≥3 requiring more than 1 drug or more intensive therapy

    - Grade 4 hypertension

13. Eye disorders

    - Retinopathy or retinal detachment Grade ≥3, confirmed by ophthalmic examination

- Retinal vein disorder including RVO, confirmed by ophthalmic examination
- Visual disturbances without ocular (retinal) changes
- Blurred vision, flashing lights, floaters: Grade ≥3
- Other (not listed above)
- Grade ≥3 for >21 consecutive days
- Grade 4 confirmed by ophthalmic examination

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

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.

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 prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.10.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 21 consecutive days during the 3-week cycle.
- 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.
- Confirmed radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 8.3.
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Investigator's decision to discontinue the participant.
- Recurrent Grade 2 pneumonitis.
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) by local investigator assessments and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of selumetinib beyond the date when the initial CR was declared.
- Completion of 35 treatments with pembrolizumab.
    - Note: 35 cycles (approximately 2 years) are calculated from the first dose.
- Side effects and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment (exceptions are permissible but should be discussed with the Sponsor).

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in Section 1.3 – SoA, and Section 8.10.3 – Discontinued Participants Continuing to be Monitored in the Study, should be completed.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, 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.

Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

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 or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

- 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 signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study is outlined in the Procedures 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 consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised

consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

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

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

8.1.4 Medical History

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in Section 1.3 – SoA, and Section 8.10.3 – Discontinued Participants Continuing to be Monitored in the Study, should be completed.

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 the first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study intervention(s), the study intervention(s) should be discontinued and the participant will move into the survival follow-up phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the study intervention, the 30-day Safety Follow-up visit should occur before the first dose of the new therapy.

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 prior to study intervention assignment. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

8.1.8.1 Oral medication: Selumetinib

Selumetinib is an oral medication, and is supplied as hard-shell capsules in strength of 25 mg. Participants should be instructed to take selumetinib capsules BID, in the morning and in the evening at approximately the same times every day.

Participants will be given clear instructions on how and when to take their study intervention. Participants will self-administer selumetinib except when a clinic visit is scheduled. During on-site visits, administration of study medication will be witnessed by the investigator and/or trial staff. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF.

For non-visit days, selumetinib will be taken at home. The participant will note the number of capsules taken, the time of administration, as well as any reactions including the date/time. Participants will be instructed to notify study site personnel of missed doses.

Study site staff will conduct capsule counts at regular intervals during study treatment. After the capsule count is performed, the remaining capsules will not be returned to the participant but will be retained by the investigative site until reconciliation is completed by the study monitor.

When a participant attends a study visit, he/she will bring any unused capsules. All participants must return their bottle(s) of selumetinib at the appropriate scheduled visit, when a new bottle will be dispensed.

8.1.8.2 Infusion: Pembrolizumab

Administration of study medication will be witnessed by the investigator and/or study staff. The total volume of study intervention infused will be compared to the total volume prepared to determine compliance with each dose administered.

Refer to Section 6 for dose and treatment details.

8.1.8.3 Timing of Dose Administration

8.1.8.3.1 Timing for Administration of Selumetinib (MK-5618)

Participants should be instructed to take selumetinib capsules 12 ± 2 hours apart with a large glass of water (approximately 250 mL) in the morning and in the evening at approximately the same time every day.

On clinical day on which PK samples are scheduled, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken.

Selumetinib will be taken BID for the first 2 weeks of every 3-week treatment cycle. Selumetinib will be administered prior to the pembrolizumab infusion on days when study treatments are administered on the same day. The Pharmacy Manual contains specific instructions for selumetinib storage, administration, and administration sequence for combination administration.

Escalation/dosing schedule (eg, direction of dose escalation, BID on/off intermittent dosing schedule) may be adjusted based on totality of data (PK, PD and safety) emerging throughout the study. Any adjustment made to the dosing schedule will be initiated through an amendment to this protocol.

8.1.8.3.2 Timing for Administration of Pembrolizumab (MK-3475)

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10

minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for pembrolizumab preparation of the infusion fluid and administration.

Every effort should be made to begin the first dose of study treatment on the day of allocation, but if this is not achieved, trial therapy should be initiated no later than 3 days from the date of allocation. All subsequent cycles of study treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the Investigator's judgment.

All study interventions will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as detailed on the SoA – Section 1.3. All study interventions will be administered on an outpatient basis.

The Pharmacy Manual contains specific instructions for pembrolizumab storage and administration.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to 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 8.10.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Domiciling

Not applicable.

8.1.12 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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the iCRO can be found in the Site Imaging Manual. Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

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

Imaging of chest, abdomen, and pelvis is typical. The Site Imaging Manual will include detailed instructions for specific tumor types and clinical scenarios.

Although RECIST 1.1 references to a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of Cycle 1 Day 1 (C1D1).

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of C1D1.

Participants with previously treated brain metastases may participate provided they have stable brain metastases (ie, without evidence of progression by imaging confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of study intervention. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to study initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of first dose of study drug intervention. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 8.2.3), disease progression should be confirmed by the site 4 to 8 weeks site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed provided they have met the conditions detailed in Section 8.2.3. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed disease progression by iRECIST as assessed by the site will discontinue the treatment. Exception is detailed in Section 8.2.3.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of intervention discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging the investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (see Section 8.2.1.2) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.2 RECIST 1.1 Assessment of Disease

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

8.2.3 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by investigator/local radiology reviewers to assess tumor response and progression, and to make treatment decisions. This protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be collected captured in the clinical database.

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management, see Table 7).

This decision by the investigator should be based on the participant's overall condition

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from trial treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST per investigator assessment. Images should continue to be sent in to the iCRO for potential retrospective blinded, independent central review.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 7.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening:
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5mm, compared to any prior iUPD time point.
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
        - Any new factor appears that would have triggered PD by RECIST 1.1.
- Any new factor appears that would have triggered PD by RECIST 1.1.

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND

- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management following the confirmatory imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from trial treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3, SoA, and submitted to the central imaging vendor.

Detection of progression at visits after pseudo progression resolves

After resolution of pseudoprogression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (20% and 5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The

nadir is always the smallest SOD seen during the entire trial, either before or after an instance of pseudoprogression.

- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD. Factors above indicate iUPD, the iUPD evaluation process repeats, just as on the first occurrence of iUPD. iUPD must be confirmed before iCPD can occur.

Additional details about iRECIST are provided in the iRECIST publication.

Table 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST, per local assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows iUPD by iRECIST, per local assessment	Repeat imaging at 4-8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the local site investigator's discretion	Repeat imaging at 4-8 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST, per local assessment	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule
iCPD = immune confirmed progressive disease; iCR = immune complete response; iPR = immune partial response; iRECIST = immune-related response evaluation criteria in solid tumors; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; PD = progressive disease; PFS = progression-free survival				

8.2.4 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status at screening ≤3 days prior to dosing on Day 1 Cycle 1, on Day 1 of each treatment cycle visit prior to the administration of study intervention, and during the follow-up period as specified in the SoA (Section 1.3).

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. Safety assessments are obtained on the specified treatment cycle visit prior to administration of study intervention, unless otherwise specified. 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 Procedures Manual.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as 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.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam 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.

8.3.1.2 Directed Physical Examination

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

8.3.2 Full Ophthalmic Examination

Full ophthalmic examination, including best corrected visual acuity for distance testing, automated visual field testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially retinal pigment epithelial detachment, serous detachment of the retina and RVO, will be performed by an ophthalmologist at screening, Cycle 2 Day 1 and then every 8 weeks (±7 days) from Cycle 2 Day 1 and end of treatment (EOT). An ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EOT (±7 days). For all

participants, ophthalmic assessments may be performed more frequently per system organ class or if clinically indicated for evaluation of any visual signs or symptoms.

8.3.3 Additional Testing

Participants with clinical suspicion of retinal abnormalities (ie, retinal pigment epithelial detachment, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity), must complete at least one of the following additional assessments:

- For non-vascular abnormalities: OCT of the macula (spectral domain OCT recommended)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.
- Images/results of the ophthalmic examinations (at a minimum, OCT and/or fluorescein angiography) should be sent to the study site and be maintained in the participant's source document file. These images/results may be requested to be sent to the Sponsor or designee.

8.3.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Height will be measured at Visit 1 only.

Blood pressure and pulse measurements should be performed with a completely automated device. Manual techniques will be used only if an automated device is not available. The participant should be in a semi-recumbent or supine position for at least 10 minutes prior to having the measurement performed. The correct size of the blood pressure cuff and correct positioning of the participant's arm are essential to the accuracy of the blood pressure measurement.

8.3.5 Electrocardiograms

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

- A standard 12-lead ECG will be performed using local standard procedure.
- The ECG measurement performed at the Screening Visit will be used to determine eligibility.
- The ECG measurement at any time point should be used for AE grading and recommended dose modifications.

- When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

- Triplicate 12-lead ECGs will be obtained at screening only.

    - Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Refer to Section 5.2 (Exclusion Criterion 13 for QTcF withdrawal criteria).

- ECG will be performed predose at every visit starting at Cycle 2 Day 1.

8.3.6 Echocardiogram/Multigated Acquisition Scan

Cardiac ejection fraction will be assessed by transthoracic ECHO or MUGA scans at the time points specified in Section 1.3 - SoA. The same method should be used throughout the study. Participants who develop signs/symptoms of congestive heart failure at any point during the study are required to have an evaluation of LVEF measurement by ECHO or MUGA.

8.3.7 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 case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.7.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

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

Laboratory tests for screening should be performed within 3 days prior to the first dose of study intervention. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted in the SoA.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

8.3.7.2 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours or the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death as described in Section 8.4.6 and Appendix 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/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 allocation/randomization through 30 days following 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 following cessation of study intervention or 30 days following 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 allocation/randomization through 120 days following cessation of study intervention, or 30 days following 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 of the time period specified above must be reported immediately to the Sponsor if the event is considered drug-related.

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 he/she 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 8.

Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (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
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs),

cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards 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 wth 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 suspected unexpected serious adverse reactions (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 SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

8.5.1 Treatment of Overdose for Selumetinib

For the purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for selumetinib ≥20% of the indicated dose. No specific information is available on the treatment of overdose for selumetinib. In the event of overdose, selumetinib should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5.2 Treatment of Overdose for Pembrolizumab

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose for 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.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma Selumetinib and Serum Pembrolizumab

Sample collection, storage, and shipment instructions for pharmacokinetic samples will be provided in the operations/laboratory manual.

Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants. The exact time of sample collection and time of administration of selumetinib and pembrolizumab will be recorded. Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants.

Blood samples for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib. Other metabolites (eg, selumetinib amide) may also be determined. Plasma samples for selumetinib and N-desmethyl selumetinib will be obtained from consenting participants. Serial plasma samples for PK analysis of selumetinib and N-desmethyl selumetinib will be collected C1D1: Pre-dose at time 0 and post-dose at 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). Additional samples will be collected at C2D1, C2D14, C5D1 and C5D14 at time 0 pre-dose (± 10 minutes). Morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn.

Blood samples for determination of serum concentrations of pembrolizumab will be obtained from consenting participants. Serial serum samples for PK analysis of pembrolizumab will be collected at pre-dose (trough) PK and samples within 24 hours before infusion at Cycles 1, 2, 3, 5, 8, and every 4 cycles thereafter.

If ongoing PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover specimens listed in Section 8.10, Biomarkers

8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

CCI

8.10.1 Screening

Approximately 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements (with the exception of MSI status, ophthalmologic examination, and MUGA/ECHO will be evaluated within 42 days) as set forth in Sections 5.1 and 5.2. Screening procedures may be repeated after consultation with the Sponsor. Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine 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 prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 3 days prior to the first dose of study intervention. An exception is hepatitis testing, which may be done up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 3 days prior to the first dose of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study intervention. Newly obtained tumor tissue may be obtained within 90 days of study intervention initiation.

8.10.2 Treatment Period

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

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.10.4 Safety Follow-up Visit

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

All AEs that occur prior to the Safety Follow-up Visit should be recorded (up to 30 days following end of treatment). Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anticancer therapy, whichever occurs first. SAEs that occur within 30 days (90 days following administration of pembrolizumab) of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

8.10.5 Imaging Follow-up Visit

Participants who discontinue study intervention for reasons other than verified PD should continue with imaging assessments per the protocol-defined schedule until: (1) PD is verified or further confirmed by the investigator, (2) initiation of a new anti-cancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

8.10.6 Survival Follow-up Visit

Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The Sponsor may request survival status be assessed at additional time points during the study. For example, these additional time points may be requested prior to an efficacy interim analysis, and/or final analysis. All participants who are not known to have died prior to the request for these additional survival status time points will be contacted at that time

8.10.7 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate supplemental Statistical Analysis Plan (sSAP).

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, will be documented in the sSAP as needed and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Study Design Overview	Phase 1b trial of selumetinib in combination with pembrolizumab in participants with histologically or cytologically confirmed diagnosis of metastatic/advanced solid tumor. The study applies an mTPI design for dose escalation and confirmation of RP2D.
Treatment Assignment	Participants will be allocated centrally through IVRS/IWRS to selumetinib in combination with pembrolizumab.
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT) PK (Secondary): Per-Protocol (PP) Efficacy (Exploratory): Full Analysis Set

Primary Endpoint(s)	• Dose-limiting toxicities (DLTs) • Adverse events (AEs) • Study drug discontinuations due to an AE
Secondary Endpoints	Pharmacokinetic parameters including area under the curve (AUC), minimum concentration (C_{min}) and maximum concentration (C_{max})
Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	Efficacy analyses are documented in the sSAP. PK parameters of study medicines will be summarized by planned visit and time for each dose separately.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints. The pool-adjacent-violators-algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of selumetinib (MK-5618) in combination with pembrolizumab (MK-3475) and the 80% Bayesian credible intervals for the estimate will be provided for each treatment arm.
Interim Analyses	An interim analysis may be conducted to enable future trial planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose-finding decisions.
Multiplicity	No multiplicity adjustment is planned in this Phase 1b trial.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of selumetinib in combination with pembrolizumab. A target sample size of 50 participants will be used for study planning purposes.

9.2 Responsibility for Analyses/In-house Blinding

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

The trial is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

9.3 Hypotheses/Estimation

There is no hypothesis testing in this study. Objectives of the study are outlined in Section 3 – Hypotheses, Objectives, and Endpoints.

9.4 Analysis Endpoints

9.4.1 Pharmacokinetics/Efficacy Endpoints

Pharmacokinetic endpoint is secondary CCI for selumetinib CCI CCI Pharmacokinetic profile of selumetinib CCI will be characterized. The PK concentrations of selumetinib (and its metabolites) CCI CCI will be used to derive PK parameters of the agents (such as C_{max}, AUC and/or C_{min}). Furthermore, the results of these analyses will be potentially used in conjunction with the pharmacodynamics, safety, and exploratory endpoint data to help assess future dosing strategies for selumetinib.

CCI

9.4.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3 – Safety Assessments.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The All-Participants-as-Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study treatment.

The DLT evaluable population includes APaT participants that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 6.6.2.2 for details.

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

9.5.2 Pharmacokinetic Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of PK and target engagement data in this study. The PP population consists of the subset of participants who complied with

the protocol sufficiently to ensure that their data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance includes such considerations as exposure to treatment, availability of measurements, and the absence of major protocol violations. Any participants or data values excluded from the analyses will be identified, along with the reasons for exclusion, in the CSR. At the end of the study, all participants who were compliant with the study procedures and have available data from at least 1 treatment will be included in the PP analysis dataset.

9.5.3 Efficacy Analysis Populations

The Full Analysis Set population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline scan that demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study medicine.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analysis

The statistical methods for efficacy analyses will be documented in the sSAP.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements, and physical examinations.

Adverse events will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized.

Dose limiting toxicities will be listed and summarized by dose level. The isotonic regression with pool-adjacent-violators-algorithm [Ji Y, Li Y, Bekele BN 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analysis

9.6.3.1 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

Pharmacokinetic parameters of study medicines will be summarized by planned visit and time for each dose separately.

9.7 Interim Analyses

An interim analysis may be conducted to enable future trial planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose finding decisions.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

With a maximum sample size of 14 at each dose level, the overall sample size for this Phase 1 trial is expected to be approximately 50. The maximum overall sample size is 84. The actual sample size depends on the safety profiles and number of doses studied.

9.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, 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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) 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 (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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 to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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. 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.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), 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.

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 chart review 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 (eg, 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, commonly 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

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 prior to 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 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 International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, 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 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 trial directive 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 directive, 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.

10.1.6 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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 Studies.

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.

10.1.7 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 signed ICF, 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.

10.1.8 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.

10.1.9 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

Table 9 provides a summary of the laboratory tests performed by the local laboratory.

- If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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.
- The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Table 9 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	Alanine aminotransferase	Protein	PT/INR
WBC (total and differential)[d]	Aspartate aminotransferase	Specific gravity	aPTT or PTT
	Bicarbonate	Microscopic exam, if abnormal results are noted	[FT3]), Total T4 (or Free T4 [FT4]), and TSH[b,c]
RBC	Calcium		
Absolute lymphocyte count[d]	Chloride		Creatine kinase
	Creatinine		
	Glucose		
Absolute neutrophil count[d]	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin		
	Total protein		
	Blood urea nitrogen		

a. Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
b. T3 and T4 are preferred; if not available, Free T3 and T4 may be tested.
c. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Procedure Manual.
d. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

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

10.3.1 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 (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 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 pre-existing condition that has not worsened is not an SAE. A pre-existing 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.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.4 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 Common Terminology for Adverse Events (CTCAE), version 4.0. 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 activities of daily living (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 Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product 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 Sponsor's product and the AE; the greater the correlation with the components and their

respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- Exposure: Is there evidence that the participant was actually exposed to the Sponsor's product 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 Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- 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 Sponsor's product 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 Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- Rechallenge: Was the participant re-exposed to the Sponsor's product in this study?

- If yes, did the AE recur or worsen?

- If yes, this is a positive rechallenge.

- If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT 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 INIRB/IEC.

• Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product 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 his/her 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 Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:

- There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship:

- Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

• For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

• 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 his/her 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.

10.3.5 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 electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 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 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
    - Male condom with cap, diaphragm, or sponge with spermicide.
    - Male and female condom cannot be used together.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • Intrauterine hormone-releasing system (IUS)[c,e] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse 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.
1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. 2. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). a) Male condoms must be used in addition to the hormonal contraception. b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c) IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, sympothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment additional pregnancy testing will be performed if clinically warranted and at monthly intervals as defined by local regulations where applicable, during the treatment period plus 30 days (a menstruation cycle) after the last dose of study intervention, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ART	anti-retroviral therapy
APaT	All-Participants-as-Treated
aPTT	Activated Partial Thromboplastin Time
AUC	area under the curve
BID	twice daily
C_{min}	minimum concentration
C_{max}	maximum concentration
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EOT	end of treatment
ERK	extracellular signal-regulated kinase
FBR	Future Biological Research
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iCPD	immune confirmed progressive disease
iCR	immune complete response
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
iPR	immune partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified RECIST 1.1 for immune-based therapeutics
iSD	immune stable disease

Abbreviation	Expanded Term
IUD	intrauterine device
iUPD	immune unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
LGG	low-grade glioma
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated extracellular signal-regulated kinase
MEKi	mitogen-activated extracellular signal-regulated kinase inhibitor
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	no observed adverse effect level
NSCLC	Non-small cell lung cancer
OCT	ocular coherence tomography
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	Taken by mouth; oral
PP	Per-Protocol
QTcF	QT interval calculated according to the Fridericia method
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
RP2D	Recommended Phase 2 dose
RTK	receptor tyrosine kinase
RVO	retinal vein occlusion
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
WOCBP	woman/women of childbearing potential

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