Official Protocol Title:	A Phase 2 Precision Oncology Study of Biomarker-Directed, Pembrolizumab- (MK-3475, SCH 900475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (KEYNOTE-495; KeyImPaCT)
NCT number:	NCT03516981
Document Date:	30-Apr-2025

Title Page

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Protocol Title: A Phase 2 Precision Oncology Study of Biomarker-Directed, Pembrolizumab- (MK-3475, SCH 900475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (KEYNOTE-495; KeyImPaCT)

Protocol Number: 495-09 / E7080-G000-223

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

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

Regulatory Agency Identifying Number(s):

IND NUMBER: 138,542

EudraCT NUMBER: 2017-003134-85

EU CT NUMBER: 2022-500990-16-00

Approval Date: 30 April 2025

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

I agree to conduct this clinical trial 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 09 / EU-specific Amendment	30-APR-2025	Text was updated to comply with EU regulation CTR 536/2014. Note: Amendment 08 was not submitted under EU CTR. Therefore, changes from both Amendment 08 and Amendment 09 are included in the summary of changes below.
Amendment 08	10-MAR-2025	Added text to allow eligible participants move to an extension study.
Amendment 07	03-AUG-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Additional changes were made throughout to align with the European Union Clinical Trials Regulation (EU CTR).
Amendment 06	20-APR-2021	Updated the dose modification guidelines for immune-related adverse events to align with the current recommendations for pembrolizumab
Amendment 05	06-SEP-2019	To increase dose of MK-4280 from 200 mg to 800 mg Q3W based on new RPD2.
Amendment 04	04-MAR-2019	Addition of pembrolizumab plus MK-1308 combination treatment.
Amendment 03	31-JUL-2018	Amendment 03 streamlined the exploratory biomarker plan and schedule of activities for lenvatinib combination groups.
Amendment 02	03-MAY-2018	Amendment 02 addressed changes requested by the FDA.
Amendment 01	29-MAR-2018	Amendment 01 updated background information and dose justification for MK-1308, MK-4280, and lenvatinib.
Original Protocol	25-SEP-2017	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendment:

Text was updated to comply with EU regulation CTR 536/2014.

Note: Amendment 08 was not submitted under EU CTR. Therefore, changes from both Amendment 08 and Amendment 09 are included in the summary of changes below.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment 09		
Section 9.3.4, Regulatory Reporting Requirements for SAE	Text added confirming the Sponsor will report SUSARs to the Eudravigilance database.	This change addresses incorrect standard text. Text was updated to comply with EU regulation CTR 536/2014.
Primary Reason for Amendment 08		
Section 5.3, Beginning and End of Study Definition	Added text indicating that eligible participants will be allowed to enroll in an extension study.	This change addresses a change in strategy.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 9.3.1, Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information	Added text for collecting safety information through consent for the extension study.	Collection of AE information in this study ends when the participant consents to the extension study.
	Added a row for potential DILI/DILI event reporting in Table 10.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
	Removed DILI reporting from events of clinical interest in Table 10.	Due to the addition of the new row for potential DILI/DILI events.
Section 9.3.3, Follow-up of AE, SAE and Other Reportable Safety Event Information	Added potential DILI/DILI to list of reportable safety events.	Refer to rationale for Section 9.3.1, potential DILI/DILI reporting.

Section Number and Name	Description of Change	Brief Rationale
Section 9.3.7, Events of Clinical Interest (ECI)	Updated bullet #2 and added reporting requirements for potential DILI/DILI events.	Refer to rationale for Section 9.3.1, potential DILI/DILI reporting.
Section 9.10.3.2, Efficacy Follow-Up Visits	Added text for collecting radiographic imaging through consent for the extension study.	Collection of radiographic imaging in this study ends when the participants consents to the extension study.
Section 12.3, Appendix 3: Study Governance Considerations	Code of Conduct for Clinical Trials: Added Regulation (EU) 536/2014 to the regulations listed in the Purpose of this section.	Refer to rationale for Section 9.3.4.
	Data Protection: Text added to acknowledge corporate privacy policies in place that provide data protection for participants in the EU.	To meet EU data protection guidelines.
	Compliance with Trial Registration and Results Posting Requirements: Text added regarding results reporting for studies conducted under the EMA Clinical Trials Regulation 536/2014.	Refer to rationale for Section 9.3.4.
	Compliance with Law, Audit, and Debarment: Text added regarding serious breach reporting requirements.	Refer to rationale for Section 9.3.4.
	Data Quality Assurance: Specified EU retention period for records and documents as 25 years.	Refer to rationale for Section 9.3.4.
Section 12.4, Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updated definition of other important medical events to include potential DILI/DILI.	Refer to rationale for Section 9.3.1, potential DILI/DILI reporting.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 Synopsis

Protocol Title:

A Phase 2 Precision Oncology Study of Biomarker-Directed, Pembrolizumab- (MK-3475, SCH 900475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (KEYNOTE-495; KeyImPaCT)

Short Title:

KeyImPaCT: Keytruda Immunotherapy Personalized and Combination Treatment

Objectives/Hypotheses and Endpoints:

In study participants with advanced non-small cell lung cancer (NSCLC) without prior systemic treatment for their advanced disease:

Objective/Hypothesis	Endpoint
Primary	

• Objective: To evaluate the clinical activity (as assessed by objective response rate [ORR]) of specific pembrolizumab-based combinations.
  • Primary Hypotheses:
  • The ORR will be greater than CCI among participants with low gene expression profile (GEP) and low tumor mutational burden (TMB) receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
  • The ORR will be greater than CCI among participants with low GEP and high TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
  • The ORR will be greater than CCI among participants with high GEP and low TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
	• ORR: Participants who have a confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) as assessed by local site.

• The ORR will be greater than [CCI] among participants with high GEP and high TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.	
Secondary	
• Objective: To evaluate the clinical activity (as assessed by progression-free survival [PFS] and overall survival [OS]) of specific pembrolizumab-based combinations. PFS and OS to different specific pembrolizumab-based combinations will be assessed independently in each biomarker-defined group.	• PFS: Time from randomization to the first documented disease progression per RECIST 1.1 as assessed by local site or death, whichever occurs first. • OS: Time from randomization to death due to any cause.
• Objective: To determine the safety and tolerability of pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib. Safety and tolerability to different specific pembrolizumab-based combinations will be assessed independently in each biomarker-defined group.	• Number of Participants Experiencing Adverse Events (AEs). • Number of Participants Discontinuing Study Drug due to AEs.

Overall Design:

Study Phase	Phase 2
Clinical Indication	Treatment of advanced NSCLC
Population	Study participants with advanced NSCLC without prior systemic treatment for their advanced disease
Study Type	Interventional
Type of Design	Adaptive randomization design
Type of Control	No treatment control
Study Blinding	Unblinded Open-label

Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 6 years (or until the last survival data are available) from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit. This duration includes an enrollment period of approximately 24 months.

Number of Participants:

Approximately 318 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Pembrolizumab 200 mg every 3 weeks (Q3W) + MK-1308 25 mg every 6 weeks (Q6W) Pembrolizumab 200 mg Q3W + MK-4280 either 200 or 800 mg Q3W • Participants enrolled under Amendment 05 or later will be treated with MK-4280 800 mg Q3W. • Participants enrolled prior to Amendment 05 were initially treated with MK-4280 200 mg Q3W. Upon approval of Amendment 05, participants currently treated with MK-4280 200 mg can choose to stay at MK-4280 200 mg Q3W or increase the dose to MK-4280 800 mg Q3W. Pembrolizumab 200 mg Q3W + lenvatinib 20 mg once daily
Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 28 days, each participant will be assigned to receive study treatment until disease progression is confirmed by the site per Immune Response Evaluation Criteria in Solid Tumors (iRECIST), unacceptable AEs, intercurrent illness that prevents further administration of treatment, Investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, withdrawal of consent, or until the participant has received 35 administrations of pembrolizumab (approximately

	2 years). For the lenvatinib combination arm, if a participant completes 35 infusions of pembrolizumab, they may continue with lenvatinib alone until disease progression or toxicity. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3. Participants who discontinue for reasons other than disease progression will have post-treatment follow-up imaging until disease progression is documented radiographically per iRECIST, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study.

A list of abbreviations used in this document can be found in Appendix 1.

2 Schedule of Activities (SoA)

2.1 Schedule of Activities - Pembrolizumab Plus MK-1308

Table 1 Study Flow Chart – Pembrolizumab + MK-1308

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Administrative Procedures													
Informed Consent Form	X												If the investigator plans to treat beyond disease progression, additional consent is required.
Future Biomedical Research ICF	X												This is optional for the participant.
Inclusion/Exclusion Criteria	X												
Participant ID Card	X												
Demographics and Medical History	X												
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		
NSCLC Disease Details and Prior Treatment	X												
Subsequent Antineoplastic Therapy Status									X	X	X	X	

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Survival Status		←	—	—	—	—	—	→		←	—	→	X	After Investigator determines PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X		If Discon visit ≥30 days from last dose of study treatment, Safety Follow-up Visit is not required. SAEs followed for 90 days post-treatment.
Full Physical Examination	X												To be performed within 7 days prior to start of study treatment.
Directed Physical Examination		X	X	X	X	X	X	X	X	X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all participants. VS to be done prior to the administration of each infused study treatment.
Height	X												

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
12-Lead ECG	X	X	X	X					X	X			At indicated times and when clinically indicated.
MUGA or ECHO LVEF assessment	X												
Assess NYHA cardiac disease classification	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		Perform within 7 days prior to first dose in study
Laboratory Procedures/Assessments													Performed by local laboratory
MK-1308 PK and ADA Sampling		X				X		X					Predose trough PK and ADA samples at Cycles 1, 5, and every 4 cycles thereafter. All predose trough samples should be drawn within 24 hours before MK-1308 infusion. PK and ADA should only be collected in participants enrolled under Amendment 5 and later.
Pregnancy Test – Urine or Serum β-HCG	X												WOCBP requires negative test within 24 h prior to first dose in study. Test monthly if required by local regulations (see Appendix 7).

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Hepatitis B & C Serology	X												Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SOC). May use central lab only if local lab is not capable. Not required unless mandated by local health authority (see Appendix 7).
HIV Testing	X												Not required unless mandated by local health authority (see Appendix 7). May use central lab only if local lab is not capable.
EGFR, ALK, ROS1	X												Not required for participants with squamous histology or KRAS mutation.
B-Raf	X												

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
PT/INR and aPTT	X												Perform eligibility laboratory tests within 10 days prior to first dose in study. After first dose, may collect up to 3 days prior to dosing pembrolizumab. Chemistry Panel described in Appendix 2. Additional testing for coagulation factors can be performed as clinically indicated in participants taking anticoagulation therapy.
CBC with Differential	X	X	X	X	X	X	X	X	X	X			
Chemistry Panel	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X												If not done within 10 days prior to C1D1, a urine dipstick is required within 10 days before C1D1.
Urine dipstick testing		X	X	X	X	X	X	X	X	X			
T3 or FT3, FT4, TSH, ACTH, and cortisol	X	X		X		X		X	X	X			Every other cycle. May use central laboratory only if local laboratory is not capable.
Lipase and Amylase	X												
Study Treatment Administration- treatments based on assignment, all patients will not receive all treatments													
Pembrolizumab 200 mg		X	X	X	X	X	X	X					Pembrolizumab Q3W
MK-1308 25 mg		X		X		X		X					MK-1308 dosed Q6W, dosed every other cycle.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Efficacy Measurements													
Tumor Imaging and iRECIST and RECIST 1.1 Assessments	X				X			X	X		X		Every 9 wk through W54, then Q12W. If within 4 wk of Discon, the Discon scan is not required. Timing should follow the calendar and not be adjusted for delays in cycle starts.

Study Period		Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit			C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 and Beyond	Dis-con	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduling Window:		–28 to –1 d	+3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	At Dis-con	30 d Post Discon +14 d	Q12W ±7 d	Q12W ±7 d	
Protocol-specific Specimen Collection														
Biopsy	Archived tissue or new biopsy for GEP, TMB, PD-L1	X												A tumor specimen for biomarker assessment will be required for enrollment of all participants. A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study), is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the participant (including, but not limited to, biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel), an archival specimen should be submitted. GEP, TMB, and PD-L1 status will be centrally determined

Study Period		Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit			**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Scheduling Window:		**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Blood	Whole blood for DNA for exploratory biomarkers		X	X	X			X		X				Streck tube
	Whole blood for DNA for planned genetic analysis		X											Pax Gene DNA tube
	Whole blood for RNA analysis		X	X	X			X		X				Pax Gene RNA tube

Abbreviations: ACTH = adrenocorticotropic hormone; aPTT = activated partial thromboplastin time; β-HCG = beta human chorionic gonadotropin; B-Raf = B isoform of rapidly accelerated fibrosarcoma; CBC = complete blood count; CPT = cell preparation tubes; d= days; Discon= discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; GEP = gene expression profile; h or hr = hours; HBV/HCV=hepatitis B/C virus; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identification; IHC = immunohistochemistry; iRECIST = immune Response Evaluation Criteria in Solid Tumors; min = minutes; INR = International Normalized Ratio; MO = months; NSCLC = non-small cell lung cancer; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PT = prothrombin time; Q or q = every; RECIST = Response Evaluation Criteria in Solid Tumors; ROS1 = c-ros oncogene 1; T3 = triiodothyronine; TMB = tumor mutational burden; TSH = thyroid-stimulating hormone; V = visit; wk = week; WOCBP = women of child-bearing potential.

2.2 Schedule of Activities – Pembrolizumab Plus MK-4280

Table 2 Study Flow Chart – Pembrolizumab + MK-4280

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Administrative Procedures													
Informed Consent Form	X												If the investigator plans to treat beyond disease progression, additional consent is required.
Future Biomedical Research ICF	X												This is optional for the participant.
Inclusion/Exclusion Criteria	X												
Participant ID Card	X												
Demographics and Medical History	X												
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		
NSCLC Disease Details and Prior Treatment	X												
Subsequent Antineoplastic Therapy Status									X	X	X	X	
Survival Status		⟷								⟷		X	After Investigator determines PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X		If Discon visit ≥30 days from last dose of study treatment, Safety Follow-up Visit is not required. SAEs followed for 90 days post-treatment.
Full Physical Examination	X												To be performed within 7 days prior to start of study treatment.
Directed Physical Examination		X	X	X	X	X	X	X	X	X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all participants. VS to be done prior to the administration of each infused study treatment. VS also performed 2 and 4 hr post infusion for MK-4280 for C1 D1.
Height	X												
12-Lead ECG	X	X	X	X					X	X			At indicated times and when clinically indicated.
MUGA or ECHO LVEF assessment	X												
Assess NYHA cardiac disease classification	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		Perform within 7 days prior to first dose in study

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Laboratory Procedures/Assessments													Performed by local laboratory
MK-4280 PK and ADA Sampling		X			X			X					Predose trough PK and ADA samples at Cycles 1, 4, and every 4 cycles thereafter. All predose trough samples should be drawn within 24 hours before MK-4280 infusion. PK and ADA should only be collected in participants enrolled under Amendment 5 and later.
Pregnancy Test – Urine or Serum β-HCG	X												WOCBP requires negative test within 24 h prior to first dose in study. Test monthly if required by local regulations (see Appendix 7).
Hepatitis B & C Serology	X												Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SOC). May use central lab only if local lab is not capable. Not required unless mandated by local health authority (see Appendix 7).

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
HIV Testing	X												Not required unless mandated by local health authority (see Appendix 7). May use central lab only if local lab is not capable.
EGFR, ALK, ROS1	X												Not required for participants with squamous histology or KRAS mutation.
B-Raf	X												
PT/INR and aPTT	X												Perform eligibility laboratory tests within 10 days prior to first dose in study. After first dose, may collect up to 3 days prior to dosing pembrolizumab. Chemistry Panel described in Appendix 2. Additional testing for coagulation factors can be performed as clinically indicated in participants taking anticoagulation therapy.
CBC with Differential	X	X	X	X	X	X	X	X	X	X			
Chemistry Panel	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X												If not done within 10 days prior to C1D1, a urine dipstick is required within 10 days before C1D1.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
T3 or FT3, FT4, TSH	X	X		X		X		X	X	X			Every other cycle. May use central laboratory only if local laboratory is not capable.
ACTH and cortisol	X												
Lipase and Amylase	X	X	X	X	X	X	X	X	X	X			
Study Treatment Administration- treatments based on assignment, all patients will not receive all treatments													
Pembrolizumab 200 mg		X	X	X	X	X	X	X					Pembrolizumab Q3W
MK-4280 200 or 800 mg		X	X	X	X	X	X	X					MK-4280 Q3W
Efficacy Measurements													
Tumor Imaging and iRECIST and RECIST 1.1 Assessments	X				X			X	X		X		Every 9 wk through W54, then Q12W. If within 4 wk of Discon, the Discon scan is not required. Timing should follow the calendar and not be adjusted for delays in cycle starts.

Study Period		Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit			C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 and Beyond	Dis-con	Safety Follow-up	Follow-up	Survival Follow-up	
Scheduling Window:		–28 to –1 d	+3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	At Dis-con	30 d Post Discon +14 d	Q12W ±7 d	Q12W ±7 d	
Protocol-Specific Specimen Collection														
Biopsy	Archived tissue or new biopsy for GEP, TMB, PD-L1	X												A tumor specimen for biomarker assessment will be required for enrollment of all participants. A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study), is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the participant (including, but not limited to, biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel), an archival specimen should be submitted. GEP, TMB, and PD-L1 status will be centrally determined

Study Period		Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit			C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 and Beyond	Dis-con	Safety Follow-up	Follow-up	Survival Follow-up	
Scheduling Window:		–28 to –1 d	+3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	At Dis-con	30 d Post Discon +14 d	Q12W ±7 d	Q12W ±7 d	
Blood	Whole blood for DNA for exploratory biomarkers		X	X	X			X		X				Streck tube
	Whole blood for DNA for planned genetic analysis		X											Pax Gene DNA tube
	Whole blood for RNA analysis		X	X	X			X		X				Pax Gene RNA tube

Abbreviations: ACTH = adrenocorticotropic hormone; aPTT = activated partial thromboplastin time; β-HCG = beta human chorionic gonadotropin; B-Raf = B isoform of rapidly accelerated fibrosarcoma; CBC = complete blood count; CPT = cell preparation tubes; d= days; Discon= discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; GEP = gene expression profile; h or hr = hours; HBV/HCV=hepatitis B/C virus; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identification; IHC = immunohistochemistry; iRECIST = immune Response Evaluation Criteria in Solid Tumors; min = minutes; INR = International Normalized Ratio; MO = months; NSCLC = non-small cell lung cancer; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PT = prothrombin time; Q or q = every; RECIST = Response Evaluation Criteria in Solid Tumors; ROS1 = c-ros oncogene 1; T3 = triiodothyronine; TMB = tumor mutational burden; TSH = thyroid-stimulating hormone; V = visit; wk = week; WOCBP = women of child-bearing potential.

2.3 Schedule of Activities – Pembrolizumab Plus Lenvatinib

Table 3 Study Flow Chart – Pembrolizumab + Lenvatinib

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Administrative Procedures													
Informed Consent Form	X												If the investigator plans to treat beyond disease progression, additional consent is required.
Future Biomedical Research ICF	X												This is optional for the participant.
Inclusion/Exclusion Criteria	X												
Participant ID Card	X												
Demographics and Medical History	X												
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		
NSCLC Disease Details and Prior Treatment	X												
Subsequent Antineoplastic Therapy Status									X	X	X	X	
Survival Status		⟷								⟷		X	After Investigator determines PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X		If Discon visit ≥30 days from last dose of study treatment, Safety Follow-up Visit is not required. SAEs followed for 90 days post-treatment. SAEs followed for 120 days post-treatment for participants treated with lenvatinib. Participants in the lenvatinib group will be contacted by telephone or have a visit on C1D8 ± 3d to assess for development of early toxicity. An unscheduled visit can occur prior to C1D15 ± 3d if deemed necessary by the investigator
Full Physical Examination	X												To be performed within 7 days prior to start of study treatment. The physical exam must include an oral exam.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Directed Physical Examination		X	X	X	X	X	X	X	X	X			Participants in the lenvatinib group will also have a physical examination on D15 ±3d of C1 & C2. The physical exam must include an oral exam.
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all participants. For lenvatinib combination, D15 ± 3d visit is mandatory in C1 and C2. During C3 and subsequent cycles, lenvatinib participants may return for the D15 ± 3d visit if BP monitoring is required. Lenvatinib arm participants with initial or recurrent systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on D15 (or more frequently as clinically indicated) until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for 2 consecutive treatment cycles. The D15 ± 3d test can be performed at local physician or clinic as long as documented. See Section 7.2.2.1 for management of hypertension.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Height	X												
12-Lead ECG	X	X	X						X	X			At indicated times and when clinically indicated. For lenvatinib, ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk patients (as defined in Section 9.5.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are no longer required.
MUGA or ECHO LVEF assessment	X												For lenvatinib group, also performed at safety follow-up (within 30 days post discontinuation).
Assess NYHA cardiac disease classification	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		Perform within 7 days prior to first dose in study

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Laboratory Procedures/Assessments													Performed by local laboratory
Pregnancy Test – Urine or Serum β-HCG	X												WOCBP requires negative test within 24 h prior to first dose in study. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Appendix 2. Test monthly if required by local regulations (see Appendix 7). Participants will be tested at least every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Hepatitis B & C Serology	X												Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SOC). May use central lab only if local lab is not capable. Not required unless mandated by local health authority (see Appendix 7).
HIV Testing	X												Not required unless mandated by local health authority (see Appendix 7). May use central lab only if local lab is not capable.
EGFR, ALK, ROS1	X												Not required for participants with squamous histology or KRAS mutation.
B-Raf	X												

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
PT/INR and aPTT	X												Perform eligibility laboratory tests within 10 days prior to first dose in study. After first dose, may collect up to 3 days prior to dosing pembrolizumab. Chemistry Panel described in Appendix 2. For lenvatinib arm, participants must also have D15 ±3d samples collected for C1 & C2. Additional testing for coagulation factors can be performed as clinically indicated in participants taking anticoagulation therapy.
CBC with Differential	X	X	X	X	X	X	X	X	X	X			
Chemistry Panel	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X												If not done within 10 days prior to C1D1, a urine dipstick is required within 10 days before C1D1.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
Urine dipstick testing		X	X	X	X	X	X	X	X	X			If urinalysis is done within 3 days of C1D1 urine dipstick does not need to be done on C1D1. Repeat testing for participants with proteinuria ≥2+ should be performed on D15 ±3d (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. D15 ±3d visit is mandatory in C1 and C2. During C3 and subsequent cycles, participants may return for the D15 ±3d visit if monitoring is required as specified above. The D15 ±3d test can be performed at local physician or clinic as long as documented. See Section 7.2.2.2 for management of proteinuria by dipstick, UPCR and/or 24-hour urine collection.

Study Period	Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 and Beyond**	**Dis-con**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduling Window:	**–28 to –1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**At Dis-con**	**30 d Post Discon +14 d**	**Q12W ±7 d**	**Q12W ±7 d**	
T3 or FT3, FT4, TSH	X	X		X		X		X	X	X			Every other cycle. May use central laboratory only if local laboratory is not capable.
ACTH, cortisol, amylase, lipase	X												
Study Treatment Administration- treatments based on assignment, all patients will not receive all treatments													
Pembrolizumab 200 mg		X	X	X	X	X	X	X					Pembrolizumab Q3W
Lenvatinib 20 mg		X	X	X	X	X	X	X					Lenvatinib once daily
Efficacy Measurements													
Tumor Imaging and iRECIST and RECIST 1.1 Assessments	X				X			X	X		X		Every 9 wk through W54, then Q12W. If within 4 wk of Discon, the Discon scan is not required. Timing should follow the calendar and not be adjusted for delays in cycle starts.

Study Period		Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit			C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 and Beyond	Dis-con	Safety Follow-up	Follow-up	Survival Follow-up	
Scheduling Window:		–28 to –1 d	+3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	At Dis-con	30 d Post Discon +14 d	Q12W ±7 d	Q12W ±7 d	
Protocol-Specific Specimen Collection														
Biopsy	Archived tissue or new biopsy for GEP, TMB, PD-L1	X												A tumor specimen for biomarker assessment will be required for enrollment of all participants. A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study), is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the participant (including, but not limited to, biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel), an archival specimen should be submitted. GEP, TMB, and PD-L1 status will be centrally determined

Study Period		Screen Phase	Treatment Period Cycle = 21 Days							EOT	Posttreatment Visits			Notes
Visit			C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 and Beyond	Dis-con	Safety Follow-up	Follow-up	Survival Follow-up	
Scheduling Window:		–28 to –1 d	+3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	At Dis-con	30 d Post Discon +14 d	Q12W ±7 d	Q12W ±7 d	
Blood	Whole blood for DNA for exploratory biomarkers		X	X	X			X		X				Streck tube
	Whole blood for DNA for planned genetic analysis		X											Pax Gene DNA tube
	Whole blood for RNA analysis		X	X	X			X		X				Pax Gene RNA tube

Abbreviations: ACTH = adrenocorticotropic hormone; aPTT = activated partial thromboplastin time; β-HCG = beta human chorionic gonadotropin; B-Raf = B isoform of rapidly accelerated fibrosarcoma; CBC = complete blood count; CPT = cell preparation tubes; d= days; Discon= discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; GEP = gene expression profile; h or hr = hours; HBV/HCV=hepatitis B/C virus; HIV= human immunodeficiency virus; ICF = informed consent form; ID = identification; IHC = immunohistochemistry; iRECIST = immune Response Evaluation Criteria in Solid Tumors; min = minutes; INR = International Normalized Ratio; MO = months; NSCLC = non-small cell lung cancer; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PT = prothrombin time; Q or q = every; RECIST = Response Evaluation Criteria in Solid Tumors; ROS1 = c-ros oncogene 1; T3 = triiodothyronine; TMB = tumor mutational burden; TSH = thyroid stimulating hormone; UPCR= urine protein-to-creatinine ratio; V = visit; wk = week; WOCBP = women of child-bearing potential.

3 Introduction

3.1 Study Rationale

Multiple anti-programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) based combination therapies show promise in the clinic. However, it is not clear which patients are most likely to respond to which pembrolizumab-based combinations. This study will investigate the utility of biomarker-based triage for study participants with advanced non-small cell lung cancer (NSCLC) without prior systemic therapy. Study participants within groups defined by a biomarker-based classifier (gene expression profile [GEP] and tumor mutational burden [TMB]) will be randomized to receive specific combination treatments, and the utility of each combination treatment in each biomarker-defined group will be assessed using an adaptive randomization design. Successful subsequent studies or expansion biomarker groups may be used to determine the full diagnostic utility of these biomarkers for triaging patients to specific combinations.

3.2 Rationale for Enrollment Biomarkers

PD-1/PD-L1–directed checkpoint blockade therapies such as pembrolizumab have demonstrated clinical benefit in patients with advanced NSCLC. However, only a subset of patients benefit from PD-1/PD-L1 antibody therapy, presumably due to multiple resistance mechanisms that are active at the level of the host or the tumor microenvironment. Pembrolizumab-based combination regimens may potentially overcome resistance mechanisms. However, such resistance mechanisms are likely to be heterogeneous, and therefore different patients may benefit optimally from different combination regimens. Studies evaluating different pembrolizumab combinations in PD-1/PD-L1–naïve participants have shown preliminary evidence of clinical activity in participants with recurrent and/or metastatic disease. Validated biomarkers may ultimately be needed to guide patients, physicians, and payers through an expanding armamentarium of combination options. Two clinically validated, next-generation biomarkers independently predict response to pembrolizumab: T cell–inflamed GEP and TMB. Tumors defined by a GEP and TMB-based classifier ($GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$) have different biological properties that suggest unique, targetable resistance mechanisms. This study will investigate specific pembrolizumab-based combinations in which each study participant will be assigned to a biomarker group defined by a biomarker-based classifier (GEP and TMB) and randomized within-group to receive a combination treatment of pembrolizumab and MK-1308 (anti–CTLA-4), MK-4280 (anti–LAG-3), or lenvatinib (receptor tyrosine kinase [RTK] inhibitor).

Recent clinical studies have demonstrated that GEP is significantly associated with an increased probability of overall response and longer PFS among pembrolizumab-treated patients across multiple tumor types [Ayers, M., et al 2016]. Tumor mutational burden derived by whole exome sequencing was also significantly associated with clinical activity to pembrolizumab across multiple indications. Moreover, TMB and GEP were only modestly correlated and were each independent predictors of response to anti–PD-1 therapy [Cristescu, R., et al 2016]. The response rates to pembrolizumab monotherapy were strikingly different across the groups identified by the 2 biomarkers, varying from approximately 50% in the group with both biomarkers positive to 0% in the group with both biomarkers negative.

Therefore, GEP and TMB may have utility when used together to identify discrete categories of tumors that may exhibit different dominant resistance mechanisms. Indeed, analysis of large tumor genomic and gene expression databases has demonstrated that different GEP- and TMB-defined groups of tumors are enriched for different types of potentially targetable resistance biology. In this study, pembrolizumab-based combinations will be evaluated in 4 biomarker-defined groups ($GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$) with the goal of determining which combination works best for each subset of participants. These data may inform additional, future cohorts or independent clinical studies that more fully define the performance characteristics of GEP and TMB as biomarkers to enable future precision medicine approaches to combination immunotherapy.

3.2.1 Gene Expression Profile (GEP)

NanoString gene expression profiling is a platform widely used by both clinical and laboratory researchers to perform mid-density GEP using RNA obtained from limited amounts of formalin-fixed paraffin-embedded (FFPE) tumor tissue. The GEP technology uses a set of combination barcoded and single molecule imaging to count hundreds of unique RNA transcripts in a single reaction (up to 800 transcripts can be evaluated on a single platform). The GEP platform is very sensitive and is capable of quantifying low input RNA amounts similar to what can be detected by reverse transcription polymerase chain reaction (RT-PCR). This is important because RNA obtained from FFPE tumor tissue specimens is generally lower in abundance and more degraded relative to newly obtained tissue specimens collected in RNA preservatives. Therefore, an assay utilized for FFPE-based experiments must be able to evaluate gene expression levels from genes expressed at low abundance and from partially degraded RNA. The GEP platform has been previously applied in the clinical setting, specifically for analysis of a multi-gene expression marker set predicting prognosis in breast cancer. Thus, the GEP platform may provide a path toward development of a multi-gene (signature) companion diagnostic assay that could potentially be applied in the clinic for making pembrolizumab treatment decisions.

Associations between clinical response to pembrolizumab and gene expression signatures of IFN-γ signaling an activated T cell biology were evaluated using RNA isolated from FFPE baseline samples of patients with multiple tumor histologies [Ayers, M., et al 2017]. Gene expression was analyzed on the NanoString nCounter system. Preliminary signatures, comprised of genes associated with IFN-γ and activated T cell biology, were initially evaluated in a discovery set of 19 patients with melanoma and subsequently validated in an independent cohort of 62 melanoma patients. Refined versions of these signatures were independently tested and shown to predict objective response and PFS in 40 patients with head and neck squamous cell carcinoma (HNSCC) and 33 patients with gastric cancer. Using data combined from 220 pembrolizumab-treated patients across 9 cancer types, a final 18-gene GEP was derived that included immune-related genes related to antigen presentation, chemokine expression, cytotoxic activity, and adaptive immune resistance. The predictive value of the GEP compared favorably with that of PD-L1 immunochemistry when evaluated in an additional independent cohort of PD-L1–unselected HNSCC patients (n=96). The pan-tumor GEP described in this study, typified by indicators of a T cell–inflamed microenvironment, captures hallmark characteristics of tumors that are responsive to anti-PD-1 therapy. Sponsor data suggest that these immune-related components are generally necessary, but not always sufficient, for clinical response to pembrolizumab. The

GEP represents a potential tumor type-agnostic determinant of response to PD-1 checkpoint blockade and has undergone analytical validation as a potential diagnostic assay with a clinical utility profile that suggests good performance for maintaining high negative-predictive value and sensitivity.

The clinical utility of the GEP is being assessed prospectively across multiple tumor types in the KEYNOTE-158 study. Although a dedicated 18-gene GEP assay is being evaluated in this context, we have shown, by a prespecified evaluation of concordance, that a comparable GEP score can be derived using the 17 genes of the GEP that are part of the commercially available NanoString PanCancer panel, which also allows for simultaneous assessment of many additional immune-related genes [Ayers, M., et al 2017]. Therefore, the 17-gene version of the GEP will be used in this study.

3.2.2 Tumor Mutational Burden (TMB)

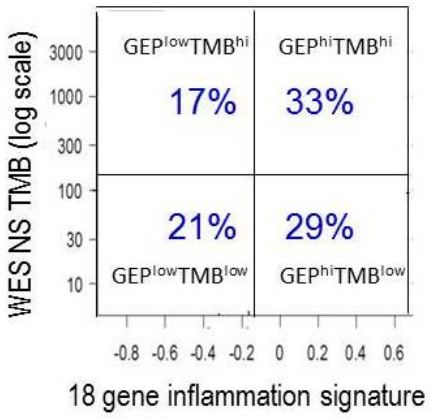
Tumor rejection antigens allow tumors sufficiently distinct from normal tissue to activate the immune system and induce an efficient antitumor response. Tumor mutated specific antigens (neoantigens) are major tumor rejection antigens [Schumacher, T. N. 2015] [Castle, J. C., et al 2012]. The recent development of innovative deep sequencing technologies (at an affordable cost) along with advances in bioinformatics has enabled systemic analysis of nonsynonymous somatic TMB and identification of potentially immunogenic neoantigens. The genetic landscape and the full spectrum of genomic alterations in each individual tumor provide the guidance for personalized cancer immunotherapy [Yuan, J., et al 2016].

Two pilot studies in mouse models first demonstrated that whole exome sequencing is able to identify neoantigen specific CD8+ T cells associated with tumor response [Matsushita, H., et al 2012] [Castle, J. C., et al 2012]. Several clinical studies demonstrated the feasibility and importance of understanding the immunogenicity of neoantigens and their potential clinical application in patients treated with tumor-infiltrating lymphocyte adoptive cell therapy [Robbins, P. F., et al 2013] [Tran, E., et al 2014] [Linnemann, C., et al 2015]. Tumor mutational burden was associated with clinical outcome to immune checkpoint blockade cancer immunotherapy in patients with advanced melanoma, NSCLC, and colorectal cancer [Snyder, A., et al 2014] [Rizvi, N. A., et al 2015] [VanAllen, E. M., et al 2015]. Patients with mismatch repair deficiency tumors likewise had high rates of clinical response to PD-1 blockade [Le, D. T., et al 2015].

We have evaluated the TMB in relationship with response to pembrolizumab in a subset of participants from KEYNOTE-012/KEYNOTE-028 for which whole exome sequencing was available (N=100 with evaluable DNA and RECIST response available). The analysis showed that TMB strongly associated with response and had potential clinical utility [Cristescu, R., et al 2018].

The estimated percentages of study participants (Figure 1) within each of the 4 biomarker-defined groups ($GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$) are from TCGA, based on 175 TMB cut-off and –0.16 GEP equivalent cut-off. The percentage of participants in $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ biomarker groups are 21%, 17%, 29%, and 33%, respectively (Figure 1).

Figure 1 Estimated Percentage of Study Participants with Advanced Non-small Cell Lung Cancer in the Four Biomarker-defined Groups



GEP=gene expression profile; TMB=tumor mutational burden.

3.3 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

In this study, pembrolizumab will be administered in combination with MK-1308, MK-4280, or lenvatinib (also known as E7080 or MK-7902). MK-1308 is a humanized, antagonist mAb that binds cytotoxic T-lymphocyte–associated antigen–4 (CTLA-4) and blocks its interaction with both of its ligands, CD80 (B7.1) and CD86 (B7.2). MK-4280 is a potent and highly selective antagonistic humanized mAb of the IgG4/kappa isotype with a hinge stabilized (Ser228Pro) modification designed to directly block the interaction between lymphocyte-activation gene 3 (LAG-3) and its ligand, major histocompatibility complex (MHC) Class II. Lenvatinib inhibits the kinase activity of vascular endothelial growth factor (VEGF) receptors (eg, VEGFR1 [FLT1], VEGFR2 [KDR], and VEGFR3 [FLT4]). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1 to 4, platelet-derived growth factor (PDGF) receptor α, KIT, and rearranged during transfection (RET) [Matsui, J., et al 2008] [Matsui, J., et al 2008a] [Okamoto, K., et al 2013] [Okamoto, K., et al 2014].

Refer to the Investigator's Brochures (IBs) for detailed background information on MK-1308, MK-4280, pembrolizumab (MK-3475), and lenvatinib.

3.3.1 Pharmaceutical and Therapeutic Background

3.3.1.1 Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T regs) correlates with improved prognosis and long-term survival in solid malignancies. These include ovarian, colorectal, pancreatic; hepatocellular; melanoma, and renal cell carcinomas. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced NSCLC.

3.3.1.2 MK-1308 (Anti–CTLA-4)

MK-1308 is a humanized, antagonist IgG1 mAb that binds CTLA-4 and blocks its interaction with both of its ligands, CD80 (B7.1) and CD86 (B7.2).

CTLA-4 is a negative regulator of T-cell function and proliferation. It is found on the surface of activated T cells and T_{regs} as a single-pass transmembrane protein belonging to the immunoglobulin superfamily. CTLA-4 was identified as a second receptor for both CD80 and CD86 and shares some structural homology with the activating co-receptor, CD28.

Unlike CD28, which is expressed on naïve T cells, the cell surface expression of CTLA-4 is both transient and tightly regulated. The opposing responses mediated by these 2 receptors are capable of coordinating the strength of the immune system's response.

As part of the adaptive immune response, T cells are central to mounting a defense against tumor growth. Activation of T cells is achieved via the dual engagement of both the T-cell receptor and CD28 receptor on the T cell to mount a full immunogenic response. CD28 binds to either CD80 or CD86 molecules expressed on antigen-presenting cells, leading to T-cell specific expression and presentation of CTLA-4, which then competes with CD28 to bind these activating molecules with a high affinity, thereby dampening the activation signal for the T cell, moving it to a more tolerogenic state. Therefore, blocking this immune checkpoint, allowing T cells to remain active, would allow the immune system to mount a more competent and durable antitumor response.

CTLA-4 suppression is thought to be primarily at sites of T-cell activation, eg, secondary lymph organs rather than within the tumor microenvironment; however, inhibition of CTLA-4 results in substantial increases of T cell infiltrates within tumor tissues. This contrasts with the presumed inhibition of T-cell function via PD-1 engagement, which occurs within the tumor microenvironment between T cells interacting with both antigen-presenting cells and the tumor cells themselves. Differences in mechanism and expression of these receptors and their ligands suggest that these differential mechanisms of action may underlie the observed clinical benefit when used as combination therapy above their respective monotherapies.

The humanized anti-human CTLA-4 antibody is being proposed for development in combination with the Sponsor's anti–PD-1 mAb, pembrolizumab. Two human mAbs targeting CTLA-4, ipilimumab (IgG1) and tremelimumab (IgG2), have been and continue to be evaluated in the clinic for the treatment of various oncology indications. Ipilimumab was approved for melanoma patients alone and in combination with the anti–PD-1 antibody. Ipilimumab demonstrates efficacy with doses from 1 to 10 mg/kg, with lower toxicity rates at lower doses. In Checkmate 227, the Phase 3 study of the combination in NSCLC, ipilimumab is being administered at a 1 mg/kg dose every 6 weeks (Q6W) [ClinicalTrials.gov 2017]. The combination of ipilimumab and nivolumab is being actively pursued in clinical studies in multiple cancer types.

3.3.1.3 MK-4280 (Anti–LAG-3)

MK-4280 is a potent and highly selective antagonistic humanized mAb of the IgG4/kappa isotype with a hinge stabilized (ser228Pro) modification designed to directly block the interaction between LAG-3 and its ligand, MHC Class II.

Lymphocyte-activation gene 3 (LAG-3) is an inhibitory immune modulatory receptor that regulates effector T cell homeostasis, proliferation, and activation, and has a role in the suppressor activity of regulatory T cells (T_{regs}) [Huang, C. T., et al 2004] [Baixeras, E., et al 1990] [Goldberg, M. V. and Drake, C. G. 2011]. Lymphocyte-activation gene 3 is expressed on activated $CD8^+$ and $CD4^+$ T cells, T_{regs} and the T_r1 regulatory T cell population, as well as on natural killer cells and a subset of tolerogenic plasmacytoid dendritic cells. Because of its proposed role on both effector T cells and T_{regs}, LAG-3 is one of several immune checkpoint

molecules where simultaneous blockade of both cell populations has the potential to enhance antitumor immunity [Andrews, L. P., et al 2017].

LAG-3 is structurally related to cluster of differentiation 4 (CD4) and a member of the immunoglobulin (Ig) superfamily. Like CD4, its ligand is MHC Class II molecules [Huard, B., et al 1995] [Triebel, F., et al 1990]. Interaction with its ligand leads to dimerization and signal transduction resulting in altered T cell activation. Following T cell activation, LAG-3 is transiently expressed on the cell surface. A large proportion of LAG-3 molecules are found in intracellular stores and can be rapidly translocated to the cell membrane upon T cell activation [Woo, S. R., et al 2010]. LAG-3 expression is regulated at the cell surface by extracellular cleavage to yield a soluble form of LAG-3 (sLAG-3), which can be detected in serum [Li, N., et al 2007]. Expression of LAG-3 is tightly regulated and represents a self-limiting mechanism to counter uncontrolled T cell activity.

LAG-3 is commonly co-expressed with PD-1 on anergic/exhausted T cells, and both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 can have a synergistic impact on reversing tumor-specific anergy [Pardoll, D. M. 2012] [Blackburn, S. D., et al 2009] [Grosso, J. F., et al 2009]. Indeed, LAG-3 was selected as an initial target of interest based on published data indicating that the addition of an anti-LAG-3 antibody could enhance the activity of an anti–PD-1 antibody in rodent, preclinical tumor models. In addition to the data from preclinical models using anti-mouse antibodies, data from double knock-out mice (LAG-$3^{-/-}$PD-$1^{-/-}$) show the ability to resist growth of various tumor implants, indicating a clear synergy between these molecules [Woo, S. R., et al 2012]. These data support the rationale of the combination MK-4280 (anti-LAG-3) with pembrolizumab in this study.

3.3.1.4 Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1-3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. and Hicklin, D. J. 2008] [Tammela, T. and Alitalo, K. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. and Claesson-Welsh L. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various

human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in human umbilical vein endothelial cell (HUVEC) models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

3.3.2 Preclinical and Clinical Studies

3.3.2.1 Pembrolizumab (MK-3475)

Information regarding preclinical studies with pembrolizumab may be found in the current edition of the IB.

3.3.2.2 MK-1308

The monovalent affinities of MK-1308 against human CTLA-4 are approximately 2- to 3-fold tighter CCI MK-1308 showed comparable binding to human and CCI

The ability of the antibodies to block binding of human CTLA-4 to its natural ligands, CD80 and CD86, was assessed by cell-based enzyme-linked immunosorbent assay (ELISA) using CCI MK-1308 also induce the upregulation of IL-2 in a dose-dependent manner with a comparable potency to either clinical standard. Consistent with this finding, CCI induced dose-dependent IFN-gamma production from CD4+ T cells in a mixed lymphocyte reaction (MLR)-based assay, using activated CD4+ T cells and allogenic differentiated monocytes to serve as DCs. MK-1308 induced the upregulation of IFN-gamma in a dose-dependent manner with observed efficacy CCI The inclusion of pembrolizumab in combination with either MK-1308 CCI resulted in a substantial and synergistic increase in IFN-gamma production in the current MLR format.

CCI

More detailed information of preclinical studies with MK-1308 may be found in the current edition of the IB.

3.3.2.3 MK-4280

Efficacy studies in mouse models have shown that administration of antibodies blocking LAG-3/MHC Class II interaction in combination with anti–PD-1 antibodies enhances immune responses and leads ultimately to tumor rejection. Anti-mouse LAG-3 antibodies have demonstrated antitumor responses as combination therapy with anti–PD-1 in syngeneic tumor models of multiple cell-type origins (eg, fibrosarcoma, renal cell carcinoma, bladder carcinoma, and colorectal carcinoma). Preclinical models have shown both overall tumor growth inhibition and an increase in the number of tumor-free mouse treatment groups (Bristol Myers Squibb Company LAG-3 Antibody Patent; International Publication Number: WO 2015/042246 A1).

3.3.2.4 Lenvatinib

In preclinical models, lenvatinib showed a superior antitumor activity in immune-competent mice compared to in immune-deficient mice suggesting that lenvatinib may have immune modulating effects. Indeed, lenvatinib decreased the tumor associated macrophage (TAM) population while increasing the percentage of IFN-gamma producing CD8+ T cells in regional lymph nodes [Kato, Y., et al 2015]. The antitumor activity of lenvatinib, single-agent anti-mouse PD-1 mAb and the combination treatment of lenvatinib and anti-mouse PD-1 mAb was examined in syngeneic mouse models [Kato, Y., et al 2015]. Combination of lenvatinib with PD-1 mAb showed more potent inhibitory activity against tumor growth in 3 syngenic mouse models (LL/2 murine lung carcinoma, H22 murine hepatocellular carcinoma, and CT26 murine colon cancer) compared with each single agent alone [Kato, Y., et al 2016]. While single agent PD-1 mAb treatment resulted in an increase in both Th1 and Th2 cytokines, lenvatinib monotherapy alone decreased Th2 cytokines, and combination treatment increased Th1 cytokines but decreased Th2 cytokines [Kato, Y., et al 2016].

As noted in the prescribing information for LENVIMA® (lenvatinib) capsules, for oral use, lenvatinib is currently used to treat “patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC” [differentiated thyroid cancer] and is used “in combination with everolimus” to treat “patients with advanced RCC [renal cell carcinoma] following one prior anti-angiogenic therapy.”

3.3.3 Ongoing Clinical Studies

3.3.3.1 Pembrolizumab (MK-3475)

Over 300 interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications, as well as in hematological malignancies. For further details, please refer to the current edition of the IB.

3.3.3.2 MK-1308

The first human clinical study with MK-1308 is currently ongoing (MK-1308-001). This Phase 1 study evaluates MK-1308 as monotherapy for 1 cycle and in combination with pembrolizumab in study participants with advanced solid tumors. The study is a multi-site, open-label study of MK-1308 monotherapy and MK-1308 in combination with pembrolizumab (Part 1, dose escalation) followed by dose confirmation therapy of MK-1308

and pembrolizumab (Part 2, Arms A, B, C). Dose confirmation for Arms A, B, and C include first-line, treatment-naïve, advanced/metastatic NSCLC. Study participants will be treated with 200 mg pembrolizumab Q3W plus MK-1308 25 mg Q3W (Arm A), 25 mg Q6W (Arm B), and 75 mg Q6W (Arm C). From a preliminary analysis of MK-1308-001 safety, anti-tumor activity, PK and pharmacodynamic biomarker data collected during the Dose Escalation and Dose Confirmation phases of the study the RP2D for MK-1308 to carry forward was determined to be 25 mg given every 6 weeks. The ORR of MK-1308 25 mg administered every 6 weeks in the advanced 1L NSCLC population (Arm B) was similar to that of the 75 mg dose level given every 6 weeks (36% versus 28%) at this data cutoff date. The safety at this dose and schedule however was superior, with a 14% Grade 3-5 related adverse event rate (Arm B) versus a 28% Grade 3-5 adverse event rate (Arm C).

3.3.3.3 MK-4280

The first clinical study with MK-4280 is currently ongoing. The safety and tolerability of MK-4280 as monotherapy and in combination with pembrolizumab are evaluated in study participants with advanced solid tumors. This is a Phase 1, multi-site, open-label study of MK-4280 monotherapy (Part A, Arm 1) and MK-4280 in combination with pembrolizumab (Part A, Arm 2) followed by dose confirmation of the combination (Part B) with expansion cohorts to assess antitumor efficacy.

Preliminary PK data from participants treated during Part A of MK-4280-001 (MK-4280 alone and in combination with pembrolizumab) at doses from 7 mg to 700 mg showed that serum MK-4280 exposures increased in a dose-dependent manner and preliminary PK analysis of MK-4280 exposures suggest that target receptor-mediated clearance of MK-4280 was saturated at the 210 mg and 700 mg doses. Also, preliminary data for the exploratory target engagement pharmacodynamic marker from participants treated during Part A of MK-4280-001 also showed a dose-dependent increase in total soluble LAG-3 in serum, generally approaching saturation at the 210 mg and 700 mg doses. MK-4280-001 has also shown the combination of MK-4280 and pembrolizumab to be well tolerated, with no DLTs observed in any participants (N=277) treated with escalating doses of MK-4280 (ranging from 7 mg to 800 mg) as monotherapy and in combination with pembrolizumab as of the data cutoff of 04-JAN-2019. Thirty-nine participants with gastric cancer have been treated with MK-4280 700 mg Q3W as noted in the MK-4280 IB.

Based on a preliminary analysis of DLTs and safety data, along with preliminary PK and exploratory pharmacodynamic observations, a preliminary RP2D of 200 mg Q3W was determined for MK-4280. Later, based on accumulating data from the study, the Sponsor elected to revise the preliminary RP2D for MK-4280 to 800 mg Q3W. As of 09-AUG-2019, 61 participants have been treated with the 800 mg MK-4280 dose in the MK-4280-001 study, including 20 on monotherapy and 41 on combination therapy with pembrolizumab. Twenty participants have passed the DLT period; 10 participants on monotherapy and 10 participants on combination therapy, and there have been 0 DLTs. Therefore, the proposed dose of MK-4280 is changed to 800 mg Q3W in this protocol amendment.

3.3.3.4 Lenvatinib

Lenvatinib was chosen for this study based on the results of the Phase 1b portion of KN146/HOPE111, the primary endpoint of which was to determine the MTD and RP2D for

lenvatinib when used in combination with pembrolizumab 200 mg IV, Q3W. Thirteen participants (lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W: n=3; lenvatinib 20 mg/day + pembrolizumab 200 mg: n=10) were enrolled in the Phase 1b portion of the study. Eight of the participants had RCC, 2 had NSCLC, 2 had EC, and 1 had melanoma. There were 2 dose-limiting toxicities (DLTs) at the lenvatinib 24 mg/day + pembrolizumab 200 mg dose IV Q3W (1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue); hence, this was defined as the toxic dose. No DLTs were reported in the next 10 participants (expansion part), all of whom received the lenvatinib 20 mg/day plus pembrolizumab 200 mg IV Q3W dose. Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given IV Q3W. In Phase 1b, 2 of 13 participants had NSCLC (1 PR and 1 stable disease) [Taylor, M., et al 2016]. Lenvatinib demonstrated meaningful antitumor activity and an acceptable safety profile in a Phase 2 study in patients with RET fusion-positive lung adenocarcinoma. A response rate of 16% and median PFS of 7.3 months with median OS not reached was observed after up to 24 months of follow-up. Overall survival at 24 months was 54.5%, not yet reached in the Other RET fusion group and 11.4 months in the KIF5B-RET fusion group. Lenvatinib has also been studied in unselected patients with non-squamous NSCLC (i.e., not screened for the presence of RET-fusions) who have failed at least two prior systemic anticancer regimens. In this study, the observed ORR was 10.1%, and the median PFS was 5.2 months [Havel, L., et al 2014]. Additionally, there is a Phase 3 clinical study ongoing for lenvatinib combined with pembrolizumab in renal cell carcinoma. These clinical data suggest a value in pembrolizumab combined with lenvatinib, and therefore this agent was selected for further study.

3.4 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.

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

4 Objectives/Hypotheses and Endpoints

This study will evaluate study participants with advanced non-small cell lung cancer (NSCLC) without prior systemic treatment for their advanced disease:

Objective/Hypothesis	Endpoint
Primary	

• Objective: To evaluate the clinical activity (as assessed by objective response rate [ORR]) of specific pembrolizumab-based combinations.
• Primary Hypotheses:
  • The ORR will be greater than CCI among participants with low GEP and low TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
  • The ORR will be greater than CCI among participants with low GEP and high TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
  • The ORR will be greater than CCI among participants with high GEP and low TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
  • The ORR will be greater than CCI among participants with high GEP and high TMB receiving pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib.
	• ORR: Participants who have a confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) as assessed by local site.

Objective/Hypothesis	Endpoint
Secondary	
• Objective: To evaluate the clinical activity (as assessed by progression-free survival [PFS] and overall survival [OS]) of specific pembrolizumab-based combinations. PFS and OS to different specific pembrolizumab-based combinations will be assessed independently in each biomarker-defined group.	• PFS Time from randomization to the first documented disease progression per RECIST 1.1 as assessed by local site or death, whichever occurs first. • OS: Time from randomization to death due to any cause.
• Objective: To determine the safety and tolerability of pembrolizumab in combination with MK-1308, MK-4280, or lenvatinib. Safety and tolerability to different specific pembrolizumab-based combinations will be assessed independently in each biomarker-defined group.	• Number of Participants Experiencing Adverse Events (AEs). • Number of Participants Discontinuing Study Drug Due to AEs.
Tertiary/Exploratory	
Biomarkers for different specific pembrolizumab-based combinations will be assessed independently in each biomarker-defined group. • Objective: To evaluate the clinical activity (as assessed by ORR and PFS) using modified RECIST 1.1 for immune-based therapeutics (iRECIST) [Seymour, L., et al 2017], as assessed by local site review. • Objective: To evaluate clinical responses based upon individual biomarkers (PD-L1 immunohistochemistry [IHC] GEP and TMB). • Objective: To explore additional classifiers of primary resistance to PD-1 blockade beyond GEP and TMB based on additional immune evaluation of baseline tissue. • Objective: To assess the concordance in neoantigen mutation load as measured by TMB gene panel vs whole exome sequencing/RNA-seq	• Clinical activity (as assessed by ORR and PFS) of specific pembrolizumab-based combinations using modified RECIST 1.1 for immune-based therapeutics (iRECIST), as assessed by local site review.

Objective/Hypothesis	Endpoint
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab based combinations.	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other blood-derived biomarkers.
• Objective: To collect and build on the pharmacokinetic (PK) and anti-drug antibody (ADA) experiences of MK-1308 and MK-4280 in combination with pembrolizumab.	• PK profiles and ADA rates of MK-1308 and MK-4280 in combination with pembrolizumab

5 Study Design

5.1 Overall Design

This is a group-sequential, adaptive randomization, multi-site, open-label study of pembrolizumab (MK-3475) in combination with MK-1308, MK-4280, or lenvatinib in participants with advanced NSCLC who have not received prior systemic therapy for advanced disease and for whom an FDA- or EMA-approved targeted therapy (eg, erlotinib, crizotinib, etc.) is not indicated as first-line (1L) therapy based on defined oncogenic mutation (nonsquamous NSCLC only).

Participants will be screened for the status of 2 clinically validated, independent next-generation biomarkers: T cell–inflamed GEP and TMB. A tumor specimen for biomarker assessment will be required for enrollment of all participants. A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study), is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the participant (including, but not limited to, biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel), an archival specimen should be submitted.

Participants will be assigned to 1 of 4 biomarker-defined groups ($GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$). TMB status will be derived from a 507-gene panel developed by PGDx, Inc. (Baltimore, MD, United States). Testing will be done centrally in their CLIA facility. GEP status will be derived from the signature genes present on the NanoString Pan Cancer Immune Panel. This assay will be run centrally at the Almac Diagnostic Services facility (Durham, NC, United States). Participants then will be randomized within biomarker-defined group to treatment with 1 of the pembrolizumab-based combination regimens, and adaptive design elements will be used to adjust the randomization based on objective responses.

Each biomarker-defined group will be capped (ie, enrollment into that biomarker group will stop) after a minimum number of participants are enrolled to ensure adequate statistical

power to assess the response rate of each combination therapy relative to the expected response rate for pembrolizumab. Estimates of pembrolizumab monotherapy response rates are CCI [redacted] for biomarker-defined groups $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$, respectively. Based on these estimates, without including 30 participants currently treated with pembrolizumab in combination with 200 mg MK-4280, the study requires approximately 66 participants in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups and approximately 90 participants in the $GEP^{hi}TMB^{hi}$ group for adequate statistical power (details provided in Section 10). Once a biomarker-defined group has reached this number (approximately 66 for $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups, and approximately 90 for the $GEP^{hi}TMB^{hi}$ group) of participants, the group will be closed to new participants. Additionally, within each biomarker-defined group, each combination therapy will be capped. Once a combination therapy has reached this number (approximately 25 for $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups, and approximately 40 for the $GEP^{hi}TMB^{hi}$ group), the combination therapy will be closed to new participants.

Pembrolizumab will be combined with MK-1308 (anti–CTLA-4), MK-4280 (anti–LAG-3) or lenvatinib (RTK inhibitor) in this study.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

This study will use an adaptive design based on prespecified criteria. Within each biomarker-defined group, the first 36 study participants will be randomized equally among the three combination therapies. The randomization is modified to accommodate the delayed introduction for pembrolizumab in combination with MK-1308. Details are provided in Appendix 9.

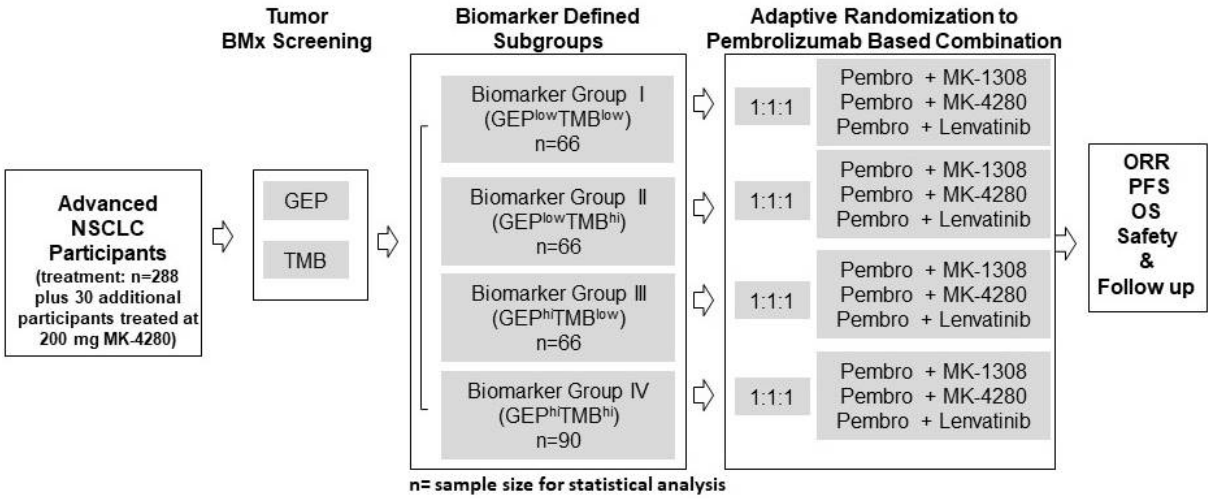
The first interim analysis for each combination therapy will occur after at least 10 participants have at least 12 weeks of follow-up. Participants' response data will be closely monitored throughout the study and subsequent interim analyses may be performed when response data are available for at least 2 additional participants in each combination therapy. The actual number of interim analyses depends on the actual accrual rate, study duration, and the actual performance of combination therapies.

Results of the interim analyses will determine the randomization ratio among the treatment arms according to the prespecified algorithm described in detail in Section 10 – Statistical Analysis Plan. Results of the interim analysis will be used to determine whether to continue, modify, or end the study according to the plan described briefly in Section 5.1.1 – Study Diagram and in detail in Section 10 – Statistical Analysis Plan.

5.1.1 Study Diagram

The study diagram is depicted in Figure 2.

Figure 2 Study Diagram



GEP=gene expression profile; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; TMB= tumor mutational burden; PFS=progression-free survival.

Note: The estimated percentages at tumor biomarker screening are based on stratification in the Cancer Genome Atlas (TCGA) using cut-point equivalent to the ones relevant for this study. Biomarker Group I consist of study participants with $GEP^{low}TMB^{low}$ tumors, Biomarker Group II with $GEP^{low}TMB^{hi}$ tumors, Biomarker Group III with $GEP^{hi}TMB^{low}$ tumors, and Biomarker Group IV with $GEP^{hi}TMB^{hi}$ tumors. The approximate number of participants in each group is indicated above. The estimated prevalences of Biomarker Group I, II, III, and IV are 21%, 17%, 29%, and 33%, respectively. Currently, 30 participants are being treated with MK-4280 200 mg Q3W, including 10, 7, 8, and 5 participants in Biomarker Group I, II, III, and IV, respectively. These 30 participants treated with MK-4280 200 mg Q3W may be replaced with 30 additional participants treated with MK-4280 at 800 mg Q3W after the approval of Amendment 05. The replacement number may depend on results of interim analyses, including estimated posterior probabilities of meeting the target response rate at the 800 mg dose. Consequently, the total treated sample size is changed from 288 to 318. Due to the different start time of the 3 combination treatments, an unequal randomization ratio may be used first and then randomization schedules will be adjusted to equalize treatment arm enrollment per biomarker-defined group depending on the time of introducing the delayed combination treatments in order to meet study analysis milestones.

5.2 Number of Participants

Without including 30 participants currently treated with pembrolizumab in combination with 200 mg MK-4280, approximately 288 participants will be randomized within each tumor biomarker-defined group to treatment with 1 of the pembrolizumab−based combinations. Currently, 30 participants are being treated with MK-4280 200 mg Q3W, including 10, 7, 8, and 5 participants in Biomarker Group I, II, III, and IV, respectively. These 30 participants treated with MK-4280 200 mg Q3W may be replaced with 30 additional participants treated with MK-4280 at 800 mg Q3W after the approval of Amendment 05. The replacement number may depend on results of interim analyses, including posterior probabilities of meeting the target response rate at the 800 mg dose. Consequently, the total treated sample size is changed from 288 to 318.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent.

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator) or the last participant in follow-up is offered enrollment in an extension study.

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

5.3.1 Clinical Criteria for Early Study Termination

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

- All pembrolizumab-based combination therapies being studied meet either the futility bar or safety or if the maximum number of participants has been reached (details in Section 10 - Statistical Analysis Plan).

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

This study will use ORR based on RECIST 1.1 criteria as the primary endpoint and PFS as a secondary endpoint. Study participants will be defined as having an objective response if they have best response as CR or PR based on RECIST 1.1 at any time during the study prior to initiation of follow-up therapy. Objective response rate and PFS based on iRECIST will be used for an exploratory objective endpoint. Objective response rate or progression-free survival is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. Overall survival is also a secondary endpoint in the study. Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

RECIST 1.1 will be used when assessing images for efficacy measures and by the local site when determining eligibility (Section 9.2.1.4). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

RECIST 1.1 will be adapted to account for the unique tumor response seen following treatment with pembrolizumab (Section 9.2.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific

immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and participants can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that considers the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. Immune Response Evaluation Criteria in Solid Tumors will be used by investigators to assess tumor response and progression and make treatment decisions as well as for exploratory efficacy analyses where specified.

5.4.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/serious adverse events (SAEs); and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, v 4.0.

5.4.1.3 Pharmacokinetic Endpoints

An exploratory objective of this study is to characterize the PK profile of MK-1308 and MK-4280 when administered in combination with pembrolizumab. PK samples (Cycles 1, 5 and every 4 cycles thereafter for MK-1308 and Cycles 1, 4 and every 4 cycles thereafter for MK-4280) will be collected in participants enrolled under Amendment 5 and later. The serum concentrations of each antibody will be used to determine PK parameters (eg, C_{max}, area under the curve [AUC]) for MK-1308 and MK-4280. Furthermore, the results of these analyses may be used in conjunction with PD, safety, and ADA endpoints to help assess dosing strategies for MK-1308 and MK-4280 in combination with pembrolizumab.

5.4.1.4 Pharmacodynamic Endpoints

Pharmacodynamic markers will be interrogated to gain a better understanding of response and resistance biology. Tumor biopsy will be performed at baseline (archival tissue acceptable for this sample). Blood samples for exploratory biomarkers and planned genetic

analysis will be collected prior to treatment on C1D1, C2D1, C3D1, C6D1 and at end of treatment/progression. Detailed endpoints are described below in the biomarker section (Section 9.9).

Formation of ADAs can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicity. ADA samples (Cycles 1, 5, and every 4 cycles thereafter for MK-1308 and Cycles 1, 4 and every 4 cycles thereafter for MK-4280) will be collected in participants enrolled under Amendment 5 and later. Anti-drug antibody response at the beginning of some prespecified cycles of drug administration will be determined to understand drug metabolism, exposure, and safety of the combination therapy. Anti-drug antibody response to MK-1308 and MK-4280 will be evaluated.

5.4.1.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical studies. These efforts will identify novel predictive/PD biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components and tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

5.4.1.5.1 Germline (Blood) Genetic Analyses (eg, Single Nucleotide Polymorphism [SNP] Analyses, Whole Exome Sequencing, Whole Genome Sequencing)

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

5.4.1.5.2 Genetic (DNA) Analyses from Tumor

The application of new technologies, such as next-generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, and microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T cells in the tumor microenvironment. Increased tumor mutational burden (sometimes referred to as a ‘hyper-mutated’ state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome.

5.4.1.5.3 Genetic (DNA) Analyses from Blood

Genetic analysis on blood samples including but not limited to assays on circulating free DNA, and T cell receptor sequencing may be performed.

5.4.1.5.4 Tumor and Blood RNA Analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued.

5.4.1.5.5 Proteomics and Immunohistochemistry (IHC) Using Blood or Tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

5.4.1.5.6 Other Blood-Derived Biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in blood. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

5.4.1.5.7 Epigenetic Analyses

Epigenetic analyses may also be performed as these are important biomarkers for some cancers.

5.4.1.6 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease

being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

5.4.1.7 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

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

5.4.2 Rationale for the Use of Comparator/Placebo

This study will not use a comparator or placebo.

5.5 Justification for Dose

5.5.1 Rationale for Pembrolizumab Fixed-Dose (Standard of Care and Combination-Based Therapy)

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 pharmacokinetic [PBPK] 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 vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of 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 (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK 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.

5.5.2 Rationale for Combination Agent Dose Selection

In this study, pembrolizumab will be combined with MK-1308, MK-4280 or lenvatinib. The rationale for the dose and schedule of each agent combining with pembrolizumab is provided in subsequent sections.

5.5.2.1 Pembrolizumab Plus MK-1308 (Anti–CTLA-4)

The first human clinical study with MK-1308 is currently ongoing. Pembrolizumab is dosed first, followed by a 30-minute break and then the MK-1308 infusion. It is reasonable to expect MK-1308 to be consistent with that of other humanized mAbs that typically have a low clearance and a limited volume of distribution. Using a population PK model of ipilimumab, distribution of exposures from the 25 mg MK-1308 fixed-dose considerably overlaps those obtained with the 0.3 mg/kg weight-based ipilimumab dose and exposures from the 75 mg MK-1308 fixed-dose considerably overlap those obtained with the 1.0 mg/kg

weight-based ipilimumab dose [Feng, Y., et al 2014]. Similar to pembrolizumab, a fixed-dose regimen of MK-1308 is expected to reduce complexity in the logistical chain at treatment facilities and reduce waste.

From a preliminary analysis of MK-1308-001 safety, anti-tumor activity, PK and pharmacodynamic biomarker data collected during the Dose Escalation and Dose Confirmation phases of the study the RP2D for MK-1308 to carry forward was determined to be 25 mg given every 6 weeks. The ORR of MK-1308 25 mg administered every 6 weeks in the advanced 1L NSCLC population (Arm B) was similar to that of the 75 mg dose level given every 6 weeks (36% versus 28%) at this data cutoff date. The safety at this dose and schedule, however, was superior, with a 14% Grade 3-5 related adverse event rate (Arm B) versus a 28% Grade 3-5 adverse event rate (Arm C). Based on MK-1308-001, a dose and schedule of 25 mg Q6W in combination with 200 mg pembrolizumab Q3W was selected for this study.

5.5.2.2 Pembrolizumab Plus MK-4280 (Anti–LAG-3)

Based on a preliminary analysis of DLTs and safety data along with preliminary PK and exploratory pharmacodynamic observations from the Part A portion of the MK-4280-001 study, a preliminary RP2D of 200 mg Q3W was determined for MK-4280. Later, based on accumulating data from the study, the Sponsor elected to test an additional higher dose of MK-4280 in Part B (800 mg).

Preliminary PK analysis of MK-4280-001 exposures suggest that target receptor-mediated clearance (reflecting target engagement of membrane LAG-3) of MK-4280 was saturated at doses higher than 200 mg, considering PK trough variability observed in study participants. Additionally, preliminary data for the exploratory target engagement pharmacodynamic marker from participants treated during Part A and Part B of MK-4280-001 demonstrate a dose-dependent increase in total sLAG-3 in serum (reflecting target engagement of sLAG-3), with the saturation likely sustained over the dosing interval at doses higher than 210 mg.

Preliminary efficacy data from the dose comparison cohort in gastric cancer in MK-4280-001 also suggests a trend towards better efficacy at 700 mg MK-4280. An interim analysis of the randomized dose-comparison of MK-4280-001 (MK-4280 200 mg vs 700 mg plus a fixed 200 mg dose of pembrolizumab) was performed on 04-JAN-2019 as part of the annual MK-4280 IB update. At the time of the analysis, 39 gastric cancer participants per arm (78 total), had been treated with MK-4280. Though not statistically significant, these data demonstrated trends towards improved disease control at the higher dose, including an ORR by RECIST 1.1 of 7.7% (95% CI: 1.6, 20.9) versus 15.4% (95% CI: 5.9, 30.5), and mean change in target lesion size of 29.9 cm (95% CI: 10.2, 49.7) versus 6.4 cm (95% CI: 9.3, 22.1) for 200 mg and 700 mg MK-4280, respectively. No significant difference in safety has been observed at the 200 mg dose in comparison to the 700 mg dose in the randomized dose comparison cohort in gastric cancer.

Based on a preliminary population PK analysis, the distribution of predicted MK-4280 serum concentrations at the 700 mg and 800 mg doses is expected to be similar, resulting in substantial overlap between the exposures at these 2 doses. Due to the predicted exposure overlap between the 700 mg and 800 mg doses based on MK-4280 drug concentrations, a similar safety profile for the 700 mg and 800 mg doses is anticipated.

Therefore, based on the totality of preliminary data accumulated so far, the Sponsor has elected to change the recommended Phase 2 dose of MK-4280. In order to minimize dosing complexity and lessen the risk of dosing errors given the 200 mg vial size, an 800 mg Q3W dose of MK-4280 alone or in combination with pembrolizumab has been selected as the RP2D and the combination of MK-4280 and pembrolizumab will be tested in the KEYNOTE-495 study.

As of 09-AUG-2019, 61 participants have been treated with 800 mg of MK-4280 in MK-4280-001, including 20 on monotherapy and 41 on combination therapy with pembrolizumab. Twenty participants have passed the DLT period; 10 participants on monotherapy and 10 participants on combination therapy and there have been 0 DLTs.

Participants enrolled under Amendment 05 or later will be treated with pembrolizumab plus MK-4280 800 mg Q3W. Participants enrolled prior to Amendment 05 were initially treated with pembrolizumab plus MK-4280 200 mg Q3W. Upon approval of Amendment 05, participants currently treated with MK-4280 200 mg can choose to stay at this dose level or start MK-4280 800 mg Q3W.

5.5.2.3 Pembrolizumab Plus Lenvatinib

The dosing regimen of lenvatinib was selected based on the results of the Phase 1b portion of Phase 1b/2 Study 111/KEYNOTE-146, the primary endpoint of which was to determine the MTD and RP2D for lenvatinib in combination with pembrolizumab 200 mg Q3W. Thirteen participants (lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W: n=3; lenvatinib 20 mg/day + pembrolizumab 200 mg: n=10) were enrolled in the Phase 1b portion of the study. Eight of the participants had RCC, 2 had NSCLC, 2 had EC, and 1 had melanoma. There were 2 DLTs at the dose of lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W (1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue); hence, this was defined as the toxic dose. No DLTs were reported in the next 10 participants (expansion part), all of whom received the lenvatinib 20 mg/day + pembrolizumab 200 mg Q3W dose.

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W. Based on the promising anti-tumor efficacy and tolerable safety profile seen in both the EC and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], two Phase 3 studies have been initiated for both of these tumor types, Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-307/KEYNOTE-581.

For the current study, participants will receive 200 mg pembrolizumab Q3W plus 20 mg/day lenvatinib. Pembrolizumab plus lenvatinib will be dosed for up to 35 cycles. If participants complete 35 infusions of pembrolizumab, they may continue with lenvatinib alone until disease progression or toxicity.

5.5.3 Rationale for Dose Intervals and Study Design

As explained in Section 5.5.1, Rationale for Pembrolizumab Fixed-Dose (Standard of Care and Combination-Based Therapy), pembrolizumab will be administered at a dose of 200 mg IV Q3W. The doses and dosing intervals of the combination agents are explained in Section 5.5.2, Rationale for Combination Agent Dose Selection. Study participants will be

treated with a maximum of 35 treatments (approximately 2 years) of pembrolizumab. Combination treatment with MK-1308 or MK-4280 also will be given for a maximum duration and discontinued upon completion of the 35th cycle of pembrolizumab. For the lenvatinib combination arm, if a participant completes 35 infusions of pembrolizumab, they may continue with lenvatinib alone until disease progression or toxicity.

6 Study Population

As stated in the Code of Conduct for Clinical Trials (Appendix 3), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male/Female study participants at least 18 years of age with NSCLC will be enrolled in this trial.

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

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Have a histologically or cytologically confirmed diagnosis of Stage IV (American Joint Committee on Cancer [AJCC] v. 8) NSCLC and study participants should not have had prior systemic therapy for advanced disease.
2. Have confirmation that epidermal growth factor receptor– (EGFR-), anaplastic lymphoma kinase– (ALK-), c-ros oncogene 1 (ROS1), or B isoform of rapidly accelerated fibrosarcoma (B-Raf) directed therapy is not indicated as primary therapy. Documentation of absence of tumor activating EGFR mutations, B-Raf mutations, ALK gene rearrangements, and ROS1 gene rearrangements. If participant's tumor is known to have a predominantly squamous histology, molecular testing for EGFR mutation and ALK and ROS1 translocations will not be required, as this is not part of current diagnostic guidelines.
3. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

Demographics

4. Male/female participants who are at least 18 years of age on the day of signing the informed consent.

Male participants:

5. A male participant must agree to use a contraceptive as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

6. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of study treatment.

Informed Consent

7. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for Future Biomedical Research. However, the participant may participate in the main study without participating in Future Biomedical Research.

Additional Inclusion Criteria

8. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Newly obtained biopsies are preferred to archival tissue. Repeat samples may be required if adequate tissue is not provided.
   Note: If sending newly cut slides, they should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).
9. Participants must have adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week prior to randomization.
10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
11. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start of study treatment.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	⩾9.0 g/dL or ⩾5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has significant cardiovascular impairment within 12 months of the first dose of study drug: such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebrovascular accident (CVA) stroke, cardiac arrhythmia associated with hemodynamic instability, or a left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition scan (MUGA) or echocardiogram.

2. Prolongation of QTc interval to >480 ms.
3. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
4. Has had an allogenic tissue/solid organ transplant.
5. 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 will be required. Note: in the event that 24 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.
6. Participants with proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 h will be ineligible.
7. Participants who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy. Participants who have had major surgery within 3 weeks prior to first dose of study intervention. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
8. Has preexisting ≥Grade 3 gastrointestinal or non-gastrointestinal fistula, gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
9. Radiographic evidence of major blood vessel invasion/infiltration. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
10. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

Prior/Concomitant Therapy

11. Has received prior systemic chemotherapy treatment for metastatic/recurrent NSCLC.

    Note: Prior treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic/recurrent NSCLC.
12. Has current NSCLC disease that can be treated with curative intent with surgical resection, localized radiotherapy, or chemoradiation.
13. Is expected to require any other form of systemic or localized antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).

14. Has received prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (eg, CTLA-4, OX 40, CD137).
15. Has received previous treatment with another agent targeting the LAG-3 receptor.
16. Has received previous treatment with another agent targeting VEGF or the VEGF receptor.
17. Has received prior anticancer therapy including investigational agents within 4 weeks prior to randomization.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

    Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
18. Has received prior radiotherapy within 2 weeks of start of study treatment or received lung radiation therapy of >30 Gy within 6 months prior to the first dose of study intervention. Participants must have recovered from all radiation-related toxicities to Grade ≤1, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
19. Has received a live or live-attenuated vaccine within 30 days before the first dose of study treatment. Administration of killed vaccines are allowed.

Prior/Concurrent Clinical Study Experience

20. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

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

Diagnostic assessments

21. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment.
22. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
23. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated CNS metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by

repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 28 days prior to first dose of study treatment.

24. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, MK-1308, MK-4280, or lenvatinib and/or any of their excipients.
25. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
26. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
27. Has an active infection requiring systemic therapy.
28. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
29. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.
30. Has a known history of active tuberculosis (TB; Bacillus tuberculosis)
31. 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, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
32. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

Other Exclusions

33. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days for females and 120 days for males after the last dose of study treatment.

6.3 Lifestyle Restrictions

No lifestyle restrictions are required.

6.3.1 Meals and Dietary Restrictions

6.3.1.1 Diet

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

6.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions for caffeine and tobacco. There are no alcohol restrictions for pembrolizumab plus MK-1308, MK-4280, or lenvatinib.

6.3.3 Activity

There are no restrictions on activity.

6.3.4 Contraception

Pembrolizumab, MK-1308, and MK-4280 may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab, MK-1308, and MK-4280 have transient adverse effects on the composition of sperm.

Based on its mechanism of action, lenvatinib can cause fetal harm when administered to a pregnant woman. Lenvatinib may also result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues leading to reduced fertility of unknown duration. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

For this study, male study participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Refer to Appendix 5 for approved methods of contraception.

6.3.5 Pregnancy

If a study participant inadvertently becomes pregnant while on treatment with a pembrolizumab-based combination treatment, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 9.3.6.

6.3.6 Use in Nursing Women

It is unknown whether pembrolizumab, MK-1308, MK-4280, or lenvatinib is excreted in human milk. In animal studies, lenvatinib has been shown to be excreted in milk. In rat studies, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, study participants who are breastfeeding are not eligible for enrollment.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Participants may be rescreened once prior to being considered a screen failure. 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 adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

A participant who discontinues study treatment or withdraws from the study will not be replaced.

7 Treatments

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

7.1 Treatments Administered

The combination study treatments to be used in this trial are outlined below in Table 5.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab (MK-3475)	Biological/ vaccine	Solution for Infusion	100 mg/vial (25 mg/mL, 4 mL vial)	200 mg	IV infusion	Q3W	Test Product	IMP	Central
Arm 1	Experimental	MK-1308	Biological/ vaccine	Solution for Infusion	50 mg/mL	25 mg	IV infusion	Q6W	Test Product	IMP	Central
Arm 2	Experimental	Pembrolizumab (MK-3475)	Biological/ vaccine	Solution for Infusion	100 mg/vial (25 mg/mL, 4 mL vial)	200 mg	IV infusion	Q3W	Test Product	IMP	Central
Arm 2	Experimental	MK-4280	Biological/ vaccine	Solution for Infusion	25 mg/mL	200 or 800 mg	IV infusion	Q3W	Test Product	IMP	Central
Arm 3	Experimental	Pembrolizumab (MK-3475)	Biological/ vaccine	Solution for Infusion	100 mg/vial (25 mg/mL, 4 mL vial)	200 mg	IV infusion	Q3W	Test Product	IMP	Central
Arm 3	Experimental	Lenvatinib	Drug	Capsule	4 mg, 10 mg	4, 8, 10, 14, or 20 mg	Oral	Once daily	Test Product	IMP	Central

EEA =European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks' Q6W=every 6 weeks.

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

All supplies indicated in Table 5 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number.

Refer to section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification (Escalation/Titration/Other)

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

The investigator may attribute each toxicity event to pembrolizumab, MK-1308, MK-4280, or lenvatinib alone or to the pembrolizumab-based combination treatment. Study participants may not have any dose reductions of pembrolizumab, MK-1308, or MK-4280 in this study. Interruption of either pembrolizumab, MK-1308, or MK-4280 administration or administration of corticosteroids and/or other supportive care is allowed. If toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from the agent. Dose interruptions and reductions of lenvatinib are allowed throughout the study. Holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both drugs should be held according to recommended dose modifications.

7.2.1.1 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.

In these cases where the toxicity is attributed to pembrolizumab coformulations or IO combinations, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

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 6.

For additional guidance on lenvatinib, see Section 7.2.2.

Table 6 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 [a]	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 [b] or 4 [c]	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 [d]	• 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 [d]		
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 [d]		

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		
Ophthalmologic Uveitis, iritis, episcleritis	Grade 2	Withhold	• Administer corticosteroid eye drops to participants who develop uveitis, iritis, or episcleritis • Permanently discontinue study drugs for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy	• Monitor for signs and symptoms of ophthalmologic disorders
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 [e]		
	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

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

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

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

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

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

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

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

7.2.1.2 Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab, MK-1308, and MK-4280

Pembrolizumab, MK-1308, and MK-4280 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, MK-4280, and MK-1308-associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab, MK-1308, and MK-4280 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of either pembrolizumab, MK-1308, or MK-4280 with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
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 participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study treatment**.	No subsequent dosing
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		

7.2.1.3 Other Allowed Dose Interruption for Pembrolizumab, MK-1308, MK-4280 and Lenvatinib

Pembrolizumab, MK-1308, MK-4280, and lenvatinib may be interrupted for situations other than treatment-related AEs, such as medical/surgical events and/or unforeseen circumstances not related to study treatment. However, intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

7.2.2 Dose Modifications for Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 8. An interruption of study treatment for more than 28 days will require Sponsor's approval before treatment can be resumed.

Adverse events will be graded using NCI CTCAE Version 4.0. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

The starting dose of lenvatinib is 20 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the Sponsor. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, Sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 7.2.2.1), proteinuria (Section 7.2.2.2), diarrhea (Section 7.2.2.3), hepatotoxicity (Section 7.2.2.4), thromboembolic events (Section 7.2.2.5), posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 7.2.2.6), hypocalcemia (Section 7.2.2.7), hemorrhage (Section 7.2.2.8), gastrointestinal perforation (7.2.2.9), and osteonecrosis of the jaw (7.2.2.10) as appropriate, before consulting the dose modification table (Table 8).

Table 8 Adverse Events Requiring Dose Modification of Lenvatinib

Adverse Event	NCI CTCAE Grade	Action	Dose Adjustment/ Resume Lenvatinib
Hypertension	Grade 3[a]	Hold	Resume at reduced dose when hypertension resolves to Grade 0, 1, or 2
	Grade 4	Discontinue	Do not restart treatment
Cardiac dysfunction	Grade 3	Hold	Resume at reduced dose when cardiac dysfunction resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do not restart
Arterial thrombotic event	Any grade	Discontinue	Do not restart
Hepatotoxicity	Grade 3	Hold OR discontinue	Consider resuming at a reduced dose if resolves to Grade 0 to 1 or baseline
	Grade 4	Discontinue	Do not restart
Hepatic failure	Grade 3 or 4	Discontinue	Do not restart
Proteinuria	≥2g/24 hours	Hold	Resume at reduced dose when proteinuria resolves to <2 g/24 hours
	Grade 4	Discontinue	Do not restart
Nephrotic syndrome	N/A	Discontinue	Do not restart
Nausea, vomiting, or diarrhea[b]	Grade 3	Hold	Resume at reduced dose when nausea, vomiting, diarrhea resolves to Grade 0, 1, or baseline
Vomiting and diarrhea[b]	Grade 4	Discontinue	Do not restart
Renal failure or impairment	Grade 3	Hold OR discontinue	Consider resuming at a reduced dose if resolves to Grade 0-1 or baseline
	Grade 4	Discontinue	Do not restart
GI perforation	Any grade	Discontinue	Do not restart
Fistula	Grade 3 or 4	Discontinue	Do not restart
QTc prolongation	>500 ms	Hold	Resume at reduced dose when QTc prolongation resolves to <480 ms or baseline
RPLS	Grade 1, 2 or 3	Hold or discontinue	Upon resolution, resume at a reduced dose or discontinue depending on the severity and persistence of neurologic symptoms
	Grade 4	Discontinue	Do not restart
Hemorrhage	Grade 3	Hold	Resume at reduced dose when haemorrhage resolves to Grade 0 or 1
	Grade 4	Discontinue	Do not restart
Other intolerable Grade 2[c,d,e] or Grade 3 adverse reactions [f,g] - first occurrence	Grade 2 or 3	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day [e]
Other intolerable Grade 2[c,d,e] or Grade 3 adverse reactions [f,g] - Second occurrence (same toxicity or new toxicity)	Grade 2 or 3	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day [e]

Adverse Event	NCI CTCAE Grade	Action	Dose Adjustment/ Resume Lenvatinib
Other intolerable Grade 2[c,d,e] or Grade 3 adverse reactions [f,g] - Third occurrence (same toxicity or new toxicity)	Grade 2 or 3	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day [e]
Other intolerable Grade 2[c,d,e] or Grade 3 adverse reactions [f,g] - Fourth occurrence (same toxicity or new toxicity)	Grade 2 or 3	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[h]	Grade 4	Discontinue	Discuss with Sponsor

CTCAE = common terminology criteria for adverse events; GI = gastrointestinal; N/A = not applicable; NCI = National Cancer Institute; RPLS=reversible posterior leukoencephalopathy syndrome.

a. Grade 3 despite optimal anti-hypertensive therapy
b. Initiate prompt medical management for nausea, vomiting, or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management.
c. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism, and/or diarrhea prior to any lenvatinib interruption or dose reduction.
d. Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
e. Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they reach at least a BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.
f. For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.
g. For Grade 3 thromboembolic event, permanently discontinue lenvatinib/matching placebo. See Section 7.2.2.5
h. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3

Note: For grading see National Cancer Institute Common Toxicity Criteria for Adverse Events, v 4.0. Collect all CTCAE grades of AEs, decreasing and increasing grade.

Note: An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

7.2.2.1 Dose Modifications for Lenvatinib Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling.

Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have blood pressure (BP) of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Activities and in Section 9.5.2. Hypertension will be graded using CTCAE v4.0, based on BP measurements only (and not on the number of antihypertensive medications). Management of lenvatinib administration will be based on the grade of hypertension according to Table 8 in the Dose Modification Guidelines.

If the participant's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as one BP assessment. If the BP

assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mmHg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles.

Under exceptional circumstances, participants will have the option of having BP measured between visits obtained locally by a health care professional. A BP log will be provided to capture the blood pressure evaluations between study visits. The health care professional will provide documentation of the BP measurement to the study-site.

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on 2 measurements after at least 30 minutes:

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.
2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction dose only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
- Additional dose reduction should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life threatening consequences):

1. Institute appropriate medical management

2. Discontinue study drug.

7.2.2.2 Dose Modifications for Lenvatinib Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA in Section 2. Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing per the SoA in Section 2
2. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:
    - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
    - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
    - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v4.0 will be based on the 24-hour urinary protein result if one has been obtained. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 8.

Monitoring

- Urine dipstick testing for participants with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued

7.2.2.3 Dose Modifications for Lenvatinib Management of Diarrhea

Instructions in Table 8 should be followed for the management of diarrhea. An anti-diarrheal agent should be recommended to the participant at the start of study treatment and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 8 should be followed.

7.2.2.4 Dose Modifications for Lenvatinib Management of Hepatotoxicity

Regular monitoring of liver function tests (eg, alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the SoA in Section 2. If signs/symptoms indicating liver injury occur, instructions contained in Table 8 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, lenvatinib must be discontinued.

7.2.2.5 Dose Modifications for Lenvatinib Management of Thromboembolic Events

Participants should be advised to pay attention to the symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, and deep vein thrombosis (DVT) signs including lower-extremity swelling, redness, and warmth to touch or tenderness. Participants should be instructed to report any of these signs and symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 8 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study treatment must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

7.2.2.6 Dose Modifications for Lenvatinib Management of Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior reversible encephalopathy syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. A magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In participants with signs or symptoms of PRES, instructions in Table 8 should be followed.

7.2.2.7 Dose Modifications for Lenvatinib Management of Hypocalcemia

Serum calcium should be monitored Q3W as detailed in the SoA in Section 2. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v 4.0, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$$

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead. Hypocalcemia should be treated per institutional guidelines (eg, using, as appropriate, calcium, magnesium, and vitamin D supplementation) until resolution.

7.2.2.8 Dose Modifications for Lenvatinib Management of Hemorrhage

Instructions in Table 8 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

7.2.2.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or ≥Grade 3 fistula.

7.2.2.10 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution.

7.2.2.11 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example,

hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following two scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

   If the participant recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

   If an AE is suspected to be treatment-related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Participants receiving the combination therapy (pembrolizumab + lenvatinib) must discontinue study therapy if any of the following occur:

   1) ALT or AST >5 X ULN for more than 2 weeks.
   Pembrolizumab will have already been permanently discontinued per Table 6, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

   2) ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
   Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 8 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

7.2.2.12 General Guidelines for Holding Periods of Lenvatinib Due to Procedures

If the study participant is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: Stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of

bleeding. Needle biopsies (fine needle aspirations and core needle aspiration) are usually considered minor procedures.

- For major procedures: Stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding. It is up to the investigator to determine if it is a major or minor procedure. Usually, a major procedure implies general anesthesia.

7.3 Method of Treatment Assignment

Initially, all eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization 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/randomization number.

Treatment randomization will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS).

7.3.1 Adaptive Randomization

Study participants will first be assigned to a biomarker-defined group ($GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, or $GEP^{hi}TMB^{hi}$) based on screening test results of TMB and GEP assays.

Due to the different start time of three combination treatments, unequal randomization ratio may be used first, and then randomization schedules will be adjusted to equalize treatment arm enrollment per biomarker-defined group depending on the time of introducing the delayed combination treatments in order to meet study analysis milestones.

For each biomarker-defined group, the first interim analysis will occur after at least 10 participants in each treatment combination have at least 12 weeks of follow-up. After the first interim analysis, participants' response data will be closely monitored throughout the study, and the subsequent interim analyses may be performed with a minimum of 2 additional participants achieving 12 weeks of follow-up for each combination therapy that still remains in the study. At each interim analysis, there will be an opportunity to drop individual treatment combinations within biomarker-defined groups or entire biomarker-defined groups for futility or safety. As long as any biomarker-defined group and treatment combination are retained in the study, enrollment will continue with equal randomization to the remaining treatment arms (see details in Section 10.7).

7.3.2 Stratification

Treatment randomization will be stratified based on the assigned biomarker-defined group based on screening test results of TMB and GEP assays.

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Details on preparation and administration of pembrolizumab, MK-1308, MK-4280, and lenvatinib are provided in the Pharmacy Manual.

The rationale for selection of doses to be used in this trial is provided in Section 3.3 – Background. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial 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 trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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 treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

Interruptions from the protocol-specified treatment plan for pembrolizumab, MK-1308 or MK-4280 greater than 12 weeks and for lenvatinib greater than 28 days require consultation between the Investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.6.1 Administration and Compliance of Intravenous Study Treatments (Pembrolizumab, MK-1308, and MK-4280)

Administration of IV pembrolizumab, MK-1308, and MK-4280 will be witnessed by the Investigator and/or study staff. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. Pembrolizumab, MK-1308, and MK-4280 will be administered on an outpatient basis.

Instructions for preparing and administering pembrolizumab, MK-1308, and MK-4280 are provided in the Pharmacy Manual.

7.6.2 Administration and Compliance of Oral Study Treatment (Lenvatinib)

Study participants will take the dose of lenvatinib on Day 1 of each cycle after completion of pembrolizumab. Lenvatinib will be taken once a day with water at approximately the same time each day. If a dose is missed and cannot be taken within 12 hours, study participants should skip that dose and take the next dose at the usual time of administration.

Records of treatment compliance for each participant will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

7.7 Concomitant Therapy

7.7.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a study participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription medications, over-the-counter medications, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage frequency, route, and date will also be included on the CRF.

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control is not permitted during the study. Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted if considered medically necessary by the treating physician as long as the lesions are NOT a RECIST 1.1–defined target lesion. Study therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study therapy. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 28 days before the first dose of study treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 9.3.

7.7.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination

may be required. The Investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the study participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the Investigator, the Sponsor, and the participant.

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab, MK-1308, MK-4280, and lenvatinib
- Oncologic surgery for tumor control
- Radiation therapy for disease control
  - Note: Radiation therapy to symptomatic lesions or to the brain may be allowed at the Investigator's discretion, provided the lesions were not previously defined by the site as target lesions.
- Live or live attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study
  - NOTE: killed vaccines are allowed.
- Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an AE, SAE, or ECI or for use as a premedication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (eg, for COPD exacerbation).
  - Replacement doses of steroids (eg, prednisone 10 mg daily) are permitted while on study, as is the use of local steroids.

Participants who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but continue in study for assessment of disease status and survival.

The exclusion criteria describe other medications which are prohibited in this study.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

7.7.3 Rescue Medications & Supportive Care

Study participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology and AEs related to lenvatinib are outlined along with the dose modification guidelines in Section 7.2. 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 treatment, the Investigator does not need to follow the treatment guidance. For information regarding dose modification and supportive care, for pembrolizumab refer to Section 7.2.1, for MK-1308 refer to Section 7.2.1, for MK-4280 refer to Section 7.2.1, and for lenvatinib, refer to Section 7.2.2.

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

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

8 Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - Schedule of Activities and Section 9.10.3.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment 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 treatment.

- ALT or AST elevation meeting the following criteria:
  - ALT or AST >5 × ULN for more than 2 weeks
    Pembrolizumab will have already been permanently discontinued per Table 6, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
  - ALT or AST >3 × ULN and (TBL > 2 X ULN or INR > 1.5)
    Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 8 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.
- The participant interrupts pembrolizumab, MK-1308, or MK-4280 administration for more than 12 consecutive weeks for an irAE or for more than 3 consecutive weeks for administrative reasons, unless approved with written documentation from the Sponsor.
- The participant interrupts lenvatinib administration for more than 28 consecutive days, unless approved with written documentation from the Sponsor.
- Clinical conditions described in Section 7.2 Dose Modification
- 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 treatment.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study.
- Confirmed radiographic disease progression outlined in Section 9.2.1.4 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment
- Noncompliance with study treatment or procedure requirements
- Any study treatment-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 7.2.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab. Combination treatment with MK-1308 or MK-4280 will be discontinued upon completion of the 35th cycle of pembrolizumab. For the lenvatinib combination arm, if a participant completes 35 infusions of pembrolizumab, they may continue with lenvatinib alone until disease progression or toxicity.

Discontinuation of treatment may be considered for participants who have attained a confirmed CR by local investigator assessment and have been treated for at least 8 cycles and received at least 2 cycles beyond the date when the initial CR was declared.

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

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

8.2 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 treatment 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 9.1.9 – Withdrawal/Discontinuation. 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 8.3.

8.3 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, phone 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 amount of missing data for the participant will be managed via the prespecified data handling and analysis guidelines.

9 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 assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of trial site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before 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 subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Administrative and General Procedures

9.1.1 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 trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

9.1.1.1 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 trial.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. 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.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level. Participants currently on pembrolizumab plus 200 mg MK-4280 will be reconsented and will discuss with the Investigator the choice of continuing 200 mg MK-4280 Q3W or switching to 800 mg MK-4280 Q3W.

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

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

9.1.2 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.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain trial site contact information (including direct telephone numbers) to be utilized 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 treatment 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 health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

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

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

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

9.1.5.2 Concomitant Medications

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

9.1.6 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 randomization. Each participant will be assigned only one 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 visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization 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/randomization number.

9.1.8 Treatment Administration

Administration of IV study medication (pembrolizumab MK-1308, and MK-4280) will be monitored by the Investigator and/or study staff. Administration of lenvatinib will be witnessed by the Investigator and/or study staff for the dose on C1D1 and C2D1, but otherwise self-administered.

Study treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

9.1.8.1 Timing of Dose Administration

9.1.8.1.1 Timing of Dose Administration of Pembrolizumab

Study treatment with pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the SoA (Section 2). All study treatments will be administered on an outpatient basis. Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for C1D1, where the window is +3 days from randomization.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. 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.

9.1.8.1.2 Timing of Dose Administration of MK-1308 and MK-4280

The Pharmacy Manual contains specific instructions for preparation and administration of MK-1308 and MK-4280. The MK-1308 (anti-CTLA-4 antibody) drug product should only be diluted with saline.

MK-4280 will be dosed 30 minutes (± 10 minutes) after the pembrolizumab infusion has completed. Whenever possible, for MK-4280 the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes (-15 and +30 minutes).
MK-1308 will be dosed 30 minutes (-5 and +10 minutes) after the pembrolizumab infusion has completed. Whenever possible, for MK-1308 the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes (-5 and +10 minutes).

9.1.8.1.3 Timing of Dose Administration of Lenvatinib

On Day 1 of each cycle, lenvatinib will be administered after completion of pembrolizumab. Lenvatinib will be taken once a day with water at approximately the same time each day for 21 days in each cycle.

The participant must be instructed in the handling of study drug as follows:

- To store the study treatment at room temperature.
- To make every effort to take doses on schedule.
- To report any missed doses.
- If the participant vomits after taking study treatment, the participant should not take another dose that day.
- To keep study treatment in a safe place and out of reach of children.
- If a dose of lenvatinib is missed by more than 12 hours, that dose should be skipped, and the next scheduled dose should be administered at the usual time.

9.1.9 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the trial, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events, Serious Adverse Events and Other Reportable Safety Events.

9.1.9.1 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 trial. If medical records for the main trial are still available, the investigator will contact the Sponsor

using the designated mailbox (clinical.specimen.management@msd.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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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.

9.1.10 Participant Blinding/Unblinding

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

9.1.11 Calibration of Equipment

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

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

All imaging will be completed and read locally. Additionally, images will be collected and stored at a central imaging vendor for potential future use. The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM).

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same 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.

All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for

other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization.

Tumor imaging performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of randomization. If brain imaging is performed to document the stability of existing metastases, MRI is preferred; however, CT imaging is acceptable if MRI is medically contraindicated.

9.2.1.2 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 randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 1 year, participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). 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 (unless the site Principal Investigator [PI] elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

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, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging (ie, 9 or 12 weeks later) if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 9.2.1.5), disease progression in participants treated with pembrolizumab should be confirmed by the site 4 to 8 weeks after 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 site Investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 9.2.1.5. Participants who obtain a confirmation scan 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 as assessed by the site will discontinue study treatment. Exceptions are detailed in Section 9.2.1.5.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

9.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response and date of disease progression, Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

9.2.1.5 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 the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD considers 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. This data will be captured in the clinical database.

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 study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor 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 to the central imaging vendor for potential retrospective use.

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.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study 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 2 and submitted to the central imaging vendor.

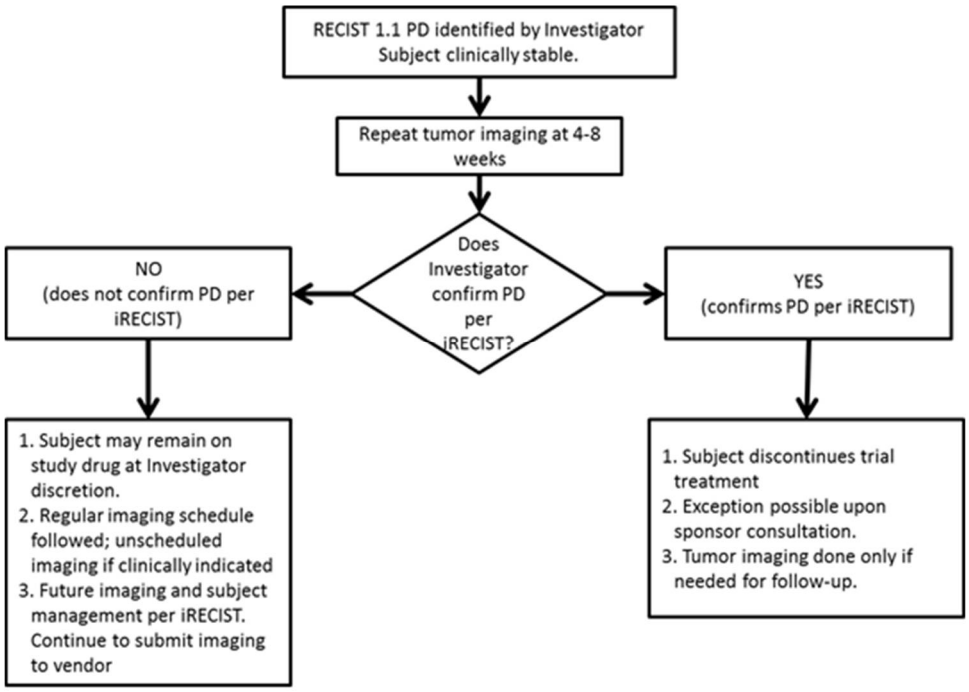
A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 9 and illustrated as a flowchart in Figure 3.

Table 9 Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator

	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 investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the 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 imaging should occur according to the regular imaging schedule.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

Figure 3 Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Site



iRECIST=Immune Response Evaluation Criteria in Solid Tumors; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors.

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

The definitions of an adverse event (AE) or serious adverse event (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 4.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 9.3.3.

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

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

9.3.1 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 treatment 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 trial, 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 treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator. For participants treated with lenvatinib, all AEs meeting serious criteria, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment 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 treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment 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 to be drug-related.

Investigators are not obligated to actively seek AE or SAE 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 treatment or study participation, the investigator must promptly notify the sponsor.

Once a participant has been consented for the extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 10.

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

Table 10 Reporting Time Periods and Timeframes 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 AE Collection Period	Reporting Time Period: After the Protocol Specified AE Collection Period		Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious 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
Potential DILI/DILI (requiring regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - potential DILI/DILI -to be reported as SAE with OME criteria in the absence of serious criteria	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 - Require regulatory reporting	Previously reported – Follow to completion/ termination; report outcome		Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - those not requiring regulatory reporting	Not required		Within 5 calendar days of learning of event

DILI=drug-induced liver injury; OME=other important medical event.

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

9.3.3 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. SAEs and other reportable safety events including potential DILI/DILI, pregnancy and exposure during breastfeeding, ECI, 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 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 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 treatment 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 treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

9.3.5 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.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

9.3.6 Pregnancy and Exposure During Breastfeeding

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

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. An overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. All events of potential DILI/DILI will be reported as an SAE with OME criteria in the absence of other serious criteria. Potential DILI/DILI events are defined as 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 trial site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.4 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose ≥1000 mg (5 times the dose) of pembrolizumab; by ≥50% the prescribed dose for MK-1308; by ≥20% of MK-4280; any dose higher than 20 mg of lenvatinib. No specific information is available on the treatment of overdose of pembrolizumab, MK-1308, MK-4280, or lenvatinib. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer and RCC.

If an AE(s) is associated with ("results from") the overdose of Sponsor's product, pembrolizumab, MK-1308 or MK-4280, the AE(s) is reported as an SAE, even if no other seriousness criteria are met. **Overdoses associated with lenvatinib should be reported as a non-serious Event of Clinical Interest (ECI), unless the AE itself meets criteria for an SAE.**

All reports of pembrolizumab, MK-1308, or MK-4280 overdose with and without an AE and all reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Reports of pembrolizumab, MK-1308, or MK-4280 overdose without any associated clinical symptoms or abnormal laboratory results, should be reported using the terminology "accidental or intentional overdose without adverse effect".

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Exam

The Investigator or medically 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 2. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

For participants receiving lenvatinib, the full physical exam must include an oral exam.

9.5.1.2 Directed Physical Exam

For cycles that do not require a full physical exam as defined in Section 2, the Investigator or medically qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

For participants receiving lenvatinib, the directed physical exam must include an oral exam.

9.5.2 Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each infused study treatment, and during the Follow-up period as specified in the SoA. For participants who receive MK-4820, vital signs will be performed at 2 and 4 hr post infusion on Day 1 of C1. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight will be measured at each visit. Height will be measured at Screening only.

Blood pressure (BP) and pulse should be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

For lenvatinib combination, blood pressure measurement is also performed on D15 for C1 and C2. Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BR <90 mm Hg. If the participant's initial BP measurement is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Under exceptional circumstances, participants will have the option of having BP measured between visits obtained locally by a health care professional. A BP log will be provided as a tool to aid the participant in collecting BP evaluations between study visits.

9.5.3 Electrocardiograms

Baseline ECGs will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at Screening, Day 1 of C1-2, end of treatment, and at the 30-day safety follow-up with additional ECGs obtained as clinically indicated for all participants. Participants receiving MK-1308 and MK-4280 also need ECG on Day 1 of C3. Participants in the lenvatinib treatment group also need ECGs every fourth cycle beginning with Cycle 6 (eg, C6, C10, C14, etc. QTc prolongation has been seen in some lenvatinib studies. Monitor ECGs every cycle (as specified in the Schedule of Assessments) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Please refer to the lenvatinib IB.

New clinically significant abnormal findings during study should be recorded as an AE. The 12-lead ECGs will be interpreted by the Investigator at the site and will be used for immediate participant management. The decision to include or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the Investigator, in consultation with the Sponsor's medical monitor, as appropriate. The correction method (Fridericia) used for calculating QTc will be provided in the eCRF.

9.5.4 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess left ventricular ejection fraction (LVEF) as designated in the SoA (Section 2). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

9.5.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol 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 treatment, 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.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Trial Procedures Manual. Refer to the SoA (Section 2) for the timing of laboratory assessments.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. Please refer to Section 7.2.2.2 Dose Modifications for Lenvatinib - Management of Proteinuria.

Please note that only safety labs affecting potential treatment need to be reviewed prior to study therapy administration following the Screening visit. Labs which would not affect potential treatment of the participant can be reviewed in a timely manner by the Investigator after the date of study therapy administration. This review must occur prior to the start of the next cycle. Similarly, in cases in which a site is not able to obtain thyroid, ACTH, and cortisol results prior to scheduled dosing, review of these after dosing is acceptable and poses no additional immediate safety risk to participant.

For lenvatinib combination, urine dipstick testing for participants with proteinuria is specified in Appendix 2 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed preferably at the investigational site (but may be performed locally by the primary

care physician or a local laboratory if the participant does not have to come for a visit to the site).

9.5.5.2 Pregnancy Test

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 24 hours of the first dose of study treatment. 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 regulations. For lenvatinib arm, following initiation of treatment, additional pregnancy testing will be performed during the treatment period and at least every 30 days up to 120 days after the last dose of study medication or the start of a new anticancer therapy, whichever comes first.

9.5.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

The Investigator or qualified designee will assess ECOG status at screening (within 7 days prior to the first dose of study treatment but before randomization), prior to the administration of each dose of study treatment, and during the Follow-up period as specified in the SoA. The ECOG performance scale is outlined in Appendix 10.

9.6 Pharmacokinetics

Sample collections are planned for PK and ADA analysis for MK-1308 and MK-4280 in combination with pembrolizumab according to the Schedule of Activities described in Section 2. PK and ADA should only be collected in participants enrolled under Amendment 5 and later. Blood samples will be obtained to measure the PK of serum MK-1308 and MK-4280. If ongoing ADA and/or PK results for either MK-1308 and/or MK-4280 are deemed to be unnecessary by the Sponsor, it may be decided to discontinue or reduce further sample collection in this study. Should this occur, it will be communicated by an administrative memo. The results of these analyses, if performed, will be reported separately.

9.6.1 Blood Collection for Serum MK-1308

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure and/or laboratory manuals.

9.6.2 Blood Collection for Serum MK-4280

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure and/or laboratory manuals.

9.6.3 Blood Collection for Anti-MK-1308 Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure and/or laboratory manuals. Anti-MK-1308 antibody samples should be drawn according to the ADA collection schedule for participants who receive MK-1308 in combination with pembrolizumab. Simultaneous PK sampling is required for interpretation of ADA analysis.

9.6.4 Blood Collection for Anti-MK-4280 Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure and/or laboratory manual. Anti-MK-4280 antibody samples should be drawn according to the ADA collection schedule for participants who receive MK-4280 in combination with pembrolizumab. Simultaneous PK sampling is required for interpretation of ADA analysis.

9.7 Pharmacodynamics

Pharmacodynamic markers will be evaluated to gain a better understanding of response and resistance biology. Tumor biopsy will be performed at baseline (archival tissue acceptable for this sample). Blood samples for exploratory biomarkers and planned genetic analysis will be collected prior to treatment on C1D1, C2D1, C3D1, C6D1, and at end of treatment/progression. Detailed endpoints are described below in the biomarker section (Section 9.9).

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover RNA
- Leftover tumor

9.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (e.g., protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants in this study as specified in the SoA. Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

- Blood for Genetic Analysis
- Blood for RNA analyses
- Whole blood for DNA for exploratory biomarkers
- Archival or newly obtained tumor tissue

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures manual. The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. Whole blood for planned genetic analysis will be collected at C1D1 for DNA and RNA and at C2D1, C3D1, C6D1 and end of therapy for RNA only. 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.

9.9.2 Enrollment Biomarkers

A tumor specimen for biomarker assessment will be required for enrollment of all participants. A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study), is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the participant (including, but not limited to, biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel), an archival specimen should be submitted.

Archived tissue (or fresh biopsy) is required at screening for GEP and TMB testing. These tests are required for enrollment. Sample collection, storage and shipment instructions are provided in the procedure manual.

9.9.3 PD-L1 IHC

Archived tissue (or fresh biopsy) is required at screening. Part of this sample will be used for retrospective testing of PD-L1 IHC. Sample collection, storage and shipment instructions are provided in the procedure manual. Historical PDL-1 results may be used with Sponsor approval.

9.9.4 Exploratory Biomarkers

Archived tissue (or fresh biopsy) is required at screening for GEP, TMB, and PD-L1 IHC testing. Residual tissue will be used for exploratory biomarker assays.

Whole blood will be collected for planned genetic analysis and exploratory biomarkers. Whole blood samples for nucleic acid will be collected at C1D1, C2D1, C3D1, C6D1, and end of the treatment.

Tissue and blood sample collection, storage and shipment instructions are provided in the procedure manual.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Approximately 28 days prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1.

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 clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study treatment. An exception is HIV and hepatitis testing, which may be done up to 28 days prior to the first dose of study treatment.
- Evaluation of ECOG is to be performed within 7 days prior to date of allocation/randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study treatment. 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 treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Screening procedures may be repeated after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol SOA, including consent review. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

9.10.2 Treatment Period

Visit requirements are outlined in the Study Flow Chart (Section 2). Specific procedure-related details are provided in Section 9.1.

9.10.3 Post-Treatment Visit

9.10.3.1 Safety Follow-up Visit

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

9.10.3.2 Efficacy Follow-Up Visits

Participants who complete the protocol-required cycles of study treatment or who discontinue study treatment for a reason other than disease progression will begin Efficacy Follow-Up and should be assessed approximately every 12 weeks by radiographic imaging to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of study as detailed in Section 2 (SoA).

Information regarding post-study anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Once a participant has been consented for the extension study, radiographic imaging will be collected as instructed in the extension study.

9.10.3.3 Survival Follow-up Assessments

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

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

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

9.10.4 Vital Status

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

9.10.5 Study Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9.11 Medical Resource Utilization and Health Economics

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

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

- All-cause hospitalizations and emergency room visits, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment, if the participant initiates new anticancer therapy, whichever is earlier.

10 Statistical Analysis Plan

10.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategy and procedures for the study. Changes in analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the clinical study report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. The study will use an adaptive approach, with on-treatment data guiding study adaptation and success or futility of each combination in each study subpopulation. Currently, 30 participants are being treated with MK-4280 200 mg Q3W, including 10, 7, 8, and 5 participants in Biomarker Group I, II, III, and IV, respectively. These 30 participants treated with MK-4280 200 mg Q3W may be replaced with 30 additional participants treated with MK-4280 at 800 mg Q3W after the approval of Amendment 05. Consequently, the total treated sample size is changed from 288 to 318. The replacement number may depend on results of interim analyses, including estimated posterior probabilities of meeting the target response rate at the 800 mg dose. All key statistical elements in this section including, but not limited to, statistical efficacy, futility, sample size and power are based on participants receiving pembrolizumab at a dose of 200 mg Q3W in combination with 25 mg MK-1308 Q6W, 800 mg Q3W MK-4280 and lenvatinib daily. The combination with MK-4280 in this section is specifically referring to the participants treated with the combination pembrolizumab with 800 mg MK-4280 Q3W from C1D1 unless more details are provided.

Key elements of the SAP are summarized below; comprehensive details are provided in Sections 10.2 through 10.12.

Study Design Overview	This is an unblinded, open-label adaptively randomized Phase 2 study of a biomarker-directed, pembrolizumab-based (MK-3475–based) combination therapy in study participants with advanced NSCLC.
Treatment Assignment	All participants will be selected by a clinical classifier based on GEP and TMB. Participants will be assigned to 1 of 4 biomarker-defined groups and will be randomized to receive pembrolizumab at a dose of 200 mg IV Q3W in combination with MK-1308 (anti–-CTLA-4), MK-4280 (anti–LAG-3), or lenvatinib. Randomization to treatment will be done using a prespecified adaptive randomization algorithm in an unblinded fashion. Furthermore, due to the different start time of 3 pembrolizumab-based combination treatments, an unequal randomization ratio may be used first and then randomization schedules will be adjusted to equalize treatment arm enrollment per biomarker-defined group depending on the time of introducing the delayed combination treatments in order to meet study analysis milestones.
Analysis Populations	Efficacy and Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. ORR based on RECIST 1.1 as assessed by local site review
Key Secondary Endpoints	1. PFS based on RECIST 1.1 as assessed by local site review 2. OS 3. Safety as assessed by the number of participants experiencing AEs and the number of participants discontinuing study drug due to AEs.

Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	In each of the 4 biomarker-defined groups, the primary hypothesis that the ORR is greater than CCI within the $GEP^{low}TMB^{low}$ group, CCI within the $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$ groups, and CCI within the $GEP^{hi}TMB^{hi}$ group will be evaluated using a Bayesian posterior probability. For the primary hypothesis, the ORR in each pembrolizumab-combination therapy group will be considered significantly larger than that expected from historical pembrolizumab monotherapy (CCI in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively) if there is at least 95% posterior probability that the true ORR is greater than CCI for the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively.
Statistical Methods for Key Safety Analyses	Safety will be evaluated using descriptive statistics.
Interim Analyses	The study incorporates an adaptive randomization design, in which multiple interim analyses may be performed. The primary endpoint of ORR will be used for all interim analyses. The first interim analysis for each combination therapy will occur after at least 10 participants have at least 12 weeks of follow-up. Participants' response data will be closely monitored throughout the study and subsequent interim analyses may be performed with a minimum of 2 additional participants in each combination therapy achieving 12 weeks of follow-up. At each interim analysis, either combination therapy arm in any biomarker-defined group may be terminated due to either futility, safety, or if the maximum number of participants for the combination therapy has been reached. Any biomarker-defined group may be terminated due to futility or safety of all three combination therapies or the maximum number of participants for each biomarker-defined group has been reached.
Multiplicity	This is an adaptive randomization study. No multiplicity adjustment will be employed. Estimates of the false positive rate (probability of incorrectly selecting any futile combination therapy) were derived via simulation studies, and details are provided in Section 10.8.
Sample Size and Power	The estimated historical control ORRs for study participants on pembrolizumab monotherapy treatment are CCI in $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$, respectively. The decision rules for futility and efficacy were derived using these underlying assumptions. Table 12 shows the operating characteristics of this design with maximum sample size of approximately 66 for the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups, and maximum sample size of approximately 90 for $GEP^{hi}TMB^{hi}$ group. The probability of correctly selecting the combination therapy when the true ORR for that combination therapy is increased approximately 25 to 30 percentage points over estimated historical control ORR is approximately CCI in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively. The probability of correctly selecting all combination therapies when the true ORR for all combination therapies is increased approximately 25 to 30 percentage points over the estimated historical control ORR is approximately CCI in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively. The average sample size for each combination therapy under various assumptions is also provided in Table 12.

10.2 Responsibility for Analyses/In-House Blinding

The interim and final statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department of the Sponsor.

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

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4 – Objectives/Hypotheses & Endpoints.

10.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by descriptions of the derivations of selected endpoints.

10.4.1 Efficacy Endpoints

The primary efficacy endpoint is objective response rate. Study participants will be defined as having an objective response if they have the best response as CR or PR based on RECIST 1.1 at any time during the study prior to initiation of follow-up therapy. The objective response for the primary analysis will be determined by local site radiologic review, with confirmatory assessment as required per RECIST 1.1. Participants with unknown or missing response information will be treated as nonresponders.

Secondary efficacy endpoints include the following:

(1) Progression-free survival, defined as the time from allocation to the first documented disease progression according to RECIST 1.1, as assessed by local site radiologic review, or death due to any cause, whichever occurs first.

(2) Overall survival, defined as the time from the date of allocation to the date of death due to any cause.

10.4.2 Safety Endpoints

A description of safety measures is included in Section 9.3 and Section 9.5. The analysis strategy for safety parameters is summarized in Section 10.6.2.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The ASaT population will be used for the analysis of efficacy in this study. The ASaT population consists of all allocated study participants who have received study treatment.

10.5.2 Safety Analysis Population

The ASaT population will also be used for the analysis of safety data in this study. 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.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analysis

10.6.1.1 Objective Response Rate (ORR)

In each of the 4 biomarker-defined groups, the primary hypothesis that the ORR is greater than [redacted] within the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively, will be evaluated using a Bayesian posterior probability. The ORR in each of the pembrolizumab-combination therapies will be considered larger than [redacted] within the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively, if there is at least 95% posterior probability supporting the hypothesis. A Beta [redacted]), Beta ([redacted]), Beta [redacted]), and Beta [redacted] prior distribution will be used for the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively. For the primary hypothesis, study participants without disease assessment after the start of treatment will be considered as nonresponders in ORR estimation. When computing the ORR at the interim analyses, only study participants with adequate follow-up (at least 12 weeks) will be included in the denominator. Participants with confirmed or unconfirmed response, if confirmation is not available at the time of the interim analyses, will be included in the numerator. At the final analysis, all enrolled participants who received at least one dose of study drug will be included in the denominator and only participants with confirmed response will be included in the numerator. A confirmed response will be counted as a response regardless of relapse at a later point during the course of the study. The posterior distribution of ORR for all combination therapies will also be provided at the final analysis, as well as the [redacted] percentile and the [redacted] percentile of the distribution. The frequentists' [redacted] confidence interval (CI) will also be estimated and reported.

10.6.1.2 Progression-Free Survival (PFS)

The Kaplan-Meier method will be used to estimate the PFS curve. The median PFS and its associated [redacted] confidence interval (CI) will be estimated and reported. The Kaplan-Meier estimates of the PFS rate at 6 months and other time points of interest will also be reported. Because disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For this analysis, for study participants who have PD, the true date of disease progression will be approximated by the date of first assessment at which PD is objectively documented using RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Participants without documented PD/death will be censored at the last disease assessment date. In the event that participants without documented PD/death have new anticancer treatment initiated, the

participants will be considered censored at last disease assessment before new anticancer treatment.

10.6.1.3 Overall Survival (OS)

The Kaplan-Meier method will be used to estimate the OS curve. The median OS and its associated [redacted] CI will be estimated and reported. The Kaplan-Meier estimates of the OS rate at 6 months and other time points of interest will also be reported. A sensitivity analysis of OS that censors study participants at the time of initiation of new anticancer treatment will also be performed. Table 11 summarizes the efficacy analyses.

Table 11 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1				
Overall response rate (ORR) by RECIST 1.1 as assessed by local site	P	Bayesian Approach	ASaT	Study participants with missing data are considered nonresponders
Secondary Endpoints				
Secondary Objectives				
Progression-free-survival (PFS) by RECIST 1.1 as assessed by local site	P	Kaplan-Meier method for PFS curve estimation and summary statistics with [redacted] will be reported.	ASaT	Censored at last assessment (before new anticancer treatment)
Overall survival (OS)	P	Kaplan-Meier method for OS curve estimation and summary statistics with [redacted] will be reported.	ASaT	Censored at last date
Overall survival (OS)	S	Kaplan-Meier method for OS curve estimation and summary statistics with [redacted] will be reported.	ASaT	Censored at last assessment (before new anticancer treatment)

[a] P=Primary approach; S=Supportive approach.

10.6.2 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. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of study participants screened and allocated, the primary reasons for screen failure, and the primary reasons for discontinuation will be displayed.

Demographic variables (such as age), baseline characteristics, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

10.7 Interim Analyses

The study incorporates a group-sequential adaptive randomization design, in which multiple interim analyses may be performed. The primary endpoint of ORR will be used for all interim analyses.

Due to the different start time of 3 combination treatments, unequal randomization ratio may be used first and then randomization schedules will be adjusted to equalize treatment arm enrollment per biomarker-defined group depending on the time of introducing the delayed combination treatments in order to meet study analysis milestones. For each biomarker-defined group, the first interim analysis will occur after at least 10 participants in each treatment combination have at least 12 weeks of follow-up. Participants' response data will be closely monitored throughout the study; the subsequent interim analyses may be performed with a minimum of 2 additional participants achieving 12 weeks of follow-up for each combination therapy that still remains in the study. When computing the ORR at the interim analyses, only study participants with adequate follow-up (at least 12 weeks) will be included in the denominator. Participants with confirmed or unconfirmed response, if confirmation is not available at the time of the interim analyses, will be included in the numerator.

Without including those 30 participants receiving pembrolizumab in combination with 200 mg MK-4280 at C1D1, a maximum of approximately 66 participants will be enrolled in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups, and a maximum of approximately 90 participants will be enrolled in the for $GEP^{hi}TMB^{hi}$ group. Additionally, a maximum of approximately 25 participants will be randomized into any one combination therapy arm within the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups, and a maximum of approximately 40 participants will be randomized into any one combination therapy arm within the $GEP^{hi}TMB^{hi}$ group.

At each interim analysis, any combination therapy arm in any biomarker-defined group may be terminated due to the following reasons:

1. Futility may be declared if there is at least a CCI posterior probability that the ORR is less than CCI in the $GEP^{low}TMB^{low}$ group, less than CCI in the $GEP^{low}TMB^{hi}$ and $GEP^{hi}TMB^{low}$ groups and less the CCI in the $GEP^{hi}TMB^{hi}$ group.
2. The maximum number of participants for the combination therapy has been reached.

In addition, a biomarker-defined group may be terminated if:

1. All combination therapies in the group are terminated due to the reasons described above.
2. The maximum number of participants for the biomarker-defined group has been reached.

As long as either treatment combination in any of the biomarker-defined groups remains in the study, enrollment will continue with participants allocated to any combination therapy that has not been terminated after the first interim analysis.

10.8 Multiplicity

No multiplicity adjustment will be employed. Estimates of the false positive rate (probability of incorrectly selecting any futile combination therapy) were derived via simulation studies. There is an estimated [CCI] false positive rate when all three combination therapies have ORRs equal to [CCI] for $GEP^{low}TMB^{low}$ group, [CCI] when all three combination therapies have ORRs equal to [CCI] for $GEP^{low}TMB^{hi}$ group, [CCI] when all three combination therapies have ORRs equal to [CCI] for $GEP^{hi}TMB^{low}$ group, and [CCI] when all three combination therapies have ORRs equal to [CCI] for $GEP^{hi}TMB^{hi}$ group [CCI]

10.9 Sample Size and Power Calculations

The estimated historical control ORRs for study participants on pembrolizumab monotherapy treatment are [CCI] in $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$, respectively. The decision rules for futility and efficacy were derived using these underlying assumptions.

Table 12 shows the operating characteristics of this design with maximum sample size of approximately 66 for the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, and $GEP^{hi}TMB^{low}$ groups, and maximum sample size of approximately 90 for the $GEP^{hi}TMB^{hi}$ group. The results are based on 10,000 simulated trials. The probability of correctly selecting a combination therapy when the true ORR for that combination therapy is increased approximately 25 to 30 percentage points (ie, 25 for $GEP^{low}TMB^{low}$ and $GEP^{hi}TMB^{hi}$ groups, 30 for $GEP^{low}TMB^{hi}$ and $GEP^{hi}TMB^{low}$ groups, Table 12) over estimated historical control ORR is approximately [CCI] in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively. The probability of correctly selecting all combination therapies when the true ORR for all combination therapies is increased approximately 25 to 30 percentage points (ie, 25 for $GEP^{low}TMB^{low}$ and $GEP^{hi}TMB^{hi}$ groups, 30 for $GEP^{low}TMB^{hi}$ and $GEP^{hi}TMB^{low}$ groups, Table 12) over estimated historical control ORR is approximately [CCI] in the $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively. The average sample size for each combination therapy under varying assumptions is also provided in Table 12.

The simulation assumes that:

(1) The total enrollment of 70 participants from Week 1 to Week 15, 50 participants from Week 16 to Week 27, 150 participants from Week 28 to Week 57, and 115 participants from Week 58 to Week 80. The entering time is uniformly distributed within each time period.

(2) The prevalence is 21%, 17%, 29% and 33% in $GEP^{low}TMB^{low}$, $GEP^{low}TMB^{hi}$, $GEP^{hi}TMB^{low}$, and $GEP^{hi}TMB^{hi}$ groups, respectively.

(3) Responses will be observed within 12 weeks.

(4) The first 20 study participants randomized to combination 1 and combination 2 using the ratio 1:1. The randomization ratio of 2:2:12 will be used to randomize the 21st-36th participant to combination 1, 2, and 3, respectively. The first interim analysis will occur for combination 1 and combination 2 when the 20th participant has 12 weeks of follow-up. Subsequent interim analyses will be performed approximately every 6 weeks using available response data. The first interim analysis for combination 3 will occur in one of the subsequent interim analyses when at least 10 participants have at least 12 weeks of follow-up (further details are in Appendix 9).

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[redacted]

10.10 Subgroup Analyses

No subgroup analyses are planned for this study.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (eg, N, mean, median, standard deviation, etc.) for duration of treatment in cycles.

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12 Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation/Term	Definition
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASaT	All-subjects-as-treated
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
AxMP	auxiliary medicinal product
BCG	Bacille Calmette Guerin
β-hCG	β-human chorionic gonadotropin
BP	Blood pressure
B-Raf	B isoform of rapidly accelerated fibrosarcoma
BUN	Blood urea nitrogen
CBC	Complete blood count
CD3ζ	CD3 zeta
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPT	Cell preparation tube
CrCl	Creatinine clearance
CR	Complete response
CRA	Clinical Research Associate
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated Antigen-4
CVA	Cerebrovascular accident
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity

Abbreviation/Term	Definition
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid cancer
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
EU	European Union
EU CTR	European Union Clinical Trials Regulation
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAA	Food and Drug Administration Amendment Act
FFPE	Formalin-fixed, paraffin embedded
FGF	Fibroblast growth factor
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
GEP	Gene expression profile
GFR	Glomerular filtration rate
GI	Gastrointestinal
H	Hours
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Head neck squamous cell carcinoma
HRT	Hormonal replacement therapy
HUVEC	Human umbilical vein endothelial cell
IB	Investigator's Brochure
IC_{50}	Mean inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
ICSR	Individual case safety report
ID	Identification
IEC	Independent Ethics Committee
IFNγ	Interferon gamma

Abbreviation/Term	Definition
Ig	Immunoglobulin
IgV	Immunoglobulin variable
IHC	Immunohistochemistry
IL	Interleukin
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IUD	Intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
IVD	In vitro diagnostic
IVRS	Interactive voice response system
IWRS	Integrated web response system
KRAS	Kirsten rat sarcoma viral oncogene homolog
1L	First-line
LAG-3	Lymphocyte-activation gene 3
LAM	Lactational amenorrhea method
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MHC	Major histocompatability complex
MLR	Mixed lymphocyte reaction
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OME	Other important medical events
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically based pharmacokinetic
PD	Progressive disease
PD-1	Programmed cell death protein 1
PDGF	Platelet-derived growth factor
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic(s)

Abbreviation/Term	Definition
PKCθ	Protein kinase C-theta
PR	Partial response
pRBC	packed red blood cell
PT	Prothrombin time
PKCθ	protein kinase C-theta
PRES	Posterior reversible encephalopathy syndrome
pRP2D	Preliminary recommended Phase 2 dose
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during transfection
RNA	Ribonucleic acid
RNA-seq	RNA sequencing
ROS1	c-ros oncogene 1
RPLS	Reversible posterior leukoencephalopathy syndrome
RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SNP	Single nucleotide polymorphism
SoA	Schedule of Activities
sSAP	Supplementary Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reactions
T3	Free triiodothyronine
T1DM	Type 1 diabetes mellitus
TAM	Tumor associated macrophages
TB	Tuberculosis
TMB	Tumor mutational burden
TMDD	Target-mediated drug disposition
TRAEs	Treatment-related AEs
T_{reg}	Regulatory T cell
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein-to-creatinine ratio
US	United States
V	Visit
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WOCBP	Woman of childbearing potential

Abbreviation/Term	Definition
ZAP70	Zeta-chain-associated protein kinase

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Central laboratory results are only required in the event that the local laboratory results are not available in time for either study treatment administration and/or response evaluation.
- Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)[a]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[b]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) Alkaline phosphatase	Total Protein
	Glucose	Calcium	Amylase[c] Lipase[c]	Cortisol[d] ACTH[d]
	Magnesium[e]			

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal) • For lenvatinib combination, if urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection or an immediate spot urine protein-to-creatinine (UPCR) test should be done to quantify the 24-hour urine protein excretion. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4. See Section 7.2.2.2.
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential) within 24 hours of first dose Thyroid panel: TSH, FT4, FT3/T3Serology

ACTH=adrenocorticotropic hormone; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; TSH=thyroid-stimulating hormone; WBC=white blood cell.

a. Urea is acceptable if BUN is not available as per institutional standard.

b. Performed only if considered the local standard of care.

c. Performed at screening on all participants and then only for pembrolizumab plus MK-4280 treatment arm

d. Performed at screening on all participants and then only for pembrolizumab plus MK-1308 treatment arm

e. Only required for participants receiving pembrolizumab plus lenvatinib.

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (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 and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. 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, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

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 and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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.

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 which 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 institutional review board, ethics review committee (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 trial 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.

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 trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form 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 trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

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.

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

central contact number for further information on appropriate trial locations and trial site contact information.

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

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

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

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

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.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

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 (eg, EU CTR: 25 years after the end of the study). 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.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

Definition of AE

AE Definition
● An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. ● 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 treatment. ● NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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 treatment 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 treatment or a concomitant medication. ● For all reports of overdose (whether accidental or intentional) with an associated adverse event, 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). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of 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 9.3.5 for protocol specific exceptions

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

A 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 patient'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) which 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 one 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. All events of potential DILI/DILI will be reported as an SAE with OME criteria in the absence of other serious criteria.

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE
● In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe 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.

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 Adverse Event case report forms/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
● 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 adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. ● Grade 1: Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or 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 adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event 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 adverse event:
    - **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 trials 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 trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment 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 one 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 adverse event 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 adverse event 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.

Reporting of AE, SAE, 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 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection 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 Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection 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 Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol-defined time frame in section 6.1:

- 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 woman of childbearing potential who is not currently pregnant.
    - The following are not acceptable methods of contraception:
        - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea 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

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 14 during the protocol-defined time frame in Section 6.1.

Table 14 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral [a,b] (with additional barrier method for participants on lenvatinib treatment) ○ Intravaginal ○ Transdermal ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [c] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner 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.
● **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 treatment. 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.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Must be on a stable dose of the same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug and for the duration of the study. b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment.

Pregnancy Testing

WOCBP should be included only after a negative highly sensitive urine or serum pregnancy test within 24 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable. For lenvatinib arm, following initiation of treatment, additional pregnancy testing will be performed as indicated in Section 2 during the treatment period and at least every 30 days up to 120 days after the last dose of study medication or the start of a new anticancer therapy, whichever comes first.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected and as required locally.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Samples 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[3, 4]

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial 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 trial site under secure storage for regulatory reasons.

A template of each trial 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 electronic Case Report Forms (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 trial purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment 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 trial 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 trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

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

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for 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 trial. If

medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to 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 trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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 trial 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 trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to

rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main study.

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 e-mailed directly to clinical.specimen.management@msd.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonisation: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.7 Appendix 7: Country-specific Requirements

12.7.1 Spain-specific, United Kingdom-specific, and Italy-specific Requirement

Pregnancy testing in WOCP is to be done monthly during the treatment period.

12.7.2 Ireland-specific Requirement

Pregnancy testing in WOCP is to be done monthly during the treatment period.

Hepatitis B and hepatitis C testing should be performed at Screening.

12.7.3 Russia-specific Requirement

Hepatitis B, hepatitis C and HIV testing should be performed at Screening.

12.7.4 South Africa-specific Requirement

HIV testing should be performed at Screening.

12.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

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 9 and Figure 3). This decision by the investigator should be based on the participant's overall clinical 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 study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor 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 to the central imaging vendor for potential retrospective use.

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 participant 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 ≥5 mm, 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 ≥5 mm 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

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 imaging 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, participants will be discontinued from study 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 study 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 2 and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudo-progression Resolves

After resolution of pseudo-progression (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 pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- 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 have 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.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

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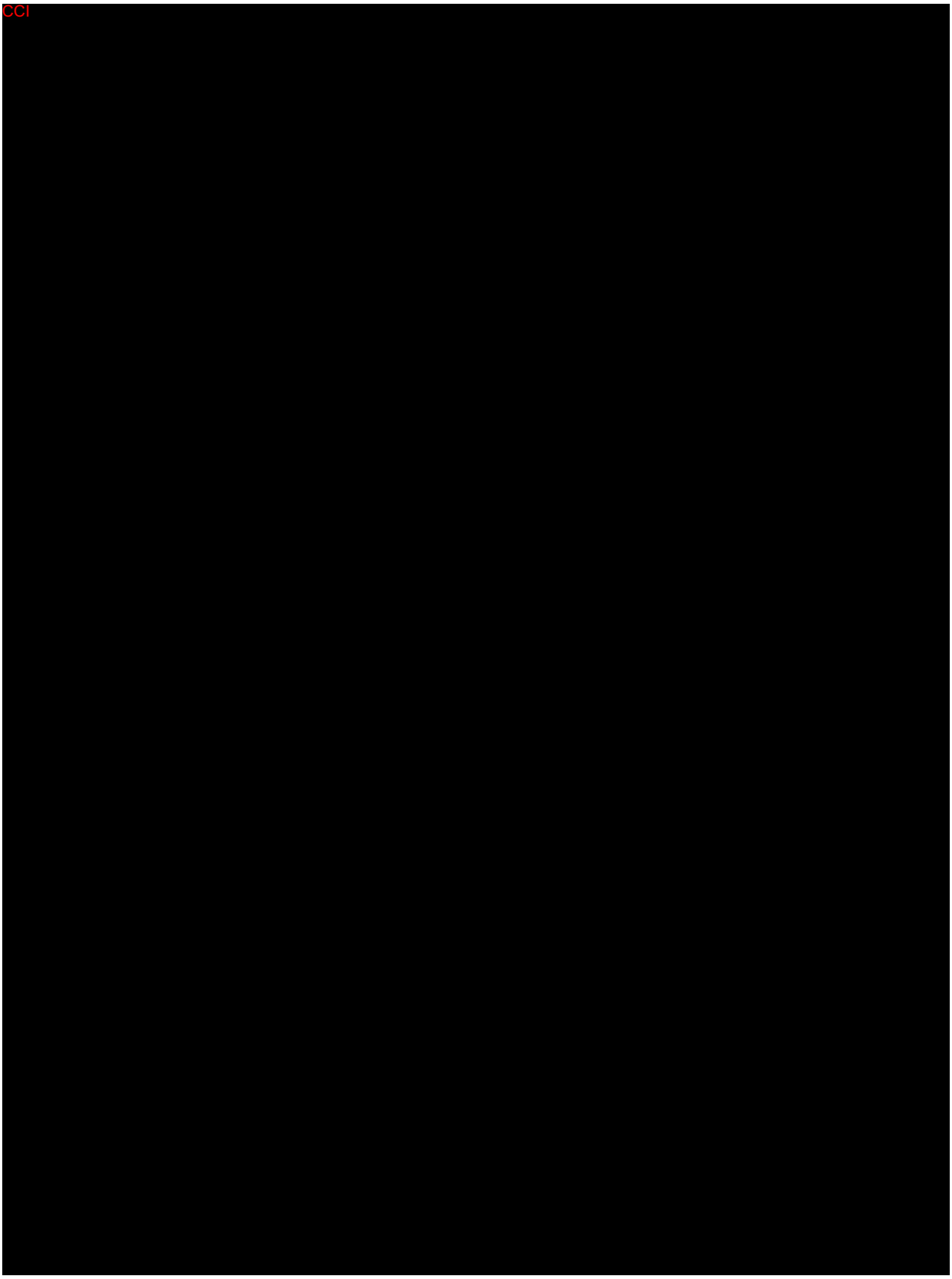

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12.10 Appendix 10: Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.