Official Protocol Title:	A Multicenter, Open-label, Phase 2 Trial to Assess the Efficacy and Safety of Lenvatinib (E7080/ MK-7902) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced Melanoma Previously Exposed to an Anti-PD-1/L1 Agent
NCT number:	NCT03776136
Document Date:	15-JUL-2022

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Multicenter, Open-label, Phase 2 Trial to Assess the Efficacy and Safety of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced Melanoma Previously Exposed to an Anti-PD-1/L1 Agent (LEAP-004)

Protocol Number: MK-7902-004-05 (E7080-G000-225)

Compound Number: MK-7902 (E7080/lenvatinib) and MK-3475 (pembrolizumab)

Sponsor Name:

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

The study is co-funded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	140155
EudraCT	2018-002518-10

Approval Date: 15 July 2022

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
7902-004-05	15-JUL-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA.
7902-004-04	09-JUN-2021	To update the pembrolizumab dose modification and toxicity management guidelines for irAEs and table, to add MK-7902 program-level updates.
7902-004-03	19-MAR-2020	Amendment 3
7902-004-02	01-APR-2019	Amendment 2
7902-004-01	07-DEC-2018	Amendment 1
7902-004-00	11-SEP-2018	Original Protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA.
Section 10.1.1 Code of Conduct for Clinical Trials	The Code of Conduct for Clinical Trials was updated.	To align with the current Code of Conduct.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicenter, Open-label, Phase 2 Trial to Assess the Efficacy and Safety of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced Melanoma Previously Exposed to an Anti-PD-1/L1 Agent (LEAP-004)

Short Title: Phase 2 study of lenvatinib plus pembrolizumab for advanced melanoma in anti-PD-1/L1-exposed participants

Acronym: Protocol 004 (E7080-G000-225)

Hypotheses, Objectives, and Endpoints:

In all participants with advanced melanoma previously exposed to an anti-PD-1/L1 agent, and following administration of lenvatinib in combination with pembrolizumab:

Primary Objectives	Primary Endpoints
- Objective: To evaluate ORR as assessed by BICR per RECIST 1.1.	- Objective Response: CR or PR.
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate PFS as assessed by BICR per RECIST 1.1.	- PFS: The time from first day of study intervention to the first documented disease progression or death due to any cause, whichever occurs first.
- Objective: To evaluate OS.	- OS: The time from first day of study intervention to death due to any cause.
- Objective: To evaluate the DOR as assessed by BICR per RECIST 1.1.	- DOR: For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
- Objective: To assess safety and tolerability of treatment with lenvatinib in combination with pembrolizumab.	- Adverse events. - Study drug discontinuations due to AEs.
- Objective: To characterize the population PK of lenvatinib when co-administered with pembrolizumab.	- Plasma concentration of lenvatinib.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of advanced melanoma
Population	Participants previously exposed to anti-PD-1/L1 agents for treatment of their advanced melanoma
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 36 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 100 participants will be allocated.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose</th><th>Dose Frequency</th><th>Route of Administration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="2">Arm 1</td><td>Pembrolizumab</td><td>200 mg</td><td>Q3W</td><td>IV</td><td>~2 years</td><td>Experimental</td></tr>
<tr><td>Lenvatinib</td><td>20 mg</td><td>QD</td><td>orally</td><td>≥2 years</td><td>Experimental</td></tr>
<tr><td colspan="7">Abbreviations: IV = intravenous; Q3W = every 3 weeks; QD = once daily</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>1 arm</td></tr>
<tr><td>Duration of Participation</td><td>After a Screening Phase of up to 28 days, each participant will receive lenvatinib (also known as E7080 or MK-7902), hereafter referred to as lenvatinib, in combination with pembrolizumab for up to 35 pembrolizumab administrations (approximately 2 years) or until disease progression, unacceptable toxicity, investigator decision or participant decision, withdrawal of consent, or death whichever occurs first. After completion of approximately 2 years, participants may receive lenvatinib monotherapy until disease progression or unacceptable toxicity. All participants who continue lenvatinib monotherapy will be monitored per the SoA. Disease progression per RECIST 1.1 should be radiographically documented. Disease progression can be confirmed by the site per RECIST 1.1 for immune-based therapeutics (iRECIST) when clinically appropriate. Participants may also discontinue treatment due to unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator’s decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment. Participants may interrupt or discontinue pembrolizumab due to toxicity and continue with lenvatinib. Similarly, participants may interrupt or discontinue lenvatinib due to toxicity and continue with pembrolizumab. Participants who attain an investigator-determined confirmed CR may consider stopping study intervention with pembrolizumab and/or lenvatinib after at least 24 weeks of lenvatinib in combination with pembrolizumab have been administered (Note: participants may continue to receive lenvatinib monotherapy until disease progression or unacceptable toxicity). In addition, if a confirmed CR per RECIST 1.1 is attained, at least 2 additional doses of pembrolizumab in combination with lenvatinib must be received after CR is first documented.</td></tr>
</table>

	Participants will be permitted to continue study intervention beyond RECIST 1.1-defined disease progression as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment as per iRECIST, and the participant is tolerating study intervention. All decisions to continue treatment beyond 2 consecutive scans (at least 4 weeks apart) showing progression must be approved by the Sponsor (Section 8.2.1). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up, whichever occurs first. Participants who discontinue due to radiographic disease progression will move to Survival Follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of the study. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Study Governance Committees:

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

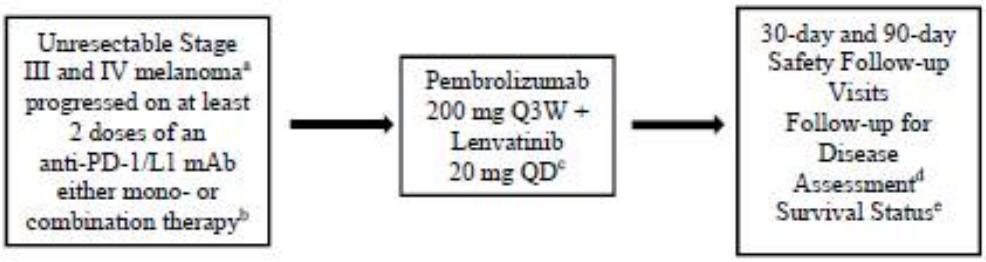
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



Abbreviations: BICR: blinded independent central review; BRAF = proto-oncogene B-raf; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; mAb = monoclonal antibody; MEKi = mitogen-activated protein kinase inhibitor; PD = progressive disease; PD-1 = programmed cell death 1; Q3W = every 3 weeks; QD = once daily; Q12W = every 12 weeks.

a All-comers with regards to PD-L1 and BRAF status.
b Prior BRAF/MEKi, anti-CTLA-4, and anti-CTLA-4+PD-1/L1 agents allowed; the proportion of participants who have received combination anti-CTLA-4+PD-1/L1 therapy will be capped at 25%. Disease progression on anti-PD-1/L1 mAb (alone or in combination) for treatment of advanced melanoma must be documented within 12 weeks following the participant's last dose with an anti-PD-1/L1 mAb (RECIST 1.1) and confirmed by a second scan showing progression no less than 4 weeks after the first scan (in the absence of rapid clinical progression [iRECIST]).
c Participants will receive lenvatinib in combination with pembrolizumab for up to 35 administrations of pembrolizumab (approximately 2 years) or until disease progression or unacceptable toxicity. After completion of approximately 2 years, participants may receive lenvatinib monotherapy until disease progression or unacceptable toxicity.
d For participants discontinuing for reasons other than PD, tumor imaging should be performed Q12W or more frequently ids clinically indicated until PD.
e For participants in Survival Follow-up, they will be contacted approximately Q12W or sooner to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Administrative Procedures												
Informed consent	X											Documented informed consent can be provided at any time prior to any protocol-specific screening procedures being performed. Additional consent is required at disease progression.
Inclusion/exclusion criteria	X											
Participant identification card	X											
Medical/surgical history	X											Significant medical/surgical history will be captured for the last 10 years.
Demographics	X											
Staging	X											At initial diagnosis and study entry.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
BRAF testing	X											BRAF V600 mutation analysis should be performed locally by the sites during Screening in participants without documented BRAF status. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central laboratory for testing.
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X		Concomitant medications will be recorded for 30 days after last dose.
Pembrolizumab + lenvatinib administration/ dispensing		X			X		X					Pembrolizumab 200 mg Q3W; lenvatinib 20 mg QD; 21-day cycle. On C1D1 and C2D1, lenvatinib will be taken 0-4 hours after completion of pembrolizumab administration. Lenvatinib will be taken in the clinic on C1D1, C1D15, and C2D1.

Study Period	**Screening**	**Treatment Cycle = 21 days**						**EOT[b]**	**Posttreatment Visits**			**Notes**
									Safety[b,c]	**Efficacy Follow-up Visits[d]**	**Survival**	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Subsequent antineoplastic treatment									X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Phone Contact Visit			X									Telephone contact or visit on C1D8 will assess participants for development of early toxicity. An unscheduled phone call or visit can occur prior to C1D15 or at any time if deemed necessary by the investigator.
Survival status												Participants may be contacted for survival status at any time during the study.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Efficacy/Immunogenicity Procedures												
Submission of initial imaging	X											The site's study team must have reviewed initial images that are of diagnostic quality from at least 3 dates to determine that radiographic progression has occurred per RECIST 1.1 and confirmed per iRECIST no less than 4 weeks from the date of the first documented PD in the absence of rapid clinical progression. The CIV must have received these scans and have confirmed that they are of acceptable diagnostic quality prior to allocation in this study for a retrospective analysis of the eligibility criterion that participants must be refractory to anti-PD-1/L1 agents. The CIV will not be confirming this eligibility prior to allocation.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Tumor assessment chest, abdomen and pelvis (CT/MRI)	X	←					→			X		Scans performed within the screening period but before providing documented informed consent may be used if consistent with protocol requirements per SIM. Investigators must receive confirmation of measurable disease by BICR prior to allocation. All imaging visits have a scheduling window of ±7 days. Imaging to be performed Q9W from the date of allocation until Week 54 of study intervention; Q12W thereafter or sooner if clinically indicated until Week 102; and Q24W thereafter or sooner if clinically indicated until disease progression per RECIST 1.1. For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
												Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit. Imaging of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted to the CIV.
Brain MRI[e]	X	←					→	X		X		All imaging visits have a scheduling window of ±7 days. A brain MRI will be required at screening and at all subsequent tumor assessment time points only if brain disease was observed at screening or if clinically indicated. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Safety Procedures												
AE monitoring	X	X	X	X	X	X	X	X	X	X		AEs: monitored up to 90 days after last dose or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Full physical examination	X											To be performed within 7 days prior to start of study intervention.
Directed physical examination		X		X	X	X	X	X	X			In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during the study, as clinically indicated.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Vital signs (resting BP, heart rate, RR, and temp) and weight	X	X		X	X	X	X	X	X			Blood pressure and pulse will be measured after the participant has been resting for 5 minutes. See Section 6.6.2.1 for management of hypertension and Section 8.3.2 for vital signs. Height measured at Screening only.
12-lead ECG	X	X			X		X	X	X			Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG at Screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and Safety Follow-up. For high-risk participants (Section 8.8.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits. Additional assessments may be performed if clinically indicated. At C1D1 only, an additional 2-hour post-lenvatinib dose ECG is required.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
MUGA or ECHO for LVEF assessment	X							X				Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study.
Hematology and clinical chemistry laboratory assessment	X			X	X	X	X	X	X			Procedures/assessments should be performed within 3 days prior to administration of first dose of study intervention and prior to all subsequent scheduled visits. Every effort should be made to collect samples at the same time of day. LDH is only required at Screening.
Urine dipstick testing	X			X	X	X	X	X	X			Performed locally within 3 days prior to administration of first dose of study intervention and prior to all subsequent scheduled visits. Participants with >1+ proteinuria on urine dipstick during Screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. See Sections 6.6.2.2 for management of proteinuria and Section 8.3.5.2 for dipstick testing.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
PT/INR and aPTT/PTT	X											Screening samples collected within 3 days of administration of first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Total T3, FT4, TSH	X				X		X	X	X			Screening samples to be collected within 3 days of C1D1. Subsequently, thyroid function tests will be performed at Cycle 2 and every other cycle thereafter (eg, C4, C6, etc.), at the time of discontinuation (EOT), and at the 30-and 90-day Safety Follow-up visits. Free T3 is acceptable where Total T3 cannot be determined. After C1, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Pregnancy test (WOCBP only)	X				X		X	X	X	X		To be assessed prior to all subsequent scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. Postmenopausal women who have not had menses for >12 months must have 2 FSH tests.
HIV, HBV, HCV	X											Testing is not required unless mandated by the local health authority.
ECOG performance status	X				X		X		X			To be assessed within 3 days of administration of first dose of study intervention and prior to dosing during all subsequent scheduled visits.
Pharmacokinetics/Pharmacodynamics/Biomarkers												
Pembrolizumab pharmacokinetics		X			X		X					Predose C1D1, C2D1, and C8D1
Pembrolizumab antidrug antibodies		X			X		X					Predose C1D1, C2D1, and C8D1

Study Period	**Screening**	**Treatment Cycle = 21 days**						**EOT[b]**	**Posttreatment Visits**			**Notes**
									Safety[b,c]	**Efficacy Follow-up Visits[d]**	**Survival**	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Lenvatinib PK blood sample		X		X	X							C1D1: 0.5-4 hours and 6-10 hours postdose (Note: no predose sampling on C1D1). C1D15: predose, and 2-12 hours postdose. C2D1: predose, 0.5-4 hours and 6-10 hours postdose. Note: postdose samples not needed if lenvatinib administration is skipped. Note: all predose samples should be collected within 2 hours of lenvatinib dosing.
Blood for serum biomarker		X		X	X		X	X				Collect predose on C1D1, C1D15, C2D1, C3D1, C5D1, and at EOT.
Blood for RNA analysis		X			X		X	X				Collect predose on C1D1, C2D1, C3D1, C5D1, and at EOT.
Blood for circulating tumor nucleic acids		X			X		X	X				Collect predose. C1D1, C2D1, C3D1, C5D1, and then D1 every 3 cycles, and at EOT.

Study Period	Screening	Treatment Cycle = 21 days						EOT[b]	Posttreatment Visits			Notes
									Safety[b,c]	Efficacy Follow-up Visits[d]	Survival	
Visit Timing/Cycle Number	**-28 to -1**	**1**			**2**		**Cycle 3 Onwards[a]**	**At DC**	**30 Days and 90 Days After Last Dose**	**Q12W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**					
Scheduling Window (Days)	**-28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	
Blood for plasma biomarker		X			X		X	X				Collect predose. C1D1, C2D1, C3D1, C5D1, and then D1 every 3 cycles, and at EOT
Blood for genetic analysis		X										Collect predose. See Sections 8.8 and 8.9 for additional information.
Tumor blocks or slides	X											Collected during Screening for confirmation of adequacy of tumor tissue at a central pathology laboratory and for other tumor biomarker assessments.
Stool analysis (optional)		X										Predose (at home within 1 week before infusion) on C1D1.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BICR = blinded independent central review; BP = blood pressure; C = Cycle; CIV = central imaging vendor; CR = complete response; CT = computed tomography; D1 = Day 1; D15 = Day 15; D8 = Day 8; DC = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxine; FSH = follicle-stimulating hormone; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD = progressive disease; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = Site Imaging Manual; SoA = Schedule of Activities; SOC = standard of care; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

a Participants who continue treatment with lenvatinib beyond ~2 years will follow the same SoA except for the following: 1) thyroid labs beyond ~2 years will be performed per SOC or as clinically indicated 2) Circulating tumor nucleic acids will no longer be collected. Participants who attain an investigator-determined CR and stop study intervention with pembrolizumab + lenvatinib will have Safety Follow-up visits and move to follow-up per SoA.

b If EOT visit occurs ~30 days from last dose of study intervention, a Safety FU visit at 30 days is not required. In this situation, all procedures required at both the EOT visit and the Safety FU visit at 30 days should be performed. EOT will be defined as the date when the participant discontinues all study interventions.

c Safety FU will occur during 2 separate visits: 30 days AND 90 days after last dose. If the 90-day Safety FU visit falls within the same window as the imaging FU visit, these visits may be combined. All procedures required at the Safety FU visit at 90 days will be performed at the imaging FU.

d For participants who discontinue study intervention for reasons other than progressive disease, follow-up visits to monitor disease status continue until progressive disease or initiation of a new anticancer therapy. Participants who discontinue study intervention with progressive disease proceed directly to Survival Follow-up.

e Brain MRI must be performed at Screening. Brain MRI should then be performed Q9W until Week 54 or sooner if clinically indicated; Q12W thereafter until Week 102; following Week 102, imaging should be performed every Q24W, or sooner if clinically indicated only for participants with brain disease present at Screening. Brain CT scan should only be used when MRI is contraindicated. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the trial to optimize the visualization of existing and new tumor burden.

2 INTRODUCTION

2.1 Study Rationale

Pembrolizumab (MK-3475/Keytruda) was approved by the US Food and Drug Administration (FDA) as the first anti- programmed cell death 1 (anti-PD-1) agent for the treatment of unresectable or metastatic melanoma in all lines of therapy. The European Commission has also approved pembrolizumab for both first-line and previously treated patients with advanced melanoma. However, there remains a large population (~60%) of patients who do not respond to anti-PD-1 therapy, and data suggest that the combination or sequencing of immune checkpoint inhibitors may be used to restore activity in participants who have progressed on a particular inhibitor. This strategy may also offer a more powerful tool to induce immune activity in tumors that respond poorly, (ie, those that may have a greater level of immune suppression) [Pennock, G. K. 2015]. The response rates in anti-PD-1 agent-exposed patients to other available checkpoint inhibitors (CTLA4, CTLA4+PD-1 combination) remain unsatisfactory, 16% and 21% respectively [Zimmer, L., et al 2017]. Therefore, there is a large unmet medical need for novel therapies or combinations in anti-PD-1 agent-exposed patients.

The current study is designed to further evaluate the safety and efficacy of combination therapy of lenvatinib and pembrolizumab following approximately 2 years of pembrolizumab therapy and approximately 2 years or more lenvatinib therapy in adult participants with unresectable or advanced melanoma who have been exposed to anti-PD-1/L1 agents approved for unresectable or metastatic melanoma.

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2).

Lenvatinib (also known as E7080 or MK-7902) inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors 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, 2, 3, and 4; platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in cell lines dependent on activated fibroblast growth factor receptor (FGFR) signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation. Once daily (QD) dosing of lenvatinib combined with pembrolizumab is currently being developed for the treatment of melanoma.

Refer to the respective IB/approved labeling for detailed background information on pembrolizumab and lenvatinib.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 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. 2008] [Tammela, T. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. 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 to 22 nmol/L, respectively[Yamamoto, Y., et al 2014]. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of human umbilical vein endothelial cell (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 mitogen-activated protein kinase (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), renal cell carcinoma (RCC), hepatocellular carcinoma (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 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.

2.2.1.2 Pembrolizumab

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 Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon

engagement of its ligands (PD L1 and/or PD-L2) [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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 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, protein kinase C-theta, and zeta-chain-associated protein kinase, 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 melanoma.

2.2.1.3 Pembrolizumab Plus Lenvatinib

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 cluster of differentiation (CD)8+ T cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (Tregs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. 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].

In preclinical models, lenvatinib decreased the tumor-associated macrophage (TAM) population, which is known as an immune-regulator in the tumor microenvironment. The decrease in TAM population was accompanied by increases in activated cytotoxic T-cell populations through stimulation of interferon-gamma signaling, resulting in increased immune activation [Kimura, T., et al 2018]. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. The effect of combining lenvatinib with an anti-human PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared with control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T cells compared with that of the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well tolerated and severe body weight loss was not observed.

2.2.1.4 Melanoma: Epidemiology and Current Therapeutic Options

Melanoma is the most serious form of skin cancer and impacts adults of all ages. The 5-year prevalence of melanoma in the EU is approximately 326,000 patients with an incidence of approximately 83,000 per year and approximately 16,000 deaths annually [WHO Health Organization 2012]. Melanoma accounts for approximately 5% of all new cases of cancer in the US. The incidence of melanoma continues to rise by almost 3% per year in the US. This translates to 76,000 new cases a year with 9,000 associated deaths. The male-to-female incidence ratio of melanoma is 1.4:1, respectively [Siegel, R., et al 2012]. The 5-year survival rate is 17% for distant-stage disease [American Cancer Society 2016].

High-dose interleukin-2 was the first immune-modulating treatment to modify the natural history of patients with metastatic melanoma and may be curative for a small fraction of patients. However, its severe toxicity limits its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. More recent research led to the development of immunotherapy using checkpoint inhibitors such as anti-PD-1 antibodies (pembrolizumab and nivolumab), the anti-CTLA-4 antibody ipilimumab, and to MAPK pathway targeted therapy with BRAF and/or MEK inhibition (dabrafenib and/or trametinib, respectively). Both of these approaches prolong PFS and OS compared with chemotherapy [UpToDate, Inc. 2015] [Ugurel, S., et al 2017]; thus, they are standard therapeutic options for patients with melanoma refractory to anti-PD-1/L1 agents.

Ipilimumab, an anti-CTLA-4 antibody, was the first checkpoint inhibitor to demonstrate OS benefit in a randomized, comparative Phase 3 registration study. In the Phase 3 study MDX010-20, ipilimumab monotherapy demonstrated a hazard ratio (HR) of 0.66 and a 4-month median OS benefit compared with gp100 in pretreated advanced melanoma participants [Hodi, F. S., et al 2010]. Grade 3 to 4 immune-related AEs included colitis (3.2%), diarrhea (4.5%), endocrinopathies (1.1%), and rash (1.3%). In the US, 3 mg/kg of ipilimumab was approved for advanced melanoma based on data from MDX010-20 and without restriction to line of therapy, in part because of the results of an additional Phase 3 randomized ipilimumab clinical study, CA184024. In the CA184024 study, treatment-naïve advanced melanoma participants treated with 10 mg/kg ipilimumab in combination with dacarbazine demonstrated an HR of 0.72 and a 2-month median OS benefit compared with monotherapy dacarbazine [Robert, C., et al 2011]. In the EU, ipilimumab is currently approved for the treatment of advanced (unresectable and metastatic) melanoma in adults who have received prior therapy.

Approximately 50% of cutaneous melanoma cases are BRAF V600E mutation positive. Vemurafenib was initially approved in the US and in the EU for the treatment of BRAF V600E mutation-positive advanced melanoma participants regardless of line of therapy [U.S. Prescribing Information 2015]. In the BRIM-3 Phase 3 study, vemurafenib demonstrated a 48% response rate and an increased OS benefit compared with dacarbazine with an HR of 0.37, but with inadequate follow-up. More recently, the combination of a BRAF inhibitor plus a MEK inhibitor demonstrated an increased efficacy and a better safety profile compared with BRAF inhibition alone as first-line therapy in patients with advanced melanoma. Both the combination of dabrafenib and trametinib or vemurafenib and

cobimetinib are approved as first-line therapy in BRAF V600E mutation-positive melanoma patients [Robert, C., et al 2014] [Robert, C., et al 2015] [Larkin, J., et al 2014].

Pembrolizumab has shown in a randomized Phase 3 study (KEYNOTE-006) a significant benefit in OS, PFS, and response rate in patients with unresectable or metastatic melanoma compared with ipilimumab. The estimated PFS rate was 46.4% at 6 months for pembrolizumab 10 mg/kg every 3 weeks versus 26.5% for ipilimumab. The ORR was 32.9% for pembrolizumab 2 mg/kg Q3W versus 11.9% for ipilimumab. Responses were ongoing in 96.7% of participants after a median follow-up of 7.9 months. Median PFS were 4.1 months for pembrolizumab versus 2.8 months for ipilimumab. The HR for disease progression for pembrolizumab Q3W versus ipilimumab was 0.58 (95% CI, 0.46 to 0.72; $p<0.001$). The 1-year estimate of survival for participants receiving pembrolizumab Q3W was 68.4% compared with 58.2% for ipilimumab (HR for death as compared with ipilimumab group 0.69; 95% CI, 0.52 to 0.90; $p=0.0036$). Because the OS results were superior to those for the ipilimumab group the IDMC recommended stopping the study early to allow patients in the ipilimumab group the option of receiving pembrolizumab [Robert, C., et al 2015].

Similarly, nivolumab was studied in participants with previously untreated advanced melanoma compared with dacarbazine. The median PFS was 5.1 months compared with 2.2 months for the dacarbazine group. The ORR were 40% in the nivolumab group and 13.9% in the dacarbazine group. At 1 year, the overall rate of survival was 72.9% for the nivolumab group compared with 42.1% in the dacarbazine group. Nivolumab significantly improved OS and PFS compared with dacarbazine among previously untreated patients who had metastatic melanoma without BRAF mutation [Robert, C., et al 2014].

In 2014, the FDA approved both nivolumab and pembrolizumab, PD-1 blocking antibodies, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600E mutation-positive, a BRAF inhibitor. Both approvals were under the accelerated approval process and were based on tumor response rates and durability of response. Both pembrolizumab and nivolumab received National Comprehensive Cancer Network (NCCN) compendia listing recommendations for use in the first-line metastatic melanoma setting based on these data. In November 2015, nivolumab received approval for first-line treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma. In December 2015, the pembrolizumab label was expanded to include first-line treatment of patients with unresectable or metastatic melanoma regardless of BRAF status. The European Commission also approved pembrolizumab and nivolumab for both first-line and previously treated patients with advanced melanoma.

There remains a high unmet medical need for efficacious combination therapies in patients not responding or refractory to anti-PD-1 agents. A retrospective analysis in advanced melanoma patients after anti-PD-1 treatment failure showed objective response rates for ipilumab alone and in combination with nivolumab as 16% and 21%, respectively. One-year OS rates for the ipilimumab and the combination-group were 54% and 55%, respectively [Zimmer, L., et al 2017]. Thus, although ipilimumab should be considered as a viable treatment option for patients with failure to prior anti-PD-1 therapy, the combination of ipilimumab and nivolumab appears significantly less effective in this setting compared with treatment-naïve patients.

2.2.1.5 Scientific Rationale for the Combination of Lenvatinib with Pembrolizumab

In preclinical models, lenvatinib decreased the TAM population, which is known as an immune-regulator in the tumor microenvironment. By decreasing TAMs, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/PD-L1 signal inhibitors. The effect of combining lenvatinib with anti-PD-1/PD-L1 agents has been investigated in the CT26 colorectal cancer syngeneic model (anti-PD-L1 agent) as well as the LL/2 lung cancer syngeneic model (anti-PD-1 agent). Combination treatment with lenvatinib and either an anti-PD-1 or anti-PD-L1 agent showed significant and superior antitumor effects compared with either compound alone in these 2 syngeneic models [Kato, Y., et al 2015].

Based on these results, an open-label, Phase 1b/2 study (Study E7080-A001-111 [Study 111]) to assess the safety and preliminary antitumor activity of the combination of lenvatinib + pembrolizumab in participants with selected solid tumors is currently ongoing. Phase 1b of this study determined the MTD and recommended Phase 2 dose (RP2D) as 20 mg lenvatinib QD in combination with 200 mg of pembrolizumab given IV Q3W. The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (ie, NSCLC, RCC, EC, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

2.2.1.6 Clinical Data on Lenvatinib in Combination with Pembrolizumab for the Treatment of Melanoma

E7080-A001-111/KEYNOTE-146 is an ongoing multi-cohort Phase 2 study to assess the efficacy and safety of lenvatinib in combination with pembrolizumab in 6 types of biomarker-unselected metastatic solid tumors, including melanoma (excluding uveal melanoma), that have progressed after treatment with approved therapies or for which there are no standard effective therapies available. The study is ongoing but is no longer enrolling melanoma patients.

Eligible participants were aged 18 years or older and had histologically confirmed non-uveal melanoma, 0 to 2 prior systemic anticancer regimens and ECOG 0 or 1. The primary endpoint is ORR at Week 24 based on Response Evaluation Criteria in Solid Tumors 1.1 for Immune-based Therapeutics (iRECIST), as determined by investigator-read tumor assessments performed at baseline, every 6 weeks until Week 24, and then every 9 weeks thereafter. Secondary endpoints include ORR, DOR, PFS, OS, and safety and tolerability of the combination. All participants received lenvatinib 20 mg daily in combination with 200 mg pembrolizumab IV Q3W. At data cutoff (01-MAR-2018), 21 metastatic melanoma participants were enrolled, and 38% of participants had 1 or more prior anticancer therapy.

For all enrolled participants (N=21), the ORR_{Week24} was 47.6% (95% CI: 25.7%, 70.2%) using iRECIST by investigator review. Of the 10 confirmed responses, 9 (42.9%) were PR, and 1 (4.8%) was CR. Stable disease was observed in 7 (33.3%) participants, and 3 (14.3%) experienced PD. One participant (4.8%) had an unknown response. Median duration of

objective response was 12.5 months (95% CI: 2.7 months, NE). Median PFS observed was 7.6 months (95% CI: 2.6 months, 15.8 months).

All participants experienced ≥1 TRAE. There were no fatal TRAEs. The most common any-grade TRAEs were fatigue (52%), decreased appetite (48%), diarrhea (48%), hypertension (48%), dysphonia (43%), and nausea (43%). Dose reduction and interruption due to TRAEs occurred in 13 (62%) and 10 (47.6%) participants, respectively.

The safety profile of lenvatinib in combination with pembrolizumab appears manageable in patients with malignant melanoma and other tumor types and is consistent with each agent's safety profile when administered as monotherapy.

2.2.2 Preclinical and Clinical Studies

Refer to the respective IBs for preclinical and clinical study data for pembrolizumab and lenvatinib.

2.3 Benefit/Risk Assessment

Beneficial effects of pembrolizumab have been seen in several melanoma trials to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in single-arm and randomized studies as monotherapy (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006).

As discussed in Sections 2.2.1.3 and 2.2.1.4, both lenvatinib and pembrolizumab in combination have shown promising efficacy in participants with melanoma and preliminary safety data of the combination of lenvatinib and pembrolizumab suggest toxicity is manageable. Given the relevance of improving and expanding treatment options for patients with advanced melanoma, there is an unmet medical need for novel combinations in this setting. The existing data suggest that inhibiting angiogenesis in combination with PD-1 blockade is a promising therapeutic strategy and the benefit:risk assessment for participants included in this study is considered to be favorable. No unexpected risks have been reported in melanoma with other immune check point inhibitors other than transient elevations in ALT and AST.

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 IB and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In all participants with advanced melanoma previously exposed to an anti-PD-1/L1 agent, and following administration of lenvatinib in combination with pembrolizumab:

Objectives	Endpoints
Primary	
• Objective: To evaluate ORR as assessed by BICR per RECIST 1.1.	• Objective Response: CR or PR.
Secondary	
• Objective: To evaluate PFS as assessed by BICR per RECIST 1.1.	• PFS: The time from first day of study intervention to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To evaluate OS.	• OS: The time from first day of study intervention to death due to any cause.
• Objective: To evaluate the DOR as assessed by BICR per RECIST 1.1.	• DOR: For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
• Objective: To assess safety and tolerability of treatment with lenvatinib in combination with pembrolizumab.	• Adverse events. • Study drug discontinuations due to AEs.
• Objective: To characterize the population PK of lenvatinib when co-administered with pembrolizumab.	• Plasma concentration of lenvatinib.
Tertiary/Exploratory	
• Objective: To evaluate ORR, PFS, and DOR per iRECIST as assessed by investigator review.	• Objective Response: CR or PR. • PFS: The time from first day of study intervention to the first documented disease progression or death due to any cause, whichever occurs first. • DOR: For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause (whichever occurs first).

Objectives	Endpoints
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of lenvatinib and pembrolizumab.	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

4 STUDY DESIGN

4.1 Overall Design

This is an open-label study to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab in participants with advanced melanoma previously exposed to an anti-PD-1/L1 agent. All-comers with regards to PD-L1 and BRAF status are eligible for enrollment if they meet all of the inclusion and none of the exclusion criteria. Disease progression on an anti-PD-1/L1 mAb (alone or in combination) for the treatment of advanced melanoma must be documented within 12 weeks following the participant's last dose with an anti-PD-1/L1 mAb (RECIST 1.1) and confirmed by a second scan showing progression no less than 4 weeks after the first scan (in the absence of rapid clinical progression) (iRECIST). The proportion of participants who have received combination anti-CTLA-4+PD-1/L1 therapy will be capped at 25%.

Approximately 100 participants will be enrolled into the study. After a Screening Phase of up to 28 days, participants will be treated with the combination of lenvatinib and pembrolizumab for up to 35 administrations of pembrolizumab (approximately 2 years) or until disease progression, unacceptable toxicity, investigator decision or participant decision, withdrawal of consent, or death, whichever occurs first. After completion of approximately 2 years of combination treatment, participants may receive lenvatinib monotherapy until disease progression or unacceptable toxicity. Participants may interrupt or discontinue pembrolizumab due to toxicity and continue with lenvatinib. Similarly, participants may interrupt or discontinue lenvatinib due to toxicity and continue with pembrolizumab. Participants may also discontinue study intervention due to unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment.

The primary endpoint of OR will be assessed by BICR per RECIST 1.1 criteria. The secondary endpoints are PFS, OS, and DOR. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements, as appropriate.

After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4.

Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up, whichever occurs first.

Participants will be permitted to continue study intervention beyond RECIST 1.1-defined disease progression if the treating investigator considers that the participant may experience clinical benefit with continued treatment as per iRECIST, and the participant is tolerating study intervention. Treatment beyond progressive disease per iRECIST may be permitted following Sponsor consultation and approval.

All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

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

4.2 Scientific Rationale for Study Design

If the safety profile is acceptable and this combination improves ORR, this study could support the regulatory approval of the combination of pembrolizumab and lenvatinib in participants with unresectable or advanced melanoma previously exposed to an anti-PD-1/L1 mAb.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use OR, defined as a best overall response of CR or PR, as assessed by BICR per RECIST 1.1 criteria as the primary endpoint.

Progression-free survival (PSF), OS, and DOR are secondary endpoints.

Progression-free survival (PFS) 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. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site. Overall survival (OS) has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. Duration of response as assessed by BICR per RECIST 1.1 will serve as an additional measure of efficacy and is a commonly accepted endpoint by both regulatory authorities and the oncology community.

iRECIST will also be used by the local site to make treatment decisions once PD has been documented per RECIST 1.1 and verified by BICR.

OS is defined as the time from the first day of study intervention to death due to any cause.

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

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and when determining eligibility (Section 8.2.1.5). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.1.2 RECIST 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.1.5). 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 patients treated with pembrolizumab may 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 fully capture the treatment benefits from 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 by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with disease progression 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 takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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 nontarget 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. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions as well as for exploratory efficacy analyses, where specified.

4.2.1.2 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/SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

4.2.1.3 Pharmacokinetic Endpoints

Based on PK data obtained in this study and from other studies, a population PK analysis will be performed to characterize PK parameters of lenvatinib when co-administered with pembrolizumab to support the proposed dosing regimen.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.5 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, including novel combinations with antiangiogenesis therapy, 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 and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, 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:

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy 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.

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, microsatellite instability) contributing toward the development/progression of cancer

and/or driving response to therapy. Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased 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. Evaluation of molecular targets and signaling pathways including angiogenesis and growth factor related signaling pathways related to pembrolizumab and lenvatinib may also be explored. 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. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

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 and growth factor signaling pathways (eg, VEGF and FGF) may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling.

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 indicates 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 and lenvatinib combination therapy. 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) and lenvatinib combination therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1, circulating cytokines and angiogenic factors, and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunosorbent assay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab and lenvatinib combination 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.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Biomarker Research using Stool

Landmark studies have demonstrated that the gut microbiome can shape anti-tumor immunity and responses to immune checkpoint blockade in mouse models, and that modulation of the gut microbiome may enhance responses to immune checkpoint blockade. This has also been studied in patients on immune checkpoint blockade (anti-CTLA-4 and anti-PD-1), with evidence that differential bacterial signatures exist in responders versus non-responders to therapy (with responders having higher diversity of the gut microbiome and differential composition compared with non-responders). Importantly, these differences in the gut microbiome are associated with differential immune signatures in the tumor microenvironment [Lynch, S. V. 2016].

4.3 Justification for Dose

4.3.1 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the pembrolizumab 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 Q2W,

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

- Pharmacology data showing full target saturation in both systemic circulation (inferred PK data) and tumor (inferred from physiologically based PK [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 versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). 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 conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, 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.

4.3.2 Lenvatinib

The dosing regimen of lenvatinib was selected based on the results of the Phase 1b portion of Study 111, 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. Neither of these participants had melanoma. 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 23 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.

4.3.3 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for approximately 2 years. The maximum dose/exposure of lenvatinib allowed in this study is 20 mg QD until disease progression or unacceptable toxicity.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/female participants with advanced melanoma who are at least 18 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

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

1. Have histologically or cytologically confirmed melanoma.

2. Have unresectable Stage III or Stage IV melanoma, per American Joint Committee on Cancer (AJCC) staging system version 8, not amenable to local therapy.

3. Have the presence of at least 1 measurable lesion by CT or MRI per RECIST 1.1 as confirmed by BICR. Cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol but may be considered as nontarget lesions.

    a. If participants have only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from the nontarget lesion or archival tissue.

    b. Lesions that are in an area that has been previously irradiated should not be considered measurable unless there has been documented growth of the lesions since the completion of radiation.

4. Participants must have progressed on treatment with an anti-PD-1/L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

    a. Received at least 2 doses of an anti-PD-1/L1 mAb.

b. Has demonstrated disease progression after PD-1/L1 as defined by RECIST 1.1. The initial evidence of RECIST 1.1 disease progression is to be confirmed using iRECIST by a second assessment no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression[i,ii].

   i Seymour et al, iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* (2017): 18: e143-52.

   ii This determination is made by the investigator. Once progressive disease is confirmed, the initial date of RECIST 1.1 progressive disease documentation will be considered the date of disease progression.

c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.

   Note: the proportion of participants who have received combination anti-CTLA-4+PD-1/L1 therapy will be capped at 25%.

5. Have submitted initial imaging.

   Note: The site's study team must have reviewed initial images that are of diagnostic quality from at least 3 dates to determine that radiographic progression has occurred per RECIST 1.1 and confirmed per iRECIST no less than 4 weeks from the date of the first documented progressive disease in the absence of rapid clinical progression (see Section 8.2.1.1 for further details). The CIV must have received these scans and have confirmed that they are of acceptable diagnostic quality prior to treatment allocation in this study for a retrospective analysis of inclusion criterion #4: participants must be refractory to anti-PD-1/L1 agents. The CIV will not be confirming this eligibility criterion prior to treatment allocation.

6. Have an ECOG performance status 0 to 1 (Appendix 9).

7. Have provided a baseline tumor biopsy.

   a. Must submit the tumor sample during Screening for confirmation of adequacy of tumor tissue at a central pathology laboratory. Participants who do not submit a tumor tissue sample will not be allocated to treatment. The biopsy may not be obtained from a lone target lesion. This condition can be waived if collecting a tumor sample is not feasible or not in the best interest of the participant, following Sponsor's approval.

   b. Newly obtained tissue is preferred and must be collected after progression on prior anti-PD-1/L1 agent.
   Note: Following collection of tissue at study enrollment, participants may not receive intervening treatment (local or systemic) involving the site of the tissue biopsy.

8. Have resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). If participant received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

Demographics

9. Be Male or Female and is at least 18 years of age at the time of providing documented informed consent.

Male Participants

10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 95 days, corresponding to time needed to eliminate study interventions (eg, 5 terminal half-lives) after the last dose of study intervention:

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

      OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below.

      - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. 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-vaginal penetration.

    - Male participants must also agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Female Participants

11. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

    - Not a woman of childbearing potential (WOCBP).

      OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with lower user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 95 days, corresponding to the time needed to eliminate any study interventions (eg, 5 terminal half-lives) after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum; as required by local regulations) within 24 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy test result is positive.

- Additional requirements for pregnancy testing during and after study intervention are in Appendix 5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetectable pregnancy.

Informed Consent

12. Have provided documented informed consent for the study.

Additional Categories

13. Have adequately controlled BP, with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week before Cycle 1, Day 1.

    Note: Eligibility of a participant that is receiving >3 antihypertensive medications prior to study entry will require Sponsor approval

14. Have adequate organ function as defined in Table 2. Specimens must be collected within 3 days prior to the start of study intervention.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
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 except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
AST (SGOT) and ALT (SGPT), and ALP	≤2.5× ULN (≤5 × ULN for participants with liver metastases)[c]
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)/PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ALP = alkaline phosphatase; CrCl = creatinine clearance; 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.
c Participants with ALP values >3 times the ULN and known to have bone metastases can be included.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.2 Exclusion Criteria

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

Medical Conditions

1. 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 before the first dose of study intervention.

2. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Exceptions include early stage cancers (carcinoma in situ or Stage 1, non-ulcerated primary melanoma <1 mm in depth with no nodal involvement) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.

3. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated CNS metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study intervention and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases confirmed by repeat imaging, and have not required steroids for at least 14 days before study intervention.

   Note: Participants with asymptomatic previously untreated brain metastases may participate provided there are ≤3 total lesions in the brain and their longest diameter is <1 cm. Stability of these lesions does not need to be confirmed by repeat imaging.

   Baseline MRI brain scan will be obtained for all participants. Brain CT scan should only be used when MRI is contraindicated.

4. Has ocular melanoma.

5. Has known hypersensitivity to active substances or any of their excipients including previous clinically significant hypersensitivity reaction to treatment with another monoclonal antibody. For a list of excipients, refer to the respective IB.

6. 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, etc.) is not considered a form of systemic treatment.

7. Has an active infection requiring systemic therapy.

8. Has known history of HIV (HIV 1/2 antibodies). No testing of HIV is required unless mandated by local health authority.

9. Has known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (HCV RNA [qualitative] is detected). No testing of hepatitis B or C is required unless mandated by local health authority.

10. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

11. Has a history of active tuberculosis (*Bacillus* tuberculosis).

12. Has presence of a gastrointestinal condition including malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.

13. Has had major surgery within 3 weeks prior to first dose of study interventions. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

14. Has a pre-existing Grade ≥3 gastrointestinal or nongastrointestinal fistula.

15. Has 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.

16. Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

17. Has clinically significant cardiovascular disease within 12 months from first dose of study drug, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.

    Note: Medically controlled arrhythmia would be permitted.

18. Has urine protein ≥1 g/24-hour.

    Note: Participants having >1+ proteinuria on urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria.

19. Has a prolongation of QTc interval (calculated using Fridericia's formula) of >480 msec.

20. Has LVEF below the institutional normal range as determined by MUGA or echocardiogram.

Prior/Concomitant Therapy

21. Has received prior radiotherapy within 2 weeks of Cycle 1 Day 1. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

22. Has received a live vaccine within 30 days before the first dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

23. 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 intervention.

    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

Other Exclusions

24. Had a history or has current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the 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.

25. Has had an allogeneic tissue/solid organ transplant.

26. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

Lenvatinib and pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

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 embryo toxicity 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. To participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) 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.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab and/or lenvatinib, the participant will be immediately discontinued from study intervention. 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 8.4.

5.3.4 Use in Nursing Women

It is unknown whether pembrolizumab and/or lenvatinib is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (pembrolizumab and lenvatinib) will be packaged to support enrollment Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm 1	Experi-mental	Pembrolizumab	Drug	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W	Experimental	IMP	Central
	Experi-mental	Lenvatinib	Drug	Capsule	10 mg, 4 mga	20 mg	Oral	Once daily	Experimental	IMP	Central

Abbreviations: IMP = Investigational Medicinal Product; IV = intravenous; Q3W = every 3 weeks.

a 4 mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.2.

All supplies indicated in Table 3 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. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Lenvatinib is a capsule for oral administration and does not require preparation. See the Pharmacy Manual for additional information.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an interactive response technology (IRT) system. There is one study intervention arm. Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol specified treatment: >28 days (lenvatinib) or >12 weeks (pembrolizumab) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication (including over-the-counter medications) or therapy administered to the participant during the study (starting at the date of informed consent) will be recorded on the appropriate CRF. The investigator will record the AE for which the concomitant medication/therapy was administered on the appropriate CRF. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the appropriate CRF.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study intervention and any concomitant therapy administered to the participant during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study intervention will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the participant’s health, and that is not expected to interfere with the evaluation of or interact with the study medication, may be continued during the study.

6.5.1 Allowed Concomitant Medications

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication. Anti-emetic or any other prophylaxis should be considered in accordance with institutional guidelines.

Any additional procedural or participant-specific particularities should be discussed with the investigator and the Sponsor.

6.5.2 Prohibited Concomitant Medications

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

- Concurrent anticancer therapies such as chemotherapy, targeted therapies, antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol.

  Note: Topical anticancer agents to treat skin lesions (eg, in situ melanoma or squamous cell carcinoma) are allowed, excluding skin metastasis of melanoma.

  Note: Palliative surgery to treat a nontarget symptomatic solitary lesion or to the brain will be allowed after confirmed progressive disease. Palliative surgery to treat nontarget lesions without documentation of progressive disease will need Sponsor consultation and approval. Palliative surgery of target lesions is not allowed.

- Other concurrent investigational drugs.

- Live vaccines within 30 days and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have immunologic etiology. Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during the study.

  Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.

- Palliative radiotherapy other than to treat a symptomatic solitary lesion or to the brain, and only after initial documentation of progressive disease. Palliative radiotherapy to treat nontarget lesions without documentation of progressive disease will need Sponsor consultation and approval. Palliative radiotherapy of target lesions without documentation of progressive disease is not allowed.

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of study intervention and further participation in the study must be discussed and agreed upon with the Sponsor.

If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These participants should complete all end of treatment assessments and continue to be followed for survival in the Follow-up Period.

6.5.3 Drug Interactions

There are no DDI-related concomitant medication prohibitions or restrictions.

Lenvatinib is not expected to clinically alter exposure to CYP3A4/ P-glycoprotein (Pgp) substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate). Clinical studies also showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp is not of clinical concern.

No drug interaction is expected between pembrolizumab and lenvatinib because of divergent metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (LENVIMA product information).

6.5.4 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. For participants receiving pembrolizumab + lenvatinib, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 4 in Section 6.6.1 along with the dose modification guidelines in Table 5 and Table 6 in Section 6.6.1 and Section 6.6.2, respectively. 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 or lenvatinib.

Note: If after the evaluation of an event, it is determined not to be related to pembrolizumab or lenvatinib, the investigator does not need to follow the treatment guidance. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of an event.

6.5.5 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte colony stimulating factors (G-CSF) may be used per the discretion of the treating physician and in line with local guidelines.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Pembrolizumab

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks. An interruption of study intervention for more than 12 weeks will require Sponsor approval before treatment can be resumed (see Section 6.4).

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab 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 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, 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

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

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

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

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

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

6.6.1.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the 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 drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: - Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). - Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - Epinephrine** - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the 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 drug treatment.**	No subsequent dosing

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth.
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov

Other allowed dose interruptions for pembrolizumab

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

Participants may interrupt or discontinue pembrolizumab and continue in the study with lenvatinib (see Section 4.1).

6.6.2 Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-related or lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 6. An interruption of study intervention for more than 28 days will require Sponsor approval before treatment can be resumed.

Adverse events will be graded using NCI CTCAE v4.0. 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 intervention dose has been reduced, it may not be increased at a later date unless the dose has been mistakenly decreased; in this situation, the Sponsor’s approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 6.6.2.1), proteinuria (Section 6.6.2.2), diarrhea (Section 6.6.2.3), hepatotoxicity (Section 6.6.2.4), thromboembolic events (Section 6.6.2.5), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.2.6), hypocalcemia (Section 6.6.2.7), hemorrhage (Section 6.6.2.8), gastrointestinal perforation or fistula formation (Section 6.6.2.9), and osteonecrosis of the jaw (Section 6.6.2.10) as appropriate, before consulting the dose modification table (Table 6). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.3.

Table 6 Dose Modification Guidelines for Lenvatinib-related Adverse Events

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] or Grade 3[e,g]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[f,g]: Discontinue Study Intervention		

Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.
Note: For grading see CTCAE version 4.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

a An interruption of study intervention for more than 28 days will require Sponsor's approval before treatment can be resumed.
b Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism, and/or diarrhea prior to any lenvatinib interruption or dose reduction.
c Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
d 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.
e 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.
f Excluding laboratory abnormalities judged to be nonlife-threatening, in which case manage as Grade 3.
g For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.2.5.

6.6.2.1 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 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 as detailed in the SoA (Section 1.3). Hypertension will be graded using NCI CTCAE v4.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's first BP measurement of the current assessment 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.

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 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. A diary will be provided to the participant to capture the blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

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 intervention can be continued without dose modification.

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

- If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg 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 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

- If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg 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 only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

- Additional dose reduction should be discussed with 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

6.6.2.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 1.3). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing per the SoA (Section 1.3).

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 6.

- In the event of nephrotic syndrome, lenvatinib must be discontinued.

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.

6.6.2.3 Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of study intervention, and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal 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 6 should be followed.

6.6.2.4 Management of Hepatotoxicity

Liver function tests (ALT, AST, and bilirubin levels) should be conducted as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 6 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug must be discontinued.

6.6.2.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 6 should be followed. Appropriate supportive care should be provided together with close monitoring. Lenvatinib must be discontinued for a Grade 3 thromboembolic event that requires urgent intervention. If a participant experiences a Grade 3 or a life-threatening

(Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib/placebo 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 intervention discontinuation.

6.6.2.6 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

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. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 6 should be followed.

6.6.2.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v4.0, 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 appropriate calcium, magnesium, and vitamin D supplementation) until resolution.

6.6.2.8 Management of Hemorrhage

Instructions in Table 6 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.

6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or ≥Grade 4 fistula.

6.6.2.10 Management of Osteonecrosis

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 judgment of adequate resolution (see Section 6.6.4).

6.6.3 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 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 2 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 intervention if any of the following occur:

    - ALT or AST >5 × ULN for more than 2 weeks
      Pembrolizumab will have already been permanently discontinued per Table 4, 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 × ULN or INR >1.5)
      Although Table 4 advises pembrolizumab to be withheld (interrupted), and Table 6 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.6.4 Other Allowed Dose Interruptions for Lenvatinib and Pembrolizumab

If the 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.

- 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.

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

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Progressive disease as verified by investigator.

  Note: Participants will be permitted to continue treatment beyond confirmed RECIST 1.1-defined progression if investigator-assessed clinical stability is observed, and the participant is tolerating study intervention (Section 8). Treatment beyond progressive disease per iRECIST may be permitted following Sponsor consultation and approval.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor prior to continuing therapy or remaining in follow-up.
- Recurrent Grade 2 pneumonitis and other AEs that may require treatment discontinuation per Section 6.6 (Dose Modification).

- Completion of 35 treatments (approximately 2 years) with pembrolizumab.
  Note: Participants may receive lenvatinib monotherapy until disease progression or unacceptable toxicity.

- Grade 3 thromboembolic events require permanent discontinuation of lenvatinib.

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

  - ALT or AST >5 × ULN for more than 2 weeks
    Pembrolizumab will have already been permanently discontinued per Table 4, 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 × ULN or INR >1.5)
    Although Table 4 advises pembrolizumab to be withheld (interrupted), and Table 6 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

A participant may be discontinued from study intervention but continue to be monitored in the study for the following reason:

- Discontinuation of study intervention with pembrolizumab and lenvatinib may be considered for participants who have attained a confirmed CR and have been treated for at least 24 weeks, receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

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

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

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

8.1.4 Medical History

A medical/surgical history and staging will be obtained by the investigator or qualified designee. The medical and surgical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. This will include disease staging at initial diagnosis and at study entry.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before first dose of study medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications will be recorded for 30 days after the last dose.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation.Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

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

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, 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.

8.1.8 Study Intervention Administration

Lenvatinib: Lenvatinib may be taken at home except on C1D1, C1D15, and C2D1; on these days lenvatinib will be taken in the clinic. Please refer to Section 8.1.8.1 for further details.

Pembrolizumab: Pembrolizumab will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Lenvatinib

Lenvatinib 20 mg (two 10-mg capsules) once daily will be taken orally with water (with or without food) at approximately the same time each day in 21-day cycles. Participants should not take lenvatinib on C1D1, C1D15, or C2D1 before their appointment; on C1D15 and C2D1, participants should be instructed to bring their lenvatinib to the clinic. On C1D1 and C2D1, lenvatinib will be administered in the clinic 0-4 hours after completion of pembrolizumab administration.

If a lenvatinib dose is missed and cannot be taken within 12 hours, then that dose should be skipped, and the next dose should be taken at the usual time of administration.

8.1.8.1.2 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. 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 to +10 minutes is permitted (ie, infusion time is 30 minutes: –5 min/+10 min).

After Cycle 1 Day 1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

8.1.8.2 Compliance

Lenvatinib: Lenvatinib compliance will be calculated by the Sponsor based on the study drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

Pembrolizumab: Administration of pembrolizumab will be administered by the investigator and/or qualified designee. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.1.12 Demography

Participant demography information will be collected at the Screening visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

8.1.13 Subsequent Antineoplastic Treatment

The investigator or qualified designee will review all new antineoplastic treatment initiated after the last dose of study intervention. Once new antineoplastic treatment has been initiated, the participant will move into Survival Follow-up. All antineoplastic treatment will be recorded until time of death or termination of Survival Follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the CIV can be found in the SIM. In general, imaging should include the chest, abdomen, and pelvis. Tumor imaging of the chest is to be acquired by CT scan. For the abdomen and pelvis, contrast-MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is

the strongly preferred modality for imaging the brain. Imaging of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted to the CIV. The same imaging technique regarding modality 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. Participant eligibility will be determined using prospective BICR assessment of measurable disease based on RECIST 1.1. All scheduled images for all study participants from the sites will be submitted to the CIV. 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 that demonstrate radiologic progression, should also be submitted to the CIV.

8.2.1.1 Initial Tumor Imaging

The site's study team must have reviewed images from at least 3 dates to confirm that radiographic progression has occurred per RECIST 1.1 and confirmed per iRECIST no less than 4 weeks from the date of the first documented PD in the absence of rapid clinical progression. These images should include:

1. Baseline image for prior anti-PD-1/L1 or an image showing nadir during prior anti-PD-1/L1 agent treatment

2. An image showing progression on prior anti-PD-1/L1 treatment

3. An image confirming progression on prior anti-PD-1/L1 agent treatment, no less than 4 weeks from the date of the first documented PD (Note: in rapidly progressing participants, confirmation of PD by a second scan may be waived after consultation with the Sponsor).

These images may have been collected prescreening, and the final image confirming progression may also be the baseline tumor image on trial, if collected during the 28-day screening window. The CIV must have received these scans prior to treatment allocation in this study for a retrospective analysis of the eligibility criterion of progression on prior PD-1/L1 agent. The CIV must also confirm that the images are of diagnostic quality prior to treatment allocation.

The baseline tumor image collected during the screening period must be also submitted to the CIV for confirmation of measurable disease per RECIST 1.1 for eligibility prior to treatment allocation.

Tumor imaging performed as part of routine clinical management is acceptable for use as baseline tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of treatment allocation, and can be assessed by the CIV.

A brain MRI at screening will be performed in all participants. When brain imaging is performed, MRI should be used if possible. If MRI is medically contraindicated, then CT with contrast is an acceptable alternative.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of treatment allocation. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. Following Week 54, imaging should be performed Q12W, or sooner if clinically indicated until Week 102. Following Week 102, imaging should be performed every Q24W, or sooner if clinically indicated. Imaging timing should follow calendar days from treatment allocation and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression per RECIST 1.1 is identified by the investigator (unless the investigator is able continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first.

Following initial brain imaging, subsequent brain imaging will be performed on all participants with brain disease present at screening, or as clinically indicated. This imaging will be performed every Q9W (±7 days) after treatment allocation, or sooner if clinically indicated, until Week 54. Following Week 54, imaging should be performed Q12W, or sooner if clinically indicated, until Week 102. Following Week 102, imaging should be performed every Q24W, or sooner if clinically indicated.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at the next scheduled scan or at least 4 weeks after the first indication of a response is observed. If participants confirmed PR or CR outside their regular scheduled imaging, they 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 if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 8.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease in clinically stable participants. Participants who have unconfirmed disease progression may continue on study intervention at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study intervention. Treatment beyond disease progression per iRECIST may be permitted upon Sponsor consultation and approval.

8.2.1.3 End-of-treatment and Follow-up Imaging

For participants who discontinue study intervention, 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 intervention due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST. All images should be submitted to the CIV.

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

8.2.1.4 RECIST 1.1

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

8.2.1.5 RECIST 1.1 for Immune-based Therapeutics (iRECIST)

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 study intervention despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs (including worsening of laboratory values) indicating progression of disease
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention
- 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 intervention 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 intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the CIV for retrospective BICR.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with Sponsor and after the following criteria have been met:
(1) absence of symptoms and signs (including worsening of laboratory values) indicating disease progression, and (2) absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the CIV. 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 7.

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

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention 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 intervention 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 intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

Abbreviations: BICR = blinded independent central review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = 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; VOP = verification of progression.

8.3 Safety Assessments

Progression of melanoma and signs and symptoms clearly related to the progression of melanoma should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

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

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

8.3.1 Physical Examinations

A complete physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Physical examinations (comprehensive or symptom-directed) will be performed as specified in the SoA (Section 1.3). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.

Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to participant treatment allocation will be recorded on the appropriate CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the appropriate CRF. Weight will also be measured and recorded. Height will only be measured and recorded at screening.

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at Screening, before the administration of each dose of study intervention and during the Follow-up Period, as specified in the SoA (Section 1.3). Vital signs include temperature, heart rate, respiratory rate, weight, and blood pressure. Height will be measured at Screening only.

- Blood pressure and heart rate will 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.

- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <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 diary will be provided as a tool to aid the participant in collecting BP evaluations between study visits.

8.3.3 Electrocardiograms

- Electrocardiograms will be obtained as designated in the SoA (Section 1.3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

- An ECG abnormality may meet the criteria of an AE as described in this protocol (see Appendix 3) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate CRF.

- QTc prolongation has been seen in some lenvatinib studies. Monitor ECGs every cycle (as specified in the Schedule of Assessments) in patients 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.

8.3.4 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 1.3). 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.

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

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Hematology and Clinical Chemistry

Hematology and clinical chemistry assessments will be performed within 3 days prior to administration of first dose of study intervention and prior to all subsequent scheduled visits. The results must be reviewed prior to administration of study therapy. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment.

8.3.5.2 Urine Dipstick

Urine dipstick testing will be performed locally within 3 days prior to start of treatment. At baseline, participants with >1+ proteinuria on urine dipstick during screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24-hour will not be eligible.

Once participants are allocated to treatment, 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. Urine dipstick testing should be performed at the investigational site. If a new event of proteinuria ≥2+ occurs, the participant must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles.

For participants with proteinuria ≥2+, see Section 6.6.2.2 for management of proteinuria.

8.3.5.3 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 intervention.

8.3.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status at Screening and before the administration of each cycle of study intervention and as specified in the SoA (Section 1.3).

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before 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 study or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 120 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, 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 intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside the time period specified above must be reported immediately to the Sponsor if the event is considered drug-related.

Investigators are not obligated to actively seek 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 intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 8.

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

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

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (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 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for:

- Pembrolizumab: ≥5 times the protocol-specified dose
- Lenvatinib: any dose above the protocol-prescribed dose if associated with an AE

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, RCC, and HCC.

No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib.

All reports of pembrolizumab 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 overdose without any associated clinical symptoms or abnormal laboratory results should be reported using the terminology “accidental or intentional overdose without adverse effect.”

8.6 Pharmacokinetics

Blood samples will be collected as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, blood samples for PK and ADA will be collected and may be stored only at this time. Further analysis may be performed if required and reported separately if conducted.

Blood samples will be collected from all participants. Plasma concentrations of lenvatinib when co-administered with pembrolizumab will be measured. Lenvatinib will be analyzed using a population PK approach.

Lenvatinib will be quantified by use of validated High-Performance Liquid Chromatography -tandem mass spectroscopy method.

8.6.1 Blood Collection for Serum Pembrolizumab

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

To evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this combination with lenvatinib, sample collections for analysis of ADA and PK are currently planned as shown in the SoA (Section 1.3). Blood samples will be obtained to measure PK and ADA of serum pembrolizumab. These samples collected may be stored at this time. Analysis may be performed if required. If ongoing ADA and/or PK results 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. If PK and/or ADA analyses are performed, the results of these analyses will be reported separately.

8.6.2 Blood Collection for Plasma Lenvatinib

Blood samples will be collected as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

Plasma concentrations of lenvatinib and serum concentrations of pembrolizumab will be measured. Lenvatinib will be analyzed using a population PK approach. Lenvatinib will be quantified by use of validated High-Performance Liquid Chromatography-tandem mass spectroscopy methods. If at some point prospective PK blood sample collection is no longer required, it will be notified to the sites.

8.7 Pharmacodynamics

No pharmacodynamic endpoints are planned for this study.

8.8 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection or if the IRB/IEC does not approve the collection of the sample for these purposes.

8.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for serum biomarkers
- Blood for genetic analysis
- Blood for RNA analysis
- Blood for circulating tumor nucleic acid analysis
- Blood for plasma biomarkers
- Tumor blocks or slides

  Note: Participants with a newly obtained biopsy considered not adequate may undergo re-biopsy at the discretion of the investigator. Please refer to the laboratory manual for additional details.

- Stool analysis (optional)

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the operations/laboratory manual.

8.10 Visit Requirements

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

8.10.1 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 5. Screening procedures may be repeated after consultation with the Sponsor.

Documented 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 intervention except for the following:

- Laboratory tests are to be performed within 3 days prior to the first dose of study intervention. An exception is hepatitis and HIV testing, which may be done up to 28 days prior to the first dose of study intervention. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor.

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

- Full physical examination to be performed within 7 days prior to start of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

- Newly or recently obtained tumor tissue must have been obtained prior to treatment allocation and after the latest systemic treatment for melanoma.

- If additional time is needed for initial image submission and CIV diagnostic quality review, an extension of the screening window of up to 7 days may be approved following mandatory Sponsor consultation.

8.10.1.1 Rescreening

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

8.10.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Assessments/procedures are to be performed prior to the administration of study intervention.

8.10.2.1 Phone Contact Visit

Telephone contact or visit on Cycle 1 Day 8 will be conducted to assess participants for development of early toxicity as outlined in the SoA (Section 1.3).

8.10.3 Posttreatment Visit

8.10.3.1 Safety Follow-up

Mandatory Safety Follow-up visits should be conducted approximately 30 days and 90 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first. If the EOT visit occurs approximately 30 days from last dose of study intervention, the 30-day Safety Follow-up visit is not required. In this situation, all procedures required at both the EOT visit and the 30-day Safety Follow-up visit should be performed at the EOT visit. End of treatment is defined as the date when the participant discontinues all study interventions.

If the 90-day Safety Follow-up visit falls within the same window as the imaging follow-up visit, these visits may be combined. All procedures required at the Safety Follow-up visit at 90 days will be performed at the imaging follow-up visit.

Participants who attain an investigator-determined confirmed complete response (CR) and stop study intervention with pembrolizumab + lenvatinib will have Safety Follow-up visits and move to follow-up per SoA (Section 1.3).

All AEs that occur prior to the Safety Follow-up visits should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 120 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

8.10.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the

Efficacy Follow-up Phase and should be assessed approximately Q12W (or more frequently as needed) by clinic visit to monitor disease status; if a clinic visit is not feasible, the participant may be contacted by telephone or email. After Week 102, imaging should be performed Q24W. The Sponsor may request survival status to be assessed at additional time points during the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study or if the participant begins retreatment with pembrolizumab as detailed in Section 6.6.4. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who complete all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Participants who attain an investigator-determined confirmed CR and stop study intervention with pembrolizumab and lenvatinib will have Safety Follow-up visits and move to follow-up per SoA.

8.10.3.3 Survival Follow-up

Participant survival follow-up status will be assessed approximately Q12W to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first Survival Follow-up assessment should be scheduled as described below:

- For participants who discontinue study intervention and who will not enter the Efficacy Follow-up Phase, the first Survival Follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

- For participants who complete assessments in the Efficacy Follow-up Phase, the first Survival Follow-up contact will be scheduled 12 weeks after the last assessment in the Efficacy Follow-up Visit has been performed.

8.10.4 Survival Status

To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested during the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external DMC 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 survival status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made

after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report for the study. A separate PK analysis plan as well as biomarker analysis plan may be provided. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report.

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

9.1 Statistical Analysis Plan Summary

Study Design Overview	A Multicenter, Open-label, Phase 2 Trial to Assess the Efficacy and Safety of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced Melanoma Previously Exposed to an Anti-PD-1/L1 Agent (LEAP-004)
Treatment Assignment	Approximately 100 participants will be enrolled to treatment with the combination of pembrolizumab and lenvatinib. This is an open-label study.
Analysis Populations	Efficacy and Safety: All Participants as Treated set (APaT)
Primary Endpoint(s)	OR as assessed by BICR per RECIST 1.1
Key Secondary Endpoint(s)	1. PFS as assessed by BICR per RECIST 1.1 2. OS 3. DOR as assessed by BICR per RECIST 1.1
Statistical Methods for Key Efficacy Analyses	Estimation of ORR; Estimation of PFS, OS, and DOR using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	Counts and percentages of participants with AEs will be provided.
Interim Analyses	No efficacy interim analyses are planned. The external data monitoring committee (eDMC) will conduct regular safety monitoring.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	A sample size of approximately 100 is planned. Section 9.9 provides the precision of the ORR estimates.
Abbreviations: BICR = blinded independent central review; DOR = duration of response; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1	

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. This study is being conducted as a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

There is no statistical hypothesis to be tested in this study. Objectives and endpoints of the study are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

- **Objective Response Rate (ORR) per RECIST 1.1 assessed by BICR**

Objective Response is defined as a best overall response of CR or PR. The details of the ORR analysis plan can be found in Section 9.6.1.1.

9.4.1.2 Secondary

- **Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR**

PFS is defined as the time from the first day of study intervention to the first documented disease progression or death due to any cause, whichever occurs first. See Section 9.6.1.2 for definition of censoring.

- **Overall Survival (OS)**

OS is defined as the time from the first day of study intervention to death due to any cause. Participants without documented death at the time of the final analysis will be censored at the date of the last follow-up.

- **Duration of Response (DOR) per RECIST 1.1 assessed by BICR**

For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. See Section 9.6.1.4 for definition of censoring.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The APaT population will serve as the primary population for the analysis of efficacy data in this study. The APaT population consists of all allocated participants who receive at least one dose of study intervention.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population as well. At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Population Pharmacokinetic Analysis Set

The Population Pharmacokinetic Analysis Set includes all the participants who have received at least 1 dose of study intervention with documented dosing history in the lenvatinib + pembrolizumab arm and have measurable plasma levels of lenvatinib or serum levels of pembrolizumab.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

9.6.1.1 Objective Response Rate (ORR)

ORR will be calculated as the ratio of the number of participants reported to have achieved a confirmed CR or PR verified by BICR, divided by the number of participants included in APaT population. Participants in the APaT analysis population without ORR assessments will be counted as nonresponders.

A 95% exact binomial CI (based on method Clopper and Pearson,1934) will be calculated for the true ORR.

9.6.1.2 Progression-free Survival (PFS)

The nonparametric Kaplan-Meier method will be used to estimate the PFS distribution. 95% CIs for the median PFS and PFS point estimates at various follow-up times from first day of study intervention will be calculated.

Since disease progression is assessed periodically, progressive disease can occur any time in the time interval between the last assessment where progressive disease was not documented and the assessment when progressive disease is documented. The true date of progressive disease will be approximated by the date of the first assessment at which progressive disease is objectively documented based on RECIST 1.1 by BICR. Death is always considered as a PFS event. Participants who do not experience a PFS event will be censored at the last disease assessment.

For the analysis of PFS, if the events (progressive disease or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The censoring rule is summarized in Table 9. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 9 Censoring Rules for Analysis of Progression-free Survival

Situation	Date of Progression or Censoring
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
Abbreviations: PD = progressive disease; PFS = progression-free survival	

9.6.1.3 Overall Survival (OS)

The nonparametric Kaplan-Meier method will be used to estimate the OS distribution. 95% CIs for the median OS and OS point estimates at various follow-up times from first day of study intervention will be calculated.

9.6.1.4 Duration of Response (DOR)

DOR will be summarized descriptively using the nonparametric Kaplan-Meier method. Only the subset of participants who show a CR or PR will be included in this analysis. Censoring rules for DOR are summarized in Table 10.

Table 10 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (nonevent)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (nonevent)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (nonevent)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	Progressive disease or death	End of response (Event)

Abbreviations: DOR = duration of response

Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.5 Analysis Strategy for Key Efficacy Endpoint

Table 11 summarizes the primary analysis approach for key efficacy endpoints.

Table 11 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Endpoints			
ORR per RECIST 1.1 by BICR	Exact method based on binomial distribution (Clopper-Pearson method)	APaT	Participants without assessments are considered nonresponders.
Key Secondary Endpoint			
PFS per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	APaT	Primary censoring rule. (More details are provided in Table 9.)
OS	Summary statistics using Kaplan-Meier method	APaT	Censored at the last known alive date.
DOR per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	APaT	Nonresponders are excluded from analysis. Responders are censored according to the censoring rules listed in Table 10.

Abbreviations: APaT=All Participants as Treated; BICR = blinded independent central review; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

a Statistical models are described in further detail in the text.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences and laboratory parameters.

The broad AE categories consisting of the percentage of participants with any AE, any drug-related AE, any Grade 3 to 5 AE, any serious AE, any AE that is both drug-related and Grade 3 to 5, any AE that is both drug-related and serious, any discontinuation due to an AE, and death will be summarized via point estimates with 95% CIs (Table 12).

Table 12 Analysis Strategy for Safety Parameters

Safety Endpoint	Within Group 95% CI	Descriptive Statistics
Any AE	X	X
Any Serious AE	X	X
Any Grade 3-5 AE	X	X
Any Drug-related AE	X	X
Any Serious and Drug-related AE	X	X
Any Grade 3-5 and Drug-related AE	X	X
Discontinuation due to AE	X	X
Death	X	X
Specific AEs, SOCs, or PDLCs		X
Change from Baseline Results (Labs, Vital Signs)		X

Abbreviations: AE = adverse event; CI = confidence interval; PDLC = predefined Limit of Change; SOC = System Organ Class.

Note: 95% CIs will be calculated using the Clopper-Pearson method.
X = results will be provided

For continuous measures such as changes from baseline in laboratory parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format.

9.6.3 Demographics and Baseline Characteristics

The number and percentage of participants screened, allocated, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for all enrolled participants.

9.7 Interim Analyses

No interim efficacy analyses are planned for this study. The external data monitoring committee (eDMC) will conduct regular safety monitoring as specified in the DMC charter. However, unblinded efficacy endpoints will be made available to the DMC upon request to enable a benefit-risk assessment.

9.8 Multiplicity

No multiplicity adjustment is planned for this study.

9.9 Sample Size and Power Calculations

In this study, approximately 100 participants will be enrolled. Table 13 shows the 2-sided 95% CI of ORR with 100 participants for different observed response rates based on the method of Clopper and Pearson (1934).

Table 13 Two-sided 95% Confidence Interval of ORR with 100 Participants

Number of Observed Responders	ORR Estimates	95% CI of ORR
20	20%	(12.7%, 29.2%)
25	25%	(16.9%, 34.7%)
30	30%	(21.2%, 40.0%)
35	35%	(25.7%, 45.2%)
40	40%	(30.3%, 50.3%)
45	45%	(35.3%, 55.3%)
50	50%	(39.8%, 60.2%)
55	55%	(44.7%, 65.0%)

Abbreviations: CI = confidence interval; ORR = objective response rate.

9.10 Subgroup Analyses

To determine whether the response rate is consistent across various subgroups, the estimate of the response rate (with a nominal 95% CI) for the primary endpoint will be estimated within each category of the following classification variables:

- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)

- Race (white vs. nonwhite)
- Disease stage (III vs. IVM1a vs. IVM1b vs IVM1c)
- Brain metastasis (yes vs. no)
- ECOG status (0 vs. 1)
- PD-L1 status (positive vs. negative [includes indeterminate])
- Geographic region of enrolling site (US vs. ex-US)
- Prior adjuvant exposure to checkpoint inhibitor (yes vs. no)
- BRAF wild type vs. BRAF mutant (no prior treatment) vs. BRAF mutant, prior adjuvant BRAFi/MEKi treatment, no BRAFi/MEKi treatment for metastatic disease vs. BRAF mutant, prior BRAFi/MEKi treatment for metastatic disease, no adjuvant BRAFi/MEKi treatment vs. BRAF mutant, prior adjuvant BRAFi/MEKi treatment and BRAFi/MEKi treatment for metastatic disease.
- Lactate dehydrogenase (≤ULN vs. >ULN but <2 × ULN vs. ≥2 × ULN)
- Participant progressed on prior treatment with CTLA-4+PD-1 combination therapy (nivolumab and ipilimumab) (yes vs. no)

A Forest plot will be produced, which provides the estimated point estimates and CIs for the treatment effect across the categories of subgroups listed above.

Any specified subgroups that have less than 10 participants will be excluded from analysis.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure for lenvatinib will be summarized as duration of treatment in days. The extent of exposure for pembrolizumab will be summarized as duration of treatment in cycles. Summary statistics will be provided on Extent of Exposure for APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for 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), 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 pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

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

III. Participant Protection

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. 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.

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) will receive and decide upon any recommendations made by the DMC regarding the study. Additional details regarding the EOC can be found in the DMC charter.

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov,

www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: 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 study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

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

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

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

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

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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.

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the local laboratory.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively, 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 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[c] MCH[c] %Reticulocytes[c]	WBC count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)[b]	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[c]	Chloride[c]	Phosphorous[c]
	Creatinine[d]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein[c]
	Glucose	Calcium	Alkaline phosphatase	Magnesium
	Thyroid-stimulating hormone	Free thyroxine[e]	Lactate dehydrogenase[c]	Amylase
	Lipase[j]	Cholesterol[c]	Triglycerides[c]	CPK[f]
	Pregnancy test	Triiodothyronine (Total T3)[e]		
Routine Urinalysis[g]	Specific gravity pH, glucose, protein[h], hemoglobin or blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	PT/INR and aPTT/PTT[i] Serology (HIV RNA, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody). Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP).			

a Absolute or % acceptable per institutional standard.
b Urea is acceptable if BUN is not available as per institutional standard.
c Performed only if considered local standard of care.
d GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
e Free T4, Total T3, and TSH levels will be performed during screening and then repeated on Day 1 of Cycle 2 and then every other cycle (starting Cycle 2), at the time of discontinuation (end of treatment), and at the Safety Follow-up visits. Free T3 is acceptable where Total T3 cannot be determined. There may be instances when sites are unable to obtain thyroid function testing results prior to the scheduled dosing. After C1, review of thyroid function test results after dosing is acceptable.
f CPK isoenzymes (CK-MB) should be evaluated if CPK is greater than 3 × ULN.
g If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
h 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
i Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulation therapy.
j If amylase is not per institutional standards then lipase is sufficient.

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

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, 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 intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

d. **Results in persistent or significant disability/incapacity**

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

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

10.3.4 Recording AE and SAE

AE and SAE recording

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

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- 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.

Assessment of causality

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of 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 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

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

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

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception that has a low user dependency as described in Table 15 during the protocol-defined time frame in Section 5.1.

Table 15 Highly Effective Contraception Methods

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

10.5.3 Pregnancy Testing

Pregnancy testing is required for only WOCBP.

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test assessed within 24 hours of treatment initiation.

Following initiation of treatment pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the SoA, and as required locally.

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Canada

Please refer to the current lenvatinib product monograph for management of AEs associated with lenvatinib administration.

- Section 6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formulation

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

10.8 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 intervention until repeat imaging is obtained (using iRECIST for participant management [see Table 7]). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs (including worsening of laboratory values) indicating progression of disease
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention
- 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 intervention 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 intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for retrospective BICR.

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 nontarget 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 nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, 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 – Nontarget.

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 iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared with any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared with 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 nontarget 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 intervention may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit [*For those studies in which PFS is the primary endpoint, add the following:* or if RECIST 1.1 PD has not been verified centrally], an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention 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 trial, either before or after an instance of pseudo-progression.
- Nontarget lesions
    - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
    - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget 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 nontarget 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 publications [Seymour, L., et al 2017].

10.9 Appendix 9: ECOG Performance Status

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

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICR	blinded independent central review
BP	blood pressure
BRAF	proto-oncogene B-raf
C	cycle
CD	cluster of differentiation
CI	confidence interval
CIV	central imaging vendor
CNS	central nervous system
CR	complete response
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptors
FU	follow-up

Abbreviation	Expanded Term
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
HUVECs	human umbilical vein endothelial cell
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors
IUD	intrauterine device
IV	intravenous
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MEKi	mitogen-activated protein kinase inhibitor
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not estimable
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBPK	physiologically based PK
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PDGF	platelet-derived growth factor
PE	physical examination
PET	positron emission tomography

Abbreviation	Expanded Term
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12	every 12 weeks
QD	once daily
OS	overall survival
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	respiratory rate
RTK	receptor tyrosine kinase
SAE	serious adverse event
SIM	Site Imaging Manual
SoA	schedule of activities
SOC	standard of care
TBL	total bilirubin lab
Tregs	regulatory T cells
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WOCBP	woman/women of childbearing potential

11 REFERENCES

[American Cancer Society 2016]	American Cancer Society. Cancer facts and figures 2016 [Internet]. Atlanta (GA): American Cancer Society, Inc.; 2016. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf.	[04H5YL]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Cross, M. J. 2001]	Cross MJ, Claesson-Welsh L. FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. Trends Pharmacol Sci. 2001 Apr;22(4):201-7.	[04XKP6]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Ellis, L. M. 2008]	Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008 Aug;8:579-91.	[04XKPD]
[Ferrara, N., et al 2003]	Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003 Jun;9(6):669-76.	[04XKQ2]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Hodi, F. S., et al 2010]	Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711-23.	[058SQR]

[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Kato, Y., et al 2015]	Kato Y, Tabata K, Hori Y, Tachino S, Okamoto K, Matsui J, et al. Effects of lenvatinib on tumor-associated macrophages enhance antitumor activity of PD-1 signal inhibitors [abstract A92]. Poster session presented at: AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2015 Nov 5-6; Boston, MA.	[04T3PH]
[Kato, Y., et al 2019]	Kato Y, Tabata K, Kimura T, Yachie-Kinoshita A, Ozawa Y, Yamada K, et al. Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8(+) T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. PLoS One. 2019 Feb 27;14(2):e0212513.	[057JXY]
[Kimura, T., et al 2018]	Kimura T, Kato Y, Ozawa Y, Kodama K, Ito J, Ichikawa K, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. Cancer Sci. 2018;109:3993-4002.	[057LPH]
[Larkin, J., et al 2014]	Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014 Nov 13;371(20):1867-76.	[04B8P2]
[Lieu, C., et al 2011]	Lieu C, Heymach J, Overman M, Tran H, Kopetz S. Beyond VEGF: inhibition of the fibroblast growth factor pathway and antiangiogenesis. Clin Cancer Res. 2011 Oct 1;17(19):6130-9.	[04XKQM]

[Limaverde-Sousa, G., et al 2014]	Limaverde-Sousa G, Sternberg C, Ferreira CG. Antiangiogenesis beyond VEGF inhibition: a journey from antiangiogenic single-target to broad-spectrum agents. Cancer Treat Rev. 2014;40:548-57.	[04XKQW]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Pennock, G. K. 2015]	Pennock GK, Chow LQM. The evolving role of immune checkpoint inhibitors in cancer treatment. Oncologist. 2015;20:812-22.	[04XQM6]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Robert, C., et al 2011]	Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-26.	[04V60R]
[Robert, C., et al 2014]	Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2014 Nov 16. [Epub ahead of print].	[0428NK]
[Robert, C., et al 2014]	Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2014 Nov 16. [Epub ahead of print]	[0429F6]

[Robert, C., et al 2015]	Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015 Jan 1;372(1):30-9.	[04XT73]
[Robert, C., et al 2015]	Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521-32.	[04G7B7]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Siegel, R., et al 2012]	Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012 Jan-Feb;62(1):10-29.	[03ZND3]
[Tammela, T. 2010]	Tammela T, Alitalo K. Lymphangiogenesis: molecular mechanisms and future promise. Cell. 2010 Feb 19;140:460-76.	[04XKRB]
[U.S. Prescribing Information 2015]	U.S. Prescribing Information: ZELBORAF (vemurafenib) tablet for oral use: 2015.	[049YCH]
[Ugurel, S., et al 2017]	Ugurel S, Loquai C, Terheyden P, Schadendorf D, Richtig E, Utikal J, et al. Chemosensitivity-directed therapy compared to dacarbazine in chemo-naive advanced metastatic melanoma: a multicenter randomized phase-3 DeCOG trial. Oncotarget. 2017 Jun 27;8(44):76029-43.	[04XT75]

[UpToDate, Inc. 2015]	Sosman JA. Overview of the management of advanced cutaneous melanoma [Internet]. Waltham (MA): UpToDate, Inc.; c2015 [last updated 2015 Nov 17]. Available from: http://www.uptodate.com/contents/overview-of-the-management-of-advanced-cutaneous-melanoma.	[04B664]
[WHO Health Organization 2012]	WHO Health Organization. GLOBOCAN 2012: Country Fast Stat: European Union (Fact sheet No. EU-28). 2012.	[03TVSV]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Yamamoto, Y., et al 2014]	Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014;6:18.	[04XQ0S]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]
[Zimmer, L., et al 2017]	Zimmer L, Apuri S, Eroglu Z, Kottschade LA, Forschner A, Gutzmer R, et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer. 2017;75:47-55.	[04XT76]