Official Protocol Title:	A Phase 3 Randomized, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) and Lenvatinib (E7080/MK-7902) Versus Pembrolizumab Alone as First-line Intervention in Participants with Advanced Melanoma (LEAP-003)
NCT Number:	NCT03820986
Document Date:	16-Feb-2024

TITLE PAGE

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Protocol Title: A Phase 3 Randomized, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) and Lenvatinib (E7080/MK-7902) Versus Pembrolizumab Alone as First-line Intervention in Participants with Advanced Melanoma (LEAP-003)

Protocol Number: 003-09 (E7080-G000-312)

Compound Number: MK-7902

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

This study is co-funded by MSD and Eisai.

Legal Registered Address:

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P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	03820986
EU CT	Not applicable
EudraCT	2018-002520-16
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	140155

Approval Date: 16 February 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 9	16-FEB-2024	The changes in this amendment are related to study extension. The changes allow additional data collection and longer follow-up for all participants enrolled in China.
Amendment 8	26-OCT-2023	This change was made to address incorrect standard text that was inadvertently changed in Amendment 07. The language was reverted to text provided in Amendment 06 to maintain consistency within the study.
Amendment 7	26-JUN-2023	Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to lack of efficacy.
Amendment 6	08-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 5 – UK specific	21-OCT-2021	To address feedback from UK regulatory authority.
Amendment 4	18-AUG-2021	Due to slower than expected Overall Survival event rate, a third IA for Overall Survival was added. IA strategies were adjusted to achieve optimal timing for IAs.
Amendment 3	10-MAY-2021	To update the Dose Modification and Toxicity Management Guidelines for irAEs and table for alignment with the USPI as requested by the FDA.
Amendment 2	26-MAR-2020	To clarify AE safety follow-up timelines, to clarify allowed concomitant medications, and to add MK-7902 program level updates.
Amendment 1	10-JAN-2019	To address feedback from regulatory authority and add MK-7902 program level updates.
Original Protocol	26-SEP-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendment:

The changes in this amendment are related to study extension. The changes allow additional data collection and longer follow-up for all participants enrolled in China.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.7.1. Country-specific Requirements, China	Updated to reflect additional data collection and longer follow-up for all participants enrolled in China.	The changes in this amendment are related to study extension. The changes allow additional data collection and longer follow-up for all participants enrolled in China.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 1.1, Synopsis	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 1.2, Schema	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 1.3, Schedule of Activities	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 3, Hypotheses, Objectives, and Endpoints	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 4.1, Overall Design	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 4.3.3, Maximum Dose Exposure for This Study	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 6.1, Study Intervention(s) Administered	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 6.6, Dose Modification	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added a cross-reference to Appendix 7 for country-specific requirements.	Refer to the rationale for Section 10.7.1.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes (including cross-reference corrections) were made throughout the documents.	To ensure clarity and accurate interpretation of the intent of the protocol

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) and Lenvatinib (E7080/MK-7902) Versus Pembrolizumab Alone as First-line Intervention in Participants with Advanced Melanoma (LEAP-003)

Short Title: Pembrolizumab plus Lenvatinib as First-line Intervention for Advanced Melanoma

Acronym: Protocol 003 (E7080-G000-312)

Hypotheses, Objectives, and Endpoints:

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (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 unresectable advanced melanoma following administration of pembrolizumab in combination with lenvatinib versus pembrolizumab in combination with placebo:

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-003 (data cutoff 18-JAN-2023), eDMC recommended stopping the study due to lack of efficacy because pembrolizumab in combination with lenvatinib did not demonstrate an improvement in OS, one of the trial's dual primary endpoints, compared to pembrolizumab plus placebo and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded as of 27-MAR-2023. The prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter sent to investigators on 3-APR-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit). All participants should stop ongoing treatment with lenvatinib/placebo. Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have completed 35 cycles of pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after unblinding and completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of

Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time. All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study; however, standard safety reporting should continue, as applicable. As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants who are still on study medication should continue tumor imaging assessment per protocol. For participants no longer on study medication, local tumor imaging assessments should continue per SOC schedule. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up is the last required visit. Updated analyses are described in Section 9.

See Appendix 7 for country-specific requirements.

Primary Objective	**Primary Endpoint**
Objective: To compare progression-free survival (PFS) as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Hypothesis (H1): The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo assessed by PFS per RECIST 1.1 by BICR.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective: To compare the combination of pembrolizumab and lenvatinib to pembrolizumab and placebo with respect to overall survival (OS). Hypothesis (H2): The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo assessed by OS.	OS: Defined as the time from date of randomization to date of death from any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare objective response rate (ORR) per RECIST 1.1 by BICR. Hypothesis (H3): The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo as assessed by ORR per RECIST 1.1 by BICR.	Objective response, defined as best overall response of either complete response or partial response.

Objective: To assess duration of response (DOR) per RECIST 1.1 by BICR.	DOR, determined by disease assessment defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first.
Objective: To assess safety and tolerability.	Adverse events (AEs) Discontinuations due to AEs.
Objective: To compare the mean change from baseline in PRO scores in global health status/quality of life (QoL) and physical functioning.	European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30]: - Global health status/QoL scale (items 29 and 30) - Physical functioning scale (items 1 to 5).
Objective: To compare the time to true deterioration (TTD) in global health status/QoL and physical functioning.	TTD is the time from baseline to first onset of 10 points or more decrease from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline for EORTC QLQ-C30: - Global health status/QoL scale (items 29 and 30) - Physical functioning scale (items 1 to 5)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Melanoma
Population	Participants with no prior systemic therapy for their advanced melanoma (prior adjuvant therapy is permitted)
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Investigator Participant Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 69 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. Extension portion of the study in China: The Sponsor estimates that the trial will require approximately 2 additional years from the time the first participant provides documented informed consent until the last participant's last visit.

Number of Participants:

Approximately 660 participants will be randomized as described in Section 9.1.

Extension portion of the study in China: China will enroll participants in the global study. Once the sample size for the global study has been achieved (n=~660); the study will continue to enroll participants from China in the extension portion of the study until the overall sample size for China reaches ~130 (up to 137) participants in the global study and the extension portion of the study combined.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Q3W	Test Product
Arm A	Lenvatinib	10 mg, 4 mg	20 mg	Oral	QD	Test Product
Arm B	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Q3W	Comparator
Arm B	Placebo	0 mg	0 mg	Oral	QD	Placebo

Abbreviations: EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/ auxiliary medicinal product; Q3W=every 3 weeks; QD=once daily.

Total Number of Intervention Groups/Arms	2 arms
Duration of Participation	After a Screening phase of up to 28 days, each participant will be randomized to receive intervention with pembrolizumab + lenvatinib or pembrolizumab + placebo until disease progression is radiographically documented and verified by BICR per RECIST 1.1, unacceptable adverse event(s) (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. Pembrolizumab treatment will be discontinued once the participant has received 35 administrations (approximately 2 years). Participants may continue treatment with lenvatinib or placebo beyond approximately 2 years if they experience clinical benefit until unacceptable toxicity or disease progression upon Sponsor consultation and approval. All participants who continue on lenvatinib or placebo monotherapy will be monitored per the SoA. Participants who attain an investigator-determined confirmed complete response (CR) may consider stopping study intervention with pembrolizumab + lenvatinib or pembrolizumab + placebo, after at least 24 weeks of study intervention has been administered. In addition, if a confirmed CR per RECIST 1.1 is attained, at least 2 additional doses of pembrolizumab must be received after CR is first documented. Note: Participants receiving lenvatinib who experience disease progression per RECIST 1.1 must be discontinued from lenvatinib. If they are

	concurrently receiving pembrolizumab, they may continue receiving pembrolizumab per iRECIST as outlined in the protocol. 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, and the participant is tolerating study intervention as per iRECIST. Treatment beyond disease progression per iRECIST may be permitted upon Sponsor consultation and approval and per criteria in Section 8.2.1.5. 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 and verified by BICR, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up. Participants who discontinue due to radiographic disease progression will move to posttreatment Survival Follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of the study. The study will be considered positive if either one of the primary endpoints (PFS or OS) meets the criteria for statistical significance per Section 9. Extension portion of the study: After the enrollment of the global study is completed, participants from China will continue to be enrolled in an extension portion of the study designed to meet local regulatory requirements. Additional details are in Section 4.1 and Section 9.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

As of Amendment 07, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.

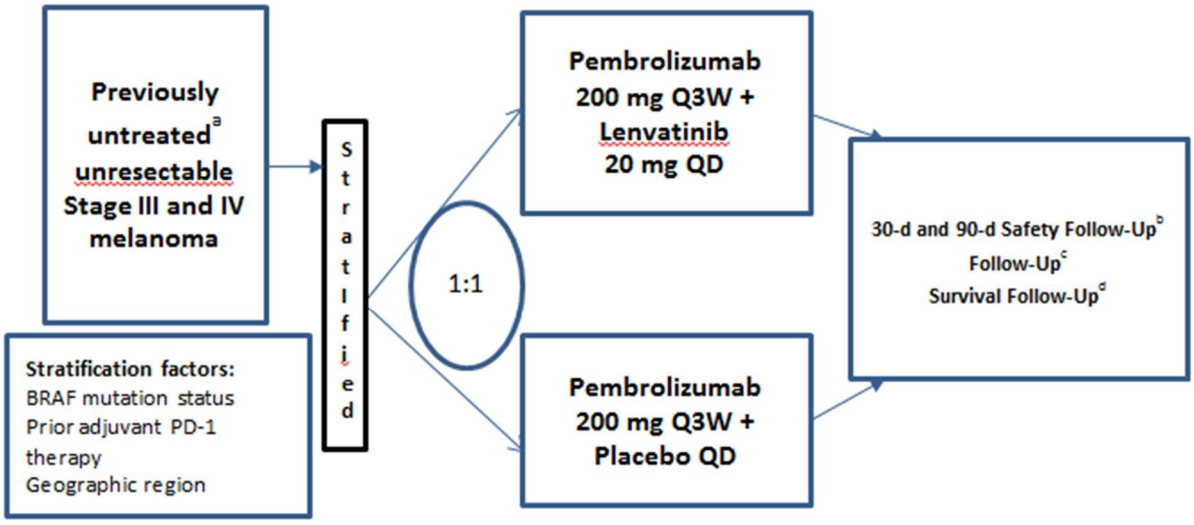
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The original study design is depicted in Figure 1. See Appendix 7 for country-specific requirements.

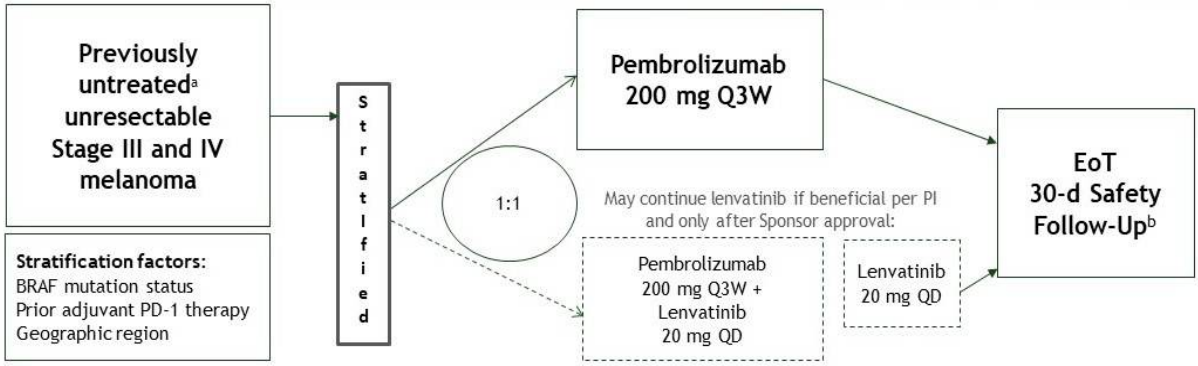
Figure 1 Original Study Design



a. Prior adjuvant BRAF/MEK, PD-1 and CTLA-4 inhibitors may be allowed.
b. If End of Treatment visit occurs ~30 days from last dose of study treatment, a safety follow-up visit at 30 days is not required.
c. For participants discontinuing for reasons other than BICR-verified PD, tumor imaging should be performed Q12W, or more frequently if clinically indicated, until BICR-verified PD. If the 90 day-safety FU visit falls within the same window as the imaging FU visit, these visits may be combined.
d. Participants in Survival Follow-up will be contacted approximately Q12W or sooner to assess for survival status until death, withdrawal of consent, or the end of study, whichever occurs first.
Abbreviations: BICR = blinded independent central review; CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; d = day; PD = progressive disease; PD-1 = programmed cell death 1; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QD = daily; RECIST = Response Evaluation Criteria in Solid Tumors.

The new study design per Amendment 07 is depicted in Figure 2.

Figure 2 New Study Design



a. Prior adjuvant BRAF/MEK, PD-1 and CTLA-4 inhibitors may be allowed.
b. If End of Treatment visit occurs ~30 days from last dose of study treatment, a safety follow-up visit at 30 days is not required.

Abbreviations: BICR = blinded independent central review; CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; d = day; PD = progressive disease; PD-1 = programmed cell death 1; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QD = daily; RECIST = Response Evaluation Criteria in Solid Tumors.

1.3 Schedule of Activities

As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be sent to the iCRO. Participants who are still on study medication should continue tumor imaging assessment per protocol. For participants no longer on study medication, local tumor imaging assessments should continue per SOC schedule. In addition, Efficacy Follow-up, 90-day Follow-up and Survival Follow-up Visits will no longer be conducted. Biomarker samples (blood for genetic analysis, RNA analysis, plasma/serum biomarker analysis, and ctDNA analysis) are discontinued. The following parameters will be assessed as follows:

Summary of changes in SoA:

- **Imaging: while still on treatment per protocol (both pembrolizumab and lenvatinib) (not submitted to iCRO), then SOC**
- **PE, Vital signs: while still on treatment, then 30-day Safety FU, then SOC**
- **ECG, MUGA: while still on lenvatinib treatment then 30-day Safety FU, then SOC**
- **Urinary laboratory tests, including 24-hour urine collection as specified per protocol: while still on lenvatinib treatment, then 30-day Safety FU, then SOC**
- **Hematology/Chemistry: while still on treatment, then 30-day Safety FU, then SOC**
- **T3, FT4, TSH: while still on treatment, then 30-day Safety FU, then SOC**
- **HIV, HBV, HCV: while still on treatment, then 30-day Safety FU, then SOC**
- **ECOG: while still on treatment, then 30-day Safety FU, then SOC**

See Appendix 7 for country-specific requirements.

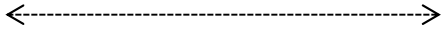
The full SoA table below is retained for reference.

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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											Informed consent must be documented prior to any protocol-specific procedures are 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 last 10 years.
Demographics	X											
Staging	X											At initial diagnosis and at study entry.
BRAF status	X											At 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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		Concomitant medications taken during the study and for 30 days after the last dose of study intervention will be recorded.
Randomization		X										Participants may be randomized up to 3 days prior to C1D1 and after confirmation of eligibility. All procedures and assessments on C1D1 should be performed after randomization.
Pembrolizumab plus lenvatinib or placebo Administration/ Dispensing		X			X		X					Pembrolizumab 200 mg Q3W; lenvatinib or placebo 20 mg QD. Lenvatinib/placebo will be taken in the clinic on C1D1, C1D15, and C2D1. On C1D1 and C2D1, lenvatinib/placebo will be taken 0 to 4 hours after completion of pembrolizumab administration.

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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 Follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Phone contact visit			X									A phone visit will be scheduled to report blood pressure and record AEs. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee during phone contact. Participants will be contacted by telephone on C1D8 to assess for development of early toxicity. If early toxicity is suspected, an unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.
Survival status		<---------->										Participants may be contacted for survival status at any time during the course of 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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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												
Tumor assessment – chest, abdomen and pelvis (CT/MRI)	X	<---------->						X		X		Prior scans performed within the Screening period but before signing informed consent may be used if consistent with protocol requirements per SIM. All imaging visits have a scheduling window of ±7 days. Imaging to be performed Q9W or sooner if clinically indicated from the date of randomization until Week 54 of study intervention, Q12W or sooner if clinically indicated thereafter until Week 102 until BICR verification of disease progression per RECIST 1.1. Progression will be verified by BICR prior to DC of study intervention. For participants who DC for reasons other than BICR-verified progressive disease, imaging should be performed Q12W until BICR-verified progressive

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
												disease. After Week 102 of FU, imaging should be performed Q24W or sooner if clinically indicated. 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. Required at Screening and at all subsequent tumor assessment time points only if brain disease was present 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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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		Report nonserious AEs occurring within 90 days after the last dose of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier. Report SAEs occurring within 120 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Full physical examination	X											At Screening, perform within 7 days prior to C1D1.
Directed Physical Examination		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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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), weight and height	X	X		X	X	X	X	X	X			BP and heart rate 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 is measured at Screening only.

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
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. ECG at C1D1 and C2D1 should be performed approximately 2 hours post lenvatinib/placebo dose. For high-risk participants (Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib/placebo is discontinued, ECGs are only required at the EOT and Safety Follow-up Visits. Additional assessments may be performed if 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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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 may be performed as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study.
Hematology and chemistry laboratory assessment	X			X	X	X	X	X	X			To be assessed within 7 days prior to first dose of study intervention. Every effort should be made to collect samples at the same time of day. LDH is only required at Screening. Refer to Appendix 7 for country-specific Requirements.

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
Urine dipstick testing	X			X	X	X	X	X	X			Performed locally within 7 days prior to start of intervention. After Screening, urine dipstick testing for protein will be performed within 3 days before Day 1 of every cycle while participants are taking lenvatinib/placebo. 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.
PT/INR and aPTT/PTT	X											Perform eligibility labs within 7 days prior to C1D1. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
T3, FT4, TSH	X				X		X	X	X			Screening samples to be collected within 7 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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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 (POCBP only)	X				X		X	X	X	X		POCBP require negative test prior to randomization. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention A serum or urine pregnancy test will be performed per Appendix 2. To be assessed prior to all subsequent scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, and up to 120 days post 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 during Screening. See Appendix 7 for country-specific guidelines.

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
HIV, HBV, HCV	X											Not required unless mandated by local health authorities. See Appendix 7 for country-specific guidelines.
ECOG performance status	X				X		X		X			To be assessed within 7 days of C1D1 and prior to dosing during all subsequent scheduled visits.
Pharmacokinetics/Pharmacodynamics/Biomarkers												
CCI [redacted]												

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		3 Onwards[a]	At D/C	30 Days and 90 Days After Last Dose	Q12W (± 7 d)	Q12W (± 7 d)	All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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	
CCI												

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		3 Onwards[a]	At D/C	30 Days and 90 Days After Last Dose	Q12W (± 7 d)	Q12W (± 7 d)	All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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	
CCI												

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	
Patient-reported Outcomes (HRQoL Measures)												
EORTC QLQ-C30		X			X		X	X	X			Patient-reported outcomes will be assessed on Day 1 (prior to first dose of study intervention) of every cycle during Year 1 (Cycles 1 to 17), every other cycle during Year 2 (Cycles 19, 21, 23, 25, 27, 29, 31, 33, and 35), and at treatment discontinuation visit and the 30-day and 90-day Safety Follow-up Visits. If the EOT visit occurs 30 days from the last dose of study intervention, a 30-day Safety Follow-up Visit is not required, ePROs do not need to be repeated. See additional details in Section 8.2.2.
EuroQoL (EQ-5D-5L)		X			X		X	X	X			

Abbreviations: AE=adverse event; BICR=blinded independent central review; BP=blood pressure; C1=Cycle 1; C2=Cycle 2; C3=Cycle 3; C5=Cycle 5; CIV=central imaging vendor; CT=computed tomography; ctDNA=circulating tumor DNA; ctRNA=circulating tumor RNA; D1=Day 1; D15=Day 15; D8=Day 8; DC=discontinue/discontinuing; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; ePRO=electronic patient-reported outcome; FT4=free thyroxine; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=health-related quality of life; INR=international normalized ratio; LDH=lactate dehydrogenase; 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; Q24W=every 24 weeks; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RR=respiratory rate; SAE=serious adverse event; SIM=site imaging manual; T3=triiodothyronine; TSH=thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; POCBP=participant of childbearing potential;

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**		**3 Onwards[a]**	**At D/C**	**30 Days and 90 Days After Last Dose**	**Q12W (± 7 d)**	**Q12W (± 7 d)**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 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**	

[a] Participants who continue treatment with lenvatinib or placebo beyond approximately 2 years (only if they experience clinical benefit until unacceptable toxicity or disease progression and upon Sponsor consultation and approval) will follow the same SoA except for the following: 1) thyroid labs beyond approximately 2 years will be performed per SOC or as clinically indicated 2) circulating tumor nucleic acid will no longer be collected. Participants who attain an investigator-determined complete response (CR) and stop study intervention with pembrolizumab + lenvatinib or pembrolizumab + placebo will have 30-day and 90-day Safety Follow-up Visits and move to the follow-up visits per SoA.

[b] If EOT visit occurs ~30 days from last dose of study intervention a 30-day Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Visit and EOT are performed once and entered into the EOT visit only. End-of-treatment 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 an 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 DC study intervention for reasons other than BICR-verified progressive disease, follow-up visits to monitor disease status continue until BICR-verified progressive disease or initiation of a new anticancer therapy. Participants who D/C study intervention with BICR-verified 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 of study intervention or sooner if clinically indicated and Q12W thereafter until Week 102; following Week 102, imaging should be performed every Q24W, or sooner if clinically indicated only if participants had 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 study to optimize the visualization of existing and new tumor burden.

2 INTRODUCTION

2.1 Study Rationale

Pembrolizumab (MK-3475/KEYTRUDA®) is approved by the US Food and Drug Administration (FDA) and the European Commission for the treatment of both first-line and previously treated patients with advanced melanoma. However, there is a large population (~60%) of patients who do not respond to therapy with anti-PD-1 agents. Thus, combination strategies as first-line intervention are needed.

The current study is designed to evaluate the safety and efficacy of combination therapy of lenvatinib (also known as E7080 or MK-7902; hereafter referred to as lenvatinib) and pembrolizumab in adult participants with advanced melanoma.

2.2 Background

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 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 Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab and lenvatinib.

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 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 CTLA-4 that has been shown to negatively

regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

2.2.1.2 Lenvatinib

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

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

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC50 values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

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

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 CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. 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 to 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 to 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 affects adults of all ages. The 5-year prevalence of melanoma in the European Union (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 United States (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 prior to the use of anti-PD-1 agents was 17% once patients had Stage IV disease [American Cancer Society 2016].

High-dose interleukin-2 was the first 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 limited 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, and the anti-CTLA-4 antibody (ipilimumab) and to targeted therapy such as BRAF and/or MEK inhibition (dabrafenib and/or trametinib, respectively). Both of these approaches prolong progression-free survival (PFS) and overall survival (OS) compared with chemotherapy [UpToDate, Inc. 2015], thus, they are standard therapeutic options for patients with melanoma.

Ipilimumab, an anti-CTLA-4 blocking antibody, and vemurafenib, a BRAF inhibitor, were the initial agents to demonstrate OS benefit in randomized, comparative Phase 3 registration studies. In the Phase 3 study MDX010-20, ipilimumab monotherapy demonstrated a hazard ratio of 0.66 and a 4-month median OS benefit compared to gp100 in pretreated advanced melanoma subjects [Hodi, F. S., et al 2010]. Grade 3 to 4 immune-related adverse events (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 the EU, ipilimumab is currently approved for the treatment of advanced melanoma in adults who have received prior therapy.

Approximately 50% of cutaneous melanoma cases are BRAF V600E mutation-positive [Larkin, J., et al 2014]. Vemurafenib was initially approved in the US and in the EU for the treatment of BRAF V600E mutation-positive advanced melanoma subjects 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 to dacarbazine with a hazard ratio (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 to 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] [Larkin, J., et al 2014].

KEYNOTE-006 Phase 3 study demonstrated superior efficacy of pembrolizumab compared to ipilimumab in PFS, OS and objective response rate (ORR). The ORR was 32.9% for pembrolizumab versus 11.9% for ipilimumab. Median PFS were 4.1 months for pembrolizumab versus 2.8 months for ipilimumab. The HR for the disease progression for pembrolizumab every 3 weeks (Q3W) versus ipilimumab was 0.58 (95% confidence interval [CI], 0.46 to 0.72; $p<0.001$). One-year estimates of survival for subjects receiving pembrolizumab Q3W were 68.4% as compared with ipilimumab at 58.2% (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 Data Monitor Committee (DMC) 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 subjects with previously untreated advanced melanoma compared to dacarbazine and reported a 5.1-month median PFS compared to 2.2 months for

the dacarbazine. The ORR was 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 to 42.1% in the dacarbazine group. Nivolumab showed significant improvements in PFS and OS compared with dacarbazine among previously untreated patients who had metastatic melanoma without BRAF mutation [Robert, C., et al 2014a].

In 2014, the FDA approved both nivolumab and pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600E mutation-positive, a BRAF inhibitor. 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 advanced (unresectable or metastatic) melanoma regardless of BRAF status. The European Commission has also approved pembrolizumab and nivolumab, for both first-line and previously treated patients with advanced melanoma.

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 mAbs has been investigated in the CT26 colorectal cancer syngeneic model (anti-PD-L1 mAb) as well as the LL/2 lung cancer syngeneic model (anti-PD-1 mAb). Combination treatment with lenvatinib and either an anti-PD-1 or anti-PD-L1 mAb 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 plus pembrolizumab in participants with selected solid tumors is currently ongoing. Phase 1b of this study determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) as 20 mg lenvatinib once daily (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, endometrial cancer, 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 multicohort 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 patients were aged 18 years or older and had histologically confirmed nonuveal melanoma, 0 to 2 prior systemic anticancer regimens and ECOG 0 or 1. The primary endpoint is ORR at Week 24 based on RECIST 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, duration of response (DOR), PFS, OS, and safety and tolerability of the combination. All patients received lenvatinib 20 mg daily in combination with 200 mg pembrolizumab IV Q3W. At data cutoff (01-MAR-2018), 21 metastatic melanoma patients were enrolled, and 38% of patients had 1 or more prior anticancer therapy.

For all enrolled subjects (N=21), the ORRWeek24 was 47.6% (95% CI: 25.7, 70.2) using iRECIST by investigator review. Of the 10 confirmed responses, 9 (42.9%) were partial response (PR), and 1 (4.8%) was complete response (CR). Stable disease was observed in 7 (33.3%) patients, and 3 (14.3%) experienced progressive disease (PD). One patient had an unknown response. Median duration of objective response was 12.5 months (95% CI, 2.7 months, not estimable [NE]). Median PFS observed was 7.6 months (95% CI: 2.6 months, 15.8 months).

All patients experienced ≥1 treatment-related adverse event (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%) patients, 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.

2.2.3 Information on Other Study-related Therapy

Not applicable.

2.3 Benefit/Risk Assessment

Beneficial effects of pembrolizumab have been seen in several melanoma studies 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 Section 2.2.1.6, 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 alanine aminotransferase (ALT) and aspartate aminotransferase (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 informed consent documents.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-003 (data cutoff 18-JAN-2023), eDMC recommended stopping the study due to lack of efficacy because pembrolizumab in combination with lenvatinib did not demonstrate an improvement in OS, one of the trial's dual primary endpoints, compared to pembrolizumab plus placebo and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded as of 27-MAR-2023. The prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints. Biomarker specimen collection is discontinued.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (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 unresectable advanced melanoma following administration of pembrolizumab in combination with lenvatinib versus pembrolizumab in combination with placebo:

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-003 (data cutoff 18-JAN-2023), eDMC recommended stopping the study due to lack of efficacy because pembrolizumab in combination with lenvatinib did not demonstrate an improvement in OS, one of the trial's dual primary endpoints, compared to pembrolizumab plus placebo and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded as of 27-MAR-2023. The prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter sent to investigators on 3-APR-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit). All participants should stop ongoing treatment with lenvatinib/placebo. Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have completed 35 cycles of pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after unblinding and completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time. All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study; however, standard safety reporting should continue, as applicable. As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants who are still on study medication should continue tumor imaging assessment per protocol. For participants no longer on study medication, local tumor imaging assessments should continue per SOC schedule. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up is the last required visit. Updated analyses are described in Section 9.

See Appendix 7 for country-specific requirements.

Primary Objective	**Primary Endpoint**
Objective: To compare progression-free survival (PFS) as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Hypothesis (H1): The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo assessed by PFS per RECIST 1.1 by BICR.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective: To compare the combination of pembrolizumab and lenvatinib to pembrolizumab and placebo with respect to overall survival (OS). Hypothesis (H2): The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo assessed by OS.	OS: Defined as the time from date of randomization to date of death from any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare objective response rate (ORR) per RECIST 1.1 by BICR. Hypothesis (H3): The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo as assessed by ORR per RECIST 1.1 by BICR.	Objective response, defined as best overall response of either complete response or partial response.
Objective: To assess duration of response (DOR) per RECIST 1.1 by BICR.	DOR, determined by disease assessment defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first.
Objective: To assess safety and tolerability.	Adverse events (AEs) Discontinuations due to AEs.
Objective: To compare the mean change from baseline in PRO scores in global health status/quality of life (QoL) and physical functioning.	European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30]: - Global health status/QoL scale (items 29 and 30) - Physical functioning scale (items 1 to 5).

Objective: To compare the time to true deterioration (TTD) in global health status/QoL and physical functioning.	TTD is the time from baseline to first onset of 10 points or more decrease from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline for EORTC QLQ-C30: - Global health status/QoL scale (items 29 and 30) - Physical functioning scale (items 1 to 5)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

Original protocol text that is contained in this section has been retained for reference.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-003 (data cutoff 18-JAN-2023), eDMC recommended stopping the study due to lack of efficacy because pembrolizumab in combination with lenvatinib did not demonstrate an improvement in OS, one of the trial's dual primary endpoints, compared to pembrolizumab plus placebo and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded as of 27-MAR-2023. The prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter sent to investigators on 3-APR-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit). All participants should stop ongoing treatment with lenvatinib/placebo. Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have completed 35 cycles of pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after unblinding and completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time. All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study; however, standard safety reporting should continue, as applicable. As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants who are still on study medication should continue tumor imaging assessment per protocol. For participants no longer on study medication, local tumor imaging assessments should continue per SOC schedule. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up is the last required visit. Updated analyses are described in Section 9.

See Appendix 7 for country-specific requirements.

This is a randomized, placebo-controlled, parallel-group, multisite, double-blinded, efficacy, and safety study of pembrolizumab in combination with lenvatinib or pembrolizumab in combination with placebo in participants with advanced melanoma.

Approximately 660 participants will be enrolled into the study. The design also includes the option for an extension. The study will continue to enroll participants from China in the extension portion of the study until the overall sample size for China reaches approximately 130 (up to 137) participants in the global study and the extension portion of the study combined. Participants will be stratified by BRAF mutation status (BRAF mutation-positive vs BRAF wild-type or unknown), prior adjuvant therapy with a PD-1 inhibitor (no prior adjuvant therapy with a PD-1 inhibitor vs. prior adjuvant therapy with a PD-1 inhibitor), and geographic region (participants from China vs. non-China countries) prior to randomization. Note: At the time of writing Amendment 07, enrollment in the China extension was complete.

Participants will be treated with the combination of pembrolizumab + lenvatinib or pembrolizumab + placebo for approximately 2 years or until disease progression verified by BICR per RECIST 1.1, 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. Pembrolizumab treatment will be discontinued once the participant has received 35 administrations (approximately 2 years). Participants may continue treatment with lenvatinib or placebo beyond approximately 2 years if they experience clinical benefit until unacceptable toxicity or disease progression upon Sponsor consultation and approval. Participants who attain an investigator-determined confirmed CR may consider stopping study intervention with pembrolizumab + lenvatinib or pembrolizumab + placebo, after at least 24 weeks of study intervention has been administered. In addition, if a confirmed CR per RECIST 1.1 is attained, at least 2 additional doses of pembrolizumab must be received after CR is first documented.

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 is experiencing clinical benefit with continued treatment, and the participant is tolerating study intervention as per iRECIST. Treatment beyond disease progression per iRECIST may be permitted upon Sponsor consultation and approval.

After the enrollment of the global study is completed, participants from China will continue to be enrolled in an extension portion of the study designed to meet local regulatory requirements. The extension portion of the study will be identical to the global study (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures) and participants enrolled in China after completion of the global enrollment will not be included in the analyses for the global study. The purpose of the extension portion of the study is to assess the consistency of safety and efficacy in the participants enrolled in China. Participants in China will continue to be enrolled in a 1:1 ratio until the cumulative total sample size for participants enrolled in China reaches approximately 130 (up to 137) participants in the global study and the extension portion of the study combined. The efficacy and safety data from participants enrolled in China (including participants enrolled prior to and after completion of enrollment in the global study) will be analyzed separately. Additional detail regarding the analysis associated with these participants will be described in the supplemental SAP (sSAP).

The primary endpoint of PFS will be assessed by BICR per RECIST 1.1 criteria (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) by BICR. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and electrocardiogram (ECG) measurements, as appropriate.

CCI IAs are planned for this study. Results from the IAs will be reviewed by CCI CCI Further details on the IAs are provided in Section 9.7.

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

4.2 Scientific Rationale for Study Design

If the safety profile is acceptable and this combination is shown to improve PFS and/or OS, this study could support the regulatory approval of the combination of pembrolizumab and lenvatinib in participants with advanced unresectable or metastatic melanoma.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The dual primary endpoints are PFS and OS.

This study will use PFS, defined as the time from date of randomization until the earliest date of disease progression or death from any cause, whichever comes first, based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. 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. OS is defined as the time from date of randomization to date of death due to any cause.

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.

ORR and DOR are secondary endpoints.

ORR is defined as the proportion of subjects who have best response as CR or PR. Responses are based on BICR using RECIST 1.1.

DOR is defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes 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 by the local site when determining eligibility. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Eligibility will also be prospectively assessed by BICR based on RECIST 1.1. Refer to Section 8.2.1.4 for additional detail.

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 after 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 provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudoprogression. Of note, participants who had disease progression by RECIST 1.1, but not by the immune-related response criteria [Wolchok, J. D., et al 2009], had longer overall survival than participants with 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.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US FDA and the EMA [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.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated via the following assessment tools: European Organisation for the Research and Treatment of Cancer (EORTC) QoL Questionnaire-Core 30 (QLQ-C30) and European QoL 5-dimension 5-level (EQ-5D-5L) questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EQ-5D-5L

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

4.2.1.4 Pharmacokinetic Endpoints

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

The serum concentrations of pembrolizumab collected will be compared to historical data to ensure the consistency of exposure levels at 200 mg Q3W.

4.2.1.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.6 Planned Exploratory Biomarker Research

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

Programmed cell death 1 inhibition is the standard of care first-line therapy in patients with advanced melanoma. Therefore, pembrolizumab will be offered to all participants in this study. Participants will be randomized to the combination of pembrolizumab + lenvatinib or pembrolizumab + placebo. Placebo will be administered in the same manner as the investigational product. Placebo is being utilized to allow for a blinded study, thereby limiting bias and providing a comparator arm that is consistent with standard of care for patients with advanced melanoma. Placebo is a capsule for oral administration and does not require preparation.

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 KEYTRUDA® development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure efficacy relationships from 2 mg/kg Q3W to 10 mg/kg 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 from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, 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 endometrial cancer, and 1 had melanoma. There were 2 dose-limiting toxicities (DLTs) at the lenvatinib 24 mg/day + pembrolizumab 200 mg dose IV Q3W (1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue); hence, this was defined as the toxic dose. 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 plus 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

NOTE: In alignment with the study-specific investigator letter sent to investigators on 3-APR-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit). All participants should stop ongoing treatment with lenvatinib/placebo. Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have completed 35 cycles of pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after unblinding and completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of

Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time. All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study; however, standard safety reporting should continue, as applicable. As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants who are still on study medication should continue tumor imaging assessment per protocol. For participants no longer on study medication, local tumor imaging assessments should continue per SOC schedule. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up is the last required visit. Updated analyses are described in Section 9.

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 for approximately 2 years. Participants may continue treatment with lenvatinib/placebo beyond approximately 2 years if they experience clinical benefit until unacceptable toxicity or disease progression upon Sponsor consultation and approval.

See Appendix 7 for country-specific requirements.

4.4 Beginning and End-of-Study Definition

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

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

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

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. The participant must have a histologically or cytologically confirmed diagnosis of melanoma.
   Note: Mucosal melanoma is limited to ≤20% of all study participants.
2. Have unresectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer 8th edition guidelines, not amenable to local therapy.
3. Have been untreated for advanced or metastatic disease except as follows:

a. BRAF V600 mutation-positive melanoma may have received standard of care targeted therapy as first-line therapy for advanced or metastatic disease (eg, BRAF/MEK inhibitor, alone or in combination); participants that do not have a BRAF V600 mutation but did receive BRAF or BRAF/MEKi therapy are eligible to participate in this study after discussion with the medical monitor.
   Note: Prior first-line therapy for advanced or metastatic disease with targeted therapy is permitted if it was completed at least 4 weeks before randomization and all related AEs have either returned to baseline or stabilized (resolution of toxic effect(s) to Grade 1 or less [except alopecia and Grade 2 neuropathy]).

b. Prior adjuvant or neoadjuvant therapy with targeted therapy or immunotherapy (such as anti-CTLA-4, anti-PD-1 therapy or interferon). Immunotherapy will only be permitted if relapse did not occur during active treatment or within 6 months of treatment discontinuation. No other prior adjuvant or neoadjuvant therapy will be allowed.
   Note: Prior adjuvant or neoadjuvant therapy with anti-CTLA-4 in combination with anti-PD-1 therapy will not be allowed.

4. Have documentation of BRAF V600-activating mutation status or consent to BRAF V600 mutation testing during the Screening period (participants with BRAF mutation-positive melanoma as well as BRAF wild-type or unknown are eligible).
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (Appendix 9).

6. Have the presence of at least 1 measurable lesion by CT or MRI per RECIST 1.1 criteria as determined by the local site investigator/radiology assessment. Measurable disease will be verified by central imaging vendor (CIV) prior to randomization. Cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol but may be considered as nontarget lesions. Photographs of cutaneous lesions do not need to be submitted to the CIV.

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.

c. If a participant does not have measurable disease by CIV, they will not be allowed to participate in the study.

7. Provide a tumor biopsy.

a. Participants must submit tumor sample during Screening for assessment of adequacy of tumor tissue at a central pathology laboratory; central confirmation of presence of tumor tissue is not required prior to randomization. Participants who do not submit a tumor tissue sample will not be randomized. The tumor biopsy may not be obtained from a lone target lesion.

b. Newly obtained tissue is preferred (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained at time of study enrollment). Note: In cases where newly obtained tissue with no intervening local or systemic therapy is not possible to provide, an archival sample will be acceptable. If participants were treated with BRAF ± MEK targeted treatment, the archival sample could have been collected prior to BRAF ± MEK targeted treatment.

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

Male Participants

10. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is:
    - Lenvatinib/Placebo: 7 days
    - Please note that 7 days after lenvatinib/placebo is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

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

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
  - Uses a penile/external condom plus nonparticipant of childbearing potential who is not currently pregnant and should also be advised of the benefit for that partner to use an additional method of contraception, as a condom may break or leak.
    Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.
  - Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

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

- Is not a POCBP
  OR

- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib/placebo, whichever occurs last, after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

- Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5 and Appendix 2.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

12. The participant (or legally acceptable representative) has provided documented informed consent for the study.

Additional Categories

13. Have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week prior to randomization.

14. Adequate organ function as defined in the following table (Table 1). Specimens must be collected within 7 days before the start of study intervention.

Table 1 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 creatinine clearance [b] (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)	≤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)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

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

[c] Participants with ALP values >3 times the ULN and known to have bone metastases can be included.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

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 requires active treatment. Exceptions include early stage cancers (carcinoma in situ or stage 1, nonulcerated 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 central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain 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 scans 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 mAb. For a list of excipients, refer to the respective IBs.
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 human immunodeficiency virus (HIV) (HIV 1/2 antibodies). No testing of HIV is required unless mandated by local health authority. (See Appendix 7 for country-specific requirements.)
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. (See Appendix 7 for country-specific requirements.)
10. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
11. Has a history of active tuberculosis (Bacillus tuberculosis). (See Appendix 7 for country-specific requirements.)
12. Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib.
13. Has had a major surgery within 3 weeks prior to first dose of study intervention. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
14. Has preexisting Grade ≥3 gastrointestinal or nongastrointestinal fistula.
15. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation.
    Note: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.

16. Has active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study intervention.
17. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, 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 with ≥2+ (≥100 mg/dL) proteinuria on urine dipstick testing (or urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria.
19. Prolongation of QTcF interval to >480 ms.
    Note: If the QTcF is prolonged to >480 ms in the presence of a pacemaker, contact the Sponsor to determine eligibility. (See Appendix 7 for Country-specific requirements.)
20. Has left ventricular ejection fraction (LVEF) below the institutional (or local laboratory) normal range, as determined by multigated acquisition scan (MUGA) or echocardiogram.

Prior/Concomitant Therapy

21. Has received prior systemic treatment for unresectable or metastatic melanoma other than targeted therapy as noted in Inclusion Criteria #3.
22. Has received prior therapy in the adjuvant setting. Note: Targeted therapy, anti-CTLA-4, or anti-PD-1 may be allowed as noted in Inclusion Criteria #3.
23. Received prior systemic anticancer therapy including investigational agents within 4 weeks or 5 half-lives (whichever is longer) before administration of study intervention or not recovered (≤Grade 1 or at baseline) from AEs due to previously administered agents. Exception to this rule would be use of denosumab, which is not excluded.

    Note: Participants with alopecia and ≤Grade 2 neuropathy are an exception and may enroll.
24. 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.
25. Has received 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, Bacillus Calmette-Guérin (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. (See Appendix 7 for country-specific requirements.)

Prior/Concurrent Clinical Study Experience

26. 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.

Other Exclusions

27. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
28. Had an allogeneic tissue/solid organ transplant.
29. 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

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

5.3.2 Pregnancy

If a participant inadvertently becomes pregnant while on any study intervention, 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 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 as described in Section 8.4. 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.

5.3.3 Use in Nursing Women

It is unknown whether the study interventions are 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 randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

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.

Original protocol text contained in this section has been retained for reference.

Clinical supplies (pembrolizumab, lenvatinib, and placebo) 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

NOTE: In alignment with the study-specific investigator letter sent to investigators on 3-APR-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit). All participants should stop ongoing treatment with lenvatinib/placebo. Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have completed 35 cycles of pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after unblinding and completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time. All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study; however, standard safety reporting should continue, as applicable.

The study intervention(s) to be used in this study are outlined in Table 2.

See Appendix 7 for country-specific requirements.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm A	Experimental	Pembrolizumab	Drug	Solution	25 mg/mL	200 mg	IV Infusion	Q3W	Test Product	IMP	Central
Arm A	Experimental	Lenvatinib	Drug	Capsule	10 mg, 4 mg	20 mg	Oral	QD	Test Product	IMP	Central
Arm B	Active Comparator	Pembrolizumab	Drug	Solution	25 mg/mL	200 mg	IV Infusion	Q3W	Comparator	IMP	Central
Arm B	Placebo Comparator	Placebo	Drug	Capsule	0 mg	0 mg	Oral	QD	Placebo	IMP	Central

Abbreviations: EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; QD=once daily.

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

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

Note: As of PA07, use of placebo is discontinued.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 2 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

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

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

All placebos were created to match the active product.

6.1.1 Medical Devices

Not applicable.

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/placebo is a capsule for oral administration and does not require preparation. If a dose of lenvatinib/placebo is missed and cannot be taken within 12 hours from the scheduled administration, the participant should skip this dose and take the next dose at the scheduled time the next day. See 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 randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to either Arm A (pembrolizumab + lenvatinib) or Arm B (pembrolizumab + placebo).

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

BRAF mutation status:

- BRAF mutation-positive
- BRAF wild-type or unknown

Prior adjuvant therapy with a PD-1 inhibitor:

- No prior adjuvant therapy with a PD-1 inhibitor
- Prior adjuvant therapy with a PD-1 inhibitor

Geographic region:

- Participants from China
- Participants from non-China countries

6.3.3 Blinding

As of IA3, the study was unblinded. Original protocol text that is contained in this section has been retained for reference.

A double-blinding technique with in-house blinding will be used. Lenvatinib and placebo will be packaged identically so that blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

See Section 8.1.11 for the description of unblinding if a medical emergency occurs during the study.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment ≥28 days (lenvatinib/placebo) 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 case report form (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 Medication(s)

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. Bisphosphonates (including denosumab) are also allowed.

6.5.2 Prohibited Concomitant Medication(s)

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 (eg, tyrosine kinase inhibitors), 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.

- Note: Palliative surgery will be 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 are permitted only for the following purposes:

  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - As needed for the prevention of emesis
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses <10 mg/day prednisone equivalent for COPD exacerbations
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

- In addition, the following glucocorticoid use is allowed:

  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

- Palliative radiotherapy will be allowed.

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication 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 meaningfully alter exposure to CYP3A4/ P-glycoprotein (Pgp) substrates based on results from a lenvatinib drug-drug interaction (DDI) study with midazolam (a sensitive CYP3A and Pgp substrate). Clinical studies also showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are 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 nonenzymatic processes (lenvatinib IB).

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/placebo, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 3 in Section 6.6.1 along with the dose modification guidelines in Table 4 and Table 5 in Section 6.6.1 and Section 6.6.2.Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or lenvatinib/placebo.

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

6.6 Dose Modification

NOTE: In alignment with the study-specific investigator letter sent to investigators on 3-APR-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit). All participants should stop ongoing treatment with lenvatinib/placebo. Exceptions may be requested for lenvatinib for study participants who, in

the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have completed 35 cycles of pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after unblinding and completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time. All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study; however, standard safety reporting should continue, as applicable. As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants who are still on study medication should continue tumor imaging assessment per protocol. For participants no longer on study medication, local tumor imaging assessments should continue per SOC schedule. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up is the last required visit. Updated analyses are described in Section 9.

See Appendix 7 for country-specific requirements.

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

Participants who interrupt lenvatinib/placebo or pembrolizumab due to toxicity can continue with the other drug until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

Participants who discontinue lenvatinib/placebo due to untoward toxicities can continue on the study receiving pembrolizumab as monotherapy. Participants who discontinue pembrolizumab due to untoward toxicities cannot continue on the study receiving only lenvatinib/placebo.

Refer to Section 6.6.3 for dose modification guidance for overlapping toxicity for the pembrolizumab plus lenvatinib/placebo combination.

6.6.1 Dose Modification (Escalation/Titration/Other)

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 3.

See Appendix 7 for country-specific requirements.

Table 3 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		

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [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]		
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		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [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 reactions are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE v4.0 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 intervention.[a]**	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 v4.0 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 intervention.**[a]	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.

[a] Participants who discontinue pembrolizumab due to untoward toxicities cannot continue on the study receiving only lenvatinib/placebo.

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

See Section 6.6.4 for other allowed dose interruptions for pembrolizumab and lenvatinib/placebo and stop time and restart time of lenvatinib/placebo for minor/major procedures.

6.6.2 Dose Modification With Lenvatinib/Placebo

Lenvatinib/placebo dose reduction and interruption for participants who experience lenvatinib/placebo-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 5. An interruption of study intervention for more than 28 days will require Sponsor consultation and approval before treatment can be resumed. Participants who discontinue lenvatinib/placebo due to untoward toxicities can continue on the study receiving pembrolizumab as monotherapy.

The starting dose of lenvatinib/placebo is 20 mg/day. Dose reductions of lenvatinib/placebo 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, 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 encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (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), QT prolongation (6.6.2.10), and osteonecrosis of the jaw (Section 6.6.2.11) as appropriate, before consulting the dose modification table (Table 5). For overlapping toxicities of pembrolizumab and lenvatinib/placebo, please refer to Section 6.6.3.

Table 5 Dose Modification Guidelines for Lenvatinib/Placebo-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,f]		
First occurrence	Interrupt lenvatinib/placebo until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib/placebo dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib/placebo until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib/placebo dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib/placebo until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib/placebo dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib/placebo	Discuss with Sponsor
Grade 4[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/placebo 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 have a minimum 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. For Grade 3 thromboembolic event, permanently discontinue lenvatinib/placebo, see Section 6.6.2.5.

g. Excluding laboratory abnormalities judged to be nonlife-threatening, in which case manage as Grade 3.

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/placebo 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 C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib/placebo 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/placebo 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 comorbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib/placebo 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.

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 intervention and institute antihypertensive therapy for participants not already receiving antihypertensive therapy.
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/placebo 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/placebo 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/placebo 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 intervention

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:

- Perform urine dipstick testing per the SoA (Section 1.3). Urine dipstick testing is the preferred method for testing urinary protein, however, urinalysis may be used if the use of urine dipstick is not feasible.
- 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+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participants is receiving lenvatinib/placebo
  - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib/placebo dose level
  - When there has been a lenvatinib/placebo dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL)
- 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/placebo administration will be based on the grade of proteinuria according to Table 5.

Monitoring:

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on D15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib/placebo must be discontinued.

6.6.2.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study intervention and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent

should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 5 should be followed.

6.6.2.4 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], 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 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v4.0) occurs, lenvatinib/placebo 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, and DVT 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 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or life-threatening (Grade 4) thromboembolic reactions, 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 5 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 5 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib/placebo depending on the severity and persistence of hemorrhage.

6.6.2.9 Management of Gastrointestinal Perforation or Fistula

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

See Appendix 7 for country-specific requirements.

6.6.2.10 Management of QT Prolongation

Lenvatinib/placebo should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib/placebo should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

6.6.2.11 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib/placebo and periodically during lenvatinib/placebo treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib/placebo 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/placebo 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

Participants who experience an unacceptable toxicity that is attributed to lenvatinib/placebo in the opinion of the investigator and the Sponsor, may permanently discontinue lenvatinib/placebo, but may continue with pembrolizumab, upon resolution of toxicity to Grade 0 or 1 or baseline, until unacceptable toxicity or progression. Participants who discontinue pembrolizumab due to untoward toxicities cannot continue on the study receiving only lenvatinib/placebo.

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 intervention. Therefore, evaluation of attribution is important for determining the study intervention 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/placebo 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/placebo 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/placebo dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib/placebo can be interrupted and dosing of pembrolizumab should be held.

If the participant recovers from an AE in response to lenvatinib/placebo interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib/placebo. 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/placebo) 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 3, but lenvatinib/placebo 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 3 advises pembrolizumab to be withheld (interrupted), and Table 5 advises lenvatinib/placebo 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/Placebo and Pembrolizumab

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

- For minor procedures: stop lenvatinib/placebo 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/placebo at least 1 week (5 half-lives) prior to surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.
- For scheduled dental surgery or invasive dental procedures, stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

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

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice:

"You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike capsule created to resemble the drug LENVIMA® (lenvatinib) as much as possible. You did not receive the active drug LENVIMA (lenvatinib) as manufactured by Eisai."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

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 Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Any progression or recurrence of any malignancy, or any occurrence of secondary malignancy that requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated 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 and lenvatinib/placebo. Note: Participants experiencing a clinical benefit may continue on lenvatinib/placebo alone beyond this time point until unacceptable toxicity or disease progression upon Sponsor consultation and approval (see Section 4.3.3 for additional details).

- Grade 3 thromboembolic events require permanent discontinuation of lenvatinib/placebo.
- Participants receiving the combination therapy (pembrolizumab + lenvatinib/placebo) must discontinue study therapy 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 3, but lenvatinib/placebo 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 3 advises pembrolizumab to be withheld (interrupted), and Table 5 advises lenvatinib/placebo 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 any of the following reasons:

- Discontinuation of study intervention with pembrolizumab and lenvatinib/placebo 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.
- Progressive disease as verified by BICR.

  Note: Participants will be permitted to continue treatment beyond RECIST 1.1-defined progression as long as investigator-assessed clinical stability is observed, and the participant is tolerating study intervention (Section 8.2.1.5). Treatment beyond PD per iRECIST may be permitted upon Sponsor consultation and approval.

As of Amendment 07, central tumor response assessments will no longer be performed. Participants on study intervention who are deriving clinical benefit and are continuing to receive study intervention will be assessed locally by the investigator for disease progression per protocol schedule. Scans will not be sent to the iCRO.

- Participants with RECIST 1.1 progression per local investigator assessment may continue pembrolizumab per iRECIST if criteria for clinical stability are met.
- Participants with RECIST 1.1 disease progression must discontinue lenvatinib.
- At investigator-determined iCPD, pembrolizumab should be discontinued (exceptions may be made if participant is clinically stable, derives benefit and if the Sponsor approves treatment continuation beyond iCPD).

Original protocol text that is contained in this section and the following sections has been retained for reference.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study

protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

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

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

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

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

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

8.1.2 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 treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior

10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

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

8.1.5 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 starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. Concomitant medications will be recorded for 30 days after the last dose of study intervention.

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention should begin within 3 days of randomization.

Lenvatinib/Placebo: Lenvatinib/placebo may be administered at home except on C1D1, C1D15, and C2D1; on these days, lenvatinib/placebo will be taken in the clinic. Please refer to Section 8.1.8.2.1 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 Compliance

Lenvatinib compliance will be calculated by the Sponsor based on the 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.

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.

8.1.8.2 Timing of Dose Administration

8.1.8.2.1 Lenvatinib/Placebo

Lenvatinib/placebo 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. However, on C1D1, and C2D1, lenvatinib/placebo will be administered in the clinic 0 to 4 hours after completion of pembrolizumab administration. Participants should not take their study medication on C1D15 and on C2D1 before their appointment.

If a lenvatinib/placebo 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.

8.1.8.2.2 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 and +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.

8.1.9 Discontinuation and Withdrawal

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

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the discontinuation visit (EOT visit) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4. If discontinuation occurs approximately 30 days after the last dose of study intervention, the 30-day Safety Follow-up Visit (Section 8.11.3.1)

is not required. In this situation, all procedures required at the 30-day Safety Visit and EOT are performed once and entered into the EOT visit only.

8.1.10 Procedures for Negative Studies Without Safety Concerns

If the study or one study intervention group discontinues due to futility or the study does not demonstrate statistically significant efficacy results per protocol specified analyses without any urgent safety issues, one or more of the following actions may occur:

- unblinding of the participants' treatment assignment (see Section 8.1.11 blinding/unblinding)
- stopping treatment with placebo (see Sections 7.1 and 8.1.9)
- cessation of recruitment
- discontinuing participants assigned to a specific control group (see Sections 7.1 and 8.1.9) or study intervention group unless participants are deriving clinical benefit (see Section 8.1.10)
- participants may be discontinued from parent study and may be enrolled into an extension study using pembrolizumab/study intervention if participants are deriving clinical benefit

The investigator or medically qualified designee must rapidly inform each participant of these results and discuss treatment options. Additionally, the protocol is to be amended to reflect any change in the study conduct (eg, cohort changes and followup).

8.1.11 Participant Blinding/Unblinding

As of IA3, the study was unblinded. Original protocol text that is contained in this section has been retained for reference.

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding or a nonemergency unblinding that is part of the study design has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.12 Calibration of Equipment

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

8.1.13 Demography

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

8.1.14 Subsequent Antineoplastic Treatment

NOTE: As of Amendment 07, Survival Follow-up is no longer required.

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

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

As of Amendment 07: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to the iCRO nor read by BICR. Original protocol text that is contained in this section has been retained for reference.

Participants still on study treatment who are deriving clinical benefit may continue study intervention until criteria for discontinuation are met. Local tumor imaging should continue per protocol schedule while participants remain on study therapy.

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

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

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

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

Participant eligibility will be determined using investigator assessment. All scheduled scans for each participant will be submitted to the iCRO. In addition, unscheduled scans to determine disease progression and scans obtained for other reasons but demonstrate radiologic progression are to be submitted to the iCRO.

When the investigator identifies disease progression, the iCRO will verify this progression and email the results to the study site and Sponsor see Section 8.2.1.4 and Figure 3. In clinically stable participants, scans are to continue until disease progression has been verified by BICR. If investigator-assessed progression was not verified by BICR, each subsequent scan must be submitted to the iCRO. Once progression is verified by BICR, subsequent scans (if acquired) should not be submitted to the iCRO.

See Appendix 7 for country-specific requirements.

8.2.1.1 Initial Tumor Scans

The scans at screening must be submitted to the iCRO to verify that eligibility criteria (Section 5) have been met before randomization. The site study team must submit screening images to the iCRO to confirm the participant has measurable disease per RECIST 1.1 prior to randomization. Tumor imaging performed as part of routine clinical management is acceptable for use as Screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the iCRO. Brain imaging must be performed at Screening. If MRI is medically contraindicated, CT is an acceptable alternative.

Tumor imaging at baseline includes the following:

- CT (preferred) or MRI of the abdomen and pelvis, must include IV contrast
- CT of the chest
- Brain MRI (preferred) or CT of the brain, must include IV contrast

8.2.1.2 Tumor Scans During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed Q9W 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 Q24W, or sooner if clinically indicated. Imaging timing should follow calendar days from randomization 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 and verified by the iCRO (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. Radiographic PD cannot be determined by worsening of cutaneous lesions or appearance of new cutaneous lesions that cannot be observed radiographically.

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 Q9W (±7 days) from the date of randomization, 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 of 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. Note: Response does not typically need to be verified in real time by the iCRO.

Per iRECIST (Section 8.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed 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 Tumor Scans

As of Amendment 07, follow-up tumor scans are no longer required.

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

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

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

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

Participants who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed according to the rules of iRECIST, when clinically appropriate.

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5

target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

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

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

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

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

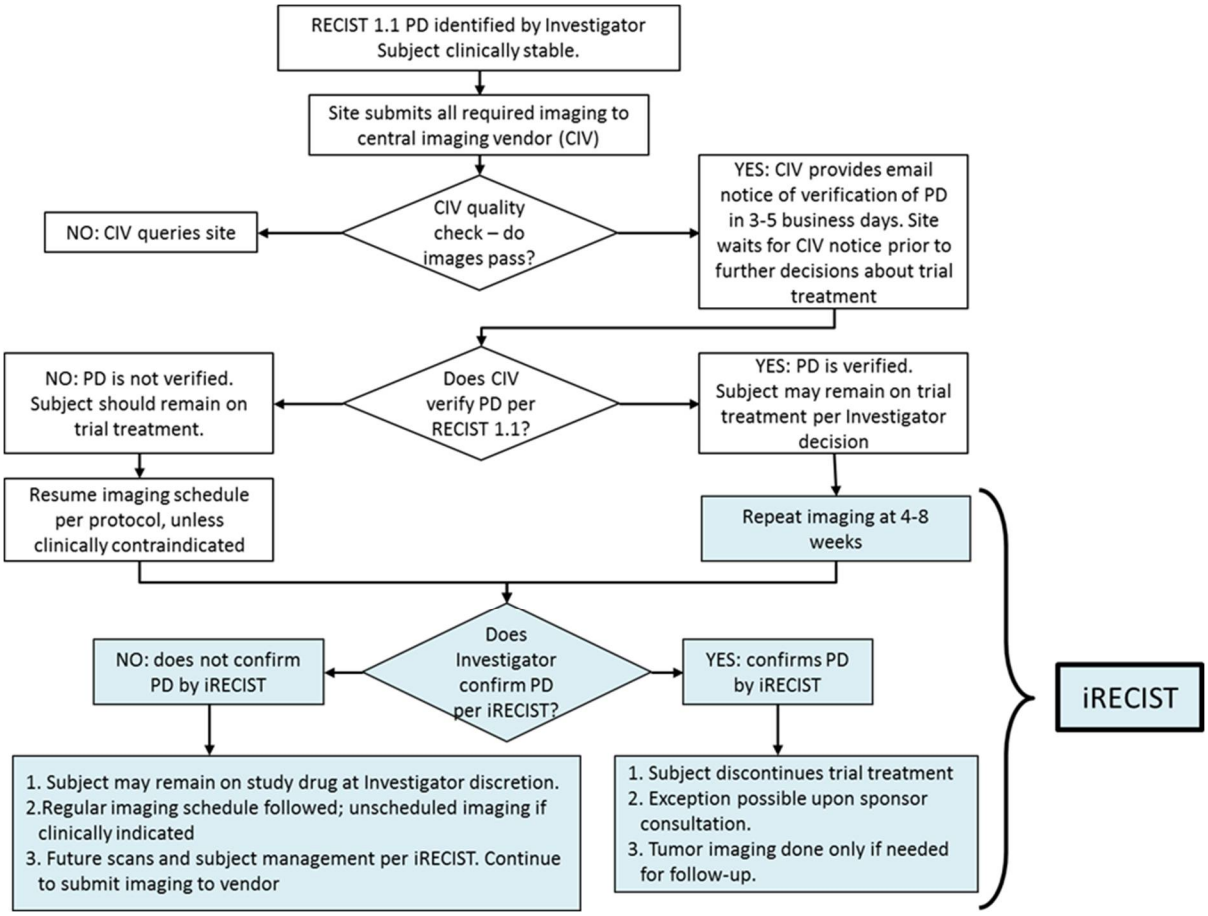
If disease progression is verified, the process continues as follows:

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

Figure 3 illustrates the study intervention decision process involving verification of disease progression for participants.

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

Figure 3 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator



CIV = central imaging vendor; iRECIST = Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors.

8.2.1.5 iRECIST Assessment of Disease

Original protocol text that is contained in this section has been retained for reference.

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 [Seymour, L., et al 2017]. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 8. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy then experience subsequent disease response. This data will be captured in the clinical database.

- If participant is clinically stable (refer to Section 8.2.1.4), continue study intervention per protocol
  - Perform scans 4 to 8 weeks after RECIST 1.1 progression
  - Continue investigator assessment per iRECIST
  - PFS endpoint: If progression is BICR-verified, stop sending scans to iCRO
- If the participant is not clinically stable, best medical practice is to be applied

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 6 and illustrated as a flowchart in Figure 3.

Table 6 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 that has been verified by BICR	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.	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.

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.

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.

8.2.2 Patient-reported Outcomes

As of Amendment 07: PROs and Quality of Life assessments will be discontinued. Original protocol text that is contained in this section has been retained for reference.

The EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then EQ-5D-5L. The questionnaires should be administered before dosing of every cycle during Year 1 (Cycles 1 to 17), every other cycle during Year 2 (Cycles 19, 21, 23, 25, 27, 29, 31, 33, and 35), at time of discontinuation (EOT visit), and the 30-day and

90-day Safety Follow-up Visits. If the EOT visit occurs 30 days from the last dose of study intervention a Safety Follow-up Visit is not required, ePROs do not need to be repeated.

Every effort should be made to administer HRQoL surveys before study intervention administration and before other assessments and procedures.

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

8.3 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all NCI CTCAE v4.0 grades (for both increasing and decreasing severity), and SAEs; regular laboratory evaluation for hematology, blood chemistry, urinalysis and thyroid function; periodic measurement of vital signs, ECGs and MUGA or echocardiogram; and the performance of physical examinations as detailed in Section 1.3. In addition, coagulation factors will be monitored at Screening, and will be assessed throughout the study as clinically indicated for participants taking anticoagulant therapy.

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) per institutional standard. Physical examinations (comprehensive/full or symptom-directed) will be performed as specified in the SoA (Section 1.3). A comprehensive/full 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. Height and weight will also be measured and recorded; height will only be measured and recorded at Screening.

A brief directed physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.2 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 BP. Height will be measured at Screening only.

- BP 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 BR <90 mm Hg. 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) shows an elevated BP (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.
- At the C1D8 telephone visit and if required between clinic visits, participants will have BP measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP retest, or other clinically appropriate intervention(s).

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 electrocardiograms 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. 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 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 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 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

CBC with differential and clinical chemistry results must be reviewed before administration of study intervention. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

8.3.5.2 Urine Dipstick

Urine dipstick testing will be performed locally within 7 days prior to start of treatment. Participants with ≥2+ (≥100 mg/dL) proteinuria on urine dipstick testing (urinalysis) 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 randomized, 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.

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

8.3.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix 9) at screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

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

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

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

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

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

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

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 participants provides documented consent 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 pembrolizumab, or 30 days following cessation of lenvatinib/placebo, whichever occurs last, must be reported by the investigator. If the participant initiates new anticancer therapy following discontinuation of study intervention, the time period for reporting pregnancies and exposure during breastfeeding is reduced to 30 days following cessation of study intervention.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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 7.

Table 7 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	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	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

DILI=drug-induced liver injury; ECI=event of clinical interest

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 AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

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

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

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

Any suspected endpoint which 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

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
2. 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 this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

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 adverse event

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

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

CCI

CCI [redacted]

8.8.1 Planned Genetic Analysis Sample Collection

CCI [redacted]

8.9 Future Biomedical Research Sample Collection

CCI [redacted]

8.10 Medical Resource Utilization and Health Economics

As of Amendment 07: Medical Resource Utilization and Health Economics data collection will be discontinued. Original protocol text that is contained in this section has been retained for reference.

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

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

All-cause hospitalizations and emergency department visits must be reported in the eCRF from the time of treatment allocation/randomization through 120 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days before intervention 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 providing documented 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 7 days of Cycle 1 Day 1. An exception is hepatitis and HIV testing which may be done up to 28 days prior to the first dose of study intervention if mandated by local health authority. 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 7 days of Cycle 1 Day 1.
- Full physical examination to be performed within 7 days of Cycle 1 Day 1.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to Cycle 1 Day 1. 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 study site laboratory).
- Tumor tissue must have been obtained prior to randomization.

8.11.1.1 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.

8.11.2 Treatment Period

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

8.11.2.1 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).

8.11.3 Posttreatment Visit

8.11.3.1 Safety Follow-up Visit

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

8.11.3.2 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 Efficacy Follow-up and should be assessed approximately Q12W (or more frequently as needed) by clinic visit to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who attain an investigator-determined CR and stop study intervention with pembrolizumab + lenvatinib or pembrolizumab + placebo will have 30- and 90-day Safety Follow-up Visits and move to follow-up visits per SoA.

After Year 3, imaging should be performed Q24W. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks).

NOTE: As of Amendment 07: Efficacy Follow-up Visits will be discontinued. The section is retained for reference.

8.11.3.3 Survival Follow-up Contacts

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

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

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

8.11.4 Survival Status

As of Amendment 07: Survival Follow-up Visits will be discontinued. Those participants remaining on study treatment at the time of Amendment 07 should continue to be monitored in the study through the AE reporting period (Section 8.4). Original protocol text that is contained in this section has been retained for reference.

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of 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.

8.11.5 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

As of Amendment 07: The Statistical Analysis Plan is amended as follows.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-003 (data cutoff 18-JAN-2023), eDMC recommended stopping the study due to lack of efficacy because pembrolizumab in combination with lenvatinib did not demonstrate an improvement in OS, one of the trial's dual primary endpoints, compared to pembrolizumab plus placebo and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded as of 27-MAR-2023. The prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. The study has been unblinded as of 27-MAR-2023. Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 07 were documented in previous protocol amendments(s) (consistent with International Conference on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized will be documented in an sSAP and referenced in the Clinical Study Report for the study. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report. Separate analysis plans (ie, separate documents from the sSAP) may be developed to detail other planned analyses.

The extension portion of the study, which includes the additional enrollment of Chinese participants, will not be included as part of the study population used to address the protocol objectives. Additional detail regarding the analysis associated with these participants will be described in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized here. The comprehensive plan is provided in Sections 9.2 through 9.12. As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints. The SAP summary has been updated accordingly.

Study Design Overview	A Phase 3 Randomized, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) and Lenvatinib (E7080/MK-7902) Versus Pembrolizumab Alone as First-line Intervention in Participants with Advanced Melanoma (LEAP-003)
Treatment Assignment	Approximately 660 participants will be randomized in a 1:1 ratio between 2 treatment groups (1) pembrolizumab + lenvatinib or (2) pembrolizumab + placebo. Stratification factors are in Section 6.3.2. This is a randomized double-blinded study with in-house blinding.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	1) PFS as assessed by BICR per RECIST 1.1 2) Overall survival (OS)
Key Secondary Endpoints	1) Objective response (OR) as assessed by BICR per RECIST 1.1 2) DOR as assessed by BICR per RECIST 1.1
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS will be evaluated by comparing pembrolizumab + lenvatinib to pembrolizumab + placebo using a stratified log-rank test. Estimation of the hazard ratio (HR) will be done using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with sample size weights will be used for the analysis of ORR.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method.
Interim Analyses	As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. CCI IAs will be performed in this study. Results will be reviewed by an CCI IAs are summarized below. Details are provided in CCI CCI [redacted]
Multiplicity	

Sample Size and Power	As of Amendment 07, the final analysis of the study described in the SAP will not be performed. The planned sample size is approximately 660 participants. CCI [redacted]

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.

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Blinding procedures related to the planned IAs are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Dual Primary

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

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 9.6.1 for the censoring rules.

Overall Survival (OS)

Overall survival is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known contact.

Secondary

Objective Response Rate (ORR) per RECIST 1.1 Assessed by BICR

Objective response rate is defined as the proportion of participants who have a CR, or a PR. Responses are based on confirmed assessments by the BICR per RECIST 1.1.

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. Response duration for participants who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Response duration will be calculated per RECIST 1.1 based on BICR by the imaging vendor.

Additional details of the efficacy measurements are described in Section 4.2.1.1.

9.4.2 Safety Endpoints

Safety parameters are described in Section 4.2.1.2.

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

9.4.3 Patient-reported Outcome Endpoints

The following secondary PRO endpoints will be evaluated:

- Global Health Status/QoL scale (EORTC QLQ-C30 items 29-30)
- Physical functioning scale (EORTC QLQ-C30 items 1-5)

The EQ-5D-5L will be evaluated as an exploratory endpoint. The EQ-5D-5L analyses will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The ITT population will serve as the population for primary efficacy analysis (PFS and OS). All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

The global study will only contain approximately 660 randomized participants. The extension portion of the study enrolling additional China participants will not be included in the global study population used as the primary population to address protocol objectives but will be analyzed as specified in the sSAP.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study medication for 1 or more cycles but receives the correct treatment for the remaining cycles will be analyzed according to the participant's randomized treatment group and a narrative will be provided for any events that occur during the cycle for which the participant was incorrectly dosed.

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.

The global study will only contain approximately 660 randomized participants. The extension portion of the study enrolling additional China participants will not be included in the global study population used as the primary population to address protocol objectives but will be analyzed as specified in the sSAP.

9.5.3 Patient-reported Outcome Analysis Populations

The PRO analyses are based on the PRO Full Analysis Set population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study medication.

9.5.4 Pharmacokinetic Analysis Population

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

9.6 Statistical Methods

NOTE: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints. Original protocol text that is contained in this section has been retained for reference.

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

The stratification factors used for randomization (Section 6.3.2) will be applied to the models for efficacy described herein. If there are a small number of responses in one or more strata,

for the purpose of analysis, strata will be combined to ensure a sufficient number of participants, responses, and events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response and event counts by stratum.

9.6.1 Statistical Methods for Efficacy Analyses

9.6.1.1 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. CCI [redacted]. The stratification factors used for randomization (see Section 6.3) will be applied to both the stratified log-rank test and the stratified Cox model.

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

CCI [redacted]

CCI

[redacted]

9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. CCI [redacted] The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model if applicable.

Participants without documented death at the time of analysis will be censored at the date of last contact.

9.6.1.3 Objective Response Rate

The stratified Miettinen and Nurminen method will be used for the comparison of the ORR between the 2 treatment groups. CCI [redacted]. The stratification factors used for randomization (Section 6.3) will be applied to the analysis.

CCI [redacted]

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis. The details of censoring rules for DOR analysis will be described in the sSAP.

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

CCI [redacted]

CCI

[redacted]

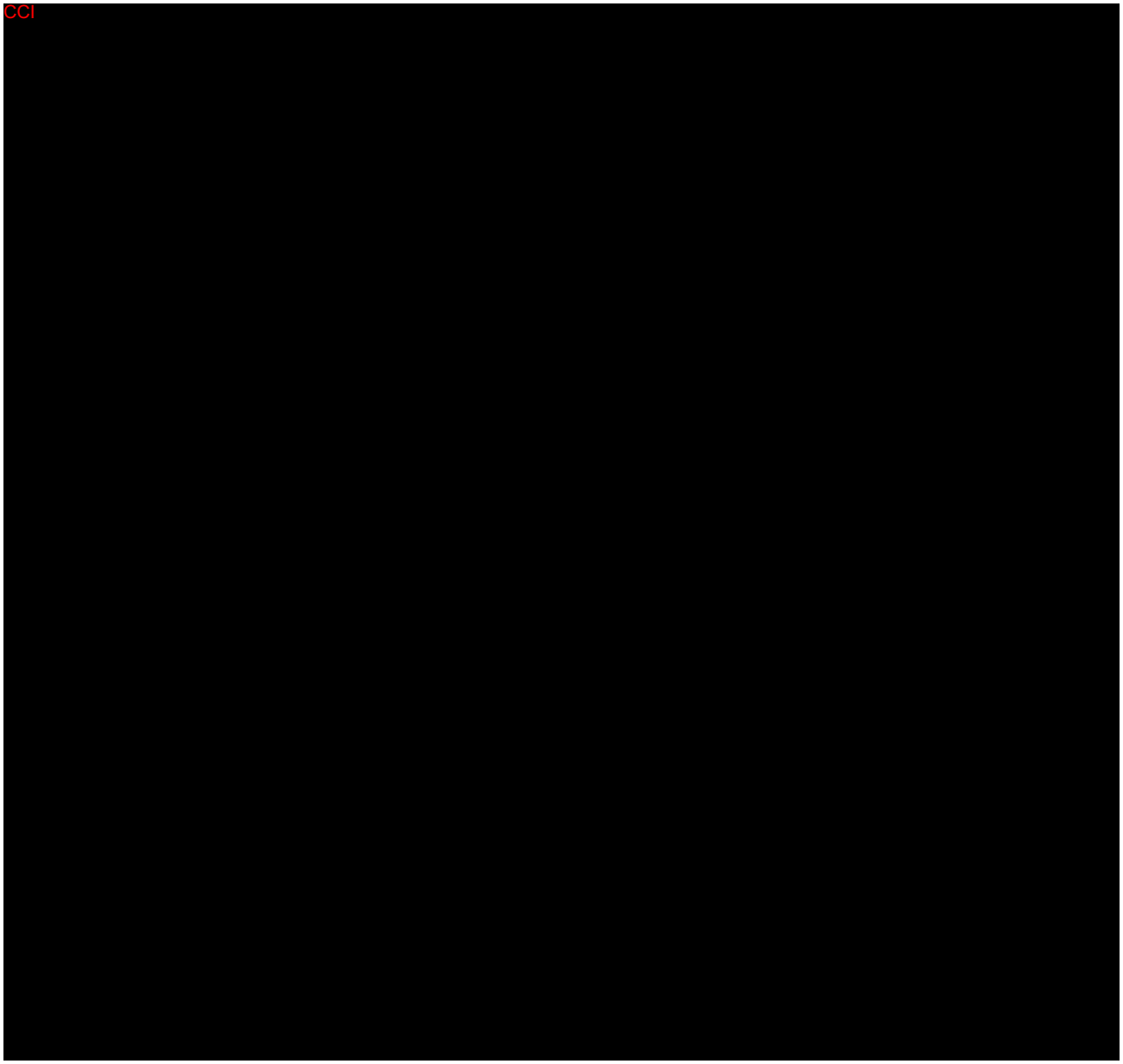
9.6.2 Statistical Methods for Safety Analyses

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

Adverse Events

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped system organ class. AEs will be graded by the investigator according to the NCI CTCAE, v4.0.

CCI



CCI

[redacted]

9.6.3 Analysis Methods for Patient-reported Outcome Endpoints

The change from baseline in the following secondary PRO endpoints from the EORTC QLQ C30 will be assessed:

- Global health status/QoL score (QLQ-C30 items 29-30)
- Physical functioning score (QLQ-C30 items 1-5)

CCI

[redacted]

9.6.4 Summaries of Demographic and Baseline Characteristics

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

9.7 Interim Analyses

NOTE: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. This section is retained for reference.

An eDMC will be convened to review the unblinded efficacy results and accumulating safety at the planned IAs. An external unblinded statistician and programmer will be responsible for conducting and presenting the IAs results to the eDMC. The eDMC responsibilities and review schedules will be outlined in the eDMC charter. The recommendation of the eDMC will be communicated to an Executive Oversight Committee. In the event of a recommendation to halt the study early due to safety concerns, the Sponsor will communicate

this to the appropriate regulatory agencies. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this Executive Oversight Committee may be unblinded to results at the treatment level in order to act on these recommendations.

A limited number of additional personnel may be unblinded, if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded to the results will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

If the eDMC makes a recommendation to alter the study conduct, it may be implemented upon EOCs advice; and health authorities and IRB/IEC will be informed accordingly.

9.7.1 Efficacy Interim Analyses

CCI

9.7.2 Safety Interim Analyses

The eDMC conducted regular safety interim analyses. The timing of these safety interim analyses was specified in the eDMC charter. No further formal efficacy analysis will be conducted. Safety monitoring will continue as per protocol.

9.8 Multiplicity

NOTE: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. Original protocol text that is contained in this section has been retained for reference.

CCI

CCI

[redacted]

9.8.1 Progression-free Survival

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.8.2 Overall Survival

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.8.3 Objective Response Rate

CCI

[redacted]

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned interim efficacy analysis; however, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for PFS adopting a conservative multiplicity adjustment will be prespecified in the sSAP. This analysis will be performed if efficacy data is requested by the eDMC during a safety evaluation to assess risk/benefit.

9.9 Sample Size and Power Calculations

NOTE: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. This section is retained for reference.

A total of approximately 660 participants will be randomized in a 1:1 ratio in the global study.

CCI [redacted]

9.9.1 Progression-free Survival

PFS is a dual primary endpoint. CCI [redacted]

CCI [redacted]

9.9.2 Overall Survival

Overall survival is a dual primary endpoint. CCI [redacted]

CCI [redacted]

CCI

[redacted]

9.9.3 Objective Response Rate

ORR is a secondary endpoint. CCI

CCI

[redacted]

9.10 Subgroup Analyses

Both efficacy and safety may be analyzed for the following subgroups as appropriate. For efficacy endpoints, the HR and two-sided 95% CI for comparing PFS as assessed by BICR and OS of combination therapy versus pembrolizumab monotherapy will be presented in forest plots for the subgroups. Median PFS and 95% CIs will be presented for all subgroups. Similar plots will be provided for OS. For safety endpoints, all treatment-emergent AEs, treatment-emergent AEs of NCI CTCAE v4.0 Grades 3 and 4, and treatment-emergent SAEs may be summarized by the subgroups.

CCI

[redacted]

CCI [redacted]

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. Dose interruption for each drug, dose reduction or dose increase for lenvatinib will be summarized. Summary statistics will be provided on extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

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

Additional details regarding the EOC can be found in the DMC charter.

10.1.4.3 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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical 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 trials 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, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 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 5.2 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 16 Protocol-required Clinical 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	Carbon Dioxide (CO_2) or 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 (FT4)[e]	Lactate dehydrogenase[c]	Cholesterol[c]
	Triglycerides[c]	CPK[f]	Pregnancy test	Triiodothyronine (Total T3)[e]
Routine Urinalysis[g]	Specific gravity Glucose, pH, protein[h], hemoglobin or blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	PT/INR and aPTT/PTT[i] Serology (HIV RNA, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody[j]). Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for POCBP).

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 with Cycle 2), at the time of discontinuation (End-of-Treatment), and at the 30- and 90-day 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 (and 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/placebo 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. Not required unless mandated by local health authorities.

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 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." Lenvatinib overdose without an associated adverse event is not reportable as an AE. Refer to Section 8.5 for the definition of overdose for lenvatinib.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

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

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

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

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

10.3.4 Additional Events Reported

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same 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 the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

No applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

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

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

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

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

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 POCBP 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 17 during the protocol-defined time frame in Section 5.1.

Table 17 Highly Effective Contraception Methods

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[a,b] • IUS[b,c] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.
[a] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [b] If hormonal contraception efficacy for a participant assigned female sex at birth is potentially decreased due to interaction(s) with study intervention(s) (eg, CYP3A4 inducers), penile/external condoms must be used in addition to POCBP's hormonal contraception. [c] IUS is a progestin-releasing IUD. Note: • Male and female condoms should not be used together (due to risk of failure with friction) • Tubal occlusion includes tubal ligation

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 China

Section 1.1 Synopsis, Section 3 Hypotheses, Objectives, and Endpoints, Section 4.1 Overall Design

LEAP-003 was unblinded per an eDMC recommendation made on 27-MAR-2023. To date, there is comparatively limited data regarding the use of pembrolizumab for melanoma in China. In addition, part of the LEAP-003 China cohort was enrolled after the global study as part of a China-specific extension, resulting in shorter follow-up. For these reasons, longer data collection and follow-up of all participants enrolled in China are scientifically justified. Therefore, as of Amendment 09, additional data collection and longer follow-up according to the SoA (Section 1.3) should be done for all participants enrolled in China.

When the extended follow-up period ends at the Sponsor's discretion, but no longer than approximately 18 months from Amendment 09 approval in China, participants enrolled in China will no longer follow Section 10.7.1 and will follow activities currently outlined for the global study.

Section 1.1 Synopsis, Section 3 Hypotheses, Objectives, and Endpoints, Section 4.1 Overall Design, Section 6.1 Study Intervention(s) Administered, Section 6.6 Dose Modification

As of Amendment 09, the sentence "All participants beyond the 30-day Safety Follow-up Visit should be discontinued from study" does not apply to participants enrolled in China.

Section 1.2 Schema

The original study design, Figure 1, applies to participants enrolled in China.

Section 1.3 Schedule of Activities

Data collection for participants enrolled in China will include all efficacy and safety evaluations per the SoA (except as noted below under "Exceptions to data collection") to support the analysis of overall survival, progression-free survival, safety, disposition, and other endpoints.

Exceptions to data collection (ie, will no longer be performed):

- ePRO (EORTC QLQ-C30; EuroQoL (EQ-5D-5L)
- Pembrolizumab PK
- Pembrolizumab antidrug antibodies
- Lenvatinib PK blood sample
- Blood for serum biomarker

- Blood for RNA analysis
- Blood for circulating tumor nucleic acids
- Blood for plasma biomarker
- Blood for genetic analysis
- Tumor blocks or slides
- Provide stool analysis informed consent and kits
- Stool analysis

Section 1.3 Schedule of Activities, Section 8.2.1 Tumor Imaging and Assessment of Disease

Oncological imaging (including non-oncological imaging incidentally found to change RECIST 1.1 assessment of tumor status) should not be submitted to the central imaging vendor but assessed locally; scans should be stored at the site.

Section 8.8 Biomarkers

As of Amendment 07, biomarkers are no longer collected globally. Clarification: The extended data collection in China as per Amendment 09 does not extend to biomarker collection.

Section 9.9 Sample Size and Power Calculations

Additional efficacy and safety data collected on participants enrolled in China may be used for supportive analyses and will not count towards the Primary Analysis.

10.7.2 France

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

Participants should be discontinued from study intervention if any of the following AEs occur:

- Recurrent Grade 3 colitis
- Grade 4 skin rash
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Please refer to the current pembrolizumab SmPC for additional guidance on management of immune-related AEs associated with pembrolizumab.

Please refer to the current lenvatinib SmPC for additional guidance on management of AEs associated with lenvatinib administration and other contraindications.

10.7.3 Germany

Participant's legally acceptable representative in Germany

As per Sections 7.1 (Discontinuation of Study Intervention), 7.2 (Participant Withdrawal from the Study, 8.1.1 (Informed Consent) and 8.1.1.1 (General Informed Consent), a participant's legally acceptable representative may sign the Informed Consent or request discontinuation of the study. *This is to clarify that in Germany participants incapable of giving informed consent for their study participation will not be enrolled into the study. In the event a participant should become incapable of giving informed consent during the study, this participant will be withdrawn from the study. Thus the "legally acceptable representative" in the above mentioned protocol sections is not applicable for Germany.*

Exclusion of MUGA (= multigated acquisition) scans at German sites

Sections 5.2 (Exclusion criteria) and 8.3 (Safety assessments) as well as other sections of the protocol refer to MUGA scans or ECHO scans for LVEF assessments. As per protocol, MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. *This is to clarify that in Germany MUGA scans are not standard practice and that therefore only ECHO scans will be done at the German sites. No MUGA scans will be done in Germany.*

Section 5.2 Exclusion Criteria

- Exclusion criterion #8 - Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required at Screening.
- Exclusion criterion #9 - Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for hepatitis B or hepatitis C is required at Screening.
- Exclusion criterion #11 - Has a known history of active tuberculosis (TB; *Bacillus* tuberculosis). Testing for tuberculosis is required at Screening.

10.7.4 United Kingdom

Section 5.2 Exclusion Criteria

- Exclusion criterion #19 - Has prolongation of QTc interval (calculated using Fridericia's formula) to >480 msec.
- Exclusion criterion #25 - Live vaccines within 30 days prior to the first dose of study intervention, while receiving study intervention, and for 90 days after the last dose of study intervention, are prohibited.

Section 5.1 Inclusion Criteria

- Inclusion criterion #11 - A pregnancy test is required every cycle for POCBP, and if urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

10.7.5 Italy

Section 6.6.1.2 Dose Modification and Toxicity Management of Infusion Reactions

Participants should be discontinued from study intervention if any of the following AEs occur:

- Recurrent Grade 3 colitis

Please refer to the current lenvatinib SmPC for management and monitoring of participants with AEs associated with lenvatinib administration.

10.7.6 Canada

Section 6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formation

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

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

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 6 and Figure 2]). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of 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 to the CIV for potential 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 PD) and iCPD (confirmed PD). 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 to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new 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 pseudoprogression, 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, 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 1.3 and submitted to the CIV.

Detection of Progression at Visits After Pseudoprogression Resolves

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

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- 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 predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (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 more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

[Oken, M. M., et al 1982]

10.10 Appendix 10: Technical Note for the Poisson Mixture Model

The Poisson mixture model is applied to account for the failure rates decreasing over time in the study, which is a mixture of patients suffering disease recurrence and others who have excellent long-term results. The survival function [de Castro, M., et al 2010] as a function of time t for a control group (c) is:

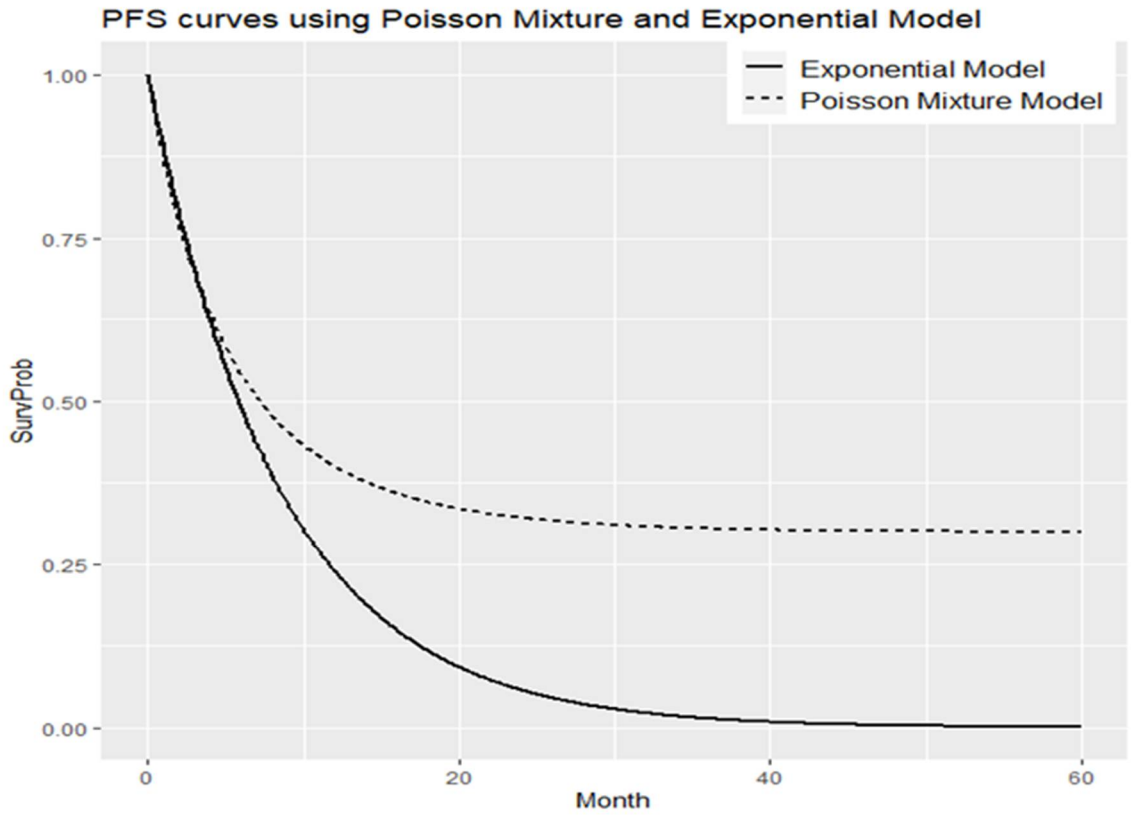
$$S(t) = \exp(-\theta(1 - \exp(-\lambda t))),$$

where $\theta = -\log(Cure\_Rate)$, λ is a constant hazard rate, and $t \geq 0$.

For the advanced melanoma setting, according to the published literature [Hurley, J., et al 2013], investigator's feedback, and study assumption, ~30% of subjects will be cured over a long-term period of time (ie, Cure_Rate = 0.3) and it is more likely after 1 to 2 years of study initiation, with minimal progression-free survival (PFS) events accumulation.

According to the published literature [Hurley, J., et al 2013], we assume PFS follows a Poisson mixture model distribution with ~40% PFS rate at 12 months in the pembrolizumab arm. shows the PFS curves using the Poisson mixture model and exponential model. The curve from the Poisson mixture model looks similar to the curve in the published literature [Hurley, J., et al 2013].

Figure 5 PFS Curves Using the Poisson Mixture Model and Exponential Model



10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICR	blinded independent central review
BP	blood pressure
BRAF	proto-oncogene B-Raf
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
C2D1	Cycle 2 Day 1
CI	confidence interval
CIV	central imaging vendor
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

Abbreviation	Expanded Term
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EFS	event-free survival
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end-of-treatment
ePRO	electronic Patient-reported Outcomes
EQ-5D-5L	European Quality of Life 5-dimension 5-level (questionnaire)
FA	Final analysis
FBR	Future biomedical research
FDA	US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle-stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
HCC	Hepatocellular Carcinoma
HCV	hepatitis C virus
HGRAC	Human Genetic Regulatory Administration of China
HR	hazard ratio
HRQoL	Health-related Quality of Life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
iCRO	imaging Contract Research Organization

Abbreviation	Expanded Term
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
iPR	iRECIST partial response
IRB	Institutional Review Board
iRECIST	RECIST 1.1 for Immune-based Therapeutics
IRT	interactive response technology
iUPD	iRECIST unconfirmed progressive disease
iSD	iRECIST stable disease
MCV	MCV = mean corpuscular volume
MEK	mitogen-activated extracellular signal-regulated kinase
MEKi	MEK 1/2 inhibitor
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not estimable
NSCLC	non-small cell lung cancer
ORR	objective response rate
ORRWeek24	objective response rate at Week 24
OS	overall survival
PBPK	physiologically based PK
PD	Progressive disease
PD-1	programmed cell death 1
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic
POCBP	Participant of childbearing potential
PR	Partial response
PRO	Patient-reported outcome

Abbreviation	Expanded Term
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RTK	Receptor tyrosine kinase
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	standard of care
TB	tuberculosis
TRAE	treatment-related adverse event
TTD	Time to true deterioration
ULN	upper limit of normal
USPI	United States Package Insert
VEGF	vascular endothelial growth factor

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