Official Protocol Title:	A Phase 2, Single-arm, Open-label Clinical Trial of Pembrolizumab Plus Lenvatinib in Participants with First-line Advanced/Metastatic Non-clear Cell Renal Cell Carcinoma (nccRCC) (KEYNOTE-B61)
NCT number:	NCT04704219
Document Date:	31-Oct-2024

Title Page

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Protocol Title: A Phase 2, Single-arm, Open-label Clinical Trial of Pembrolizumab Plus Lenvatinib in Participants with First-line Advanced/Metastatic Non-clear Cell Renal Cell Carcinoma (nccRCC) (KEYNOTE-B61)

Protocol Number: B61-04

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

Sponsor Name:

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

This study is part of a collaboration between MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT04704219
IND	122,753
EU CT	2023-504944-32-00
EudraCT	2020-004087-26

Approval Date: 31 October 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 4	31-OCT-2024	To add the option of an extension study.
Amendment 3	04-AUG-2022	To clarify that treatment may continue beyond radiographic disease progression if the participant is deriving clinical benefit and after Sponsor consultation.
Amendment 2	25-AUG-2021	Administrative changes, clarifications to protocol language and interpretation, and country-specific requirements were updated.
Amendment 1	15-APR-2021	Amendment implemented to update non-clear cell histology confirmation requirements. The revision is removing the prospective mandatory central review process during screening. This revision allows confirmation of non-clear cell RCC histology/diagnosis to be performed locally to confirm eligibility. Pembrolizumab dose modification table (DMT) updated. Additional changes were also made to align with regional authority requirements and to comply with the lenvatinib label requirements for ONJ.
Original Protocol	22-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

To add the option of an extension study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 6.7, Intervention After the End of the Study	Added extension study language for intervention after the end of the study.	To address a strategy change by providing an option for participants to roll over into an extension study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	Added NCT number.	For completeness.
	Added EU CT number.	See rational above.
Section 4.4, Beginning and End of Study Definition	Added definition of when the overall study ends for purposes of analysis and reporting.	To align with the EU CTR.
	Added definition of local start of the study for EEA countries.	See rationale above about the EU CTR.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Added a statement describing how to report SUSARs.	Refer to Section 4.4 rationale about the EU CTR.
Section 9.1, Statistical Analysis Plan Summary	Specified that no formal interim analysis is planned.	Interim analyses have been performed but were not formally planned.
Section 9.5.2, Safety Analysis Population	Removed reference to Section 9.6 for details on handling missing data for safety analyses.	To correct an error.
Section 9.7, Interim Analyses	Specified that no formal interim analyses are planned.	Refer to Section 9.1 rationale.
Section 9.7.1, Efficacy Interim Analysis	Specified that no formal interim analysis for efficacy is planned.	Refer to Section 9.1 rationale.
	Updated timing of final analysis from 24 months to approximately 36 months.	To align with the end of the study.
Section 10.1.3, Data Protection	Added text regarding Sponsor's EU-approved Binding Corporate Rules.	Refer to Section 4.4 rationale about the EU CTR.

Section Number and Name	Description of Change	Brief Rationale
Section 10.1.5, Compliance With Study Registration and Results Posting Requirements	Updated referenced EU regulation and added a submission website link.	Refer to Section 4.4 rationale about the EU CTR.
Section 10.1.6, Compliance with Law, Audit, and Debarment	Added text for investigators located in countries with serious breach reporting requirements.	Refer to Section 4.4 rationale about the EU CTR.
Section 10.1.7, Data Quality Assurance	Added the EU CTR requirement for a longer retention period for records and documents.	Refer to Section 4.4 rationale about the EU CTR.
Section 10.3.1, Definitions of Medication Error, Misuse, and Abuse	Added this section.	Refer to Section 4.4 rationale about the EU CTR.
	Renumbered former Sections 10.3.1 through 10.3.5 to current Sections 10.3.2 through 10.3.6.	Due to the addition of new Section 10.3.1.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Single-arm, Open-label Clinical Trial of Pembrolizumab Plus Lenvatinib in Participants with First-line Advanced/Metastatic Non-clear Cell Renal Cell Carcinoma (nccRCC) (KEYNOTE-B61)

Short Title: Pembro + Lenva for 1L nccRCC

Acronym: KEYNOTE-B61

Hypotheses, Objectives, and Endpoints:

In male or female participants at least 18 years of age with previously untreated histologically confirmed advanced/metastatic nccRCC:

Primary Objectives	**Primary Endpoints**
- To evaluate the ORR of pembrolizumab + lenvatinib per RECIST 1.1 by blinded independent central review (BICR)	- Objective response (OR): a confirmed complete response (CR) or partial response (PR)
Secondary Objectives	**Secondary Endpoints**
- To evaluate the DOR of pembrolizumab + lenvatinib in participants with a confirmed CR or PR per RECIST 1.1 by BICR	- DOR: the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first
- To evaluate PFS per RECIST 1.1 by BICR in participants receiving pembrolizumab + lenvatinib	- PFS: the time from first dose to the first documented PD or death from any cause, whichever occurs first
- To evaluate the overall survival (OS) of participants receiving pembrolizumab + lenvatinib	- OS: the time from first dose until death from any cause
- To evaluate the CBR of pembrolizumab + lenvatinib per RECIST 1.1 by BICR	- Clinical benefit: a confirmed CR, PR, or stable disease (SD) for at least 6 months
- To evaluate the DCR of pembrolizumab + lenvatinib per RECIST 1.1 by BICR	- Disease control: a confirmed CR, PR or SD
- To evaluate the safety of pembrolizumab + lenvatinib	- Adverse events (AEs) - Discontinuations due to AEs

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Previously untreated advanced or metastatic nccRCC
Population	Participants with previously untreated advanced or metastatic nccRCC
Study Type	Interventional
Intervention Model	Single Group This is a multisite study.
Type of Control	No Treatment Control
Study Blinding	Unblinded Open-label
Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 152 participants will be enrolled in the study.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="2">Pembrolizumab + Lenvatinib</td><td>Pembro-lizumab</td><td>400 mg</td><td>Q6W</td><td>IV</td><td>Up to 18 infusions, progressive disease or discontinuation</td><td>Experi-mental</td></tr>
<tr><td>Lenvatinib</td><td>20 mg</td><td>QD</td><td>Oral</td><td>Until progressive disease or discontinuation</td><td>Experi-mental</td></tr>
<tr><td colspan="7">IV=intravenous; Q6W=every 6 weeks; QD=every day.</td></tr>
</table>

Other current or former names or aliases for study interventions are as follows:

Pembrolizumab: KEYTRUDA®, MK-3475, lambrolizumab
Lenvatinib: LENVIMA®, Kisplyx, MK-7902, E7080</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>1</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact.

After a screening phase of up to 28 days, each participant will be assigned to receive study intervention. Study intervention with pembrolizumab will continue for up to 18 administrations (approximately 2 years) or until a discontinuation criterion is met. Study intervention with lenvatinib may continue beyond 2 years until a discontinuation criterion is met. Participants who stop study intervention after receiving 18 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a complete response and stop study intervention may be eligible for up to 9 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression (Section 8.10.3).

After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 8.4.</td></tr>
</table>

	Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, the start of a new anti-cancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

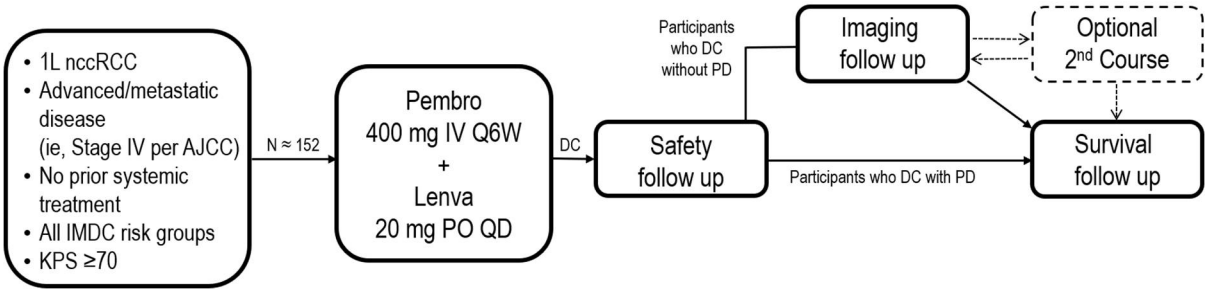
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



1L=first-line; AJCC=American Joint Committee on Cancer; DC=discontinuation; IMDC=International Metastatic RCC Database Consortium; IV=intravenous; KPS=Karnofsky Performance Status; nccRCC=non-clear cell renal cell carcinoma; PO=per oral; PD=progressive disease; Q6W=every 6 weeks; QD=every day.

1.3 Schedule of Activities

1.3.1 Initial Treatment Phase

Table 1 Schedule of Activities – Initial Treatment Phase

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Administrative Procedures																					
Informed Consent	X																				Informed consent must be obtained prior to any protocol-specific procedures. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/ Exclusion Criteria	X																				
Participant Identification Card	X	X*																			*Update with allocation number from IRT.
nccRCC Disease History	X																				
Demographics and Medical History	X																				Medical history includes substance usage (drugs, alcohol, tobacco and caffeine), family history of premature CV disease, and surgical history.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Prior/ Concomitant Medication Review	X	←														→					Record medications received within 28 days before the first dose of study intervention through 30 days after the last dose of study intervention, or >30 days for medications for SAEs and ECIs as outlined for AE monitoring timeframe below.
Treatment Allocation		X																			First dose of study treatment must be administered within 3 days of allocation.
Study Intervention Administration																					
Lenvatinib Dispensed		X			X		X	X	X	X	X	X	X	X	X	X					
Lenvatinib Container Returned					X		X	X	X	X	X	X	X	X	X	X	X				
Pembrolizumab Administration		X					X		X		X		X								

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Tumor Imaging and Efficacy Assessments																					
Imaging of chest/ abdomen/ pelvis and Response Assessment	X	←														→					The same modality should be used for all scans. The first on-treatment assessment should occur at Week 12 (84 ± 7 days) and be repeated Q6W (42 ± 7 days) until Week 54 and then Q12W (84 ± 7 days) thereafter. Schedule should follow calendar days and not be adjusted for delays in treatment.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Bone Scan	X	◄———	———	———	———	———	———	———	———	———	———	———	———	———	———	———►					Perform a screening bone scan in all participants. After allocation, only continue bone scans if participant's scan at Screening was positive. The schedule for bone scans is at Week 18 (126 ± 7 days); Q12W (84 ± 7 days) until Week 54; then Q24W (168 ± 7 days) thereafter. Perform for participants at time of CR if positive at baseline. Schedule should follow calendar days and not be adjusted for delays in treatment.
Brain Scan	X*																				*Perform at Screening ONLY for participants with previously documented brain metastases (to confirm stability) or who are clinically symptomatic. Brain scans will be performed as clinically indicated and to confirm a CR in participants with brain metastasis at baseline.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Subsequent Anticancer Therapy Status																	X	X	X	X	
Survival Status		←														→				X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures/Assessments																					
Full Physical Examination	X																X				
Directed Physical Examination		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Height	X																				
Weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			HR, DBP, SBP, RR, temperature.
ECHO/ MUGA	X																X				Additional assessments may be performed as clinically indicated.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
12-lead ECG	X	X			X		X				X*		X*		X*		X	X			*After Cycle 2, repeat ECG every other cycle (eg,C4, C6, C8, C10, etc.). For high-risk participants (Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
KPS	X																				At screening, perform within 10 days prior to first dose of study intervention.
ECOG Performance Status	X	X					X		X		X		X		X		X	X			At screening, perform within 10 days prior to first dose of study intervention.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
AE/SAE Review	X	◄———														———►		X*			*Report AEs occurring within 30 days after the last dose of study intervention treatment or before initiation of a new anticancer treatment. Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if new anticancer therapy is initiated, whichever is earlier.
Laboratory Procedures/Assessments																					
Pregnancy Test – Urine or Serum hCG (WOCBP only)	X	X*			X		X	X	X	X	X	X	X	X	X	X		X			WOCBP require negative test prior to allocation. *If more than 24 hours have elapsed prior to first dose of study intervention, another negative pregnancy test is required prior to starting study intervention. Ongoing pregnancy tests should be conducted as indicated in Appendix 2.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Urine Dipstick Testing (or Urinalysis) for Protein	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					Urinalysis as clinically indicated. See Section 6.6.2.2 for guidance on testing frequency in cases of elevated protein. Participants with proteinuria ≥2+ (≥100 mg/dL) at screening will undergo 24-hour urine collection for quantitative assessment of proteinuria.
HIV, Hepatitis B, Hepatitis C	X*																				*Only if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
Hematology	X	X		X			X		X		X		X		X		X	X			At screening, perform within 10 days prior to first dose of study intervention.
Chemistry	X	X		X			X		X		X		X		X		X	X			
Lipase and Amylase	X	X		X			X		X		X		X		X		X	X			

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
PT/INR and aPTT or PTT	X																				At screening, perform within 10 days prior to first dose of study intervention. PTT is acceptable if aPTT cannot be determined. Perform additional testing as clinically indicated for participants taking anticoagulants.
T3 or FT3, FT4, TSH	X	X					X		X		X		X		X		X	X			At screening, perform within 10 days prior to first dose of study intervention.
Biomarkers																					
Blood for Genetic Analysis		X																			This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

Trial Period	Screening	Initial Treatment Phase Cycle = 42 Days															EOT	Posttreatment			Notes
																		Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		**1**					**2**		**3**		**4**		**5 to 18**		**>18**		**At D/C**	**30 days after last dose**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**22**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Blood for Serum Biomarkers		X		X			X		X								X				
Blood for ctDNA Analysis		X					X		X		X*		X*		X*		X				* After C3D1, collect blood for ctDNA at D1 of every cycle (C4, C5, C6, etc.) up until and at C10. After C10D1, collect D1 of every other cycle (C12, C14, C16, etc.). Collect at EOT.
Archival or Newly Obtained Tumor Tissue Sample Collection	X																				Tumor tissue (archival or newly acquired core or excisional biopsy) will be obtained and submitted at screening. Tumor blocks are preferred over cut slides.

AE=adverse event; aPTT=activated PTT; C=Cycle; ctDNA=circulating tumor DNA; CR=complete response; CV=cardiovascular; D=Day; DBP=diastolic blood pressure; D/C=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event of clinical interest; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; FT3=free T3; FT4=free thyroxine; FU=follow-up; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HR=heart rate; IEC=independent ethics committee; INR=international normalized ratio; IRB=institutional review board; IRT=interactive response technology; KPS=Karnofsky performance status; MUGA=multiple gated acquisition scan; nccRCC=non-clear cell renal cell carcinoma; PT=prothrombin time; PTT=partial thromboplastin time; Q6W=every 6 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

1.3.2 Translational Oncology Research

Table 2 Schedule of Activities – Additional Biomarker Collections From Select Sites

Trial Period	Screen-ing	Initial Treatment Phase Cycle = 42 Days																EOT	Posttreatment			Notes
																			Safety FU	Efficacy FU	Survival FU	
Visit Timing/ Cycle Number		1					2		3		4		5 to 18		>18			At D/C	30 days after last dose	Per Imaging Schedule	Q12W	At selected TOR sites, all samples will be collected as indicated in the Schedule of Activities from all participants at these sites. See Procedure Manual for details of selected sites.
Cycle Day		1	8	15	22	36	1	22	1	22	1	22	1	22	1	22						
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			+7	±7	±14	
Biomarker Sample Collection																						
Blood for RNA Analysis		X		X			X											X				
Blood for PBMC		X		X			X											X				

D/C=discontinuation; EOT=end-of-treatment; FU=follow-up; PBMC=peripheral blood mononuclear cells; Q12W=every 12 weeks; RNA=ribonucleic acid; TOR=translational oncology research.

1.3.3 Second Course Treatment Phase

Table 3 Schedule of Activities – Second Course Treatment Phase

Trial Period	**Second Course Treatment Phase Cycle = 42 days**						**EOT**	**Posttreatment**			**Notes**
Visit Timing/ Cycle Number	**1**		**2**		**3 to 9**			**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**22**	**1**	**22**	**1**	**22**	**At D/C**	**30 days after D/C**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	**±7**	**±14**	
Administrative Procedures											
Informed consent	X										Obtain prior to initiating Second Course treatment. If the investigator plans to treat beyond disease progression, additional consent is required.
Second Course Eligibility Criteria	X										The Second Course eligibility criteria must be satisfied, and all safety parameters listed in the inclusion criteria and none listed in the exclusion criteria must be met.
Concomitant Medications	←		———		———	→					Record medications received within 28 days before the first dose of study intervention through 30 days after the last dose of study intervention, or >30 days for medications for SAEs and ECIs as outlined for AE monitoring timeframe below.
Study Intervention Administration											
Lenvatinib Dispensed	X	X	X	X	X	X					
Lenvatinib Container Returned		X	X	X	X	X	X				
Pembrolizumab Administration	X		X		X						
Tumor Imaging and Efficacy Assessments											
Imaging of chest/abdomen/pelvis and Response Assessment	←		———		———	→					Baseline imaging should be performed within 28 days before C1. Perform subsequent imaging Q12W (84±7 days) from C1. This schedule will be followed regardless of delays in study intervention. All imaging should be submitted for BICR.

Trial Period	**Second Course Treatment Phase Cycle = 42 days**						**EOT**	**Posttreatment**			**Notes**
Visit Timing/ Cycle Number	**1**		**2**		**3 to 9**			**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**22**	**1**	**22**	**1**	**22**	**At D/C**	**30 days after D/C**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	**±7**	**±14**	
Bone Scan	←					→					Perform a baseline bone scan within 28 days before C1. Only continue bone scans if participant has positive baseline bone scan. The schedule for on-study bone scans is Q24W (168 ± 7 days). Perform for participants at time of CR if positive at baseline. Schedule should follow calendar days and not be adjusted for delays in treatment.
Brain Scan	X*										*Perform within 28 days before C1 ONLY for participants with previously documented brain metastases (to confirm stability) or who are clinically symptomatic. Brain scans will be performed as clinically indicated and to confirm a CR in participants with brain metastasis at baseline.
Subsequent Anticancer Therapy Status							X	X	X	X	
Survival Status	←					→				X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures/Assessments											
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X		X			
Weight	X	X	X	X	X	X	X	X			
Vital Signs	X	X	X	X	X	X	X	X			HR, DBP, SBP, RR, temperature.

Trial Period	**Second Course Treatment Phase Cycle = 42 days**						**EOT**	**Posttreatment**			**Notes**
Visit Timing/ Cycle Number	**1**		**2**		**3 to 9**			**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**22**	**1**	**22**	**1**	**22**	**At D/C**	**30 days after D/C**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	**±7**	**±14**	
ECHO/MUGA	X*						X				*If a previous ECHO/MUGA in the Initial Treatment Phase was performed within 24 weeks prior to C1D1 of the Second Course Treatment Phase, this assessment does not need to be repeated. Additional assessments may be performed as clinically indicated.
12-lead ECG	X				X*		X	X			*After Cycle 1, repeat ECG every other cycle (eg, C3, C5, C7, etc.). For high-risk participants (Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
ECOG Performance Status	X		X		X		X	X			
AE/SAE Review	←					→			X*		*Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if new anticancer therapy is initiated, whichever is earlier.
Laboratory Procedures/Assessments											
Pregnancy Test – Urine or Serum hCG (WOCBP only)	X	X	X	X	X	X		X			WOCBP require negative test within 24 hours prior to first dose of intervention in the Second Course Treatment Phase. Ongoing pregnancy tests should be conducted as indicated in Appendix 2.
Urine Dipstick Testing (or Urinalysis) for Protein	X	X	X	X	X	X					Urinalysis as clinically indicated. See Section 6.6.2.2 for guidance on testing frequency in cases of elevated protein.
Hematology	X		X		X						
Chemistry	X		X		X						
Lipase and Amylase	X		X		X						

Trial Period	**Second Course Treatment Phase Cycle = 42 days**						**EOT**	**Posttreatment**			**Notes**
Visit Timing/ Cycle Number	**1**		**2**		**3 to 9**			**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**22**	**1**	**22**	**1**	**22**	**At D/C**	**30 days after D/C**	**Per Imaging Schedule**	**Q12W**	**All procedures/ assessments are to be performed prior to dosing unless otherwise indicated.**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	**±7**	**±14**	
PT/INR and aPTT or PTT	X										PTT is acceptable if aPTT cannot be determined. Perform testing as clinically indicated for participants taking anticoagulants.
T3 or FT3, FT4, TSH	X		X		X		X	X			

AE=adverse event; aPTT=activated PTT; BICR=blinded independent central review; C=Cycle; CR=complete response; DBP=diastolic blood pressure; D/C=discontinuation; ECG=electrocardiogram; ECI=event of clinical interest; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; FT3=free T3; FT4=free thyroxine; FU=follow-up; hCG=human chorionic gonadotropin; HR=heart rate; INR=international normalized ratio; MUGA=multiple gated acquisition scan; PT=prothrombin time; PTT=partial thromboplastin time; Q12W=every 12 weeks; Q24W=every 24 weeks; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

2 INTRODUCTION

This study will evaluate the efficacy and safety of pembrolizumab in combination with lenvatinib for the first-line treatment of participants with advanced/metastatic nccRCC.

2.1 Study Rationale

2.1.1 Non-clear Cell Renal Cell Carcinoma

RCC accounts for 3% to 4% of all adult malignancies, representing the sixth most common cancer in men and the eighth most common cancer in women in the US [Siegel, R. L., et al 2020]. Globally in 2018 there were an estimated 403,000 new cases of kidney cancer and 175,000 deaths due to the disease reported [Bray, F., et al 2018].

RCC originates within the renal cortex and is the most common kidney cancer constituting up to approximately 85% of primary renal neoplasms, with a median age at diagnosis of 64 years [National Comprehensive Cancer Network 2019]. Smoking, obesity, and hypertension are established risk factors for RCC development, and several hereditary conditions (eg, von Hippel-Lindau disease) also predispose patients to having an increased risk of developing RCC [National Comprehensive Cancer Network 2019]. The most important prognostic determinants of the 5-year survival rates in RCC are tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation [National Comprehensive Cancer Network 2019]. RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain [Bianchi, M., et al 2012].

At initial diagnosis, approximately two-thirds of patients with RCC present with localized disease and one-third present with unresectable or metastatic disease at diagnosis [Siegel, R. L., et al 2020]. And approximately 20% to 30% of patients with localized tumors will eventually relapse [National Comprehensive Cancer Network 2019].

Recent analyses of the SEER database indicate that the incidence of RCC has been rising on average 0.6% each year and death rates have been falling on average 0.7% each year from 2006 through 2015. [National Cancer Institute 2020]. However, although the 5-year survival for localized RCC is high at 92.6%, the 5-year survival rate for patients with distant metastasis remains dismal at 13.0% [National Comprehensive Cancer Network 2019].

The vast majority of RCC contain a clear cell histology (70% to 80%) with the remainder of cases being summarized as non-clear cell. This heterogeneous group is further subclassified into less common subtypes such as papillary (10% to 15% of all RCCs), chromophobe (5% to 7%), collecting duct (1% to 2%), renal medullary (<1%), and translocation RCC tumors (<1%) [Leibovich, B. C., et al 2010] [Lipworth, L., et al 2016] [Moch, H., et al 2000].

In the advanced/metastatic setting, survival in all subtypes of nccRCC is uniformly worse compared to ccRCC, due to the inherent aggressiveness of these cancers and a lack of effective systemic treatment options [Leibovich, B. C., et al 2010]. Median survival

following a diagnosis of metastatic nccRCC remains poor, with 5-year OS rates ranging from 7% to 12%.

2.1.2 Current Therapeutic Options for nccRCC

Currently there is no globally accepted standard of care in nccRCC, and clinical trials of immune and targeted agents have predominantly focused on patients with clear cell histology due to the higher prevalence of ccRCC compared to nccRCC. Therefore, and due to limited data in nccRCC patients, the role of various agents in the treatment of nccRCC is poorly defined and there is no standard of care. As such, treatment guidelines from the NCCN, SITC, and EAU state that enrollment in clinical trials is a preferred strategy for patients with nccRCC [National Comprehensive Cancer Network 2019].

Several studies have compared treatment with sunitinib or everolimus specifically in patients with nccRCC. In the ASPEN trial, 108 patients with nccRCC were randomized to treatment with sunitinib or everolimus. The estimated ORR for sunitinib and everolimus were 18% and 9%, respectively, with a median PFS of 8.3 months and 5.6 months, respectively (HR: 1.41; 80% CI: 1.03 to 1.92; p=0.16) [Armstrong, A. J., et al 2016]. In the ESPN trial, 68 patients were randomized to sunitinib or everolimus and an interim analysis showed that first-line therapy with sunitinib resulted in an ORR of 9.5% and a median PFS of 6.1 months versus an ORR of 2.8% and a median PFS of 4.1 months with everolimus. However, no statistically significant difference in OS (16.2 versus 14.9 months) was observed between the 2 arms [Tannir, N. M., et al 2016]. The RECORD-3 trial included a 66-patient cohort of nccRCC comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus. The median first-line PFS was 7.2 months in the sunitinib arm and 5.1 months in the everolimus arm, but this difference was not statistically significant.

Based on all of these trials, both sunitinib and everolimus are included in NCCN treatment recommendations as Category 2A options for treatment-naïve patients with Stage IV nccRCC, with sunitinib as the preferred treatment option [National Comprehensive Cancer Network 2019].

A Phase 3 trial of temsirolimus demonstrated that participants with poor prognosis risk factors may benefit from treatment with temsirolimus compared to IFNα, and therefore the NCCN recommends the use of temsirolimus in these patients [National Comprehensive Cancer Network 2019]. An exploratory retrospective subgroup analysis of different tumor histologies demonstrated a median OS of 11.6 months (95% CI: 8.9 to 14.5, N=37) in the temsirolimus arm compared to a median OS of 4.3 months (95% CI: 3.2 to 7.3, N=36) in the IFNα arm [Dutcher, J. P., et al 2009].

Cabozantinib and bevacizumab are also included in treatment recommendations, but the clinical data supporting these recommendations are very limited [National Comprehensive Cancer Network 2019].

2.1.3 Rationale for the Use of Pembrolizumab and Lenvatinib in Patients with nccRCC

KEYNOTE-427 Cohort B contains the largest cohort of participants with nccRCC in a clinical trial (n=165) providing proof of concept for clinical activity of pembrolizumab monotherapy in the first-line setting. At the 2-year follow-up, pembrolizumab demonstrated an ORR of 26.7% with a DCR of 43% and a median PFS and OS of 4.2 and 28.9 months, respectively. Clinical activity was demonstrated across key patient subgroups, including IMDC risk groups, histologic subtype, PD-L1 status, and sarcomatoid differentiation.

A single-arm Phase 2 trial of lenvatinib plus everolimus (n =31) demonstrated an ORR of 25.8% and a DCR of 71% with a median PFS of 9.2 months and median OS of 15.6 months. Given the observed ORR of everolimus as reported above, the improved ORR in this study is thought to be primarily due to the lenvatinib component. However, it is noted that in chromophobe subtypes, given the high rates of mTOR pathway alterations, the contribution of everolimus to the clinical activity might be larger.

An open-label, Phase 1b/2 study (E7080-A001-111) of the combination of lenvatinib plus pembrolizumab in participants with select metastatic tumor types, including metastatic ccRCC, is ongoing to assess the safety and efficacy of the combination of lenvatinib plus pembrolizumab. As of a data cutoff date of 12-JAN-2020, 46 of 91 evaluable participants with ccRCC had achieved a confirmed PR for an ORR of 51% with a median DOR of 9.9 months. The safety of the combination was also assessed, with the most common TRAEs (≥30%) being fatigue (49%), diarrhea (44%), proteinuria (37%), hypertension (31%), and nausea (31%). No new safety signals were observed beyond what was already known for the combination of pembrolizumab and lenvatinib.

Given the observed efficacy of PD-1/PD-L1 targeted therapies and lenvatinib in the advanced/metastatic RCC population, along with the high unmet medical need in patients specifically with non-clear cell histologies, there is strong rationale to support the exploration of the combination of pembrolizumab and lenvatinib in patients with nccRCC.

2.2 Background

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

Lenvatinib (also known as E7080 or MK-7902) inhibits the kinase activities of 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 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.

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

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, 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].

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as 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 nccRCC.

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 IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in 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

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.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab in combination with axitinib has been approved for the first-line treatment of patients with advanced RCC. Additionally, the combination of lenvatinib plus everolimus has been approved for the treatment of patients with advanced RCC following one prior anti-angiogenic treatment. In this study, the activity in nccRCC is expected to be attributed primarily to the lenvatinib given the historical response rates of everolimus in nccRCC (Section 2.1.2). And early data from KEYNOTE-427B provided signs of clinical activity of pembrolizumab monotherapy in participants with nccRCC.

The safety profile of the combination of pembrolizumab and lenvatinib has been well characterized across many indications including RCC. In KEYNOTE-146, the most common TRAEs were fatigue, diarrhea, proteinuria, hypertension, and nausea. The safety profile of the combination treatment was generally consistent with the known safety profiles of pembrolizumab and lenvatinib. Taken together, the existing data suggest that exploring the combination of pembrolizumab + lenvatinib in participants with first-line nccRCC is a promising therapeutic strategy, and the benefit/risk assessment for participants in this study is considered to be favorable.

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.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In male or female participants at least 18 years of age with previously untreated histologically confirmed advanced/metastatic nccRCC:

Objectives	Endpoints
Primary	
• To evaluate the ORR of pembrolizumab + lenvatinib per RECIST 1.1 by blinded independent central review (BICR)	• Objective response (OR): a confirmed complete response (CR) or partial response (PR)
Secondary	
• To evaluate the DOR of pembrolizumab + lenvatinib in participants with a confirmed CR or PR per RECIST 1.1 by BICR	• DOR: the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first
• To evaluate PFS per RECIST 1.1 by BICR in participants receiving pembrolizumab + lenvatinib	• PFS: the time from first dose to the first documented PD or death from any cause, whichever occurs first
• To evaluate the overall survival (OS) of participants receiving pembrolizumab + lenvatinib	• OS: the time from first dose until death from any cause
• To evaluate the CBR of pembrolizumab + lenvatinib per RECIST 1.1 by BICR	• Clinical benefit: a confirmed CR, PR, or stable disease (SD) for at least 6 months
• To evaluate the DCR of pembrolizumab + lenvatinib per RECIST 1.1 by BICR	• Disease control: a confirmed CR, PR or SD
• To evaluate the safety of pembrolizumab + lenvatinib	• Adverse events (AEs) • Discontinuations due to AEs
Tertiary/Exploratory	
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab + lenvatinib	• Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, nonrandomized, single-arm, multisite, open-label study of pembrolizumab + lenvatinib in participants with previously untreated advanced/metastatic nccRCC including all IMDC risk groups. Participants must have histologically confirmed diagnosis of nccRCC pathology to participate. Collecting duct histology is excluded.

Approximately 152 participants will be enrolled and allocated to receive treatment with pembrolizumab 400 mg Q6W and lenvatinib 20 mg QD. Pembrolizumab treatment will continue for up to ~2 years or until a discontinuation criterion (Section 7.1) is met, and lenvatinib treatment may continue beyond 2 years until a discontinuation criterion (Section 7.1) is met.

During initial treatment, participants who have been receiving study intervention for ≥24 weeks (at least 4 cycles) and who attain a CR may consider stopping pembrolizumab treatment. If a confirmed CR per RECIST 1.1 is attained after at least 24 weeks, participants must receive pembrolizumab for at least 1 additional cycle after CR is first documented.

Treatment may continue after radiographic progression of RCC per RECIST 1.1 as long as the investigator believes that the participant is still receiving clinical benefit from study intervention and that the potential benefit of continuing study intervention outweighs potential risks. Treatment beyond disease progression requires Sponsor consultation. Continued participation requires additional consent (Section 8.1.1). Participants who continue treatment beyond disease progression will continue with all protocol-required assessments and procedures, and will resume the existing imaging schedule.

Participants who stop pembrolizumab treatment after receiving 18 administrations (2 years) of pembrolizumab with SD or better, or participants who have been receiving pembrolizumab for at least 24 weeks, attain a confirmed CR, and stop pembrolizumab may be eligible for up to 9 additional cycles (approximately 1 year) of pembrolizumab upon experiencing investigator-assessed PD. This retreatment is termed the Second Course Treatment Phase and is only available if the study remains open and the participant meets the criteria in Section 6.6.5. Participants may also continue lenvatinib treatment during the Second Course Treatment Phase. If lenvatinib is continued, participants will be treated at the same dose level and frequency of lenvatinib they were receiving when PD occurred.

Imaging assessments will include chest CT and abdomen and pelvis CT/MRI throughout the study. Bone scans will be performed at screening and will only be repeated throughout the study if a participant has a positive result at screening. Brain imaging at screening is only required for participants with previously documented brain metastases. On-study brain imaging will only be performed as clinically indicated or to confirm CR in a participant with brain lesions at baseline. All imaging obtained will be submitted to the iCRO for BICR, which will assess the images per RECIST 1.1, adjusted to allow for a maximum of 10 total target lesions and a maximum of 5 target lesions per organ. However, all decisions to

discontinue study intervention(s) due to disease progression are based solely on the site radiology's assessment.

Adverse event monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the NCI CTCAE Version 5.0.

During both Initial Treatment Phase and the Second Course Treatment Phase, if pembrolizumab is discontinued because of toxicity, lenvatinib alone may be continued based on physician discretion regarding the benefits of continuing VEGFR-based oral monotherapy. If lenvatinib is discontinued due to toxicity, pembrolizumab alone may be continued.

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

4.2 Scientific Rationale for Study Design

This study is being performed as a single-arm open-label study in order to rapidly provide information on the potential benefits of the combination of pembrolizumab and lenvatinib in participants with nccRCC, a population with high unmet medical need where new treatments are sorely needed. The data from this study will provide additional information on the potential efficacy and safety of the combination treatment in participants specifically with non-clear cell histologies. A single-arm design was chosen as there is no globally accepted standard-of-care regimen for participants with previously untreated nccRCC.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use ORR based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. ORR is an acceptable measure of clinical benefit for a late stage study, 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 ORR is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review to minimize bias in the response assessments.

Secondary efficacy endpoints for this study include CBR, DCR, DOR, PFS, and OS.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. 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. Refer to Section 8.2.1.5 for additional detail.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Planned Exploratory Biomarker Research

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

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

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

Proteomics and IHC using blood or tumor

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

Other blood-derived biomarkers

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

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

4.3 Justification for Dose

4.3.1 Pembrolizumab

The planned dose of pembrolizumab is 400 mg Q6W. Based on the totality of data generated in the KEYTRUDA development program, 400 mg Q6W is an appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type based on modeling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration over the dosing interval (C_{avg}) (or AUC) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
  - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-response analysis for pembrolizumab has been demonstrated to be flat across indications, and OS predictions demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.
- Clinical safety profiles were similar between 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W in multiple tumor types based on randomized dose comparisons; hence, the safety profile at 400 mg Q6W is also expected to be similar.

Overall, a 400 mg Q6W dosing regimen for KEYTRUDA monotherapy is predicted to have a similar efficacy and safety profile compared to the currently approved 200 mg Q3W dosing regimen.

4.3.2 Lenvatinib

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

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W. Based on the promising antitumor efficacy and tolerable safety profile seen in both the endometrial carcinoma and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], 2 Phase 3 studies have been initiated for both of these tumor types, Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-307/ KEYNOTE-581.

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), or the last participant on active treatment is consented in the extension study. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the 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, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male and female participants at least 18 years of age with previously untreated and histologically confirmed diagnosis of nccRCC will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Must have a histologically confirmed diagnosis of nccRCC.

2. Has locally advanced/metastatic disease (ie, Stage IV per the American Joint Committee on Cancer).

3. Has received no prior systemic therapy for advanced nccRCC.

   Note: Prior neoadjuvant/adjuvant therapy for nccRCC is acceptable if completed >12 months prior to allocation.

Demographics

4. Is male or female, from 18 years to 120 years of age inclusive, at the time of providing informed consent.

Male Participants

5. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study intervention:

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

  OR

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

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Please note that 7 days after lenvatinib is stopped, if the male participant is on pembrolizumab only, no male contraception measures are needed.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib, whichever occurs last. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before the first dose of study intervention.

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

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

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

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

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

Additional Categories

8. Has measurable disease per RECIST 1.1 as assessed by BICR. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

9. Has submitted an archival tumor tissue sample or newly obtained core or incisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Details pertaining to tumor tissue submission can be found in the Procedures Manual.

10. Has KPS ≥70% as assessed within 10 days prior to the start of study intervention.

11. Has 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 allocation.

12. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start of study intervention.

Table 4 Adequate Organ Function Laboratory Values

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

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

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

[b] Applicable only when local guidelines require both assessments.

[c] CrCl should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has collecting duct histology.

2. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study intervention (see Appendix 2 and Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

3. Has pre-existing ≥Grade 3 gastrointestinal or non-gastrointestinal fistula.

4. Has urine protein ≥1 g/24 hours.
   Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria.

5. Has a left ventricular ejection fraction below the institutional (or local laboratory) normal range, as determined by multigated acquisition or echocardiogram.

6. Has radiographic 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.

7. Has prolongation of QTcF interval to >480 msec.

8. 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.

9. Has gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.

10. Has active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.

Prior/Concomitant Therapy

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

12. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

13. Has received prior systemic anticancer therapy including investigational agents within 4 weeks prior to allocation.

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

14. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and

not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

15. Has received a live or attenuated vaccine within 30 days before the first dose of study intervention. Note: Killed vaccines are allowed. Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

17. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention.

18. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

19. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

20. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, lenvatinib and/or any of their excipients.

21. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

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

23. Has an active infection, requiring systemic therapy.

24. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

    Refer to Appendix 7 for country-specific requirements.

25. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

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

    Refer to Appendix 7 for country-specific requirements.

26. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

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

Other Exclusions

29. Has had an allogenic tissue/solid organ transplant.

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 Contraception

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal

information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility following consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 5.

Table 5 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/ NIMP/ AxMP	Sourcing
Pembrolizumab + Lenvatinib	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	400 mg	IV Infusion	Q6W	Test product	IMP	Provided centrally by the Sponsor
Pembrolizumab + Lenvatinib	Experimental	Lenvatinib	Drug	Capsule	10 mg	20 mg	Oral	QD	Test product	IMP	Provided centrally by the Sponsor
Pembrolizumab + Lenvatinib	Experimental	Lenvatinib	Drug	Capsule	4 mg	14 mg to 8 mg	Oral	QD	Test product	IMP	Provided centrally by the Sponsor

AxMP=auxiliary medicinal product; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP=non-investigational medicinal product; Q6W=every 6 weeks; QD=every day.

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/NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 5 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements .

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IRT system. There is 1 study intervention arm that participants will be allocated into.

6.3.2 Stratification

This is a single-arm study. No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Interruptions from the protocol-specified treatment plan for >28 days for lenvatinib 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 time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants are prohibited from receiving the following therapies during the screening and treatment periods of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and lenvatinib
- Radiation therapy

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

- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, 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.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

  Refer to Appendix 7 for country-specific requirements.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study intervention.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications and fluids. If changes

occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered >30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.7.

6.5.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 6 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.5.2 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 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 their divergent metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (lenvatinib IB).

6.6 Dose Modification (Escalation/Titration/Other)

Adverse events will be graded using NCI CTCAE Version v5.0. 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 or discontinue one drug in the pembrolizumab + lenvatinib combination due to toxicity can continue with the other drug in the combination until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

Refer to Section 6.6.3 for dose modification guidance for overlapping toxicity for the pembrolizumab + lenvatinib combination.

6.6.1 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. Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

- 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.
- 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.
- The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
- If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	**Toxicity Grade (CTCAE v5.0)**	**Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations**	**Corticosteroid and/or Other Therapies**	**Monitoring and Follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	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 based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID=nonsteroidal anti-inflammatory drug; PO=orally. 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 NCI CTCAE version 5.0 at http://ctep.cancer.gov.		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted therapy within 6 weeks (42 days) of the originally scheduled dose interruption and within 12 weeks (84 days) of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Dose Modification With Lenvatinib

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

The starting dose of lenvatinib is 20 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the Sponsor. Once the lenvatinib dose has been reduced, it

may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 6.6.2.1), proteinuria (Section 6.6.2.2), diarrhea (Section 6.6.2.3), hepatotoxicity (Section 6.6.2.4), thromboembolic events (Section 6.6.2.5), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.2.6), hypocalcemia (Section 6.6.2.7), hemorrhage (Section 6.6.2.8), gastrointestinal perforation or fistula formation (Section 6.6.2.9), QT prolongation (Section 6.6.2.10), and ONJ (Section 6.6.2.11) as appropriate, before consulting the dose modification table (Table 8). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.3.

Table 8 Dose Modification Guidelines for Lenvatinib-Related Adverse Events

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

AE=adverse event; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events.

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

a. An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.
b. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.
c. Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
d. Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they 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/matching placebo. See Section 6.6.2.5.
g. Excluding laboratory abnormalities judged to be non-life-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 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 dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3.1 and Section 1.3.3). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

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

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

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored every 2 weeks (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 6 weeks. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume every 2 week evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 6 weeks.

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

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.
2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.
3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
    - Additional dose reduction should be discussed with the Sponsor.

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

1. Institute appropriate medical management
2. Discontinue study drug

6.6.2.2 Management of Proteinuria

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

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3.1 and Section 1.3.3). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible.
2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) is required in the following situations:
   - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participant is receiving lenvatinib
   - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL)
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 8.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 6 weeks.
- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

6.6.2.3 Management of Diarrhea

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

Diarrhea is a known overlapping toxicity between pembrolizumab and lenvatinib (Section 6.6.3). If the causative agent is unknown, investigators should refer to both Table 7 and Table 8 for possible supportive care guidelines to follow.

6.6.2.4 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3.1 and Section 1.3.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 8 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug must be discontinued. If hepatic failure (any grade per CTCAE v5) occurs, lenvatinib 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, 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 8 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

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

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 8 should be followed.

6.6.2.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3.1 and Section 1.3.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, 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 8 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or Grade 4 fistula. Refer to Appendix 7 for country-specific requirements.

6.6.2.10 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib 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 and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution (see Section 6.6.4).

6.6.3 Dose Modifications for Overlapping Toxicities

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

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q6W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

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

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

2. Severity of AE

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

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

   - ALT or AST >5 × ULN for more than 2 weeks.
     Pembrolizumab will have already been permanently discontinued per Table 6 but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
   - ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5).
     Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 8 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.6.4 Other Allowed Dose Interruptions

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

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.

6.6.5 Second Course Treatment Phase

All participants who have completed the first course may be eligible for up to an additional 9 cycles of pembrolizumab if there is investigator-determined progressive disease by RECIST 1.1 after initial treatment or first course has been completed or stopped for confirmed CR.

Participants may enter the Second Course if all of the following criteria are met:

- The participant received pembrolizumab, determined on unblinding if applicable
- No new anticancer treatment was administered after the last dose of study intervention
- The participant meets all of the inclusion criteria and none of the exclusion criteria
- The study is ongoing

An objective response or disease progression that occurs during the Second Course will not be counted as an event for the primary analysis of either endpoint in this study.

Participants in the Second Course Treatment Phase who continue receiving lenvatinib will be treated at the same dose and frequency of lenvatinib that they were receiving when PD occurred.

6.7 Intervention After the End of the Study

The study is complete upon consent of the last active treatment participant for an extension study using pembrolizumab monotherapy, coformulations, or in combination with a compound (eg, lenvatinib or lenvatinib alone), if available.

All study-related procedures and data collection as defined per protocol will be terminated at study completion. In addition, survival follow-up will be stopped upon study completion as defined in Section 4.4.

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts pembrolizumab for more than 12 consecutive weeks or lenvatinib for more than 28 consecutive days without prior agreement from the Sponsor.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1 (exception if the Sponsor approves treatment continuation following confirmed disease progression).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

Completion of pembrolizumab Q6W monotherapy consists of 18 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 4 cycles (at least 24 weeks), receiving at least 1 dose of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 6.6.5.

Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 18 doses may be eligible for retreatment if they progress after stopping study intervention provided they meet the requirements detailed in Section 8.10.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 9 cycles (approximately 1 year).

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.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (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 utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

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

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

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

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

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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 significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit. In addition, new medications started during the Second Course Treatment Phase through the Second Course Safety Follow-up visit should be recorded. Concomitant medications administered >30 days after the last dose of study intervention will be recorded for SAEs and ECIs as defined in Section 8.4.1. In the posttreatment follow-up period, information about new anticancer therapies will be collected.

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

The first dose of study intervention should begin as close as possible to the date of allocation but can occur up to 3 days following allocation. Every effort should be made to ensure the participants receive the first dose of study intervention on the date of allocation. Study interventions will be administered by the investigator and/or qualified study staff according to the specifications in the Pharmacy Manual.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Lenvatinib

Participants should be given clear instructions on how and when to take their study intervention. Lenvatinib will be taken orally QD, with doses taken at approximately the same time of day. Lenvatinib may be administered at home except on days when clinic visits are scheduled to occur. Study intervention on these days will occur in the clinic after completion of all other assessments.

If a dose is missed and cannot be taken within 12 hours, study participants should skip that dose and take the next dose at the usual time of administration. Participants who vomit after study drug administration should not retake that study drug dose but should resume taking study drug with the next scheduled dose. Lenvatinib can be taken without regard to food.

8.1.8.1.2 Pembrolizumab

Study treatment with pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the SoA (Section 1.3). All study treatments will be administered on an outpatient basis. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for C1D1, where the window is +3 days from allocation.

Pembrolizumab will be administered using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for preparation of the infusion fluid and administration.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are

present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue Collection

During the screening period, a tissue sample is required for each participant consisting of:

- A newly obtained core or incisional biopsy of a tumor lesion, which was not previously irradiated

  OR

- An archival tumor tissue sample if a new biopsy is unavailable.

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Newly cut unstained slides must be submitted to the central laboratory within 14 days of cut date (details pertaining to tumor tissue submission can be found in the Procedures Manual).

The central laboratory will provide consultative review to confirm nccRCC histology without any admixed clear cell component.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for image collection and transmission to the iCRO can be found in the SIM. Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging technique 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 imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

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

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

Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO, and will not be included in response assessment.

Expedited confirmation of measurable disease based on RECIST 1.1 by BICR at screening will be used to determine participant eligibility. Confirmation by BICR that the participant’s imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required before participant allocation.

All scheduled imaging for all study participants will be submitted to the iCRO. In addition, imaging that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment. All imaging acquired within the protocol-specified window of time around a scheduled imaging visit can be classified as pertaining to that visit.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging (chest, abdomen, and pelvis) at Screening must be performed within 28 days prior to the date of allocation. The screening images must be submitted to the iCRO for verification of measurable disease per RECIST 1.1 for eligibility before allocation. Tumor imaging performed as part of routine clinical management is acceptable for use as the Screening tumor imaging if it is of diagnostic quality, performed within 28 days prior to the date of allocation, and can be assessed by the iCRO.

Bone imaging will be required for all participants at Screening. Bone imaging are not required to be repeated at Screening if they were performed for standard of care within 42 days prior to allocation and meet protocol requirements.

If brain imaging is required to document the stability of existing metastases, the brain MRI should be acquired during the Screening period.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 12 weeks ([84 days ±7 days]) from the date of allocation. Subsequent tumor imaging should be performed every 6 weeks

(42 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days]), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the iCRO.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging 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 BICR.

On-study brain or bone imaging should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

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

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

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All Second Course imaging should be submitted to the iCRO for quality control, storage, and possible retrospective review.

The first on-study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, completion of Second Course treatment (9 cycles), or notification by the Sponsor, whichever occurs first.

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

For participants who discontinue Second Course study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8.2.1.5 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.

If disease progression is established by the investigator, the process continues as follows:

- investigator judgement 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 per original protocol schedule
- send scans to iCRO

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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination, including oral examination, will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

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.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination, including oral examination, during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

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

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

- Vital sign measurements (ie, systolic and diastolic BP [mm Hg], heart rate [beats per minute], respiratory rate [per minute], and body temperature) will be assessed/ obtained at the visits designated in the SoA (Section 1.3) by a validated method.

- 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 BP <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.

- Under exceptional circumstances, participants taking lenvatinib may have the option of having BP measured between visits obtained locally by a health care professional.

8.3.3 Electrocardiograms

ECGs 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 QTcF 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. For participants receiving lenvatinib, ECGs will be monitored at every cycle (as specified in the SoA in Section 1.3) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Medicinal products with a known potential to prolong the QT/QTc interval must be used cautiously. Please refer to the lenvatinib prescribing information for further details.

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 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the Study Flow Chart (Section 1.3) for the timing of laboratory assessments.

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.

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

8.3.5.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status as specified in the SoA (Section 1.3) [Oken, M.M., et al 1982].

8.3.6.2 Karnofsky Performance Status

The KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks, with scores ranging from 0 to 100% [Karnofsky, D. A., et al 1948]. A higher score means the patient is better able to carry out daily activities. The KPS will be assessed as specified in the SoA (Section 1.3). A KPS ≥70% is required for study eligibility.

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 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 participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days following cessation of study intervention must be reported by the investigator.

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

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and 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 9.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if:- participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (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
ECI (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; NSAE=nonserious adverse event; SAE=serious adverse event.

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, 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 allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply 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 SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

Efficacy endpoints 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 monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that on 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:

a. An overdose of Sponsor's product, as defined in Section 8.5.

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

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

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. For this study, an overdose of lenvatinib will be defined as any dose above the protocol-prescribed dose if associated with an adverse event.

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.

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.

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

Not applicable.

8.7 Pharmacodynamics

Not applicable

8.8 Biomarkers

- Blood for Genetic Analysis
- Blood for Serum Biomarkers
- Blood for ctDNA Analysis
- Archival or Newly Obtained Tumor Tissue Sample Collection
- Blood for RNA Analysis
- Blood for PBMC

8.8.1 Planned Genetic Analysis Sample Collection

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

8.9 Future Biomedical Research Sample Collection

Not applicable.

8.10 Visit Requirements

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

8.10.1 Screening

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the date of allocation except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of study intervention.

- Evaluation of KPS is to be performed within 10 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 10 days prior to the first dose of study intervention.

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

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

8.10.2 Treatment Period Visits

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1. Assessments/procedures will be performed, prior to the administration of study intervention.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

The investigator or qualified designee should clarify what a participant is withdrawing from, ie, treatment, follow-up visits, and/or contact. Given the importance of collecting extended follow-up data for PFS and OS in this study, efforts should be made to clarify if participants

are willing to be followed for a PFS event and/or survival and/or whether review of public records is acceptable.

8.10.4 Posttreatment Visits

8.10.4.1 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 the initiation of a new anticancer treatment, whichever comes first.

Participants who are eligible for retreatment/crossover with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Initial Treatment Phase and 1 after the Second Course Treatment Phase.

8.10.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-up Phase and should be assessed according to the SoA (Section 1.3) 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, or if the participant begins retreatment with pembrolizumab as detailed in Section 6.6.5. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or who will not have further efficacy assessments must enter the Survival Follow-up Phase.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.5 will move from the Efficacy Follow-up Phase to the Second Course Treatment Phase when they experience disease progression. Details are provided in the SoA (Section 1.3.3) for retreatment with pembrolizumab.

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

8.10.5 Survival Status

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 eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to the final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	This is a single-arm, open-label, Phase 2 clinical trial to evaluate the efficacy and safety of pembrolizumab plus lenvatinib as first-line treatment for participants with advanced/metastatic nccRCC.
Treatment Assignment	Approximately 152 participants will be allocated to receive treatment with pembrolizumab 400 mg Q6W and lenvatinib 20 mg QD.
Analysis Populations	Efficacy: APaT Safety: APaT
Primary Endpoint	Objective Response per RECIST 1.1 as assessed by BICR
Secondary Endpoints	• DOR per RECIST 1.1 as assessed by BICR • PFS per RECIST 1.1 as assessed by BICR • OS • Clinical Benefit per RECIST 1.1 as assessed by BICR • Disease Control per RECIST 1.1 as assessed by BICR • AEs and study intervention discontinuations due to AEs.
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].
Statistical Methods for Key Safety Analyses	Counts and percentages of participants with AEs will be provided.
Interim Analyses	No formal interim analysis is planned in this study.
Multiplicity	No multiplicity adjustment is planned as there is no formal hypothesis testing.
Sample Size and Power	The planned sample size is approximately 152 participants. Section 9.9 provides the precision of the ORR estimates.

9.2 Responsibility for Analyses/In-house Blinding

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

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

The Sponsor will generate the allocation schedule for study treatment assignment. The allocation will be implemented in IVRS.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. There is no formal hypothesis testing in this estimation study.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary

- **Objective Response Rate**
  The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

Secondary

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

- **Progression-free survival**
  PFS is defined as the time from the date of first dose to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

- **Overall Survival**
  OS is defined as the time from date of first dose to death due to any cause.

- **Clinical Benefit Rate**
  CBR is defined as the percentage of participants who have achieved SD of ≥6 months or CR or PR per RECIST 1.1 by BICR.

- **Disease Control Rate**
  DCR is defined as the percentage of participants who have achieved SD, CR, or PR per RECIST 1.1 by BICR.

9.4.2 Safety Endpoint

The safety endpoints include AEs, SAEs, and study treatment discontinuation due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters

including AEs, laboratory tests, vital signs, and ECGs. A description of safety measures is provided in Sections 8.3 and 8.4.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The APaT population will be used for the primary analysis of efficacy data in this study. The APaT population consists of all allocated participants who received at least 1 dose of study treatment.

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 allocated participants who received at least one dose of study treatment.

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

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the tertiary/exploratory endpoints will be described in the sSAP. This is an estimation study. No formal hypothesis tests will be conducted.

9.6.1 Statistical Methods for Efficacy Analysis

The efficacy analyses for ORR, DOR, PFS, CBR, and DCR will include responses and documented progression events that occur before Second Course treatment.

9.6.1.1 Objective Response Rate, Clinical Benefit Rate, and Disease Control Rate

The point estimate of ORR, CBR, and DCR will be provided along with the 95% CIs using the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

9.6.1.2 Duration of Response

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. Censoring rules for DOR are summarized in Table 10.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered

ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 10 Censoring Rules for Duration of Response

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

PD=progressive disease.
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.3 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve.

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 earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy prior to documented progression will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second

sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than CR, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarized in Table 11.

Table 11 Censoring Rules for Primary and Sensitivity Analysis of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression immediately after ≥ 2 consecutive missed disease assessments, or after new anticancer therapy	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD=progressive disease; PFS=progression-free survival.			

9.6.1.4 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curve. Participants without documented death at the time of analysis will be censored at the date of the last known alive date.

9.6.1.5 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy variables is provided in Table 12.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per RECIST 1.1 by BICR	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders
Secondary Analyses			
DOR per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	Responders in APaT population	Censored according to rules in Table 10
PFS per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	APaT	Censored according to rules in Table 11
OS	Summary statistics using Kaplan-Meier method	APaT	Censored at the date participant last known to be alive

APaT=all participants as treated; BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory parameters, vital signs and ECG measurements. The broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3 to 5 AE, a drug-related Grade 3 to 5 AE, and who discontinued due to an AE will be summarized. The number and percentage of participants with increased laboratory toxicity grade shift from baseline will also be provided.

The primary safety analyses will include only events that occur before Second Course treatment.

9.6.3 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

No formal interim analyses are planned for this study.

9.7.1 Efficacy Interim Analysis

No formal interim analysis for efficacy is planned for this study. The final analysis is to be performed approximately 36 months after the last participant is enrolled. Participants will continue to be followed after the final analysis until the overall study ends.

9.7.2 Safety Interim Analysis

The study team will be responsible for periodic safety monitoring and reviews. No formal interim safety analysis will be performed for this study.

9.8 Multiplicity

Since there is no formal hypothesis testing for this estimation study, no multiplicity adjustment is planned.

9.9 Sample Size and Power Calculations

In this study, approximately 152 participants with nccRCC will be enrolled.

Table 13 shows the two-sided 95% confidence intervals for ORR with 152 participants for different observed response rates based on the method of Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 13 Two-sided 95% Confidence Intervals for ORR with 152 Participants

Number of Observed Responders	ORR Estimates	95% CI of ORR (%)
53	34.9%	(27.3, 43.0)
61	40.1%	(32.3, 48.4)
64	42.1%	(34.2, 50.4)
68	44.7%	(36.7, 53.0)

CI=confidence interval; ORR=objective response rate.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of ORR (with nominal 95% CIs) will be estimated and plotted within each category of the following subgroup variables:

- Geographic region (US, EU, ROW)
- IMDC risk factor (favorable, intermediate, or poor)
- PD-L1 CPS (<1, ≥1)
- Age category (<65 years, ≥65 years)
- Sex (female, male)
- Race (white, all others)
- Histologic subtype (papillary, chromophobe, translocation, unclassified)
- Sarcomatoid Feature (with, without)

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the APaT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study treatment. Summary statistics will be provided on the extent of exposure for the overall study treatment, and for pembrolizumab and lenvatinib separately, 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 Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related

Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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.

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including 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 (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.9 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor 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 14 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/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 individual's participation in the study.

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: MCV MCH Reticulocytes[a]	WBC count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	BUN or urea[b]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate or CO_2 [c]	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting, or nonfasting)	Calcium	Alkaline phosphatase	Magnesium
	Amylase	Lipase		
Routine Urinalysis as Clinically Indicated	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick/urinalysis • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• FSH (as needed in WONCBP only) • Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP) • Serology (HIV antibody, HBsAg, and/or Hepatitis C virus antibody) as required by local health authority • T3 (or FT3 if T3 is unavailable), FT4 and TSH • PT/INR and aPTT (PTT may be performed if lab cannot perform aPTT)			

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; HBsAG=hepatitis B surface antigen; hCG=human chorionic gonadotropin; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT= partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; T3=triiodothyronine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

NOTES:

a. Report % or absolute results per standard practice. Report the results in the same manner throughout the study.
b. BUN is preferred; if not available, urea may be tested.
c. If these tests are not performed as part of standard of care in a particular country, then they do not need to be performed for sites in that country.

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 (also referred to as Sponsor's product) 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 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 pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

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

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

f. **Other important medical events**

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 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

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

- Grade 4: Life threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
    - Yes, there is a reasonable possibility of Sponsor's product relationship:
        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
    - No, there is not a reasonable possibility of Sponsor's product relationship:
        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

10.3.6 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 e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and 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.

Women in the following categories are not considered WOCBP:

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

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

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

10.5.2 Contraception Requirements

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

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 UK-specific Requirements

The UK has country-specific requirements for the protocol, which are summarized below.

Section 1.3 – Schedule of Activities

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in the UK should have the following procedures/assessments performed:

Study Period:	**Screening Phase**	**Notes**
Cycle Number/ Visit Title	Screening Visit	
Cycle Day		
Safety Procedures		
HIV, Hepatitis B, Hepatitis C	X	Required

Section 5.2 – Exclusion Criteria

For Exclusion Criteria No. 24 (HIV infection) and No. 25 (Hepatitis B and Hepatitis C infection), testing for HIV, Hepatitis B, and Hepatitis C must be performed in the UK during screening in order to determine a participant's eligibility for the study.

Section 6.5 – Concomitant Therapy

In addition to all restrictions or concomitant medications listed in Section 6.5 – Concomitant Therapy, the following restriction applies to participants in the UK:

- Live vaccines within 30 days prior to the first dose of study intervention, while participating in the study, **and for 90 days after the last dose of study treatment**, are prohibited.

10.7.2 Canada-specific Requirements

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

Section 6.6.2.9 – Management of Gastrointestinal Perforation or Fistula Formation

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

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

Not applicable.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate transaminase
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BMI	body mass index
BP	blood pressure
CBR	clinical benefit ratio
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
Cmax	maximum concentration
Cmin	minimum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPS	combined positive score
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTR	Clinical Trial Regulation
DAIDS	Division of AIDS
DCR	disease control rate
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
EAU	European Association of Urology
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded

Abbreviation	Expanded Term
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging CRO
ICSR	individual case safety report
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
IND	Investigational New Drug
INR	international normalized ratio
IO	immuno-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
KIT	mast/stem cell growth factor receptor Kit
KPS	Karnofsky performance status
LAM	lactational amenorrhoea method
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
nccRCC	non-clear cell renal cell carcinoma
NCI	National Cancer Institute
NDA	New Drug Application

Abbreviation	Expanded Term
NSCLC	non-small cell lung cancer
ONJ	osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell-death 1
PD-L1	programmed cell-death ligand 1
PD-L2	programmed cell-death ligand 2
PFS	progression-free survival
PGIC	Patient Global Impression Change
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PO	orally
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QD	every day
QOL	quality of life
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RET	proto-oncogene tyrosine-protein kinase receptor Ret
RNA	ribonucleic acid
ROW	rest of world
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results Program
SIM	Site Imaging Manual
SITC	Society for Immunotherapy of Cancer
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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