Official Protocol Title:	A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)
NCT number:	NCT03898180
Document Date:	05-Dec-2022

Title Page

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Protocol Title: A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)

Protocol Number: 011-04 (E7080-G000-317)

Compound Number: MK-7902

Sponsor Name:

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

The study is co-funded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	141237
EudraCT	2018-003752-21

Approval Date: 05 December 2022

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	05-DEC-2022	The scope of the study has been reduced. Long-term efficacy/survival data will no longer be collected; therefore, upon either completion or discontinuation of pembrolizumab, participants will have a final Safety Follow-up visit and be discontinued from the study. Participants in Efficacy Follow-up will stop efficacy assessments and be discontinued from the study. Participants in Survival Follow-up are considered to have completed the study.
Amendment 03	24-SEP-2021	To update the dose modification and toxicity management guidelines for irAEs. To make updates consistent with recommendations of the external Data Monitoring Committee (eDMC) after an interim review of the data; specifically, that all participants be unblinded and lenvatinib/placebo administration stop. The study will remain open so that participants still on study will have continued access to pembrolizumab.
Amendment 02	06-FEB-2020	To allow participants to be enrolled in China while awaiting authorization from the HGRAC to collect biomarker specimens.
Amendment 01	22-JUL-2019	Current literature supports use of this class of drugs in a higher age range for this patient population.
Original protocol	25-JAN-2019	Original Protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

The scope of the study has been reduced. Long-term efficacy/survival data will no longer be collected; therefore, upon either completion or discontinuation of pembrolizumab, participants will have a final Safety Follow-up visit and be discontinued from the study. Participants in Efficacy Follow-up will stop efficacy assessments and be discontinued from the study. Participants in Survival Follow-up are considered to have completed the study.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.1 Initial Treatment 1.3.2 Second Course Treatment 4.1 Overall Design 7.3 Lost to Follow-up 8.1.13 Subsequent Antineoplastic Treatment 8.2.1.3 End of Treatment and Follow-up Tumor Imaging 8.10.5.2 Efficacy Follow-up Visits 8.10.6 Survival Follow-up 8.10.7 Survival Status	Reduced the scope of the study. Participants who either complete administration of pembrolizumab or discontinue pembrolizumab will discontinue the study following the Safety Follow-up visit. Participants in Efficacy Follow-up will stop efficacy assessments and be discontinued from the study. Participants in Survival Follow-up are considered to have completed the study and should have a final survival contact. Revised the Schema and SoA accordingly to remove Follow-up and Safety Follow-up from the Posttreatment phase of the study.	Long-term efficacy/survival data will no longer be collected.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Initial Treatment 1.3.2 Second Course Treatment 6.5 Concomitant Therapy 8.1.5.2 Concomitant Medications 8.3.1 Physical Examination 8.3.2 Vital Signs 8.3.5.1 Hematology and Clinical Chemistry 8.3.5.3 Thyroid Function Testing 8.3.6 Eastern Cooperative Oncology Group Performance Status	Reduced the frequency that information on concomitant medication, safety laboratory parameters, physical examination, vital sign measurements, and ECOG performance status are collected for participants still receiving pembrolizumab treatment. Revised the SoA accordingly to reduce the frequency concomitant medication, safety laboratory parameters, physical examination, vital sign measurements, and ECOG performance status are collected.	Revision to align with the current standard of care for pembrolizumab administration and to ease the burden on participants and investigational sites.
1.1 Synopsis 1.3.2 Second Course Treatment 4.1 Overall Design 8.2.1.4 Second Course Treatment Tumor Imaging 8.2.1.4.1 Bone Imaging During Second Course 8.10.3 Second Course Treatment	Added a note that Second Course treatment will no longer be offered; however, any participant receiving Second Course prior to initiation of Amendment 011-04 can continue as planned.	Revision in alignment with reducing the scope of the study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 Initial Treatment 1.3.2 Second Course Treatment 8.2.1.2 Tumor Imaging During the Study 8.2.1.2.1 Bone Imaging During the Study 8.2.1.4 Second Course Treatment Tumor Imaging 8.2.1.4.1 Bone Imaging During Second Course	Removed the requirement of recording the date and assessment of imaging performed as part of standard of care.	Revision to clarify that the date and assessment of imaging performed as part of standard of care is no longer needed as Second Course treatment is no longer an option.
1.3.1 Initial Treatment 1.3.2 Second Course Treatment 8.2.1.3 End of Treatment and Follow-up Tumor Imaging	Removed the requirement for imaging at the time of discontinuation (end of treatment visit).	Imaging is no longer required at the time of discontinuation.
1.3.1 Initial Treatment 1.3.2 Second Course Treatment	Added “local” to laboratory tests that were previously required to be performed at the central laboratory.	Revision to allow investigational sites the option of sending samples to the local laboratory for all required laboratory testing while participants are on-treatment.
10.2 Appendix 2: Clinical Laboratory Tests	Removed language stipulating that, if a local laboratory is used, samples need to be collected and sent to the central laboratory in parallel.	

Section # and Name	Description of Change	Brief Rationale
4.4.1 Clinical Criteria for Early Study Termination	Added language regarding decision to stop providing pembrolizumab.	Revision to clarify that the Sponsor will provide ample notification in the event of a decision to no longer supply pembrolizumab.
6.5.2 Prohibited Concomitant Medications	Added a note regarding the concomitant use of COVID-19 vaccines.	Revision to clarify that licensed COVID-19 vaccines (including those for emergency use) are not prohibited.
8.2.1.2 Tumor Imaging During the Study	Added imaging to the list of conditions that would stop on-study imaging.	Revision to clarify that imaging would stop in the event of a pregnancy.
4.2.1.6 Planned Exploratory Biomarker Research	Text was revised to remove specific references to pembrolizumab, lenvatinib, and immunotherapy/immune-oncology.	Revision to allow more flexibility with planned exploratory biomarker research.
Title Page 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
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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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)

Short Title: Phase 3 Study of First-line Pembrolizumab With or Without Lenvatinib in Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1 and Participants Ineligible for Any Platinum-containing Chemotherapy

Acronym: MK-7902-011

Hypotheses, Objectives, and Endpoints:

The objectives and endpoints apply to a study population of male or female participants at least 18 years of age with a histologically confirmed diagnosis of advanced/unresectable or metastatic urothelial carcinoma (UC), who are cisplatin-ineligible and whose tumors express programmed death ligand 1 (PD-L1) (combined positive score [CPS] ≥10), or who are medically ineligible to receive any platinum-based chemotherapy.

This study will be considered to have met its primary objective if pembrolizumab +lenvatinib is superior to pembrolizumab + placebo for either primary endpoint.

Progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) will be assessed per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

NOTE: As of Amendment 011-03, formal comparisons between study treatment arms will no longer be conducted. Imaging, ePROs, biomarkers, and PK/ADA samples are no longer being collected. Updated analyses are described in Section 9.

Primary Objectives	Primary Endpoints
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to PFS per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by blinded independent central review (BICR). Hypothesis 1: Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to PFS per RECIST 1.1 by BICR.	PFS, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first.
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to overall survival (OS). Hypothesis 2: Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to OS.	OS, defined as the time from randomization to the date of death from any cause.
Secondary Objectives	Secondary Endpoints
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to objective response rate (ORR) per RECIST 1.1 by BICR. Hypothesis 3: Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to ORR per RECIST 1.1 by BICR.	Objective response (OR), defined as a confirmed complete response (CR) or partial response (PR).
To evaluate the safety and tolerability of treatment with pembrolizumab + lenvatinib versus pembrolizumab + placebo.	Adverse events (AEs) and discontinuations due to AEs.
To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to duration of response (DOR) per RECIST 1.1 by BICR.	DOR, defined as the time from the first documented evidence of CR or PR to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.
To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to disease control rate (DCR) per RECIST 1.1 by BICR.	Disease control, defined as a confirmed response of CR or PR or stable disease (SD).

To evaluate changes in patient-reported outcomes (PROs) from baseline, and to evaluate time to deterioration (TTD) in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) global health status/quality of life (QoL).	EORTC QLQ-C30 global health status/QoL score. TTD, defined as the time from baseline to the first onset of PRO deterioration in EORTC QLQ-C30 global health status/QoL score.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Advanced/unresectable or metastatic urothelial carcinoma
Population	Cisplatin-ineligible participants with CPS ≥10, or participants ineligible for any platinum-containing chemotherapy regardless of CPS, with advanced/unresectable or metastatic UC
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study. **Note: As of Amendment 011-03, all participants will be unblinded and receive study treatment with pembrolizumab monotherapy.**
Type of Control	Placebo **Note: As of Amendment 011-03, placebo has been removed.**
Study Blinding	Double-blind with in-house blinding **Note: As of Amendment 011-03, the study is unblinded, open-label.**
Masking	Participant or Subject Investigator Sponsor **Note: As of Amendment 011-03, the study is unblinded, open-label.**

Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant signs the informed consent until the last participant's last study-related contact or visit.

Number of Participants:

Approximately 694 participants will be randomized. As of Amendment 011-03, approximately 487 participants have been randomized and no additional participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>NOTE: As of Amendment 011-03, lenvatinib and placebo are removed. All participants remaining in the study will receive open-label pembrolizumab only.
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin</th><th>Treatment Period</th><th>Use</th></tr>
<tr><td>Arm 1 and 2</td><td>Pembrolizumab</td><td>200 mg</td><td>Q3W</td><td>IV Infusion</td><td>~2 years (initial treatment) ~1 year (Second Course)</td><td>Background Treatment</td></tr>
<tr><td colspan="7">Abbreviations: Admin = administration; IV = intravenous; Q3W = every 3 weeks.</td></tr>
</table></td></tr>
<tr><td>Total Number</td><td>Note: As of Amendment 011-03, all participants will receive open-label pembrolizumab only.
2 arms</td></tr>
<tr><td>Duration of Participation</td><td>NOTE: As of Amendment 011-03, lenvatinib and placebo are removed from study intervention. All participants remaining in the study will receive open-label pembrolizumab only.
Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact.
After a screening phase of up to 28 days, each participant will be assigned to receive pembrolizumab for up to 35 cycles or until a discontinuation criterion (Section 7.1) is met.
Participants will be permitted to continue study intervention beyond RECIST 1.1-defined PD as long as the treating investigator considers that the participant may experience clinical benefit, and the participant is</td></tr>
</table>

	tolerating study intervention. All decisions to continue study intervention beyond confirmed PD by RECIST must be approved by the Sponsor. Participants who have been receiving study intervention for ≥24 weeks (8 cycles) and who attain a CR may consider stopping pembrolizumab treatment. If a confirmed CR per RECIST 1.1 is attained, participants must receive pembrolizumab for at least 2 additional cycles after CR is first documented. Participants with investigator-determined PD by RECIST 1.1 after first course treatment with pembrolizumab treatment has been completed (i.e., 35 cycles) or stopped for confirmed CR may be eligible for up to 17 additional cycles of pembrolizumab (approximately 1 year) in the Second Course Treatment phase upon experiencing PD (Section 8.10.3). **Note: As of Amendment 011-04, Second Course will no longer be offered.** Any participant receiving Second Course treatment prior to initiation of Amendment 011-04 will be able to complete treatment as planned. After the end of study intervention, each participant will be followed for safety and spontaneously reported pregnancy as described in Section 8. Tumor imaging should be performed by site investigator/radiology assessment as per standard of care (SOC) for the disease and local guidelines. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. **Note: As of Amendment 011-04**, study participation will end after the final administration of pembrolizumab. Participants who either complete 35 administrations of pembrolizumab or discontinue pembrolizumab will discontinue from the study following the Safety Follow-up visit. AEs and spontaneously reported pregnancies will be reported and followed as described under Section 8.4. All participants in Efficacy Follow-up prior to initiation of Amendment 011-04 will stop efficacy assessments and be discontinued from the study. All participants in Survival Follow-up prior to initiation of Amendment 011-04 are considered to have completed the study and should have a final survival contact. The overall study ends when the last participant completes the last study-related contact or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Additional study governance considerations are outlined in Appendix 1 (Section 10.1.4). **As of Amendment 011-03, Executive Oversight Committee and Data Monitoring Committee are no longer applicable.**	

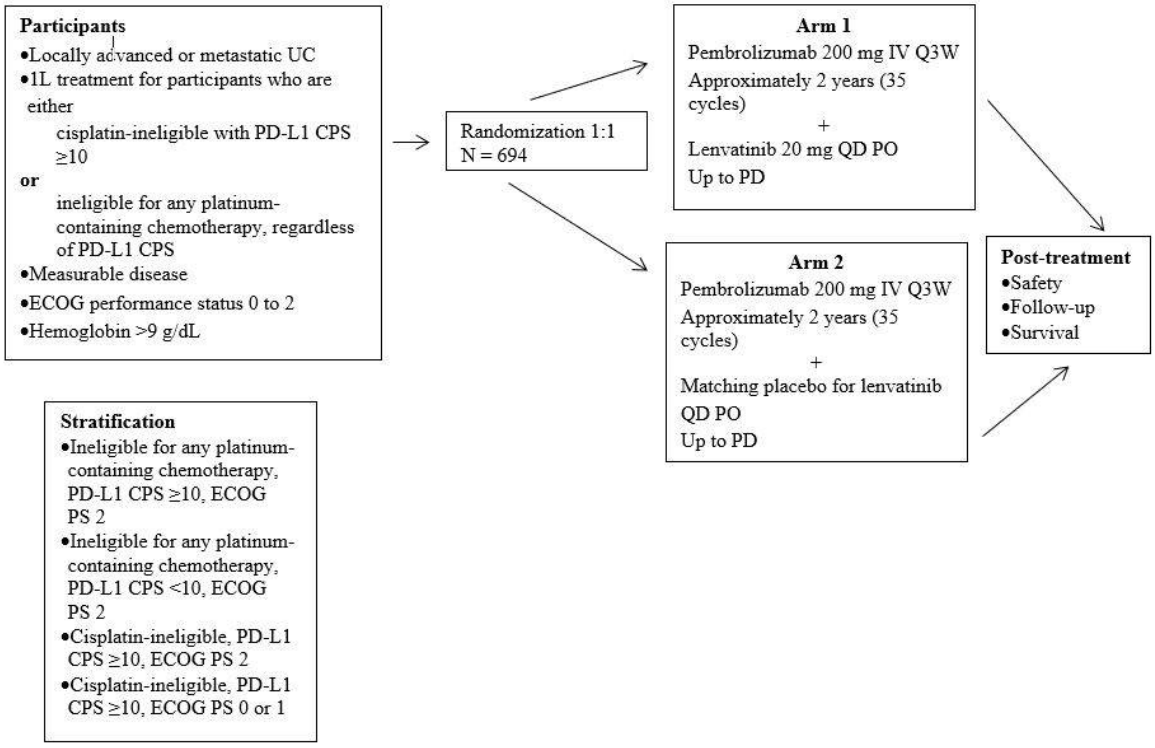
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document is in Appendix 10.

1.2 Schema

The original study design is shown in Figure 1 (Initial Treatment) and Figure 2 (Second Course). **The revised study design as of Amendment 011-04 is depicted in Figure 3 (Initial Treatment) and Figure 4 (Second Course). Note: As of Amendment 011-04, Second Course will no longer be offered.** Any participant currently receiving Second Course treatment will be able to complete treatment as planned.

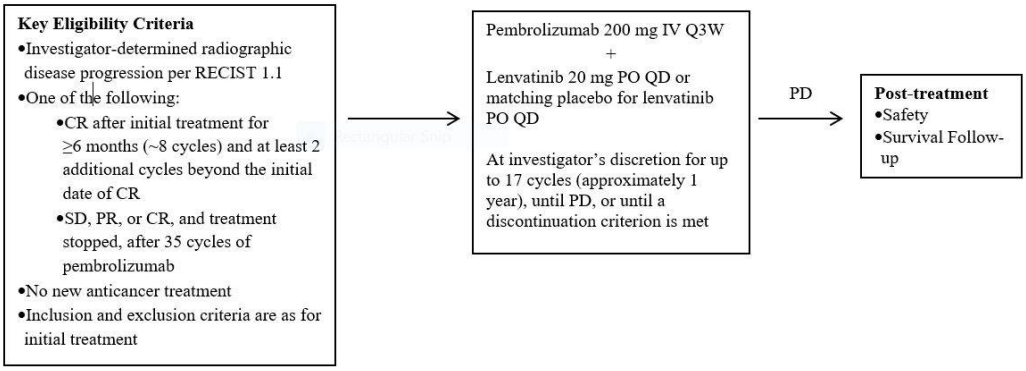
Figure 1 Initial Treatment (Original Study Design)



Abbreviations: 1L = first line; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; PD = progressive disease; PD-L1 = programmed death ligand 1; PO = orally; PS = performance status; Q3W = every 3 weeks; QD = once daily; UC = urothelial carcinoma.

If pembrolizumab is discontinued because of toxicity, participants may continue receiving lenvatinib or placebo as long as they continue to show clinical benefit from the treatment. If lenvatinib or placebo is discontinued for any reason, pembrolizumab may be continued to complete the duration of 35 cycles of therapy unless there is a reason to discontinue pembrolizumab.

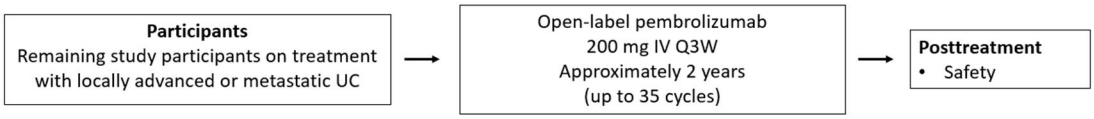
Figure 2 Second Course (Original Study Design)



Abbreviations: CR = complete response; IV = intravenously; PD = progressive disease; PO = orally; PR = partial response; Q3W = every 3 weeks; QD = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SD = stable disease.

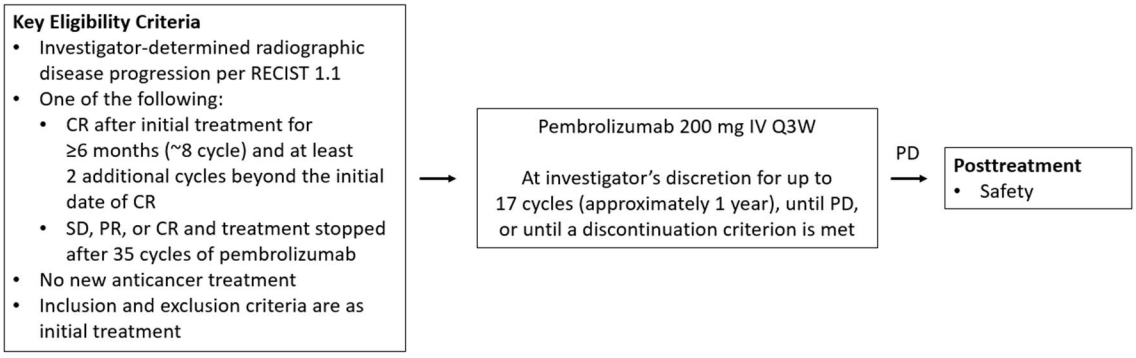
If pembrolizumab is discontinued because of toxicity, participants may continue receiving lenvatinib or placebo as long as they continue to show clinical benefit from the treatment. If lenvatinib or placebo is discontinued for any reason, pembrolizumab may be continued to complete the duration of 17 cycles of therapy unless there is a reason to discontinue pembrolizumab.

Figure 3 Initial Treatment (Amendment 011-04)



Abbreviations: IV = intravenously; Q3W = every 3 weeks; UC = urothelial carcinoma.

Figure 4 Second Course (Amendment 011-04)



Abbreviations: CR = complete response; IV = intravenously; PD = progressive disease; PR = partial response; Q3W = every 3 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SD = stable disease.

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment

As of Amendment 011-04, study participation will end after the final administration of pembrolizumab. Participants who either complete 35 cycles of pembrolizumab or discontinue pembrolizumab will discontinue from the study following the Safety Follow-up visit. AEs and spontaneously reported pregnancies will be reported and followed as described under Section 8. All participants in Efficacy Follow-up prior to initiation of Amendment 011-04 will stop efficacy assessments and be discontinued from the study. All participants in Survival Follow-up prior to the initiation of Amendment 011-04 are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information. The SoA has been amended to only show the required assessments.

Trial Period	**Screening**	**Treatment Cycle = 21 days**						**EOT**	**Posttreatment** **Safety FU[a]**	**Notes**
Visit Timing/ Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At D/C**	**30 days after last dose**	**All procedures performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**			
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	
Informed Consent										
Informed consent	X									Signed before any protocol-specific screening procedures are performed. Reconsent required at time of progression if study intervention is to be continued beyond progression.
Tumor Tissue Collection										
Archived or newly obtained tumor tissue	X									Archived tissue sample, obtained before screening as part of SOC, may be used.

Trial Period	Screening	Treatment Cycle = 21 days						EOT	Posttreatment Safety FU[a]	Notes
Visit Timing/ Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At D/C**	**30 days after last dose**	**All procedures performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**			
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	
Administrative and General Procedures										
Inclusion/ exclusion criteria	X									
Participant identification card	X	X*								*Update with randomization number from IRT.
Demographics and medical history	X									
Prior/concomitant medications	X	X								Per SOC or as clinically indicated and required to be recorded when clinically relevant to an AEOSI, SAE or ECI.
Treatment randomization		X								First dose within 3 days of randomization.
Study Intervention Administration										
Pembrolizumab administration IV Q3W		X	X	X	X	X	X			

Trial Period	Screening	Treatment Cycle = 21 days						EOT	Posttreatment Safety FU[a]	Notes
Visit Timing/ Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At D/C**	**30 days after last dose**	**All procedures performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**			
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	
Tumor Imaging										
Chest imaging (CT) and response assessment (Oral contrast is optional. IV contrast is required unless contraindicated.)	X	⟷								The same modality should be used for all scans. Perform at screening (within 28 days of randomization); thereafter imaging is to be performed as per SOC for the disease and local guidelines. Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks before EOT, a scan at EOT is not mandatory.
Abdomen/pelvis imaging (CT/MRI) and response assessment (Oral contrast is optional. IV contrast is required unless contraindicated.)	X	⟷								
Bone scan	X	⟷								Perform a baseline bone scan in all participants within 28 days prior to randomization. After randomization, if baseline scan is positive, perform bone scan as per SOC for the disease and local guidelines. This schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks prior to EOT, a scan at EOT is not mandatory.

Trial Period	Screening	Treatment Cycle = 21 days						EOT	Posttreatment Safety FU[a]	Notes
Visit Timing/ Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At D/C**	**30 days after last dose**	**All procedures performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**			
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	
Efficacy Procedures										
Subsequent anticancer therapy status								X	X	FU information may be obtained at a clinic visit or by telephone, email, or from other sources.
Survival status		←					→			
Clinical Procedures/Assessments										
Directed physical examination		X								Per SOC or as clinically indicated.
Weight	X	X								
Vital signs	X	X								
Height	X									
12-lead ECG with QTcF determination	X*									*After screening, per SOC or as clinically indicated.
MUGA scan or ECHO	X*									*After screening, per SOC or as clinically indicated.
ECOG performance status	X	X								To be performed per SOC or as clinically indicated.

Trial Period	Screening	Treatment Cycle = 21 days						EOT	Posttreatment Safety FU[a]	Notes
Visit Timing/ Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At D/C**	**30 days after last dose**	**All procedures performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**			
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	
AE/SAE review	X	←							→	Report NSAEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. 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 (Local Laboratory)										
Pregnancy test-urine or serum β-HCG (WOCBP only)	X	X								Monthly pregnancy testing should be conducted as per local regulations where applicable.
Urine dipstick testing	X									Performed locally within 7 days before first dose. Thereafter, only required per SOC or if clinically indicated.
Urinalysis	X									Performed locally within 7 days before first dose. Thereafter, only required per SOC or if clinically indicated.
Laboratory Procedures/Assessments (Local or Central Laboratory)										
HIV, hepatitis B, and hepatitis C	X									Only if mandated by local health authority.
Serum FSH (WONCBP only)	X									In the absence of 12 months of amenorrhea, confirmation with 2 FSH values in postmenopausal range is required.

Trial Period	Screening	Treatment Cycle = 21 days						EOT	Posttreatment Safety FU[a]	Notes
Visit Timing/ Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At D/C**	**30 days after last dose**	**All procedures performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**			
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	
CBC with differential	X	X								To be performed per SOC or as clinically indicated and required to be recorded when clinically relevant to an AEOSI, SAE or ECI.
Clinical chemistry	X	X								
T3 or FT3, FT4, TSH	X	X								
PT/INR and aPTT or PTT	X									Within 10 days of first dose PTT is acceptable if aPTT cannot be determined. Additional testing as clinically indicated for participants taking anticoagulants.
PK/Biomarkers (Central Laboratory)										
Blood for genetic analysis		X								Predose. See Section 8.8 of the protocol for additional information.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BP = blood pressure; β-HCG; = β human chorionic gonadotropin; CBC = complete blood count; CR = complete response; CT = computed tomography; CXDY= Cycle X Day Y; D/C = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EOT = end of treatment; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; HIV = human immunodeficiency virus; IEC = independent ethics committee; INR = international normalized ratio; IRB = institutional review board; IRT = interactive response technology; IV = intravenously; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSAE = non-serious adverse event; PD = progressive disease; PD-L1 = programmed death ligand 1; PO = orally; PT = prothrombin time; PTT = partial thromboplastin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q18W = every 18 weeks; Q24W = every 24 weeks; QD = once daily; QTcF = QT interval corrected with Fridericia's formula; RNA = ribonucleic acid; SAE = serious adverse event; SoA = schedule of activities; SOC = standard of care; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; W = week; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] If the D/C visit takes place ≥30 days from the last dose of study intervention, a safety FU visit is not required. In that event, all procedures required for both the D/C visit and the safety FU visit will be performed at the D/C visit. The D/C date is the date when the participant discontinues all study intervention.

1.3.2 Second Course Treatment

Note: As of Amendment 011-04, Second Course will no longer be offered. Any participant currently receiving Second Course treatment will be able to complete treatment as planned. Participants who either complete 17 cycles of pembrolizumab or discontinue pembrolizumab will be discontinued from the study following the Safety Follow-up visit. AEs and spontaneously reported pregnancies will be reported and followed as described under Section 8. All participants in Efficacy Follow-up prior to initiation of Amendment 011-04 will stop efficacy assessments and be discontinued from the study. All participants in Survival Follow-up are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information. The SoA has been amended to only show the required assessments.

Trial Period	**Treatment Cycle = 21 days**						**EOT**	**Post-treatment**	**Notes**
								Safety FU[a]	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At D/C**	**30 days after D/C (+ 7 days)**	**All procedures are to be performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	
Administrative and General Procedures									
Second Course eligibility criteria	X								The SC eligibility criteria must be satisfied and all safety parameters listed in the inclusion criteria, and none listed in the exclusion criteria, are met.
Concomitant medications	X								Per SOC or as clinically indicated and required to be recorded when clinically relevant to an AEOSI, SAE or ECI.
Study Intervention Administration									
Pembrolizumab 200 mg IV Q3W	X	X	X	X	X	X			Eligible participants may receive up to an additional 17 cycles of pembrolizumab.

Trial Period	Treatment Cycle = 21 days						EOT	Post-treatment	Notes
								Safety FU[a]	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At D/C**	**30 days after D/C (+ 7 days)**	**All procedures are to be performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	
Efficacy Procedures									
Chest imaging (CT) and response assessment (Oral contrast is optional. IV contrast is required unless contraindicated.)	←	—	—	—	—	→			For SC, baseline imaging is CT scan showing PD that makes SC necessary. Baseline imaging within 28 days before the first dose of treatment, in the Second Course. This may be the same day as the date of new PD. Thereafter imaging is to be performed as per SOC. This schedule should be followed regardless of treatment delays.
Abdomen/pelvis imaging (CT/MRI) and response assessment (Oral contrast is optional. IV contrast is required unless contraindicated.)	←	—	—	—	—	→			
Bone scan	←	—	—	—	—	→			Perform baseline bone scan within 28 days before SC C1 only in the situation of an actively monitored bone scan in the Initial Treatment course or any evidence of symptomatic development of bone metastases. If the scan at SC C1 is positive, a bone scan is to be performed as per SOC for the disease and local guidelines. This schedule should be followed regardless of treatment delays.
Subsequent anticancer therapy status							X	X	FU information may be obtained at a clinic visit or by telephone, email, or from other sources.
Survival status	←	—	—	—	—	→			Upon Sponsor request, participants may be contacted for survival status at any time during the study.

Trial Period	**Treatment Cycle = 21 days**						**EOT**	**Post-treatment**	**Notes**
								Safety FU[a]	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At D/C**	**30 days after D/C (+ 7 days)**	**All procedures are to be performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	
Clinical Procedures/Assessments									
Full physical examination	X						X		Within 7 days before SC C1
Directed physical examination	X								Per SOC or as clinically indicated.
Vital signs; weight	X								
ECOG performance status	X								
12-lead ECG with QTcF determination	X						X		Perform only if clinically indicated.
AE/SAE review	←							→	Report NSAEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. 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 a new anticancer therapy is initiated, whichever is earlier.
Laboratory Procedures/Assessments: (Local Laboratory)									
Pregnancy test- urine or serum β-HCG (WOCBP only)	X								Monthly pregnancy testing should be conducted as per local regulations where applicable.

Trial Period	Treatment Cycle = 21 days						EOT	Post-treatment	Notes
								Safety FU[a]	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At D/C**	**30 days after D/C (+ 7 days)**	**All procedures are to be performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**±7**	
Laboratory Procedures/Assessments (Local or Central Laboratory)									
CBC with differential	X								To be performed Per SOC or as clinically indicated and required to be recorded when clinically relevant to an AEOSI, SAE or ECI.
Clinical chemistry	X								
T3 or FT3, FT4, and TSH	X								
PT/INR and aPTT/PTT	X								Additional testing as clinically indicated for participants taking anticoagulants

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = beta human chorionic gonadotropin; BP = blood pressure; CBC = complete blood count; CR = complete response; CT = computed tomography; C1 = cycle 1; CXDY = Cycle X Day Y; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; NSAE = nonserious adverse event; PD = progressive disease; PO = orally; PT = prothrombin time; PTT = partial thromboplastin time; QD = every day; Q12W = every 12 weeks; Q24W = every 24 weeks; QTcF = QT interval corrected with Fridericia's formula; SAE = serious adverse event; SC = second course; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

[a]If the D/C visit takes place ≥30 days from the last dose of study intervention, a safety FU visit is not required. In that event, all procedures required for both the D/C visit and the safety FU visit will be performed at the D/C visit. The D/C date is the date when the participant discontinues all study intervention.

2 INTRODUCTION

2.1 Study Rationale

Urothelial carcinoma (UC), also referred to as transitional cell carcinoma, is a range of tumors that arise from the urothelial endothelium, including the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually [Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D 2011]. UC is the predominant histologic type of bladder cancer in the United States and western Europe, where it accounts for approximately 90% of bladder cancers.

UC disproportionately affects the elderly, who often have coexisting, impactful illnesses such as cardiovascular disease and impaired renal function. Such coexisting illnesses are important factors limiting treatment options for these patients [Bamias, A., et al 2007]. Many patients with UC present with advanced disease [Siegel, R. L., et al 2016]. Inoperable, metastatic disease is typically incurable; prognosis is poor and treatment options are limited. Patients receive palliative chemotherapy or best supportive care as the only options.

For nearly 30 years, the first-line standard of care treatment for patients with locally advanced or metastatic UC has been cisplatin-containing combination chemotherapy, including either gemcitabine or methotrexate/vinblastine/doxorubicin [Sternberg, C. N., et al 2006] [Logothetis, C. J., et al 1990] [von der Maase, H., et al 2000]. Median survival with cisplatin-based multi-agent chemotherapy is approximately 14 to 15 months [von der Maase, H., et al 2005]. While this result is superior to the estimated 6-month survival with metastatic disease before the development of modern chemotherapy regimens, the 5-year survival rate with contemporary regimens remains poor.

Chemotherapy, particularly with cisplatin, is toxic, and it has been estimated that only approximately 21% of patients are treated with cisplatin-based chemotherapy [Sonpavde, G., et al 2014]. Cisplatin ineligibility is commonly due to renal dysfunction (creatinine clearance [CrCl] <60 mL/min), ECOG performance status (PS) 2, or both. Hearing loss, Grade 2 neuropathy, and heart failure may also confer cisplatin ineligibility [Galsky, M. D., et al 2011] [Galsky, M. D., et al 2011] [Dash, A., et al 2006]. There is no standard of care chemotherapy for patients unable to tolerate cisplatin. Consensus guidelines, such as those of the National Comprehensive Cancer Network (NCCN), recommend participation in clinical trials of new and more tolerable therapy for patients who cannot tolerate cisplatin-based chemotherapy. As an alternative chemotherapy to cisplatin and clinical trial participation, NCCN recommends gemcitabine/carboplatin on the basis of category 2 evidence (https://www.nccn.org/professionals/physician_gls/default.aspx). The NCCN recommendation for gemcitabine/carboplatin is based on the European Organisation for Research and Treatment of Cancer (EORTC) 30986 trial, one of the largest clinical trials evaluating carboplatin-based chemotherapy in the cisplatin-ineligible population [De Santis, M., et al 2012]. In this study, 238 cisplatin-ineligible participants with UC were randomized to receive either gemcitabine/carboplatin or methotrexate/carboplatin/vinblastine. Overall, chemotherapy was active; the ORR was 36.1%. However, median survival was poor (9.3 months with gemcitabine/carboplatin, the more effective and less toxic of the 2 regimens studied) for the overall study population. Participants with baseline ECOG PS 2 and

glomerular filtration rate (GFR) <60 mL/min demonstrated a worse ORR of 26.5% and a median OS of 5.5 months (95% confidence interval [CI]: 4.1, 8.3). Participants with ECOG PS 2 and visceral metastatic disease (represented by Bajorin risk group 2 [below]) had an ORR of 26.5% and a median OS of 5.5 months (95% CI: 4.2, 7.3). The rate of severe acute toxicity, defined as death as a result of toxicity, renal toxicity (Grade 3 to 4), febrile neutropenia (Grade 3 to 4), hemorrhage/bleeding with thrombocytopenia (Grade 4), or mucositis (Grade 3 to 4) was 9.3% of the overall population in the gemcitabine/carboplatin arm of EORTC 30986. The rate of severe acute toxicity was 28% in participants with ECOG PS 2 and GFR <60 mL/min. Of the participants receiving gemcitabine/carboplatin, 72.9% required dose reduction and 21% discontinued therapy due to toxicities. In light of these results, the overall benefit derived from carboplatin is small.

Consistent with these recommendations, a risk categorization called the Bajorin risk model has been formulated and published [Bajorin, D. F., et al 1999]. The 2 risk factors in the Bajorin risk model are:

- Poor performance status (Karnofsky performance status <80%, equivalent to ECOG PS ≥2)
- Presence of visceral (lung, liver, or bone) metastasis

Patients are placed in 3 prognostic groups (Bajorin risk groups 0, 1, or 2) depending on their number of adverse prognostic factors. Because of these findings, the NCCN warns that ECOG PS ≥2 and visceral metastatic disease or ECOG PS ≥2 and GFR <60 mL/min strongly predict a poor outcome of chemotherapy and suggests that such patients might be better served with best supportive care or participation in a clinical trial [National Comprehensive Cancer Network 2016]. The results of the EORTC 30986 clinical trial demonstrate that ECOG PS 2 plus an additional prognostic factor (GFR <60 mL/min or visceral metastases) are key characteristics that define chemotherapy unfitness [De Santis, M., et al 2012] and suggested that alternative non-cisplatin-containing treatment regimens should be investigated for these patients.

Indeed, because of the frailty of this population with advanced UC and the toxicity associated with chemotherapy, it has been estimated that 48% of UC patients cannot be treated with any platinum chemotherapy at all. In addition, it has been shown that patients not treated with chemotherapy do worse than those who are able to tolerate it [Small, A. C., et al 2012] [Sonpavde, G., et al 2014] [Sonpavde, G., et al 2012]. The critical implication is that there are many patients who die not having received anticancer treatment. There are no clear guidelines or definitions of clinical characteristics for platinum-based chemotherapy ineligibility [Sonpavde, G., et al 2014]. Despite the absence of a precise definition, practicing clinical oncologists are adept at identifying patients who are good candidates for chemotherapy and do not offer chemotherapy to patients who are not good candidates for it.

The most frequently listed characteristics of patients deemed unfit for chemotherapy, and therefore of platinum ineligibility, are the following [Apolo, A. B., et al 2013]:

- ECOG PS 2 plus 1 of the following:
  - Visceral metastases
  - GFR 30 to 60 mL/min
  - Grade ≥2 audiometric hearing loss
  - Grade ≥2 peripheral neuropathy
  - Other reason for the patient's being unable to receive carboplatin safely

Recently, pembrolizumab has shown efficacy in first line (1L) and second line (2L) treatment of metastatic bladder cancer [Powles, T., et al 2014]. Pembrolizumab is indicated for the treatment of previously untreated patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10). In the US and some other regions, pembrolizumab is also indicated for patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status. Data from KEYNOTE-052 [Balar, A. V., et al 2017], a large single-arm Phase 2 study investigating pembrolizumab for the first-line treatment of advanced UC in cisplatin-ineligible participants, were the basis of approval for this indication. KEYNOTE-052 enrolled 370 participants who were cisplatin-ineligible (ECOG PS 2, CrCl ≥30 to <60 mL/min, Grade ≥2 neuropathy/hearing loss, New York Heart Association [NYHA] Class 3 heart failure), had advanced UC, and had received no prior chemotherapy for metastatic disease. Participants received pembrolizumab 200 mg IV Q3W for up to 24 months.

In KEYNOTE-052, 48% of participants (n = 179) were at least 75 years of age, and 10.8% (n = 40) were at least 85 years of age. Many participants had poor prognostic features at study entry: 41.9% (n = 155) had ECOG PS 2, 85.1% (n = 315) had visceral disease, and 20.8% (n = 77) had liver metastases. In addition, 35% of participants (n = 130) had ECOG PS 2 and visceral metastatic disease and were considered ineligible for any platinum-containing chemotherapy. In summary, these participants represented the full spectrum of cisplatin-ineligible patients, including those who likely would not have been treated with any platinum chemotherapy at all had they not been enrolled into this study.

The results of KEYNOTE-052 demonstrate compelling antitumor activity across the full spectrum of the cisplatin-ineligible population. Treatment resulted in a clinically meaningful ORR of 28.9% (95% CI: 24.3%, 33.8%). Responses were accompanied by unprecedented durability: median duration of response (DOR) was not reached, and DOR ranged from 1.4+ to 27.9+ months (+ denotes ongoing response). The median OS in the overall population was 11.5 months (95% CI: 10.0, 13.3). In comparison to the overall population, median OS was longer in the PD-L1 CPS ≥10 subgroup (18.5 months [95% CI: 12.2, not reached]) and shorter in the PD-L1 CPS <10 subgroup (10.0 months [95% CI: 7.8, 11.6]). This included participants considered cisplatin-ineligible as well as those who were ineligible for any

platinum-based combination chemotherapy. The median OS in the platinum-ineligible population was 8.3 months (95% CI: 5.2, 10.8). Due to the results of KEYNOTE-052, the NCCN recommends pembrolizumab as the standard of care for patients with cisplatin-ineligible UC and CPS ≥10 and for all platinum-ineligible patients.

Pembrolizumab is also indicated for use in patients with locally advanced or metastatic UC and disease progression during or after platinum-containing chemotherapy. KEYNOTE-045 was the basis of approval for this indication and was a multicenter, randomized, active-controlled trial in which participants had previously received platinum-based chemotherapy and were randomized to receive either pembrolizumab 200 mg Q3W (n = 270) or the investigator's choice of paclitaxel, docetaxel, or vinflunine (n = 272) [U.S. Prescribing Information. 2021].

In KEYNOTE-045 [Bellmunt, J., et al 2017], the median age of participants was 67 years in the pembrolizumab arm and 65 years in the chemotherapy arm. The majority of participants had ECOG PS 0 (44.1% for pembrolizumab and 39.0% for chemotherapy) or 1 (53.0% for pembrolizumab and 58.1% for chemotherapy). In addition, 89.2% of participants in the pembrolizumab arm and 86.0% of those in the chemotherapy arm had visceral metastases. The results of KEYNOTE-045 showed significantly superior overall survival (OS) with pembrolizumab (hazard ratio [HR] 0.73; 95% CI: 0.59, 0.91; $p = 0.002$) compared with chemotherapy. The median OS with pembrolizumab was 10.3 months (95% CI: 8.0, 11.8), versus 7.4 months with chemotherapy (95% CI: 6.1, 8.3). KEYNOTE-045 also demonstrated higher response rates and longer response duration with pembrolizumab, compared with chemotherapy. The results in the pembrolizumab arm have led to pembrolizumab's becoming a standard of care in this disease setting [Bellmunt, J., et al 2017].

Advanced/metastatic UC presents unique challenges and represents a clinical area in need of novel therapeutic approaches. The current study was originally designed to evaluate the safety and efficacy of combination therapy with pembrolizumab + lenvatinib versus pembrolizumab + placebo in cisplatin-ineligible participants whose tumors express PD-L1 (CPS ≥10) and participants ineligible for any platinum chemotherapy (eg, ineligible for cisplatin and carboplatin by virtue of comorbidities, advanced age, and clinical judgment), with pembrolizumab monotherapy as a treatment option.

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® is indicated for the treatment of patients across a number of indications, including locally advanced or metastatic UC. For more details on specific indications refer to the pembrolizumab Investigator's Brochure (IB) [IB Edition 21 2021].

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

2.2.1.2 Lenvatinib

NOTE: As of Amendment 011-03, this section is no longer applicable.

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 (VEGFRs 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.

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].

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 human umbilical vein endothelial cell (HUVEC) with IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), renal cell carcinoma (RCC), HCC, melanoma, gastric cancer, non-small cell lung 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 Combination of Pembrolizumab With Lenvatinib

NOTE: As of Amendment 011-03, this section is no longer applicable.

Early studies have shown that lenvatinib has antitumor activity in many solid tumors. Lenvatinib is a kinase inhibitor indicated as a single agent for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC), in combination with everolimus for advanced RCC following 1 prior anti-angiogenic therapy, and as a single agent for 1L treatment of unresectable hepatocellular carcinoma. In DTC and RCC, lenvatinib statistically significantly prolonged PFS [U.S. Prescribing Information 2018]. In studies with lenvatinib monotherapy, the median duration of therapy was 13.8 months for DTC and 7.3 months for hepatocellular carcinoma. In the RCC study, the median duration of therapy with lenvatinib in combination with everolimus was 7.6 months.

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

For this reason, an open-label, Phase 1b/2 study (Study E7080-A001-111 [Study 111]) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors was initiated. Phase 1b of this study determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib as 20 mg QD in combination with 200 mg of pembrolizumab IV Q3W. The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (i.e., NSCLC, RCC, endometrial cancer, UC, melanoma, and squamous cell carcinoma of the head and neck). Preliminary data show promising antitumor activity with the combination in many solid tumors. For participants with endometrial cancer that progressed with approved therapy, the combination resulted in an ORR of 48% in 23 participants [Makker, V., et al 2017]. Similarly, in 30 participants with RCC, an ORR of 63.3% was observed with combination therapy. The safety profile in participants with melanoma and RCC was consistent with the overall safety profile of the combination across tumor indications. In 20 participants with metastatic UC who received this combination the ORR at Week 24 was 25%, while an additional 45% had stable disease [Vogelzang, N., et al 2018].

2.2.2 Preclinical and Clinical Studies

NOTE: As of Amendment 011-3, information relative to lenvatinib is no longer applicable.

2.2.2.1 Completed Studies With Pembrolizumab and Lenvatinib

Refer to the respective IBs for pembrolizumab [IB Edition 21 2021] and lenvatinib [IB Edition 15-Eisai 2018] for additional preclinical and clinical study data for pembrolizumab and lenvatinib.

2.2.3 Ongoing Clinical Studies With Pembrolizumab and Lenvatinib

NOTE: As of Amendment 011-03, information relative to lenvatinib is no longer applicable.

Pembrolizumab is under evaluation in patients with metastatic UC as monotherapy and in combination with chemotherapy and targeted therapy. Lenvatinib is studied in patients with different types of solid tumors, including metastatic UC in combination with pembrolizumab (Study 111/KEYNOTE-146). Full lists of ongoing studies are in the respective IBs for pembrolizumab and lenvatinib.

Study 111/KEYNOTE-146

Study 111/KEYNOTE-146 is a multicenter, open-label, Phase 1b/2 clinical trial being conducted to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab. The primary objective of the Phase 1b portion of the study is to determine the MTD in participants with unresectable solid tumors (NSCLC, RCC, endometrial cancer, UC, melanoma, and squamous cell carcinoma of the head and neck) that had progressed after treatment with approved therapies or for which no standard effective therapies were available. The MTD of lenvatinib in Study 111/KEYNOTE-146 was 20 mg/day + pembrolizumab 200 mg Q3W and was therefore the dose selected for this Phase 3 study.

The primary endpoint of the initial part of the Phase 2 portion of the study was ORR after 24 weeks of treatment, with select secondary endpoints including ORR, DCR, PFS, and DOR.

As of the data cutoff of 01-MAR-2018, 20 participants with confirmed metastatic UC and ECOG PS 0 or 1 were enrolled [Vogelzang, N. J., et al 2018] [Vogelzang, N., et al 2018]. Of the enrolled participants, 10 (50%) were PD-L1(+), 8 (40%) were PD-L1(-), and 2 (10%) were not tested; 4 (20%) were treatment-naïve and 11 (55%) and 5 (25%) had had 1 and 2 prior lines of prior anticancer therapies, respectively. The primary endpoint of ORR at Week 24 was 25% (95% CI: 8.7%, 49.1%) with an additional 45% having stable disease. A total of 18 participants (90%) experienced treatment-related AEs (TRAEs). Grade 3 and Grade 4 TRAEs occurred in 5 (25%) and 5 (25%) participants, respectively. There was 1 fatal TRAE (gastrointestinal hemorrhage). The most common TRAEs of any grade were proteinuria (45%), diarrhea (40%), hypertension (35%), fatigue (30%), and hypothyroidism

(30%). The median PFS was 5.4 months (95% CI: 1.3, not estimable) based on investigator assessment per immune-related RECIST. The conclusion was that the combination of lenvatinib and pembrolizumab showed promising clinical activity with a manageable safety profile in previously treated participants with metastatic urothelial cancer who were not preselected for PD-L1 status, including those who had received more than 1 line of treatment.

2.3 Benefit/Risk Assessment

NOTE: As of Amendment 011-03, the risks for lenvatinib or for the combination of pembrolizumab and lenvatinib are no longer applicable.

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 has been approved for first-line treatment of patients with locally advanced or metastatic bladder cancer who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (combined positive score [CPS] ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. It is also approved for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment. There is an unmet medical need for safe and efficacious first-line therapy in patients with locally advanced or metastatic UC who are ineligible for any platinum-containing chemotherapy. As such, there is a continual need for novel therapies in this setting. The existing data suggest that inhibiting angiogenesis in combination with PD-1 blockade is a promising therapeutic strategy, and the benefit/risk assessment for participants in this study is considered to be favorable.

Additional details regarding specific benefits and risks for participants in this study are in the accompanying IBs and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The objectives and endpoints apply to a study population of male or female participants at least 18 years of age with a histologically confirmed diagnosis of advanced/unresectable or metastatic urothelial carcinoma (UC), who are cisplatin-ineligible and whose tumors express programmed death ligand 1 (PD-L1) (combined positive score [CPS] ≥10), or who are medically ineligible to receive any platinum-based chemotherapy.

This study will be considered to have met its primary objective if pembrolizumab +lenvatinib is superior to pembrolizumab + placebo for either primary endpoint.

Progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) will be assessed per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

NOTE: As of Amendment 011-03, formal comparisons between study treatment arms will no longer be conducted. Imaging, ePROs, biomarkers, and PK/ADA samples are no longer being collected. Updated analyses are described in Section 9.

Primary Objectives	Primary Endpoints
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to PFS per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by blinded independent central review (BICR). Hypothesis 1: Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to PFS per RECIST 1.1 by BICR.	PFS, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first.
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to overall survival (OS). Hypothesis 2: Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to OS.	OS, defined as the time from randomization to the date of death from any cause.
Secondary Objectives	Secondary Endpoints
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to objective response rate (ORR) per RECIST 1.1 by BICR. Hypothesis 3: Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to ORR per RECIST 1.1 by BICR.	Objective response (OR), defined as a confirmed complete response (CR) or partial response (PR).
To evaluate the safety and tolerability of treatment with pembrolizumab + lenvatinib versus pembrolizumab + placebo.	Adverse events (AEs) and discontinuations due to AEs.
To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to duration of response (DOR) per RECIST 1.1 by BICR.	DOR, defined as the time from the first documented evidence of CR or PR to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.

To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to disease control rate (DCR) per RECIST 1.1 by BICR.	Disease control, defined as a confirmed response of CR or PR or stable disease (SD).
To evaluate changes in patient-reported outcomes (PROs) from baseline, and to evaluate time to deterioration (TTD) in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) global health status/quality of life (QoL).	EORTC QLQ-C30 global health status/QoL score. TTD, defined as the time from baseline to the first onset of PRO deterioration in EORTC QLQ-C30 global health status/QoL score.
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
To identify molecular (genomic, metabolic, or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and lenvatinib in all participants.	Molecular (genomic, metabolic, or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.
To assess the pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab.	Population PK parameters including clearance, volume of distribution, and absorption rate constant.
To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to PFS per iRECIST (RECIST 1.1 for immune-based therapeutics) by investigator.	PFS, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first.
To evaluate changes in PROs from baseline using the following instruments: • EORTC QLQ-C30 • European Quality of Life Five Dimensional Five-Level Questionnaire (EuroQoL [EQ]-5D-5L).	Change in PROs from baseline in • Scores for the multi-item and single-item scales of the EORTC QLQ-C30 • EQ-5D-5L visual analog scale (VAS) score.

4 STUDY DESIGN

4.1 Overall Design

NOTE: As of Amendment 011-03, all text in this section relating to lenvatinib/placebo is no longer applicable.

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind study of pembrolizumab + lenvatinib in cisplatin-ineligible participants whose tumors express PD-L1 (CPS ≥10), and in participants ineligible for any platinum-containing chemotherapy, with advanced/unresectable or metastatic UC. This Phase 3 study will be conducted in participants with measurable disease who provide tumor tissue (newly obtained or archival formalin-fixed paraffin-embedded [FFPE] tumor biopsy) for determination of PD-L1 expression, as assessed with the diagnostic IHC 22C3 pharmDx at the central laboratory. Participants will be randomized 1:1 to Arm 1 (pembrolizumab + lenvatinib) or Arm 2 (pembrolizumab + placebo).

The original study design is shown in Figure 1 (Initial Treatment) and Figure 2 (Second Course). The current study design is shown in Figure 3 and Figure 4.

Approximately 694 participants will be enrolled. **As of Amendment 011-03**, approximately 487 participants have been randomized and no additional participants will be randomized. Stratification factors for this study are:

- Ineligible for any platinum-containing chemotherapy, PD-L1 CPS ≥10, ECOG PS 2
- Ineligible for any platinum-containing chemotherapy, PD-L1 CPS <10, ECOG PS 2
- Cisplatin-ineligible, PD-L1 CPS ≥10, ECOG PS 2
- Cisplatin-ineligible, PD-L1 CPS ≥10, ECOG PS 0 or 1

Imaging assessments will include chest CT, abdomen, and pelvis CT/MRI and bone scintigraphy at baseline, repeated based on the initial result or symptoms. The timing of imaging assessments is given in the SoA (Sections 1.3.1 and 1.3.2) and in Section 8.2.1.

Note: As of Amendment 011-04, **participants who either completed pembrolizumab administration or discontinue pembrolizumab will discontinue from the study following the Safety Follow-up visit (Section 8.10.5).** AEs and spontaneously reported pregnancies will be reported and followed as described under Section 8.4. All participants in Efficacy Follow-up prior to initiation of Amendment 011-04 will stop efficacy assessments and be discontinued from the study. All participants in Survival Follow-up prior to initiation of Amendment 011-04 are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information.

During initial treatment, participants who have been receiving study intervention for ≥24 weeks (8 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 2 additional cycles after CR is first documented.

Adverse event monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.

Treatment with pembrolizumab will continue for up to 35 cycles, or until a discontinuation criterion (Section 7.1) is met.

Participants who stop pembrolizumab treatment after receiving 35 administrations of pembrolizumab, or participants who have been receiving study intervention for at least 24 weeks, attain a confirmed CR, and stop study intervention may be eligible for up to 17 additional cycles (approximately 1 year) of pembrolizumab upon experiencing PD. This retreatment is termed the Second Course Treatment phase and is only available if the study remains open, the participant meets the criteria in Section 8.10.3 and upon consultation with the Sponsor. **Note: As of Amendment 011-04, Second Course will no longer be offered.** Any participant receiving Second Course treatment prior to the initiation of Amendment 011-04 will be able to complete treatment as planned.

Pembrolizumab will be administered for a maximum of 35 cycles during initial treatment and 17 cycles during the Second Course phase.

The study will be conducted in conformance with Good Clinical Practice (GCP).

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

NOTE: As of Amendment 011-03, all text in this section relating to lenvatinib/placebo is no longer applicable.

Patients with UC who are not eligible to receive cisplatin-based chemotherapy combinations have few options for 1L treatment of locally advanced or metastatic disease. The EORTC 30986 study demonstrated a reasonable ORR with gemcitabine and carboplatin, but the median OS remained low at 5.5 months. In participants with ECOG PS 2 and either visceral metastases or CrCl <60 mL/min, the treatment was associated with significant toxicities and poor tolerance. The KEYNOTE-052 study demonstrated improved median OS with manageable safety in participants who were cisplatin-ineligible and had PD-L1 CPS ≥10, and in participants deemed too frail to receive any platinum-based combination therapy. Pembrolizumab monotherapy is considered a standard of care for this population.

In addition, the use of a placebo control with the standard of care, pembrolizumab, will allow unbiased evaluation of the combination therapy. In Study 111, the adverse event profile of the combination of pembrolizumab with lenvatinib was not significantly greater than that of

either agent as monotherapy. This allows blinding to be an appropriate strategy for evaluation of the combined activity in this population with few options for treatment.

This Phase 3 study is being conducted to evaluate the efficacy and safety of pembrolizumab + lenvatinib compared with pembrolizumab + placebo in locally advanced or metastatic UC, to determine whether addition of lenvatinib will provide improvements to pembrolizumab monotherapy.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

NOTE: As of Amendment 011-03, efficacy endpoints will be analyzed in a descriptive fashion, without conducting any formal comparison between treatment arms. Imaging will no longer be assessed by BICR.

This study will use PFS per RECIST 1.1 assessed by BICR and OS as primary endpoints. ORR per RECIST 1.1 by BICR and DOR per RECIST 1.1 by BICR and DCR per RECIST 1.1 by BICR will be used as secondary efficacy endpoints.

PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable benefit/risk profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by an iCRO blinded to treatment assignment to minimize bias in response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than on a local site assessment. The iCRO will verify progression by RECIST 1.1 in real time.

OS has been recognized as the gold standard for demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

ORR, DOR, and DCR per RECIST 1.1 by BICR are considered preliminary and supportive evidence of efficacy. As ancillary markers of efficacy, they are also chosen to be secondary endpoints in the study.

4.2.1.1.1 Response Assessed by RECIST 1.1

As of Amendment 011-03, RECIST 1.1 will be used by the investigator when assessing images for efficacy measures and by the site when determining eligibility (Section 8.2.1.5). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.1.2 iRECIST

NOTE: As of Amendment 011-03, all images will be locally assessed using RECIST 1.1 and will no longer be submitted to the iCRO.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses to cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001, 7% of evaluable participants experienced delayed or early tumor pseudoprogression. Of note, participants with PD per RECIST 1.1 but not per immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than did participants with PD per both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses to immunotherapy and enables treatment beyond initial radiographic progression, if the patient is clinically stable.

Modified RECIST 1.1 (iRECIST) has been developed and published by the RECIST Working Group with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the EMA (European Medicines Agency) [Seymour, L., et al 2017]. Unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression occurs per RECIST 1.1. However, if a patient is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions.

4.2.1.2 Safety Endpoints

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

4.2.1.3 Rationale for Patient-reported Outcomes

NOTE: As of Amendment 011-03, ePRO assessments will no longer be collected.

Symptomatic improvement is considered a clinical benefit and is accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their health-related QoL via the EORTC QLQ-C30 and EQ-5D-5L questionnaires.

The EORTC QLQ-C30 and EQ-5D-5L PROs are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-30

The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing health-related QoL in oncology studies [Aaronson, N. K., et al 1993]. EORTC QLQ-C30 is the most widely used cancer-specific, health-related QoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health status/QoL scale [Aaronson, N. K., et al 1993].

4.2.1.3.2 EQ-5D-5L

The EuroQoL 5-Dimensional 5-Level (EQ-5D-5L) is a standardized instrument for use as a measure of health outcome and will provide data for developing health utilities to be used in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in EQ-5D-5L are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). EQ-5D-5L also includes a graded (0 to 100) vertical VAS on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies, and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Pharmacokinetic Endpoints

NOTE: As of Amendment 011-03, samples for PK and ADA assessments will no longer be collected.

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

Standard PK parameters of clearance and volume of distribution at steady state are planned to be calculated for lenvatinib in this study, using the accepted mixed effects modeling approach. PK data from this study may be combined with data from other studies and analyzed using standard population PK techniques to further characterize basic PK parameters, explore the exposure/response relationship for lenvatinib antitumor activity, evaluate the effect of extrinsic and intrinsic factors in support of the proposed dosing regimen, and evaluate safety in the proposed participant population.

4.2.1.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.6 Planned Exploratory Biomarker Research

As of Amendment 011-03, samples for exploratory biomarker research will no longer be collected.

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

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

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

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other blood-derived biomarkers

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

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

4.2.2 Rationale for the Use of Placebo

NOTE: As of Amendment 011-03, this section is no longer applicable.

The use of a placebo in combination with pembrolizumab will ensure the objectivity of the local investigators' treatment decision and AE causality assessments.

4.3 Justification for Dose

4.3.1 Lenvatinib

NOTE: As of Amendment 011-03, this section is no longer applicable.

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

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W. Based on the promising antitumor efficacy and tolerable safety profile seen in both the EC and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], two Phase 3 studies have been initiated for both of these tumor types, Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-307/KEYNOTE-581.The safety and efficacy of the combination of pembrolizumab and lenvatinib at the lenvatinib RP2D are being assessed in the Phase 2 portion of this study that includes 6 cohorts (NSCLC, RCC, endometrial carcinoma, UC, melanoma, and squamous cell carcinoma of the head and neck).

4.3.2 Pembrolizumab

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications
- Lack of clinically relevant effect of tumor burden or indication on distribution behavior of pembrolizumab, as assessed by the population pharmacokinetics (PopPK) model
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W

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

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

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

Information on pembrolizumab dose modification is in Section 6.6.1.

4.3.3 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg IV Q3W for up to 2 years (35 cycles) of initial treatment (Section 8.10.2), and for up to 1 year (17 cycles) of Second Course treatment (Section 8.10.3).

4.4 Beginning and End of Study Definition

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

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

4.4.1 Clinical Criteria for Early Study Termination

The 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.

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

5 STUDY POPULATION

The study population includes cisplatin-ineligible participants whose tumors express PD-L1 (CPS ≥10), and participants ineligible to receive any platinum-containing chemotherapy regimen, with advanced/unresectable or metastatic UC.

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

5.1 Inclusion Criteria

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

1. Have a histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter (upper urinary tract), bladder, or urethra. Both transitional cell and mixed transitional/nontransitional cell histology are allowed, but transitional cell carcinoma must be the predominant histology.

2. Have at least 1 measurable target lesion per RECIST 1.1 as assessed by the local site investigator/radiologist, per the following criteria: 1) lymph node (LN) lesion measuring ≥15 mm in the short axis; 2) non-nodal lesion measuring ≥10 mm in the longest diameter; 3) lesion suitable for repeat measurement with CT/MRI imaging. Lesions in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

3. Have provided an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated and adequate for PD-L1 evaluation. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. PD-L1 status (CPS ≥10 or CPS <10) must be obtained by the central laboratory during the screening period prior to enrollment.

    - **Note**: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date they are cut (details pertaining to tumor submission are in the Procedures Manual).

    - **Note:** If PD-L1 is not evaluable (eg, not enough tissue is provided, or the tissue is of poor quality, such that assessment of PD-L1 status is not possible) the participant will be excluded.

4. Have received no prior systemic chemotherapy for advanced or metastatic UC with the following exceptions:

    - Neoadjuvant platinum-based chemotherapy for treatment of muscle-invasive bladder cancer with recurrence >12 months from completion of the therapy is permitted.

    - Adjuvant platinum-based chemotherapy following radical cystectomy, with recurrence >12 months from completion of the therapy, is permitted.

    Note: Low-dose chemotherapy (eg, low-dose cisplatin, cisplatin plus 5-FU, mitomycin plus 5-FU, or cisplatin plus paclitaxel), given concurrently with radiation to the primary tumor site for curative intent treatment of muscle-invasive bladder cancer, is not considered systemic therapy. In the clinical setting, chemotherapy is given with the sole purpose of sensitizing the tumor to local radiation and is not administered at doses with any systemic efficacy. Surgery is not considered 1L therapy following diagnosis of advanced/metastatic disease.

5. Meet criteria for **either option a or option b (below)**:

    a. Have a tumor(s) with PD-L1 CPS ≥10 and be considered ineligible to receive cisplatin-based combination therapy, based on 1 of the following:

        - ECOG PS 2 (Appendix 9) within 7 days prior to randomization

        - CrCl (calculated or measured using the institutional standard) ≥30 to ≤60 mL/min

        - NCI CTCAE Version 4.0 Grade ≥2 audiometric hearing loss

        - NCI CTCAE Version 4.0 Grade ≥2 peripheral neuropathy

    OR

b. In the opinion of the investigator, be considered ineligible to receive any platinum-based chemotherapy (ie, ineligible for cisplatin and carboplatin) based on:

- ECOG PS 2 within 7 days prior to randomization.

  And at least 1 of the following:

- Documented visceral metastatic disease
- CrCl ≥30 to ≤60 mL/min
- NCI CTCAE Version 4.0 Grade ≥2 audiometric hearing loss
- NCI CTCAE Version 4.0 Grade ≥2 peripheral neuropathy
- Other reason, identified on the case report form (CRF), for the participant's being unable to receive both cisplatin and carboplatin safely. Additional criteria for platinum ineligibility will be considered and allowed on a case-by-case basis, following consultation with the Sponsor.

Note: Participants considered ineligible for any platinum-based chemotherapy are eligible for this study regardless of their tumor PD-L1 status.

Note: The reason(s) for ineligibility for cisplatin or any platinum-based chemotherapy must be documented in the participant's medical record and on the electronic case report form (eCRF).

Demographics

6. Be male or female and ≥18 years of age and considered an adult per local regulations on the day of signing the informed consent.

7. Have ECOG PS 0, 1, or 2 within 7 days prior to randomization and a life expectancy of ≥3 months.

Male Participants

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 30 days after the last dose of pembrolizumab or lenvatinib/placebo:

- 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.

  Please note that 30 days after lenvatinib/placebo is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

Female Participants

9. 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 her preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib/placebo. 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 in Appendix 2.

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

Informed Consent

10. The participant (or legally acceptable representative if applicable) provides documented informed consent for the study.

Medical History and Laboratory Values

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

12. Have adequate organ function as defined in Table 1.

    Note: Specimens must be collected within 7 days before the start of study intervention. Subjects may be enrolled based on local laboratory results pending central laboratory results.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine or measured or calculated[b] CrCl (GFR can be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participants with creatinine >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin >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 the participant is receiving anticoagulants, as long as PT or aPTT is within the therapeutic range for intended use of anticoagulants

Abbreviations: 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.

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

[a]This criterion must be met without erythropoietin dependency and without packed red blood cell transfusion within the last 2 weeks.

[b]CrCl should be calculated per the institutional standard.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has disease that is suitable for local therapy administered with curative intent (eg, chemotherapy and radiation for Stage 3 disease).

2. Has tumor with any neuroendocrine or small cell component.

3. Has a history of a gastrointestinal condition or procedure (eg, gastric bypass, malabsorption) that, in the opinion of the investigator, may affect oral drug absorption.

4. Has had major surgery within 3 weeks prior to the first dose of study intervention.

   Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

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

6. Has radiographic evidence of major blood vessel invasion/infiltration or has had clinically significant hemoptysis (at least 0.5 teaspoon of bright red blood) or tumor bleeding within 2 weeks prior to the first dose of study intervention. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.

7. Has had significant cardiovascular impairment within 12 months of the first dose of study intervention, such as history of NYHA >Class II congestive heart failure, unstable angina, myocardial infarction or cerebrovascular accident (CVA)/stroke, cardiac revascularization procedure, or cardiac arrhythmia associated with hemodynamic instability.

8. Has known intolerance or severe hypersensitivity (Grade ≥3) to pembrolizumab or lenvatinib or any of their excipients.

9. Has received lenvatinib as monotherapy or in combination with a PD-1/PD-L1 inhibitor or has previously been enrolled in a clinical study evaluating lenvatinib for bladder cancer, regardless of the treatment received.

10. Is a WOCBP who has a positive urine pregnancy test within 24 hours before randomization (see Appendix 5). If the urine test is positive or 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 test result is positive. If >24 hours have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative for the participant to start receiving study intervention.

Prior/Concomitant Therapy

11. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 inhibitor, indoleamine-pyrrole 2,3 dioxygenase (IDO1) inhibitor, or agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137), or any other antibody or drug targeting T-cell costimulatory pathways in the adjuvant or advanced/metastatic setting.

12. Has received prior radiotherapy to a metastatic site without the use of chemotherapy radiosensitization within 3 weeks of the first dose of study intervention, with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks before the start of study intervention. Participants must have recovered from all radiation-related toxicities and must not require corticosteroids.

13. Has received a live vaccine within 30 days prior to the first dose of study intervention (see Appendix 7 for UK-specific study requirements). Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

14. In the investigator's judgment, has not recovered from toxicity or other complications from any major surgery prior to starting study intervention.

Prior/Concurrent Clinical Study Experience

15. Is currently participating in or has participated in a trial 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

16. Has an LVEF below the institutional normal range, as determined by MUGA or ECHO.

17. Has history or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Participants with QTcF >480 msec are excluded. If a single QTcF is >480 msec, the participant may be enrolled if the average QTcF for 3 ECGs is <480 msec.

18. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (at a dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.

19. Has had an active malignancy (except locally advanced or metastatic UC) within the past 36 months.

    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) who have undergone potentially curative therapy are not excluded.

- A history of prostate cancer (T2NXMX or lower with Gleason score ≤7) treated with definitive intent (surgically or with radiation therapy) at least 1 year prior to study entry is acceptable, provided that the participant is considered prostate cancer-free and the following criteria are met:

  - Participants who have undergone radical prostatectomy must have undetectable prostate-specific antigen (PSA) for >1 year and at screening.

  - Participants who have had radiation must have a PSA doubling time >1 year (based on at least 3 values determined >1 month apart) and a total PSA value which does not meet Phoenix criteria for biochemical recurrence (ie, <2.0 ng/mL above nadir).

- Participants with untreated low-risk prostate cancer (Gleason score ≤6) on active surveillance with PSA doubling time >1 year (based on at least 3 values determined >1 month apart) are also eligible.

20. Has central nervous system (CNS) metastases, unless the participant has completed local therapy (eg, whole brain radiation therapy, surgery, or radiosurgery) and has discontinued use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study intervention.

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

22. Has a history of (non-infectious) pneumonitis that required systemic steroids, or current pneumonitis.

23. Has an active infection requiring systemic therapy.

24. Has a known history of human immunodeficiency virus (HIV) infection. Testing is not required unless mandated by the local health authority (see Appendix 7 for Germany- and UK-specific study requirements).

25. Has a known history of or is positive for active hepatitis B (hepatitis B surface antigen [HbsAg] reactive) or has active hepatitis C (HCV RNA). Testing is not required unless mandated by the local health authority (see Appendix 7 for Germany- and UK-specific study requirements).

26. Has active tuberculosis (see Appendix 7 for Germany-specific study requirements).

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.

29. Is receiving hemodialysis.

30. A participant with >1+ proteinuria on urinalysis at screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. A participant with urine protein ≥1 g/24 h will be excluded.

Other Exclusions

31. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab and lenvatinib/placebo.

32. Has had an allogeneic 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.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

NOTE: As of Amendment 011-03, only pembrolizumab will be administered. Other study treatments (prior to this amendment) have been deleted. The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP/ NIMP	Sourcing
Arm 1 and 2	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W	Background Treatment	IMP	Central

Abbreviations: IV = intravenous; Q3W = every 3 weeks.

Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

NOTE: As of Amendment 011-03, text in this section relating to dose modification of lenvatinib/placebo is no longer applicable and has been deleted.

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

The rationale for selection of doses to be used in this study is 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

NOTE: As of Amendment 011-03, this section is no longer applicable and all participants will receive open-label pembrolizumab.

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab + lenvatinib or to pembrolizumab + placebo, respectively.

6.3.2 Stratification

Stratification factors for this study are:

- Ineligible for any platinum-containing chemotherapy, PD-L1 CPS ≥10, ECOG PS 2
- Ineligible for any platinum-containing chemotherapy, PD-L1 CPS <10, ECOG PS 2
- Cisplatin-ineligible, PD-L1 CPS ≥10, ECOG PS 2
- Cisplatin-ineligible, PD-L1 CPS ≥10, ECOG PS 0 or 1.

6.3.3 Blinding

NOTE: As of Amendment 011-03, blinding is no longer applicable – all participants will receive open-label pembrolizumab monotherapy.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.3.3.1 Lenvatinib/Placebo

NOTE: As of Amendment 011-03, this section is no longer applicable.

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

6.3.3.2 Pembrolizumab

Pembrolizumab will be administered open label; therefore, its identity will be known by the participant, the investigator, the Sponsor, and delegate(s) involved in study intervention administration or clinical evaluation of participants.

6.3.3.3 CPS Results

Investigators will be alerted to completion of a participant's PD-L1 evaluation, as well as to instances where the tumor tissue sample is inadequate for PD-L1 evaluation (not evaluable).

For cisplatin-ineligible participants, the investigator will be blinded to the central vendor's PD-L1 CPS results. However, the investigator will be informed of, and accordingly unblinded to, the PD-L1 CPS category (ie, PD-L1 CPS ≥10 or <10). The inclusion criterion for cisplatin-ineligible participants states a requirement for PD-L1 CPS ≥10. Cisplatin-ineligible participants with PD-L1 CPS <10 will be excluded from the study. **Note**: Participants with PD-L1 considered to be below detectable levels will be included in the CPS <10 category.

For **platinum-ineligible participants**, the investigator will be blinded to the central vendor's PD-L1 CPS results, in an attempt to reduce bias from treatment decisions. The Sponsor acknowledges that, due to the commercial availability of PD-L1 testing assays, it is possible that the investigator may know a participant's CPS prior to screening. This risk is seen as acceptable, as the treatment interventions are hypothesized to provide benefit regardless of CPS.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for >12 weeks for pembrolizumab require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If there is a clinical indication for any medication or vaccination that is specifically prohibited, please consult the Sponsor; discontinuation from study intervention may be required.

Medication considered necessary for the participant's health and not expected to interfere with the evaluation of or interact with the study medication may be continued during the study. Palliative and supportive care is permitted during the study for underlying medical conditions and symptom management. Surgery for tumor control is not permitted during the study.

Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician, as long as the lesion is NOT a RECIST 1.1-defined target lesion and

radiotherapy is NOT administered for tumor control. Study intervention should be withheld during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study intervention. Specific details of the radiation therapy, including location, will be recorded. The investigator should discuss any questions regarding radiation therapy with the Sponsor.

The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant's receiving study intervention requires mutual agreement of the investigator, the Sponsor, and the participant.

All concomitant medications (including over-the-counter medications) administered to the participant during the course of the study will be reviewed. Concomitant medications administered throughout the Initial or Second Course phase and until study intervention discontinuation should be reviewed per SOC or as clinically indicated, and are required to be recorded on the appropriate CRF when an AE of special interest (AEOSI), SAE or event of clinical interest (ECI) occurs.

Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded.

6.5.1 Allowed Concomitant Medications

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

The following concomitant medications are also allowed:

- Hormone replacement therapy
- Thyroid hormone suppressive therapy
- Anticoagulants including low molecular weight heparin, warfarin, anti-Xa agents
- Anti-inflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the participant is enrolled)

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

6.5.2 Prohibited Concomitant Medications

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

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

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

  - Other concurrent investigational drugs.

- Live vaccines within 30 days and while participating in the study (see Appendix 7 for UK-specific study requirements). Examples of live vaccines include, but are not limited to, measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

  - **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 (i.e., those not licensed or approved for Emergency Use) are not allowed.

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

  - **Note:** Inhaled steroids are allowed for management of asthma or seasonal allergies. See Section 6.5.4 for additional information.

- Radiotherapy for disease control.

  - Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician, as long as the lesion is NOT a RECIST 1.1-defined target lesion and radiotherapy is NOT administered for tumor control.

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

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

6.5.3 Drug Interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism; food and drug-drug interactions (DDI) are not anticipated to influence exposure. No preclinical evaluations for DDI have been performed with pembrolizumab. Please refer to the labeling for SOC treatments.

6.5.4 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

For participants receiving pembrolizumab, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined, along with the dose modification guidelines in Table 3 in Section 6.6.1.1. Where appropriate, these guidelines include the use of oral or IV 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 an event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance.

Refer to Table 3 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 the evaluation of an event.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Pembrolizumab

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks (Section 6.4).

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

Dose Modification and Toxicity Management for Immune-related Adverse Events 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 3.

Of note, any serious changes to the skin, including Stevens-Johnson syndrome or toxic epidermal necrolysis, require immediate discontinuation of pembrolizumab.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

6.6.1.2 Dose Modification and Toxicity Management for 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 for pembrolizumab-associated infusion reactions are provided in Table 4.

Table 4 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 h	**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 the drug infusion, the infusion may be restarted at 50% of the original rate (eg, from 100 mL/h to 50 mL/h). Otherwise, withhold dosing until symptoms resolve, and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	The participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: - Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). - Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - Epinephrine** - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In case of anaphylaxis, epinephrine should be used immediately. **The participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO = orally. Appropriate resuscitation equipment should be available at the bedside, and a physician should be readily available during drug administration. For further information, please refer to CTCAE v4.0 at http://ctep.cancer.gov		

6.6.2 Other Allowed Dose Interruptions for Pembrolizumab

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

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

NOTE: As of Amendment 011-03, this section is no longer applicable.

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

NOTE: As of Amendment 011-03, all participants will receive open-label pembrolizumab monotherapy.

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants

who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.4.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- ALT or AST elevation meeting the following criteria:
    - ALT or AST > 5 × ULN for more than 2 weeks
    - ALT or AST > 3 × ULN and (TBL > 2 X ULN or INR > 1.5)
    - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, and/or eosinophilia (>5%)
- The participant interrupts study drug administration for >12 weeks for pembrolizumab, except if agreed to by the Sponsor.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Disease progression is radiographically documented per RECIST 1.1.

  Note: If a participant has unconfirmed PD and is clinically stable*, the assigned study intervention per protocol may be continued at the investigator's discretion until PD is confirmed at least 28 days from the date of imaging suggesting PD. If subsequent imaging does not confirm PD, the participant should continue to receive study intervention and imaging to monitor disease status should continue as per SOC.

*Clinical stability is defined as:

- Absence of symptoms and signs (including worsening of laboratory values) indicating clinically significant disease progression
- No decline in ECOG performance status
- Absence of disease progression or progressive tumor at critical anatomic sites (eg, cord compression) requiring urgent alternative medical intervention

- The participant has intercurrent illness preventing further administration of study intervention.
- The participant has any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing therapy or follow-up.
- The participant has unacceptable toxicities (Section 6.6).
- The investigator decides to discontinue study intervention.
- The participant has recurrent Grade 2 pneumonitis.

  The participants must be discontinued from pembrolizumab treatment after completing 35 cycles of Initial Treatment (approximately 2 years) with pembrolizumab, and, if applicable, after 17 cycles (approximately 1 year) of Second Course treatment with pembrolizumab (Section 4.3.3).

  Discontinuation of pembrolizumab may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

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.

The investigator or qualified designee should clarify whether a participant is withdrawing from study intervention, follow-up visits, and/or contact. Given the importance of OS in this study, efforts should be made to clarify if participants are willing to be followed for survival. For participants unwilling to be followed for survival, a review of public records is required by the investigative site.

7.3 Lost to Follow-up

Note: As of Amendment 011-04, this section is no longer applicable.

There will be no additional efforts to contact participants who are 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 decisions must be made by an investigator who is a qualified physician.

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

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

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

The maximum amount of blood collected from each participant over the duration of the study will be provided in the Laboratory Manual. Repeat or unscheduled samples may be collected for safety reasons or because of technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

The participant or his/her legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

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

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

The participant 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.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

The investigator or qualified designee will review all medications, if any, taken by the participant during the study. Concomitant medications administered throughout the Initial or Second Course phase and until study intervention discontinuation should be reviewed per SOC or as clinically indicated, and are required to be recorded on the appropriate CRF when an AEOSI, SAE or ECI occurs.

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 randomization. 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 of screening/rescreening visit requirements are provided in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Pembrolizumab: Administration of pembrolizumab will be witnessed by the investigator and/or study staff and or qualified designee per institutional guidelines and procedures.

8.1.8.1 Timing of Dose Administration

Pembrolizumab: Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target the infusion time to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes to +10 minutes is permitted (ie, infusion time is 30 minutes [-5 min/+10 min]).

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

8.1.8.2 Compliance

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

8.1.9 Discontinuation and Withdrawal

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

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

8.1.10 Participant Blinding/Unblinding

NOTE: As of Amendment 011-03, blinding is no longer applicable – all participants will receive open-label pembrolizumab alone.

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY, FOR THE WELFARE OF THE PARTICIPANT.

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

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

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

The IRT system should be used for emergency unblinding in the event that this is required for participant safety.

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

8.1.11 Calibration of Equipment

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

8.1.12 Demographics

Participant demographic information will be collected at the screening visit. Demographic information includes date of birth (or age), sex, and race/ethnicity.

8.1.13 Subsequent Antineoplastic Treatment

The investigator or qualified designee will review all new antineoplastic treatment initiated after the last dose of study intervention as outlined in the SoA (Section 1.3).

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 enters survival follow-up. The process for image collection and transmission to the iCRO is in the Site Imaging Manual. CT using IV contrast (unless contraindicated) with the use of oral contrast as optional is strongly preferred for tumor imaging; the use of oral contrast is optional. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging of the brain. The same imaging technique should be used for a participant throughout the study to optimize reproducibility of assessment of existing and new tumor burden, and to improve the accuracy of the response assessment based on imaging. N**ote**: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiologic reviewer at the site or at an offsite facility.

NOTE: As of Amendment 011-03, images for all participants should no longer be submitted to the iCRO.

Treatment and imaging should continue until PD by RECIST 1.1 per investigator assessment.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. Any imaging obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site study team must review screening images to confirm that the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable as screening imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the iCRO.

Tumor imaging at baseline includes the following:

- CT or MRI of the abdomen and pelvis
- CT of the chest
- Bone scan

Bone scans must be performed to confirm CR if positive at baseline.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative. N**ote**: for participants with stable brain metastases at randomization, repeat brain imaging must be performed to document CR.

8.2.1.2 Tumor Imaging During the Study

NOTE: As of Amendment 011-03, central review of images and iRECIST are no longer applicable. Imaging will be performed as per local SOC guidelines; however, the data will not be collected. This section has been updated accordingly.

The first on-study imaging assessment should be performed at 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed by site investigator/radiology assessment as per SOC for the disease and local guidelines. Imaging timing should follow calendar days and not be adjusted for delays in cycle starts. Imaging should continue to be performed until any of these conditions are met: disease progression is identified by the investigator, pregnancy, the start of new anticancer treatment, withdrawal of consent, or death.

8.2.1.2.1 Bone Imaging During the Study

A bone scan at screening will be performed in all participants within 28 days prior to randomization. **As of Amendment 011-03,** if the baseline scan is positive, subsequent scans will be performed by site investigator/radiology assessment as per SOC for the disease and local guidelines. This schedule should be followed regardless of treatment delays. If a bone scan was obtained within 4 weeks prior to end of treatment (EOT), a scan at EOT is not mandatory.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

If previous imaging was obtained within 4 weeks prior to the date of discontinuation, 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 study intervention without documented disease progression, every effort should be made to obtain a final image at the end of treatment visit.

8.2.1.4 Second Course Treatment Tumor Imaging

Note: As of Amendment 011-04, Second Course will no longer be offered. Any participant receiving Second Course prior to the initiation of Amendment 011-04 will be able to complete treatment as planned and should continue with tumor imaging as outlined in the SoA (Section 1.3.2).

Imaging scan showing PD in Initial Treatment phase will be considered the baseline scan for Second Course Treatment as long as it is performed within 28 days of beginning the Second Course C1D1. If imaging was conducted outside of the 28-day window, the scans should be repeated. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and response.

Subsequent tumor imaging should be performed by site investigator/radiology assessment as per SOC for the disease and local guidelines.

Imaging should continue until disease progression, the start of new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

If previous imaging was obtained within 4 weeks prior to the date of discontinuation, 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 treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging per SOC until the start of new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4.1 Bone Imaging During Second Course

Note: As of Amendment 011-04, Second Course will no longer be offered. Any participant receiving Second Course prior to the initiation of Amendment 011-04 will be able to complete treatment as planned and should continue with bone imaging (if indicated) as outlined in the SoA (Section 1.3.2).

A bone scan will be performed within 28 days before restarting study intervention only in those participants for whom bone scans were being acquired due to a positive bone scan during the Initial Treatment phase, and for all participants with new clinical symptoms prior to beginning Second Course phase. **As of Amendment 011-03**, subsequent scans will be performed by site investigator/radiology assessment as per SOC for the disease and local guidelines.

8.2.1.5 RECIST 1.1 Assessment of Disease

NOTE: As of Amendment 011-03, all images will be locally assessed using RECIST 1.1 and will no longer be submitted to iCRO.

RECIST 1.1 will be used as the primary measure of tumor response and 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. Initial tumor imaging showing site-assessed PD per RECIST 1.1 should be submitted as soon as possible, but within 72 hours of acquisition, when feasible, for BICR verification of PD. The site and Sponsor will be notified whether the BICR verifies PD using RECIST 1.1. Figure 5 illustrates the imaging flow for verification of PD for clinically stable participants.

8.2.1.6 iRECIST Assessment of Disease

NOTE: As of Amendment 011-03, iRECIST is no longer applicable.

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator working with the local radiology department, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy and then experience disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs (including worsening of laboratory values) indicating clinically significant progression of disease
- Absence of rapid progression of disease or of progressive tumor at critical anatomic sites (eg, cord compression) requiring urgent alternative medical intervention
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue study intervention, the participant may continue to receive study intervention, and tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST per investigator assessment. Images should continue to be sent to the iCRO for potential retrospective BICR in the Initial Treatment course only.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued. However, if the participant is achieving clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue at the intervals outlined in Section 1.3, and images should be submitted to the iCRO.

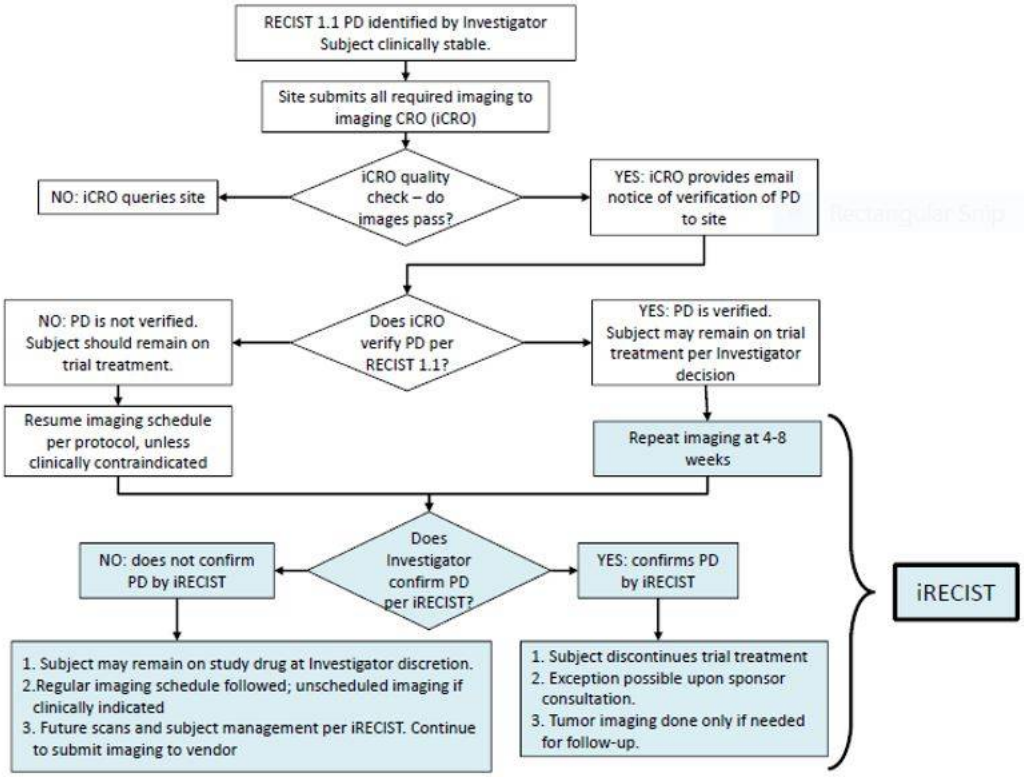
A description of the adaptations and iRECIST process is in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 5 and illustrated as a flow chart in Figure 5.

Table 5 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD per RECIST 1.1 by investigator assessment	Submit imaging for verification by BICR Repeat imaging in 4 to 8 weeks to confirm PD	May continue study intervention at investigator assessment and after participant's consent	Submit imaging for verification by BICR Repeat imaging in 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue study intervention
First radiologic evidence of PD per RECIST 1.1 verified by BICR	Repeat imaging in 4 to 8 weeks to confirm PD	May continue study intervention at investigator's discretion while awaiting confirmatory imaging by site per iRECIST	Repeat imaging in 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue study intervention
Repeat imaging confirms PD (iCPD) per iRECIST by investigator assessment	No additional imaging required	Discontinue study intervention (exception possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat imaging shows iUPD per iRECIST by investigator assessment	Repeat imaging in 4 to 8 weeks to confirm PD May take place at next regularly scheduled imaging visit	Continue study intervention at investigator's discretion	Repeat imaging in 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue study intervention
Repeat imaging shows iSD, iPR, or iCR per iRECIST by investigator assessment	Continue regularly scheduled imaging assessments	Continue study intervention at investigator's discretion	Continue regularly scheduled imaging assessments	May restart study intervention if participant's condition has improved and/or participant is clinically stable per investigator's discretion. The next imaging should take place per the regular imaging schedule.

Abbreviations: BICR = blinded independent central review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iPR = iRECIST partial response; iRECIST = modified Response Evaluation Criteria in Solid Tumors Version 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; VOP = verification of progression.
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the iCRO, but there will be no rapid review. If RECIST 1.1 disease progression has not been centrally verified, the site should continue study intervention. Whether or not study intervention continues, images should be collected and submitted to the iCRO with a request for VOP, until RECIST 1.1 progression is verified by BICR.

Figure 5 Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab After First Radiologic Evidence of Progressive Disease Assessed by the Investigator



Abbreviations: iCRO = imaging contract research organization; iRECIST = Response Evaluation Criteria in Solid Tumors Version 1.1 for immune-based therapeutics; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.\

8.2.2 Patient-reported Outcomes

NOTE: As of Amendment 011-03, PRO questionnaires will no longer be administered to participants.

The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants; EORTC QLQ-C30 should be administered before EQ-5D-5L. The questionnaires should be administered on Day 1 prior to dosing:

- In Cycle 1 to Cycle 7
- In Cycle 9
- In every 3 subsequent cycles through Cycle 18 (Cycles12, 15, and 18)

- Then in every 4 cycles until the end of study intervention (Cycles 22, 26, 30, and 34)
- At the EOT visit

It is best practice and strongly recommended that electronic patient-reported outcomes (ePROs) be determined for allocated participants before study intervention administration, AE evaluation, and disease status notification. If a participant does not complete the ePRO instruments at a scheduled time point, the MISS_MODE form must be completed to capture the reason that this assessment was not performed.

8.3 Safety Assessments

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

The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit, can be found in the laboratory manual.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per the institutional standard. Physical examinations (comprehensive or symptom-directed) will be performed at screening and EOT as specified in the SoA (Section 1.3). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a complete neurologic examination. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to participant allocation will be recorded on the appropriate CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the appropriate CRF. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted per SOC or as clinically indicated. A directed physical examination is also required to be performed when an AEOSI, SAE, or ECI occurs.

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], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as per SOC or as clinically indicated as designated in the SoA (Section 1.3). Vital sign measurements are also required to be performed when an AEOSI, SAE, or ECI occurs.

- BP and pulse 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.

8.3.3 Electrocardiograms

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 Fridericia correction method for calculating QTc will be used.

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

8.3.4 Echocardiograms or Multiple Gated Acquisition Scans

A MUGA scan (using a technetium-based tracer) or an echocardiogram will be performed to assess LVEF as designated in the SoA (Section 1.3.1). 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 on the CRF. Investigator assessment will be based on 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.

8.3.5.1 Hematology and Clinical Chemistry

Hematology and clinical chemistry assessments will be performed within 7 days prior to administration of the first dose of study intervention. Thereafter, hematology and clinical chemistry are to be performed per SOC or as clinically indicated as designated in the SoA (Section 1.3). When laboratory tests are clinically relevant (ie, inform diagnosis or management) for an AEOSI, SAE, or ECI then the laboratory test results should be entered into the eCRF.

8.3.5.2 Urine Dipstick Testing/Urinalysis

Urine dipstick testing will be performed locally within 7 days prior to the start of study intervention. Thereafter, urinalysis is only required per SOC or if clinically indicated.

Urinalysis will be performed locally within 7 days prior to the start of study intervention. Thereafter, urinalysis is only required per SOC or if clinically indicated.

8.3.5.3 Thyroid Function Testing

The screening blood sample for thyroid function testing should be obtained within 14 days before the first dose of study intervention. Thereafter, thyroid function testing will be performed per SOC or as clinically indicated. When thyroid function tests are clinically relevant (ie, inform diagnosis or management) for an AEOSI, SAE, or ECI then the test results should be entered into the eCRF.

8.3.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status at screening. Thereafter, ECOG performance status will be assessed per SOC or when clinically indicated (Section 1.3). When ECOG assessments are clinically relevant (ie, inform diagnosis or management) for an AEOSI, SAE, or ECI then the assessment should be entered into the eCRF.

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator (see Appendix 7 for Germany-specific study requirements).

All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following pembrolizumab, or 30 days following cessation of lenvatinib/placebo, whichever occurs last, must be reported by the investigator. If the participant initiates new anticancer therapy following discontinuation of study intervention, the time period for reporting pregnancies and exposure during breastfeeding is reduced to 30 days following cessation of study intervention.

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 6.

See Appendix 7 for Germany-specific study requirements.

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

It is not known whether pembrolizumab is excreted in human milk. No studies have been conducted to assess the impact of pembrolizumab on milk production or its presence in breast milk. Because many drugs are excreted in human milk, female participants must discontinue breastfeeding during treatment with pembrolizumab and for 4 months after the final dose[U.S. Prescribing Information. 2021].

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.

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that 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 purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab of ≥5 times the protocol-specified dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be withheld and the participant should be observed

closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of pembrolizumab, the AE(s) is reported as an SAE, even if no other seriousness criteria are met. An overdose associated with lenvatinib should be reported as a nonserious event of clinical interest, unless the AE itself meets criteria for an SAE.

If a dose of study drug meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a nonserious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

8.6 Pharmacokinetics

NOTE: As of Amendment 011-03, this section is no longer applicable.

Blood samples will be collected from participants as specified in the SoA for initial treatment (Section 1.3.1). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for collection, handling, and shipping of PK samples will be provided in the Laboratory Manual.

If at some point during enrollment prospective PK/ADA blood sample collection is no longer required, the sites will be notified.

8.6.1 Blood Collection for Serum Pembrolizumab

To evaluate pembrolizumab immunogenicity and exposure during treatment with lenvatinib + pembrolizumab, sample collections for analysis of ADA and PK are currently planned as shown in the SoA for initial treatment (Section 1.3.1). Blood samples will be obtained to measure PK and ADA for serum pembrolizumab. These samples may be stored, and analysis may be performed if required. If ongoing ADA and/or PK results are deemed unnecessary by the Sponsor, it may be decided to discontinue or reduce further sample collection in this study. Should this occur, it will be communicated by an administrative memo. If PK and/or ADA analyses are performed, the results of these analyses will be reported separately.

8.6.2 Blood Collection for Plasma Lenvatinib

Plasma concentrations of lenvatinib co-administered with pembrolizumab will be measured. Lenvatinib data will be analyzed using a population PK approach. Lenvatinib will be quantified by validated tandem high-performance liquid chromatography/mass spectroscopy.

8.7 Pharmacodynamics

Not applicable

8.8 Biomarkers

As of Amendment 011-03, samples for exploratory biomarker research will no longer be collected.

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

Blood for serum biomarker analyses

Blood for genetic analysis

Blood for RNA analysis

Blood for circulating tumor nucleic acids

Blood for plasma biomarker analyses

Archived or newly obtained tumor tissue

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Laboratory Manual.

8.8.1 Planned Genetic Analysis Sample Collection

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

8.9 Medical Resource Utilization and Health Economics

NOTE: As of Amendment 011-03, this section is no longer applicable.

Medical resource utilization and health economics data associated with medical encounters will be collected in the CRF by the investigator and study site personnel for all participants throughout the study.

Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses. All-cause hospitalizations and emergency department visits must be reported on the eCRF from the time of 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.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8. Unscheduled visits are permitted at any time during the study.

8.10.1 Screening

NOTE: As of Amendment 011-03, this section is no longer applicable.

Twenty-eight days prior to allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as provided in Section 5. **Note**: Screening procedures may be repeated after consultation with the Sponsor.

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

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis and HIV testing, which may be done up to 28 days prior to the first dose of study intervention. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor.

- Baseline imaging is to be performed within 28 days of randomization.

- ECOG performance status is to be evaluated within 7 days before randomization.

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

- For WOCBP, 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.

8.10.1.1 Rescreening

NOTE: As of Amendment 011-03, this section is no longer applicable.

Participants may be rescreened after initially failing to meet inclusion/exclusion criteria. Results of assessments during the original screening period are acceptable in lieu of repeat screening tests if obtained within the specified time frame and the corresponding criteria are met. Rescreened participants will retain their original screening numbers

8.10.2 Initial Treatment

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

8.10.2.1 Telephone Contact or Visit

NOTE: As of Amendment 011-03, this section is no longer applicable.

A telephone contact or visit will be conducted on Cycle 1 Day 8 to assess participants for development of early toxicity, as outlined in the SoA (Section 1.3.1).

8.10.3 Second Course Treatment

Note: As of Amendment 011-04, Second Course will no longer be offered. Any participant receiving Second Course treatment prior to the initiation of Amendment 011-04 will be able to complete treatment as planned.

All participants who have completed the first course may be eligible for up to an additional 17 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. This retreatment is the Second Course of this study.

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

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

Treatment may continue until a discontinuation criterion is met (Section 7.1).

Second Course visit requirements are outlined in the SoA (Section 1.3.2). Specific procedure-related details are provided in Sections 8.1 and 8.2.

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

8.10.4 Discontinued Participants Continuing to be Monitored in the Study

The discontinuation visit should take place at the time study intervention is discontinued for any reason. If the discontinuation visit takes place 30 days from the last dose of study intervention, at the time of the mandatory safety follow-up visit, the safety visit is not required. All procedures required at the discontinuation visit and at the 30-day safety follow-up visit should be performed.

8.10.5 Post-treatment Visits

8.10.5.1 Safety Follow-up Visit

The mandatory safety follow-up visit should take place approximately 30 days after the last dose of study intervention or before initiation of new anticancer treatment, whichever comes first.

Participants who are eligible for Second Course Treatment may have up to 2 safety follow up visits, 1 after initial treatment and 1 after Second Course treatment.

8.10.5.2 Efficacy Follow-up Visits

Note: As of Amendment 011-04, this section is no longer applicable. **Participants in Efficacy Follow-up prior to the initiation of Amendment 011-04 will stop efficacy assessments and be discontinued from the study. AEs and spontaneously reported pregnancies will be reported and followed as described under Section 8.4.**

Participants who discontinue study intervention for a reason other than PD will move into the follow-up phase and should be assessed as outlined in 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, PD, death, end of study, or the participant begins retreatment as detailed in Section 8.10.3. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible for retreatment according to the criteria in Section 8.10.3 may move from follow-up to the Second Course phase if they experience PD. Details are provided in the SoA (Section 1.3.2).

8.10.6 Survival Follow-up

Note: As of Amendment 011-04, this section is no longer applicable. Participants in Survival Follow-up prior to initiation of Amendment 011-04 are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information. AEs and spontaneously reported pregnancies will be reported and followed as described under Section 8.4.

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

8.10.7 Survival Status

Note: As of Amendment 011-04, this section is no longer applicable. Survival data is no longer being collected.

To ensure that current and complete survival data are available at the time of database locks, updated survival data may be requested during the study by the Sponsor. For example, updated survival data may be requested prior to, but not limited to, an external DMC review or an interim or final analysis. Upon Sponsor notification, all participants who do not or will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their survival status.

9 STATISTICAL ANALYSIS PLAN

NOTE: Efficacy data and non-binding futility boundaries were provided to the eDMC, in addition to safety analyses, to evaluate the benefit/risk ratio of the experimental arm relative to the control arm for LEAP-011 (data cutoff: 26-APR-2021). The interim efficacy data indicated that although the study did not meet non-binding futility boundaries for any of the analyzed endpoints, improvements of outcomes in favor of the combination are unlikely to be as high as initially hypothesized. Based upon these data and the recommendation of the eDMC, Amendment 011-03 was implemented to unblind the study and remove lenvatinib and matching placebo from the treatment arms. The prespecified interim and final analyses of the study described in the statistical analysis plan (SAP) will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy or ePRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but before any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before unblinding/final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to PK/ADA data and PROs) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)
Treatment Assignment	Approximately 694 participants will be randomized in a 1:1 ratio between 2 treatment arms: (1) pembrolizumab + lenvatinib and (2) pembrolizumab + placebo. As of Amendment 011-03, approximately 487 participants have been randomized and no additional participants will be randomized. Stratification factors are as follows: • Ineligible for any platinum-containing chemotherapy, PD-L1 CPS ≥10, ECOG PS 2 • Ineligible for any platinum-containing chemotherapy, PD-L1 CPS <10, ECOG PS 2 • Cisplatin-ineligible, PD-L1 CPS ≥10, ECOG PS 2 • Cisplatin-ineligible, PD-L1 CPS ≥10, ECOG PS 0 or 1.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	• PFS per RECIST 1.1 by BICR • OS
Key Secondary Endpoint	• ORR per RECIST 1.1 by BICR
Statistical Methods for Key Efficacy Analyses	PFS and OS will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. ORR will be estimated by treatment group with 95% CI calculated by Clopper-Pearson exact method.
Statistical Methods for Key Safety Analyses	Point estimates (count and percentage) by treatment group will be provided for safety endpoints.
Interim Analyses	There is no efficacy interim analyses. During the course of the study, DMC performed 6 quarterly safety reviews, including 4 futility analyses. The final analysis will be performed at when approximately 487 participants are randomized.
Multiplicity	There is no multiplicity adjustment.
Sample Size and Power	The total sample size is 487 participants.

9.2 Responsibility for Analyses/In-house Blinding

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

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

The Clinical Biostatistics Department will generate the randomized allocation schedule(s) for study intervention assignment.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

Primary

- **Progression-free Survival (PFS):** PFS is defined as the time from randomization to the first documented disease progression (PD) per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. See Section 9.6.1.1 for the definition of censoring.

- **Overall Survival (OS):** OS is defined as the time from randomization to death due to any cause.

Secondary

- **Objective Response Rate (ORR):** ORR is the percentage of participants with a confirmed CR or PR per RECIST 1.1 by BICR.

- **Duration of Response (DOR):** DOR is defined as the time from the first documented evidence of CR or PR to PD per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

- **Disease Control Rate (DCR):** DCR is defined as the percentage of participants with a confirmed response of CR, PR, or SD per RECIST 1.1 by BICR. Stable disease must be achieved at ≥6 weeks after randomization to be considered a best overall response.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 Patient-Reported Outcome Endpoints

As of Amendment 011-03, ePRO endpoints will not be analyzed.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The analyses of the primary efficacy endpoints are based on the intention-to-treat (ITT) population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. Details of the approach to handling missing data are provided in Section 9.6.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who receive incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study intervention for one cycle but receives the randomized study intervention for all other cycles, will be analyzed according to the randomized treatment group, and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

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

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary efficacy objectives. Methods related to exploratory objectives will be described in the sSAP. Nominal *p*-values will be computed for other efficacy analyses but should be interpreted with caution because of potential issues of multiplicity.

An OR PD that occurs during Second Course treatment will not be counted as an event for the primary analyses of either endpoint in this study.

9.6.1.1 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment comparison (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported.

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. For the primary analysis, for the participants who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR, regardless of discontinuation of study drug.

For the primary analysis, if the events (PD or death) are after more than 1 missed disease assessment, the data are censored at the last disease assessment before missing visits. Also, data after new anticancer therapy are censored at the last disease assessment before the initiation of new anticancer therapy. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules are summarized in Table 7.

Table 7 Censoring Rules for Primary Analyses of Progression-free Survival

Situation	Primary Analysis
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
PD or death documented after ≤1 missed disease assessment and before new anticancer treatment	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer treatment	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessments and new anticancer treatment

Abbreviation: PD = progressive disease.

9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the OS curve in each treatment arm. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment comparison (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. Participants without documented death at the time of analysis will be censored at the date of last known contact. Analysis using the Restricted

Mean Survival Time method may be conducted for OS to account for the possible non-proportional hazards effect.

9.6.1.3 Objective Response Rate

ORR will be estimated by treatment group. 95% CI for ORR will be provided using the Clopper-Pearson (exact) method.

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 8.

Table 8 Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
PFS per RECIST 1.1 by BICR	Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 7
OS	Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Key Secondary Analyses			
ORR per RECIST 1.1 by BICR	Estimation: Clopper-Pearson (exact) method	ITT	Participants with missing data are considered nonresponders
Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; 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 Analyses

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

Individual events and the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, a fatal AE, dose interruption due to an AE, discontinuation due to an AE, adverse event of special interest (AEOSI), clinically significant adverse event (CSAE) will be summarized by counts and percentages by treatment group (Table 9).

Table 9 Analysis Strategy for Safety Parameters

Safety Endpoint	Descriptive Statistics
Any AE	X
Any drug-related AE	X
Any Grade 3-5 AE	X
Any drug-related Grade 3-5 AE	X
Any serious AE	X
Any serious drug-related AE	X
Treatment interruption due to AE	X
Treatment discontinuation due to AE	X
Death	X
Any AEOSI	X
Any CSAE	X
Any Grade 3-5 AEOSI	X
Any Grade 3-5 CSAE	X
Any serious Grade 3-5 AEOSI	X
Any serious Grade 3-5 CSAE	X
Change from baseline results (laboratory test toxicity grade)	X
Abbreviations: AE=adverse event; AEOSI=adverse event of special interest; CSAE=clinically significant adverse event.	

9.6.3 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

NOTE: As of Amendment 03, there will be no interim efficacy analysis.

9.8 Multiplicity

NOTE: As of Amendment 03, no hypothesis testing will be performed in this study. Therefore, no multiplicity adjustment is needed.

9.9 Sample Size and Power Calculations

Note: As of Amendment 011-03, the study randomized 487 participants in a 1:1 ratio into the pembrolizumab + lenvatinib and pembrolizumab + placebo arms. Because no statistical testing will be performed, the power calculations are not applicable.

The study will randomize 694 participants in a 1:1 ratio into the pembrolizumab + lenvatinib and pembrolizumab + placebo arms. PFS and OS are primary endpoints for the study, with ORR as the key secondary endpoint.

Based on the 694 participants with at least 7 months of follow-up, the power of the ORR testing at the allocated α=0.025 is approximately 99.6% to detect a 17-percentage point difference between an underlying 30% response rate in the control arm and a 47% response rate in the experimental arm.

For the PFS endpoint, based on a target number of 558 events and 1 interim analyses at approximately 95% of the target number of events, the study has approximately 95% power to detect an HR of 0.7 at an overall α level of 0.005 (1-sided), and 99% power at an α level of 0.025 (1-sided).

For the OS endpoint, based on a target number of 552 events and 2 interim analyses at approximately 70% and 85% of the target number of events, the study has approximately 90% power to detect an HR of 0.75 at an overall α level of 0.02 (1-sided), and 91.5% power at an α level of 0.025 (1-sided).

Based on KEYNOTE-052 and KEYNOTE-361 data, the above sample size and power calculations for PFS and OS assume the following:

- PFS follows an exponential distribution with a median of 3.2 months for the control group.
- OS follows an exponential distribution with a median of 10.0 months for the control group.
- Enrollment period of 17 months.
- An annual dropout rate of 12% and 5% for PFS and OS, respectively.
- A follow-up period of 6 and 22 months for PFS and OS, respectively, after the last participant enrolls.

The sample size and power calculations were performed using R (“gsDesign” package) and EAST 6.4.

9.10 Subgroup Analyses

Note: As of Amendment 011-03, this section is no longer applicable.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles in which the participant receives the study intervention. Summary statistics will be provided for the extent of exposure in 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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC includes both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

NOTE: As of Amendment 011-03, this section is no longer applicable.

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

10.1.4.3 External Data Monitoring Committee

NOTE: As of Amendment 011-03, this section is no longer applicable.

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their

disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 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.

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10 will be performed by either the local or central laboratory except for pregnancy, urine dipstick testing, and urinalysis ,which will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2.

Prior to study treatment administration, the protocol-mandated safety laboratory tests (ie, complete blood count with differential, clinical chemistry, coagulation, and thyroid function tests, as applicable to each treatment cycle) should be performed locally per standard of care to ensure subject's safety prior to treatment.

- Treatment decisions may be made based on local laboratory results.
- Additionally, if the local laboratory results significantly disagree with those results obtained from the central laboratory and that a patient management decision was made based on local laboratory value(s), then the value(s) supporting the patient management decision are required to be entered in the relevant eCRF, as applicable.

Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events must be reported per instructions detailed in Section 8.4 and Appendix 3.

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 or serum) should be performed as required by local regulations during study treatment.
    - Pregnancy testing (urine or serum) should be performed as required by local regulations at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
    - Additional urine or serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV[c] MCH[c] % reticulocytes[c]		WBC count with differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood urea nitrogen[b]	Potassium	Aspartate aminotransferase/ serum glutamic-oxaloacetic transaminase	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[c]	Chloride[c]	Phosphorus[c]
	Creatinine[d]	Sodium	Alanine aminotransferase/ serum glutamic-pyruvic transaminase	Total Protein[c]
	Glucose	Calcium	Alkaline phosphatase	Magnesium
	Thyroid-stimulating hormone	Free thyroxine[f]	Lactate dehydrogenase[c]	Amylase
	Lipase[e]	Cholesterol[c]	Triglycerides[c]	CPK[g]
	Pregnancy test	Triiodothyronine (total T3)[f]		
Routine Urinalysis[h]	Specific gravity pH, glucose, protein[i], hemoglobin or blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	PT/INR and aPTT/PTT[j] Serology (HIV RNA, HbsAg, and hepatitis C virus antibody) (if required by local health authority) Serum or urine β human chorionic gonadotropin (β-HCG) pregnancy test (as needed for WOCBP) FSH as needed for WONCBP			

aPTT=activated partial thromboplastin time; BUN=blood urea nitrogen; CPK=creatine phosphokinase; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; HbsAg=hepatitis B surface antigen hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; TSH=thyroid stimulating hormone; ULN=upper limit of normal; UPCR=urine protein/creatinine ratio; WBC=white blood cell WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

[a] Absolute or % acceptable per institutional standard.
[b] Urea is acceptable if BUN is not available as per institutional standard.
[c] Performed only if considered local standard of care.
[d] GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
[e] After Cycle 1, retrospective review of lipase results is allowed when the results are not available during dosing.
[f] Free T4, total T3, and TSH levels will be determined during screening and then repeated on Day 1 of every cycle (starting Cycle 2), at the time of discontinuation (End of Treatment), and at the safety follow-up visits. Free T3 is acceptable where total T3 cannot be determined. There may be instances when sites are unable to obtain thyroid function testing results prior to the scheduled dosing. After C1, review of thyroid function test results after dosing is acceptable.

Laboratory Assessments	Parameters
[g] CPK isoenzymes (CK-MM and CK-MB) should be evaluated if CPK is greater than 3 × ULN. [h] If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, urine microscopy, culture, and sensitivity should be performed at the institution's laboratory. [i] If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection or an immediate spot urine protein/creatinine ratio (UPCR) test should be done to quantify the 24-hour urine protein excretion. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4. [j] Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants.	

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

For platinum-ineligible participants, the investigator will be blinded to the central vendor's PD-L1 CPS results, in an attempt to reduce bias from treatment decisions. The Sponsor acknowledges that, due to the commercial availability of PD-L1 testing assays, it is possible that the investigator may know a participant's CPS prior to screening. This risk is seen as acceptable, as the treatment interventions are hypothesized to provide benefit regardless of CPS.

For cisplatin-ineligible participants, the investigator will be blinded to the central vendor' s PD-L1 CPS results. However, the investigator will be unblinded to the PD-L1 CPS category (ie, PD-L1 CPS ≥10 or <10). The inclusion criterion for cisplatin-ineligible participants includes a requirement for PD-L1 CPS ≥10.

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

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

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

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

Is a new cancer (that is not a condition of the study)

Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity/toxicity

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

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

Assessment of causality

- Did the 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 IMP)?

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

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
    - Yes, there is a reasonable possibility of Sponsor's product relationship:
        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
    - No, there is not a reasonable possibility of Sponsor's product relationship:
        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

New or updated information will be recorded in the CRF.

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

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

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

The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.

Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

Reference Section 8.4.1 for reporting time requirements.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (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 non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • 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.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
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 Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. d 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).

10.5.3 Pregnancy Testing

- Pregnancy testing requirements for study inclusion are described in Section 5.1.

- Pregnancy testing ([urine or serum] as required by local regulations) should be conducted as indicated in Section 1.3 during the treatment period and at least every 30 days during intervention.

- Pregnancy testing ([urine or serum] as required by local regulations) should be conducted at the end of relevant systemic exposure.

- 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 subject's participation in the study.

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 Germany-specific Requirements

1. Section 5.2 - Exclusion criterion 24: HIV testing is mandatory.

2. Section 5.2 - Exclusion criterion 25: Hepatitis B and C testing is mandatory.

3. Section 5.2 - Exclusion criterion 26: Tuberculosis testing is mandatory.

4. Section 8.4.1 (Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information): All AEs meeting serious criteria are to be collected for 120 days after the last dose of study intervention.

10.7.2 UK-specific Requirements

1. Section 5.2 - Exclusion criterion 24: HIV testing is mandatory.

2. Section 5.2 - Exclusion criterion 25: Hepatitis B and C testing is mandatory.

3. Section 6.5.2 (Prohibited Concomitant Medications): Live vaccines must not be administered for 90 days after the last dose of study intervention.

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

NOTE: As of Amendment 011-03, iRECIST is no longer applicable.

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants with evidence of radiologic PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue study intervention until repeat imaging 4 to 8 weeks later is obtained (using iRECIST for participant management [Table 5 and Figure 5]). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care
- Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.
- If the investigator decides to continue study intervention, the participant may continue to receive study intervention, and tumor assessment should be repeated 4 to 8 weeks later to confirm PD per iRECIST by per investigator assessment. Images should continue to be sent to the iCRO for potential retrospective BICR, in the Initial Treatment course only.
- Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:
    - Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

      Note: "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
    - Unequivocal progression of nontarget lesion(s) identified at baseline
    - Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point.
    - For nontarget lesions, worsening is any significant growth in lesions overall compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1.
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new nontarget lesions
        - Appearance of additional new lesions

- Any new factor appears that would have triggered PD by RECIST 1.1.

Persistent iUPD

- Progression is considered not confirmed, and the overall response remains iUPD, if:
- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)
- Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits After Pseudoprogression Resolves

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

- Target lesions
    - The sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudoprogression.
- Nontarget lesions
    - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
    - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time.
    - Additional new lesions appear.
    - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum.
    - Previously identified nontarget lesions show any significant growth.

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

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

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

10.9 Appendix 9: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry out all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5;649-55. The Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.	

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
5-FU	5-fluorouracil
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AEOSI	adverse event of special interest
ALK	anaplastic lymphoma kinase gene
ALT	alanine aminotransferase
APaT	all participants as treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCG	Bacillus Calmette-Guérin
β-HCG	β human chorionic gonadotropin
BICR	blinded independent central review
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CD3ζ	CD3 zeta
CD28	cluster of differentiation 28
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CPS	combined positive score
CrCl	creatinine clearance
CR	complete response
CRF	case report form
CRP	C-reactive protein
CSAE	clinically significant adverse event
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CVA	cerebrovascular accident
CXDY	Cycle X Day Y
CYP	cytochrome P450
D/C	discontinuation
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicities
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DTC	Differentiated thyroid cancer
EC	endometrial cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram

Abbreviation	Expanded Term
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
EGFR	epithelial growth factor receptor
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	end of treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level Questionnaire
FA	final analysis
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
iCRO	imaging contract research organization
IDO1	indoleamine-pyrrole 2,3 dioxygenase inhibitor
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgV	immunoglobulin-variable
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors Version 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
ITT	intention-to-treat
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease

Abbreviation	Expanded Term
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
1L	first-line
2L	second-line
LAM	lactational amenorrhea method
LEAP	Lenvatinib And Pembrolizumab
LFTs	liver function tests
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NaF PET	^{18}F sodium fluoride positron emission tomography
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NSAE	non-serious adverse event
NSAIDS	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PDGF	platelet-derived growth factor
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PKCθ	protein kinase C-theta
PO	oral(ly)
PopPK	population PK
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PS	performance status
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once daily
QLQ-C30	Quality of Life Questionnaire Core 30 items
QoL	quality of life
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell

Abbreviation	Expanded Term
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
RTK	receptor tyrosine kinase
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	second course
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	schedule of activities
SOC	standard of care
SP-D	surfactant protein D
SpO2	peripheral capillary oxygen saturation
sSAP	supplemental Statistical Analysis Plan
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
TAM	tumor-associated macrophage
TEAE	treatment-emergent adverse event
TMDD	target-mediated drug disposition
TRAE	treatment-related adverse event(s)
TSH	thyroid-stimulating hormone
TTD	time to deterioration
UC	urothelial carcinoma
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
USA	United States of America
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VOP	verification of progression
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential
ZAP70	zeta-chain-associated protein kinase

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