Official Protocol Title:	A Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Investigational Agents in Combination with Etoposide and Cisplatin or Carboplatin for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer (KEYNOTE-B99)
NCT number:	NCT04924101
Document Date:	21-Dec-2022

Title Page

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Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Investigational Agents in Combination with Etoposide and Cisplatin or Carboplatin for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer (KEYNOTE-B99)

Protocol Number: B99-04

Compound Number: MK-3475

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	153342
EudraCT	2020-005649-17

Approval Date: 21 December 2022

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Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	21-DEC-2022	NIMP/AxMP classification corrected for Background Treatment in Study Interventions Table.
Amendment 03	10-OCT-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 02	26-JAN-2022	Participants with presence of radiographic evidence of encasement or invasion of a major blood vessel will be allowed to be randomized among the open intervention groups that do not contain lenvatinib treatment, but continue to be ineligible for randomization into Intervention Group C (pembrolizumab, lenvatinib, etoposide/platinum).
Amendment 01	02-JUN-2021	Changes made in response to FDA feedback.
Original Protocol	31-MAR-2021	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

NIMP/AxMP classification corrected for Background Treatment in Study Interventions Table.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study Intervention(s) Administered	NIMP/AxMP classification corrected for Background Treatment in Study Interventions Table (Table 7).	To apply the correct classification for each treatment.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Investigational Agents in Combination with Etoposide and Cisplatin or Carboplatin for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer (KEYNOTE-B99)

Short Title: Phase 2 First-Line ES-SCLC Platform Study

Acronym: B99

Hypotheses, Objectives, and Endpoints:

Formal hypothesis testing will not be performed in this study. The objectives will be evaluated by intervention group.

In males and females with ES-SCLC who are in need of 1L treatment:

Objectives	Endpoints
Primary	
• To estimate the objective response rate as assessed by blinded independent central review according to RECIST 1.1	• Objective response: complete response or partial response
• To estimate 6-month progression free survival rate as assessed by blinded independent central review according to RECIST 1.1	• 6-month progression free survival: survival without documented disease progression or death due to any cause at 6 months after randomization
Secondary	
• To evaluate duration of response based on RECIST 1.1 as assessed by blinded independent central review	• Duration of response: time from first documented evidence of complete response or partial response until disease progression or death due to any cause, whichever occurs first
• To evaluate progression free survival based on RECIST 1.1 as assessed by blinded independent central review	• Progression free survival: time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Objectives	Endpoints
• To evaluate overall survival	• Overall survival: time from randomization to death due to any cause
• To evaluate the best tumor size change as assessed by blinded independent central review	• Tumor size change: percent change in the sum of the diameters of the target lesions
• To evaluate the safety and tolerability of investigational treatment combinations based on proportion of adverse events	• Adverse events • Study intervention discontinuations due to adverse events
• To evaluate changes in health-related quality of life assessments from baseline using the EORTC QLQ-C30	• Change from baseline at Week 19 in the EORTC QLQ-C30 global health status/quality of life scale (items 29-30)

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	The first-line treatment of participants with extensive-stage small cell lung cancer
Population	Participants with extensive-stage small cell lung cancer
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	No treatment control
[redacted]	[redacted]
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

This study employs a design in which new intervention groups will be open for enrollment on a rolling basis to evaluate investigational agents. Therefore, the number of participants will depend on the total number of intervention groups in the study.

Approximately 40 participants will be enrolled in each study intervention group.

Intervention Groups and Duration:

Intervention Groups

This study is composed of a specific set of study intervention groups. A study intervention group refers to a combination of investigational agents.

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Intervention Group A	Pembrolizumab	200 mg	Q3W (D1 of each cycle)	IV	Up to 35 infusions or until PD or DC	TP
	[redacted]					
	Etoposide	100 mg/m^2	Q3W (D1, D2, D3 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
	Cisplatin **OR**	75 mg/ m^2	Q3W (D1 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
	Carboplatin	AUC 5 mg/mL/min	Q3W (D1 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
Intervention Group B	Pembrolizumab	200 mg	Q3W (D1 of each cycle)	IV	Up to 35 infusions or until PD or DC	TP
	[redacted]					
	Etoposide	100 mg/m^2	Q3W (D1, D2, D3 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
	Cisplatin **OR**	75 mg/ m^2	Q3W (D1 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
	Carboplatin	AUC 5 mg/mL/min	Q3W (D1 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
Intervention Group C	Pembrolizumab	200 mg	Q3W (D1 of each cycle)	IV	Up to 35 infusions or until PD or DC	TP
	Lenvatinib	8 mg during Induction; 20 mg during Maintenance	qd	Oral	Until PD or DC	TP
	Etoposide	100 mg/m^2	Q3W (D1, D2, D3 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
	Cisplatin **OR**	75 mg/ m^2	Q3W (D1 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT
	Carboplatin	AUC 5 mg/mL/min	Q3W (D1 of each cycle)	IV	Up to 4 cycles or until PD or DC	BT

AUC=area under curve, BT=background treatment, D1=Day 1, D2=Day 2, D3=Day 3, DC=discontinuation, IV=intravenous infusion, PD=progression of disease, qd=daily, Q3W=every 3 weeks, Q6W=every 6 weeks; TP= Test Product

Other current or former name(s) or alias(es) for study intervention(s) are as follows: pembrolizumab (KEYTRUDA®, MK-3475, or SCH 900475); lenvatinib (LENVIMA®, KISPLYX®, MK-7902, or E7080)

Total Number of Intervention Groups/ Arms	The total number of study intervention groups will depend on the number of investigational agents evaluated.
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. After the end-of-treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

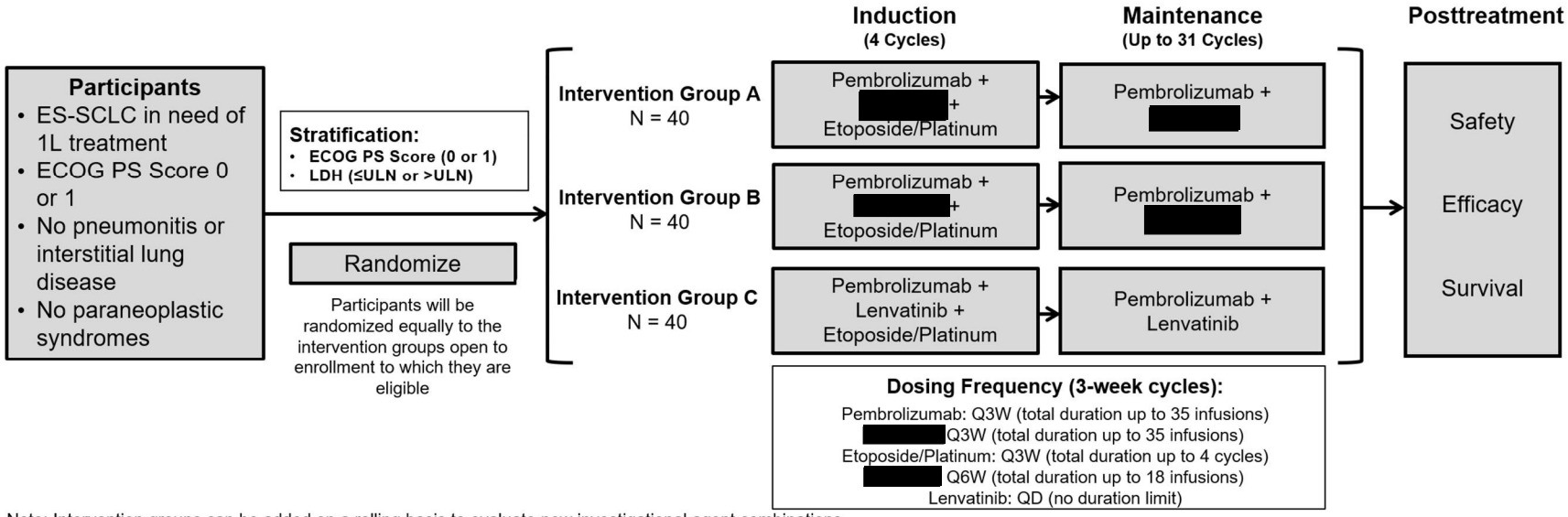
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 MK-3475-B99 Study Schema



Note: Intervention groups can be added on a rolling basis to evaluate new investigational agent combinations.

1L=first-line, ECOG-PS-Eastern Cooperative Oncology Group Performance Status, ES-SCLC=extensive-stage small cell lung cancer; LDH=lactate dehydrogenase, QD=daily, Q3W= every 3 weeks, Q6W=every 6 weeks, ULN=upper limit of normal

1.3 Schedule of Activities

The procedures for all participants in the study are outlined in Table 1. Procedures specific to Intervention Groups A, B, and C are outlined in Table 2, Table 3, and Table 4, respectively. Details of each procedure outlined in the Schedule of Activities are provided in Section 8. Please refer to Appendix 7 for country-specific requirements.

1.3.1 All Participants

Table 1 Schedule of Activities – All Participants

Study Period:	**Screening**	**Treatment (3-Week Cycles)**										**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screening	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
Administrative Procedures																
Informed Consent	X															Documented informed consent must be obtained before any protocol-specific procedures. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/ Exclusion Criteria	X	X														Verification documented by the investigator.
Participant Identification Card	X	X														Add the randomization number at the time of randomization.
Demographics and Medical History	X															

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
SCLC History Prior/ Concomitant Medication Review	X X	X	X	X	X	X	X	X	X	X	X	X	X			
Tobacco Use Assessment	X															Refer to Section 8.1.4.1 for definitions of cigarette use.
Intervention Randomization		X														Study intervention should begin within 3 days of randomization.
Anticancer Therapy Status												X	X		X	Any changes in new treatment will be collected
Vital Status		<----------									---------->				X	On Sponsor request, participants may be contacted for survival information at any time during the study.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
Tumor Scan																Scans should follow calendar days from randomization and should not be adjusted for dose delays or cycle starts. Unscheduled scans can be performed as clinically indicated. Scans must be submitted and reviewed by BICR before randomization. See Section 8.2 for full details.
CT/MRI of chest, abdomen, and pelvis	X	X												X		Use the same imaging modality for all evaluations. Perform at 6 weeks (42 days ± 7 days from randomization). Repeat Q6W (42 days ±7 days) for the first 48 weeks and Q9W (63 days ±7 days) thereafter. Details for scans following discontinuation can be found in Section 8.2.1.3.
Bone Scan	X															All participants are required to have bone scans (bone or PET scans) to assess for bone lesions during Screening. On-study bone scans should be acquired as clinically indicated or to confirm a CR when bone metastases were present at Screening.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
Brain Scan	X															All participants are required to have brain scans during Screening. For participants without brain metastases at Screening, on-study brain scans are required as clinically indicated. For participants with brain metastases present at Screening, on-study brain scans are to be acquired at all scheduled postbaseline imaging timepoints, or more often as clinically indicated, and to confirm a CR.
Safety Procedures																
Full Physical Examination	X											X				
Height	X															
Weight	X	X			X		X		X		X					If ≥10% change in body weight occurs, weight-based therapy should be readjusted.
Directed Physical Examination		X			X		X		X		X		X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X			DBP, SBP, heart rate, RR, temperature, pulse oximetry

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
12-lead ECG	X															After randomization: for participants who are assigned to Intervention Group C, refer to additional ECG schedule in Table 4. Otherwise, ECG may be performed as clinically indicated.
MUGA/ECHO Scan	X															After randomization: for participants who are assigned to Intervention Group C, refer to Table 4.
Audiometry	X												X			To be performed if this is the local standard of care only when cisplatin is chosen as the platinum agent. May be performed more often as clinically indicated.
ECOG Performance Status	X	X	X		X	X	X	X	X	X	X	X	X			At Screening, perform ≤7 days before randomization.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
Pregnancy Test – Urine or Serum hCG (WOCBP only; per local SOP)	X	X			X		X		X		X	X				Serum test is only required if urine test is positive or not evaluable. WOCBP require negative test before randomization. If more than 24 hours (urine test) or 72 hours (serum test) have elapsed before first dose of study intervention, another pregnancy test is required before starting study intervention. After Cycle 1, a negative pregnancy test is required within 24 hours (urine test) or 72 hours (serum test) before study intervention on Day 1 of each cycle. Pregnancy testing should also be conducted as outlined in Section 8.3.7.
FSH (as needed in WONCBP only)	X															Refer to Appendix 5 for additional information.
HBV, HCV, and HIV testing	X															Only perform if required by local health authority.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
Thyroid Function Tests (TSH, T3, free T4; periodically)	X				X				X		X	X	X			Screening samples must be collected ≤10 days before start of study intervention. Thyroid function tests will be performed at Screening and every other cycle thereafter (ie, C2D1, C4D1, C6D1).
Coagulation Tests (PT/INR and aPTT or PTT)	X															Screening samples must be collected ≤10 days before start of study intervention.
Urine Dipstick Testing for Protein (Urinalysis may be used if the use of urine dipstick is not feasible)	X															Screening samples must be collected ≤10days before start of study intervention. For participants who are assigned to Intervention Group C, refer to Table 4 for additional urine dipstick assessments.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X			
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X			
Creatinine Clearance (measured or calculated)	X	X			X		X		X							

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X			Record all AEs occurring within 30 days after last dose of study intervention. Record all SAEs occurring up to 90 days after last dose of study intervention or 30 days after last dose of study intervention if the participant initiates new anticancer therapy, whichever comes first. Any treatment-related SAEs must be reported regardless of time they occur.
Pharmacodynamics/Biomarkers																
Archival or Newly Obtained Tissue Collection for Biomarkers	X															A pretreatment tumor sample must be submitted before or within 4 weeks after randomization, if such sample exists (see inclusion criteria [Section 5.1]) for additional detail
[redacted]																

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**										**End-of-Treat-ment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	Screen-ing	1			2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)		1	8	15	1	8	1	8	1	8	1	EOT (±3 days)	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)	-28 to -1		±1	±1	±3	±1	±3	±1	±3	±1	±3					
[redacted]																
Patient-reported Outcomes																
[redacted]																

AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; C=cycle; CR=complete response; CT=computed tomography; [redacted] acid; D=day; DBP=diastolic blood pressure; Discon=discontinuation; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; [redacted]; EOT=end-of-treatment; free T4=thyroxine; FSH=follicle-stimulating hormone; HBV=Hepatitis B virus; hCG=human chorionic gonadotropin; HCV=Hepatitis C virus; HIV=human immunodeficiency virus; INR= international normalized ratio; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PET=positron emission tomography; PT=prothrombin time; PTT=partial thromboplastin time; Q6W=every 6 weeks; Q9W=every 9 weeks; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; SCLC=small cell lung cancer; SOP=standard operating procedure; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of child bearing potential; WONCBP=women of nonchildbearing potential.

1.3.2 Specific Intervention Groups

1.3.2.1 Intervention Group A (Pembrolizumab, [redacted], Etoposide/Platinum)

Table 2 Schedule of Activities – Intervention Group A-specific

Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
Administrative Procedures														
Pembrolizumab Administration	X		X		X		X		X					Pembrolizumab will be administered Q3W starting with C1D1 for a maximum of 35 infusions (approximately 2 years).
[redacted]														
Etoposide Administration	X	X	X	X	X	X	X	X						Etoposide will be administered Q3W on Days 1, 2, and 3 for a maximum of 4 cycles. Days 1, 2, and 3 must be consecutive days without interruption. Administration on D1 will occur after completion of the pembrolizumab [redacted] infusions. Dose should be recalculated if there is a ≥10% weight change.

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Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
Cisplatin or Carboplatin Administration	X		X		X		X							Cisplatin or carboplatin will be administered Q3W starting with C1D1, for a maximum of 4 cycles. Administration will occur after completion of the pembrolizumab [redacted] infusions. Dose should be recalculated if there is a ≥10% weight change.
[redacted]														
Pembrolizumab PK Sampling	X		X						X	X				Predose PK samples should be drawn within 24 hours before the start of infusion of pembrolizumab at C1D1, C2D1, and C8D1. Postdose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at [redacted]
[redacted]														

Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
Anti-pembrolizumab Antibody Sampling	X		X						X	X				Predose anti-pembrolizumab antibody samples should be drawn within 24 hours before start of infusion at C1D1, C2D1, and C8D1. Samples will also be drawn [redacted]
[redacted]														

C=cycle; D=day; Discon=discontinuation; EOT=end-of-treatment; [redacted]; Q3W=every 3 weeks

1.3.2.2 Intervention Group B (Pembrolizumab, [redacted], Etoposide/Platinum)

Table 3 Study Schedule of Activities – Intervention Group B-specific

Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
Administrative Procedures														
Pembrolizumab Administration	X		X		X		X		X					Pembrolizumab will be administered Q3W starting with C1D1 for a maximum of 35 infusions. (approximately 2 years).
[redacted]														

Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
Etoposide Administration	X	X	X	X	X	X	X	X						Etoposide will be administered Q3W on Days 1, 2, and 3 for a maximum of 4 cycles. Days 1, 2, and 3 must be consecutive days without interruption. Administration on D1 will occur after completion of the pembrolizumab [redacted] (if relevant) infusions. Dose should be recalculated if there is a ≥10% weight change.
Cisplatin or Carboplatin Administration	X		X		X		X							Cisplatin or carboplatin will be administered Q3W starting with C1D1, for a maximum of 4 cycles. Administration will occur after completion of the pembrolizumab [redacted] (if relevant) infusions. Dose should be recalculated if there is a ≥10% weight change.

Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
[redacted]														
Anti-pembrolizumab Antibody Sampling	X				X				X	X				Predose anti-pembrolizumab antibody samples should be drawn within 24 hours before start of infusion at C1D1, C3D1, C7D1, and C9D1. Samples will also be drawn at EOT.

Study Period:	**Treatment (3-Week Cycles)**									**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1		2		3		4		5-35	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±3		±3		±3		±3					
[redacted]														

Abbreviations: ADA=antidrug antibody; C=cycle; D=day; Discon=discontinuation; EOT=end-of-treatment; [redacted]; Q3W=every 3 weeks; Q6W=every 6 weeks

1.3.2.3 Intervention Group C (Pembrolizumab, Lenvatinib, Etoposide/Platinum)

Table 4 Study Schedule of Activities – Intervention Group C-specific

Study Period:	**Treatment (3-Week Cycles)**										**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1			2		3		4		5-35	Discont	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	15	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±1	±3		±3		±3		±3					
Administrative Procedures															
Lenvatinib Dispensed	X			X		X		X		X					Dispensed on D1 of each cycle.
Lenvatinib Container Returned				X		X		X		X	X				
Lenvatinib Administration	<----------									---------->					If dose missed for >12 hours, that dose is skipped. Lenvatinib will be dosed until confirmed disease progression is documented or a discontinuation criterion is met (Section 7.1).
Pembrolizumab Administration	X			X		X		X		X					Pembrolizumab will be administered Q3W starting with C1D1, for a maximum of 35 infusions (approximately 2 years).

Study Period:	**Treatment (3-Week Cycles)**										**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1			2		3		4		5-35	Discont	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	15	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±1	±3		±3		±3		±3					
Etoposide Administration	X	X		X	X	X	X	X	X						Etoposide will be administered Q3W on Days 1, 2, and 3 for a maximum of 4 cycles. Days 1, 2, and 3 must be consecutive days without interruption. Administration on Day 1 will occur after completion of the pembrolizumab infusion. Dose should be recalculated if there is a ≥10% weight change.
Cisplatin or Carboplatin Administration	X			X		X		X							Cisplatin or carboplatin will be administered Q3W starting with C1D1, for a maximum of 4 cycles. Administration will occur after completion of the pembrolizumab infusion. Dose should be recalculated if there is a ≥10% weight change.

Study Period:	**Treatment (3-Week Cycles)**										**End-of-Treatment**	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	1			2		3		4		5-35	Discont	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Day (in Cycle)	1	2&3	15	1	2&3	1	2&3	1	2&3	1	EOT	30 days from last dose (+7 days)	Per imaging schedule	Every 12 weeks (±7 days)	
Scheduling Window (Days)			±1	±3		±3		±3		±3					
Safety Procedures															
12-lead ECG	X			X						X	X	X			Perform ECG on C1D1, C2D1, and D1 of every fourth cycle (C6, C10, etc). ECG on C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high risk participants, conducted ECG monitoring every cycle, see Section 8.3.4. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up Visits.
MUGA/ECHO Scan												X			Additional LVEF assessments may be performed as clinically indicated.
Urine Dipstick Testing for Protein	X		X	X		X		X		X	X	X			Urine dipstick will be performed within 3 days before Day 1 of every cycle while participants are taking lenvatinib. See Section 6.6.2.4 for guidance on testing frequency in cases of elevated protein.

C=cycle; D=day; Discon=discontinuation; ECG=electrocardiogram; ECHO=echocardiogram; EOT=end-of-treatment; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition; Q3W=every 3 weeks

2 INTRODUCTION

This signal-finding clinical study will evaluate the use of investigational agents in combination with pembrolizumab and etoposide/platinum chemotherapy for the first-line treatment of participants with ES-SCLC.

2.1 Study Rationale

SCLC remains a worldwide public health problem as a major cause of cancer mortality. Studies of chemo-immunotherapy combinations for the first-line treatment of patients with ES-SCLC suggest that the combination of chemotherapy and anti-PD-1/L1 receptor therapy provides a clinically meaningful benefit in this patient population compared with chemotherapy alone. However, these regimens demonstrate short PFS and only modestly improve OS, reflecting the necessity for novel therapeutics that ideally show synergy with anti-PD-1/L1 therapeutics in this patient population.

The design of this platform study allows for testing of an investigational agent in combination with pembrolizumab and etoposide/platinum chemotherapy as first-line treatment in participants with ES-SCLC. The infrastructure of this study enables the rolling assignment of investigational agents in an efficient fashion to study the impact of each investigational agent in combination with pembrolizumab for these patients in need.

Refer to Section 2.2.3 for the rationale for use of the specific investigational agents evaluated in this study and preliminary evidence for their use in SCLC.

2.2 Background

2.2.1 SCLC Epidemiology and Current Therapeutic Options

SCLC is an aggressive neuroendocrine malignancy of the lung, which remains a worldwide public health problem as it is a major cause of cancer mortality. This malignancy accounts for approximately 13% to 17% of all lung cancer cases, with approximately 30,000 patients diagnosed annually in the US [American Cancer Society 2020] [National Cancer Institute 2014] [Zhao, H., et al 2018]. Worldwide, approximately 275,000 patients are diagnosed with SCLC annually [Majem, M. 2017]. This malignancy is strongly linked to tobacco use, with only 2% to 3% of cases occurring in never-smokers [Varghese, A. M., et al 2014] [Thomas, A., et al 2020].

SCLC is characterized by a short doubling time, high growth fraction, and early development of widespread metastases [Gazdar, A. F., et al 2017]. The overwhelming majority of patients with SCLC present with ES-SCLC, with advanced, bulky nodal disease or with tumors that have spread beyond a single tolerable radiation field in the chest. Therefore, SCLC is not considered a surgical disease and chemotherapy is the foundation of treatment [Gaspar, L. E., et al 2012]. The fundamental approach of first-line treatment of SCLC did not change in nearly 4 decades since the introduction of an etoposide/platinum doublet, which is administered to both patients with LS-SCLC (cancer confined to the chest in a single tolerable radiation field) and patients with ES-SCLC. Although first-line treatment for SCLC

yields high tumor response rates, essentially all patients with ES-SCLC, and most with LS-SCLC, develop chemoresistance and relapse within months of completing initial therapy. Once patients develop recurrent or progressive, advanced or metastatic disease, treatment options are limited, which is in stark contrast to the progress that has been made in NSCLC. Correspondingly, there has been very little improvement in survival rates; the overall 5–year survival rate of SCLC patients from diagnosis is <7% [National Cancer Institute 2014] [Gazdar, A. F., et al 2017] [American Cancer Society 2020].

The strongest predictor of outcome for patients with relapsed SCLC is the duration of remission. Patients with sensitive disease, who maintain a response to initial treatment for 3 months or more, have a response rate to additional chemotherapy of about 25% and a median survival of about 6 months from the time of relapse. In contrast, patients with refractory disease, who either have no response to initial therapy or progress within 3 months, rarely benefit from additional treatment, with response rates <10% and median survival of 4 months [Ardizzoni, A., et al 2014]. Therefore, optimal first-line treatment options are needed to improve initial responses and delay, as well as possibly prevent, progression.

Multiple efforts at improving first-line outcomes for patients with SCLC have been largely unsuccessful. OS is not improved if participants receive maintenance therapy with additional cycles of the same regimen used for induction or a different agent (eg, maintenance oral etoposide or sunitinib after an etoposide-containing first-line regimen) [Spiro, S. G., et al 1989] [Hanna, N. H., et al 2002] [Hanna, N., et al 2006], consolidation with different chemotherapeutic regimens after 4 cycles of etoposide/platinum [Beith, J. M., et al 1996] [Schiller, J. H., et al 2001], or the addition of ipilimumab in a phased fashion to etoposide and platinum [Reck, M., et al 2016]. Therefore, treatment beyond 6 cycles of etoposide/platinum chemotherapy is not recommended for ES-SCLC by the NCCN [National Comprehensive Cancer Network 2018], the ESMO Guidelines [Fruh, M., et al 2013] or the ASCO [Rudin, C. M., et al 2015]. Overall, as minimal improvement has been made in the fundamental treatment of SCLC in the past few decades since the introduction of the etoposide/platinum doublet, there remains critical need for new therapeutic approaches in the first-line treatment of this disease.

Recently, immunotherapy in combination with etoposide/platinum chemotherapy has begun to change outcomes in the first-line treatment of ES-SCLC, as shown by the IMpower133 and CASPIAN studies, which led to the approval of atezolizumab and durvalumab, respectively, in combination with etoposide and platinum therapy for first-line treatment of ES-SCLC. Atezolizumab and durvalumab given with the etoposide/platinum doublet for 4 cycles and continued as maintenance have each improved the median overall survival by 2.0 and 2.4 months, respectively (Table 5).

The randomized Phase 3 KEYNOTE-604 study also showed clinically meaningful and statistically significant improvement in PFS for pembrolizumab in ES-SCLC in combination with etoposide/platinum compared with etoposide/platinum chemotherapy alone. The addition of pembrolizumab resulted in increased and durable responses, as well as a clinically meaningful improvement in OS, compared with chemotherapy alone, further detailed in Section 2.2.3.1 and Table 5, showing clinical benefit of pembrolizumab in first-line treatment.

Table 5 Summary of Studies Evaluating Immunotherapy + Etoposide/Platinum Chemotherapy in 1L SCLC

Study	Treatment Arms	N	ORR (%)	6-month PFS Rate (%)	Median OS (Months)	OS HR (95% CI)
Impower133 [Horn, L., et al 2018]	etoposide/carboplatin/atezolizumab	202	60.2	30.9	12.3	0.70 (0.54, 0.91)
	etoposide/carboplatin/placebo	201	64.4	22.4	10.3	
CASPIAN [Paz-Ares, L., et al 2019] [Paz-Ares, L. G., et al 2020]	durvalumab/platinum-etoposide	268	68 [a]	45 [a]	12.9 [b]	0.75 [b] (0.62, 0.91)
	platinum-etoposide	269	58 [a]	46 [a]	10.5 [b]	
KEYNOTE-604 [Rudin, C. M., et al 2020]	pembrolizumab/etoposide-platinum	228	70.6	34.1	10.8	0.80 [c] (0.64, 0.98)
	placebo/etoposide-platinum	225	61.8	23.8	9.7	

1L=first-line, CI=confidence interval, HR=hazard ratio, ORR=objective response rate, OS=overall survival, PFS=progression free survival, SCLC=small cell lung cancer

a. Data from 11-MAR-2019 interim data cutoff [Paz-Ares, L., et al 2019]

b. Data from 27-JAN-2020 interim data cutoff [Paz-Ares, L. G., et al 2020]

c. OS improvement did not reach the statistical significance per the prespecified statistical plan (p=0.0164)

2.2.2 Pharmaceutical and Therapeutic Background

2.2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with its ligands PD-L1 and PD-L2. 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.

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB/approved labeling.



2.2.2.4 Lenvatinib

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGFR, 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. Also, in preclinical models, lenvatinib decreased the TAM population, which is known as an

immune-regulator in the tumor microenvironment. The decrease in TAM population was accompanied by increases in activated cytotoxic T-cell populations through stimulation of interferon-gamma signaling, resulting in increased immune activation [Kimura, T., et al 2018].

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB/approved labeling.

2.2.3 Rationale for the Use of Investigational Agents

2.2.3.1 Rationale for the Use of Pembrolizumab in SCLC

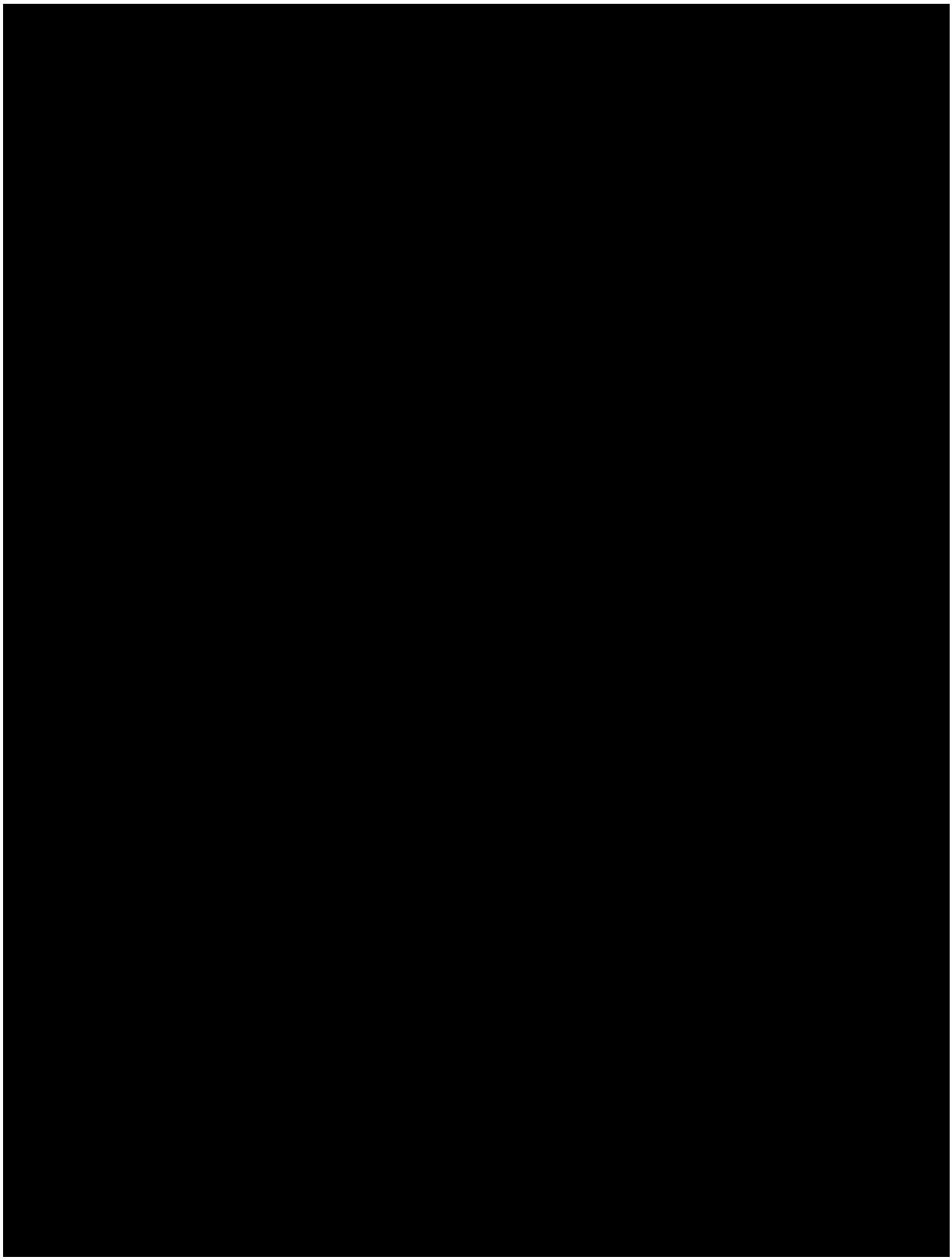
Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across several indications and has been evaluated for the treatment of ES-SCLC in both previously treated and treatment-naïve patient populations.

KEYNOTE-158 and KEYNOTE-028 are ongoing multicohort studies to evaluate the efficacy and safety of pembrolizumab monotherapy in multiple tumor types, including advanced or metastatic SCLC. In these studies, pembrolizumab monotherapy provided a clinically meaningful benefit in participants with locally advanced or metastatic SCLC who had received 2 or more lines of prior therapy, with an 18.3% ORR per RECIST 1.1 by BICR. Based on Kaplan-Meier estimation, 65.5% of responders had response durations ≥24 months, and the median response was not yet reached (4.1-35.8+ months).

Pembrolizumab has also shown benefit in the treatment of first-line ES-SCLC in KEYNOTE-604, an ongoing Phase 3, placebo-controlled, double-blind study of pembrolizumab in combination with etoposide/platinum chemotherapy compared with etoposide/platinum chemotherapy alone. The primary efficacy results from KEYNOTE-604 demonstrated clinically meaningful and statistically significant improvement of the pembrolizumab combination over chemotherapy alone for the PFS endpoint at IA2 (primary analysis). The pembrolizumab combination reduced the risk of progression or death by 25% with an HR of 0.75 (95% CI: 0.61, 0.91, p=0.00225) [Rudin, C. M., et al 2020]. PFS rates for the pembrolizumab combination were higher than the chemotherapy control (6-months [34.1% and 23.8% respectively], 9-months [17.2% and 8.0%, respectively]). At the final analysis, the pembrolizumab combination showed a clinically meaningful improvement over the control with regard to OS, with an HR of 0.80 (95% CI: 0.64, 0.98) and p-value of 0.01643 (p-value boundary: 0.01282). The magnitude of benefit for OS and PFS in KEYNOTE-604, as well as OS and PFS rates at milestone landmarks, were similar to those shown by contemporaneous studies [Horn, L., et al 2018] [Reck, M., et al 2019] [Paz-Ares, L., et al 2019][Leal, T. A., et al 2020], demonstrating the effectiveness of pembrolizumab in the first-line setting.

The benefit of pembrolizumab in ES-SCLC, both as a monotherapy and in combination with etoposide/platinum chemotherapy, provides the backbone for novel combinations with investigational agents as first-line treatment in this study.

2.2.3.2 Rationale for Combination Therapy in SCLC



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2.2.3.2.3 Rationale for the Use of Lenvatinib

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ 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 immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. The effect of combining lenvatinib with an anti-human PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared with control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T-cells compared with the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well tolerated and severe body weight loss was not observed.

In a Phase 1b/2 study of lenvatinib in combination with pembrolizumab in patients with advanced solid tumors, the ORR at Week 24 was as follows: RCC 63%, endometrial cancer 52%, melanoma 48%, SCCHN 36%, NSCLC 33%, and urothelial cancer 25% [Taylor, M. H., et al 2020]. In the Phase 2 KEYNOTE-146 study, lenvatinib plus pembrolizumab showed

promising antitumor activity and manageable toxicity in patients with previously treated advanced endometrial carcinoma [Makker, V., et al 2020].

SCLC tumors express increased levels of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR and KIT, which mediate proangiogenic pathways and tumor proliferation, and the role of different antiangiogenic agents has shown effectiveness as 2L+ therapy in ES-SCLC both as monotherapy [Cheng, Y., et al 2019] and in combination with a PD-1 inhibitor [Wang, J., et al 2020]. Therefore, the combination of lenvatinib and pembrolizumab is expected to show enhanced antitumor efficacy in treatment of 1L ES-SCLC.

2.2.4 Information on Other Study-related Therapy

Standard 1L treatment for the vast majority of patients with SCLC, regardless of stage, involves combination chemotherapy with etoposide plus cisplatin or carboplatin, a combination that has been used clinically for over 40 years [Sierocki, J. S., et al 1979].

A meta-analysis evaluated individual participant data from 4 randomized studies and found that median OS, median PFS, and response rates were similar in the cisplatin and carboplatin arms. While hematologic toxicities were higher in participants treated with carboplatin, nonhematologic toxicities were increased in participants treated with cisplatin [Rossi, A., et al 2012]. Based on these data, 4 cycles of etoposide with either cisplatin or carboplatin can be considered an appropriate 1L regimen to treat SCLC. This is also reflected in clinical utilization data and the NCCN [National Comprehensive Cancer Network 2018] and ESMO [Fruh, M., et al 2013] recommendations. Taken together, these data provide the basis for the chemotherapy induction regimen selected for KEYNOTE-B99.

2.3 Benefit/Risk Assessment

As described in Section 2.2.1, anti-PD-1/L1 therapy improves the survival of patients receiving 1L therapy for ES-SCLC. Still, these improvements have been short in duration; as a result, there is an unmet need for improving the survival of patients with newly diagnosed ES-SCLC.

The existing preclinical and early clinical data suggest that inhibiting angiogenesis or other immune checkpoint molecules in combination with PD-1 blockade is a promising therapeutic strategy and that the risk/benefit assessment for participants in this study will be favorable. Phase 1 studies have shown that MK-4830 [Siu, L. L., et al 2020] and lenvatinib [Taylor, M. H., et al 2020] as monotherapy or in combination with pembrolizumab can potentially enhance antitumor efficacy in patients with solid tumors (see Section 2.2.3.2). [redacted]. An advantage of the platform study design is that it will allow rapid, concurrent evaluation of multiple investigational agents as first-line treatment in participants with ES-SCLC. This may identify new combination interventions with improved responses over those historically achieved with current treatment options. Therefore, a potential benefit may be faster clinical development of novel interventions benefiting this particular patient population, while reducing exposure of participants to interventions that do not show improved clinical benefit.

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. Potential risks of these novel combination interventions may be increased toxicity, intolerability, or unanticipated adverse drug reactions. Each agent has been evaluated in combination with pembrolizumab or pembrolizumab and chemotherapy to support the doses planned for this study and no new safety signals have been identified with these combinations (Section 2.2.3.2). Considering the high unmet need for new and tolerable treatment options, 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 clinical study may be found in the accompanying IBs and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Formal hypothesis testing will not be performed in this study. The objectives will be evaluated by intervention group.

In males and females with ES-SCLC who are in need of 1L treatment:

Objectives	Endpoints
Primary	
• To estimate the objective response rate as assessed by blinded independent central review according to RECIST 1.1	• Objective response: complete response or partial response
• To estimate 6-month progression free survival rate as assessed by blinded independent central review according to RECIST 1.1	• 6-month progression free survival: survival without documented disease progression or death due to any cause at 6 months after randomization
Secondary	
• To evaluate duration of response based on RECIST 1.1 as assessed by blinded independent central review	• Duration of response: time from first documented evidence of complete response or partial response until disease progression or death due to any cause, whichever occurs first
• To evaluate progression free survival based on RECIST 1.1 as assessed by blinded independent central review	• Progression free survival: time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Objectives	Endpoints
• To evaluate overall survival	• Overall survival: time from randomization to death due to any cause
• To evaluate the best tumor size change as assessed by blinded independent central review	• Tumor size change: percent change in the sum of the diameters of the target lesions
• To evaluate the safety and tolerability of investigational treatment combinations based on proportion of adverse events	• Adverse events • Study intervention discontinuations due to adverse events
[redacted]	[redacted]

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, Phase 2, rolling-arm, multisite, open-label platform study of pembrolizumab in combination with investigational agents and etoposide/platinum chemotherapy in participants with ES-SCLC in need of first-line treatment.

Following a Screening of up to 28 days, treatment randomization will be stratified according to ECOG performance status (0 or 1) and LDH (≤ULN or >ULN), as described in Section 6.3.2.

Induction will consist of up to 4 cycles of concurrent etoposide/platinum (cisplatin or carboplatin) chemotherapy with pembrolizumab and investigational agent followed by a Maintenance combination of pembrolizumab (up to 31 additional infusions) with investigational agent (duration varies by agent). Refer to Section 6.1 for information on the investigational agents and intervention groups that are currently being investigated.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8. Tumor response will be evaluated per RECIST 1.1 and participants will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met (Section 8.2.1.3). All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

4.1.1 Criteria and Procedures for Adding Intervention Groups

The Sponsor will decide if other investigational agents should be evaluated in this study based on the mechanism of action, preliminary efficacy, and toxicity profile observed in other studies. Once an investigational agent has been chosen, a protocol amendment will be submitted. Refer to Section 2 for background information on the investigational agents that are currently being investigated in this study.

4.1.2 Criteria and Procedures for Stopping Enrollment in an Intervention Group

Enrollment in a specific intervention group may stop early if the extent (incidence and/or severity) of emerging effects and clinical endpoints is such that the risk/benefit ratio to the

intervention group population as a whole is unacceptable. [redacted]

If an intervention group is closed to enrollment, participants already enrolled in that group will continue on treatment until one of the conditions for discontinuation is met, unless the Sponsor determines that discontinuation of study intervention is required due to safety concerns. If treatment is discontinued, participants will continue in follow-up.

For intervention groups that end enrollment due to the criteria above, further enrollment to the group will be closed via IRT.

4.2 Scientific Rationale for Study Design

This is an open-label signal-finding study. The goal of this Phase 2 study is to evaluate the safety and efficacy of experimental combinations of investigational agents in 1L ES-SCLC.

The platform study design provides the framework for testing investigational agents in participants who might benefit from novel combination therapies (added to the backbone of concurrent PD-1 receptor blockade and etoposide/platinum chemotherapy) and who are in need of new treatment options.

The study intervention assignments are unblinded due to the differing treatment regimens between intervention groups. The results of each intervention group will be compared with those of the pembrolizumab and chemotherapy combination in KEYNOTE-604 to determine whether the novel combinations warrant further evaluation.

4.2.1 Rationale for Stratification Factors

Treatment randomization will be stratified according to ECOG-PS score (0 or 1) at Screening and LDH (≤ULN or >ULN) at Screening to ensure a balanced allocation of participants in populations with different prognosis. Elevated LDH values and higher ECOG scores are associated with higher tumor burden and decreased survival in SCLC [Zhang, X., et al 2016] [Deng, T., et al 2018] [Foster, N. R., et al 2009] [Liu, S. V., et al 2020] and were also included as stratification factors in KEYNOTE-604, which serves as a historical comparator for this study.

4.2.2 Randomization

Tumor-related bleeds, including fatal hemorrhagic events, have been reported in clinical studies and in postmarketing experience involving lenvatinib [E.U. Summary of Product Characteristics 2021] [U.S. Prescribing Information 2021]. As such, 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. Because this risk is only applicable to lenvatinib, participants with presence of radiographic evidence of encasement or invasion of a major blood vessel (Exclusion Criterion #19) are not

eligible for randomization into Intervention Group C but may enroll in the study for randomization across the other intervention groups currently enrolling. This exclusion must be documented in the eCRF.

Participants who satisfy all inclusion criteria and do not meet any exclusion criteria will continue to be randomized across all open intervention groups, including Intervention Group C.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary Efficacy Endpoints

This study will use ORR and 6-month PFS rate based on RECIST 1.1 criteria as assessed by BICR as the dual primary endpoints. The use of BICR and RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. ORR is considered an adequate endpoint to evaluate response in a signal-finding study.

PFS rate has shown strong potential surrogacy for OS in first-line treatment of ES-SCLC and is considered to be a good alternative endpoint to OS in this disease. While participants with ES-SCLC have a high initial response to anti-PD-1/L1 and chemotherapy treatment, relapse within 6 months is unfortunately common, with only 30% to 45% maintaining response after 6 months of treatment in the KEYNOTE-604, CASPIAN, and IMpower133 studies (Table 5). Therefore, 6-month PFS endpoint will allow for efficient determination of efficacy for the novel intervention groups in this study. The final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Verification of radiologic progression as determined by central review will be communicated to the site.

ORR and 6-month PFS rate are appropriate endpoints to evaluate the antitumor activity of investigational combinations. Treatment effect measured by ORR and 6-month PFS rate can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, the number of CRs, the durability of response, the disease setting, the location of the tumors, available therapy, and the risk-benefit relationship.

Secondary Efficacy Endpoints

This study will use DOR, PFS, OS, and change in best tumor size as secondary efficacy endpoints.

DOR per RECIST 1.1, as assessed by BICR, will serve as an additional measure of efficacy and is a frequently accepted endpoint by both regulatory authorities and the oncology community.

A PFS event can reflect tumor growth and be assessed before the determination of a survival benefit. Its determination is not confounded by subsequent therapy. Treatment effect measured by PFS can be a surrogate endpoint to represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, the disease setting, location of metastatic sites, available therapy, the risk-benefit relationship, and the clinical consequences of delaying or preventing progression in key disease sites (eg, delay of new lesions in the brain or spine) or delaying administration of more toxic therapies.

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

Tumor size change may detect signals of early antitumor activity [Wang, M., et al 2019] and is defined as the percent change in the sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) of the target lesions.

[redacted]

4.2.3.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.4 for additional detail.

4.2.3.2 Safety Endpoints

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

4.2.3.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL will be investigated via the EORTC QLQ-C30 questionnaire. This measure is not a pure efficacy or safety endpoint because it is affected by both disease progression and treatment tolerability.

4.2.3.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing HRQoL in oncology studies [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30

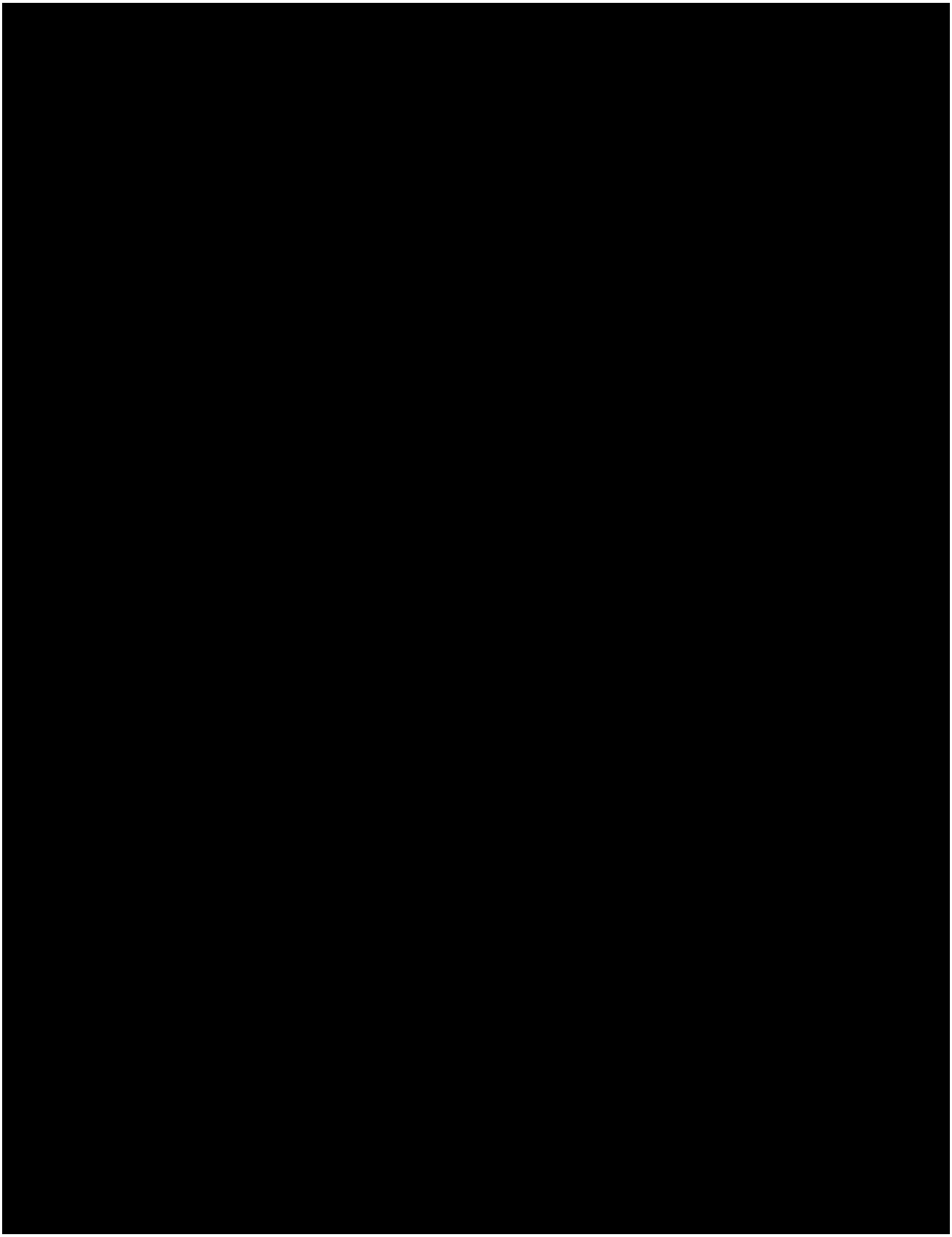
is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea,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

4.2.3.4 Pharmacokinetic Endpoints

[redacted]

4.2.3.5 [redacted]

[redacted]



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[redacted]

4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dosing

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 an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

4.3.2 [redacted]

[redacted]

4.3.3 [redacted]

[redacted]

4.3.4 Rationale for Lenvatinib Dosing

The 8 mg lenvatinib dosing regimen to be used during Induction, which is the RP2D when combined concurrently with etoposide/platinum chemotherapy and pembrolizumab, was based on experience in a Phase 1 NSCLC study in which lenvatinib was combined with paclitaxel (200 mg/m^2) and carboplatin (AUC 6 mg/mL/min) [Nishio, M., et al 2013]. In this study, the MTD was defined as 4 mg BID (equivalent to 8 mg daily). Further, the ongoing randomized, double-blind Phase 3 LEAP-006 is evaluating the combination of pembrolizumab (200 mg) and platinum doublet chemotherapy (pemetrexed [500 mg/m^2] and platinum [carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2]) with or without lenvatinib 8 mg qd in 1L treatment of metastatic NSCLC. Recent eDMC review of LEAP-006 determined that the combination was safe and well tolerated (internal MSD data).

The Maintenance 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 and pembrolizumab 200 mg IV Q3W: n = 3; lenvatinib 20 mg/day and 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 and 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 and pembrolizumab 200 mg Q3W dose [Taylor, M. H., et al 2020].

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.

4.3.5 Rationale for Etoposide/Platinum Chemotherapy Dosing

Platinum doublet chemotherapies used in this study are well-established regimen for SCLC. The regimen was first evaluated in SCLC because this combination produced synergistic activity in preclinical studies. Etoposide 100 mg/m^2 IV Q3W on Days 1, 2, and 3 in combination with either cisplatin 75 mg/m^2 IV Q3W on Day 1 or carboplatin AUC of

5 mg/mL/min IV Q3W on Day 1 are recommended by the NCCN Guidelines [National Comprehensive Cancer Network 2018].

4.4 Beginning and End-of-Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologically or cytologically confirmed diagnosis of ES-SCLC in need of first-line therapy.

2. Has extensive-stage SCLC defined as Stage IV (T any, N any, M1a/b/c) by the American Joint Committee on Cancer, Eighth Edition.

Demographics

3. Is male or female, at least 18 years of age at the time of providing documented informed consent.

Male Participants

4. Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    - Lenvatinib (7 days)

    - Etoposide, Cisplatin, or Carboplatin (180 days)

    - Pembrolizumab, [redacted] (no contraception measures)

- Refrain from donating sperm

    PLUS either:

- 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 , documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

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

    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

5. 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

- Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

    - Lenvatinib (30 days)

    - Etoposide, Cisplatin, or Carboplatin (180 days)

    - Pembrolizumab, [redacted] (120 days)

  The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours (urine test) or 72 hours (serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.

  - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.

  - Has had her medical history, menstrual history, and recent sexual activity reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

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

Additional Categories

7. Has measurable disease per RECIST 1.1 as assessed by local site investigator/radiology and verified by BICR. Lesions situated in a previously irradiated area are considered

measurable if progression has been shown in such lesions. At least 1 lesion that meets the criteria for being measurable, as defined by RECIST 1.1, must be appropriate for selection as a target lesion.

Note: metastatic lesions situated in the brain are not considered measurable and should be considered nontarget lesions.

8. Submits an archival tumor tissue sample or newly obtained core, incisional, or excisional biopsy of a tumor lesion not previously irradiated where such sample exist. The sample may be submitted after enrollment but must be submitted within 4 weeks after randomization. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

9. Has an ECOG performance status of 0 or 1 assessed within 7 days before randomization.

10. Has adequate organ function as defined in the following table (Table 6). Specimens must be collected within 10 days before the first dose of study intervention.

Table 6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥8.0 g/dL or ≥5.0 mmol/L[a]
Renal	
Measured or calculated[b] creatinine clearance	≥60 mL/min for participant receiving cisplatin ≥50 mL/min for participants receiving carboplatin
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.
[a]Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
[b]Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

11. Has adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no changes in antihypertensive medications within 1 week before randomization.

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12. Has a predicted life expectancy of >3 months.

5.2 Exclusion Criteria

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

Medical Conditions

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

2. Has a preexisting ≥Grade 3 gastrointestinal or non-gastrointestinal fistula.

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

4. Has a LVEF below the institutional (or local laboratory) normal range, as determined by MUGA or ECHO.

5. Prolongation of QTcF interval to >480 ms.

6. Has clinically significant cardiovascular disease or major arterial thromboembolic event within 12 months before first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.
   Note: Medically controlled arrhythmia would be permitted.

7. Has active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks before the first dose of study intervention.

8. Has gastrointestinal malabsorption or any other condition that might affect oral study intervention absorption.

9. Has serious nonhealing wound, ulcer, or bone fracture within 28 days before first dose of study intervention.

10. Has any major hemorrhage or venous thromboembolic events within 3 months before the first dose of study intervention. Participants with venous thrombosis diagnosed more than 3 months before the first dose of study intervention must be on stable doses of anticoagulants.

11. Has a history of inflammatory bowel disease.

12. Has a history of a gastrointestinal perforation within 6 months before the first dose of study intervention.

13. Is considered a poor medical risk due to a serious, uncontrolled medical disorder or nonmalignant systemic disease. Examples include, but are not limited to, uncontrolled major seizure disorder, unstable spinal cord compression, or superior vena cava syndrome.

Prior/Concomitant Therapy

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, anti-CTLA-4, anti-OX-40, anti-CD137, anti-CD27).

15. Has received prior treatment (chemotherapy, radiotherapy, or surgical resection) including investigational agents for SCLC.

    Note: Palliative radiation therapy is allowed until 7 days before the first dose of study intervention, provided that the radiated lesion is clinically stable and the participant is not receiving steroids for at least 7 days before the first dose of study intervention. The radiated lesion must not be an intrathoracic lesion and must not be included as a target lesion for RECIST 1.1 measurements.

    Specific treatment options allowed in the presence of brain metastases are not exclusionary (see Exclusion Criterion number 23 for details).

16. Is expected to require any other form of antineoplastic therapy for SCLC, including radiation therapy, while on study.

    Exception: radiation to the brain may be allowed during the study following Sponsor consultation. Prophylactic cranial irradiation is not permitted during the study.

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

Prior/Concurrent Clinical Study Experience

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

    Note: Participants who have entered the follow-up period 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

19. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation.
    Note: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy. In the chest, major blood vessels include the main pulmonary artery, the left and right pulmonary arteries, the 4 major pulmonary veins, the superior or inferior vena cava, and the aorta.
    Note: If a participant does not meet this exclusion criterion and is otherwise eligible for the study, the participant may be randomized into any intervention group currently open to enrollment. A participant that meets this exclusion criterion but is otherwise deemed eligible for the study may not be randomized into Intervention Group C but may be randomized across the other intervention groups currently open to enrollment. This exclusion must be documented in the eCRF.

20. Has symptomatic ascites, pleural effusion, or pericardial effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

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

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

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.

23. Has known active CNS metastases and/or carcinomatous meningitis. Participants with brain metastases may participate only if they satisfy all of the following:

    - Completed treatment (eg, whole brain radiation treatment, stereotactic radiosurgery, or equivalent) at least 14 days before the first dose of study intervention

    - Have no evidence of new or enlarging brain metastases confirmed by posttreatment repeat brain imaging (using the same modality) performed at least 4 weeks after pretreatment brain imaging, and

    - Are neurologically stable without the need for steroids for at least 7 days before the first dose of study intervention as per local site assessment.

      Note: Participants with untreated brain metastases will be allowed if they are asymptomatic, the investigator determines there is no immediate CNS-specific

treatment required, there is no significant surrounding edema, and the brain metastases are of 5 mm or less in size and 3 or fewer in number.

24. Has a history of severe hypersensitivity reaction (≥ Grade 3) to any study intervention and/or any of its excipients (refer to the IB and/or approved product label(s) for a list of excipients).

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

    Note: participants with vitiligo, Sjøgren's syndrome, Type 1 diabetes, or resolved childhood asthma/atopy will not be excluded from the study. Participants requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from the study. Participants with hypothyroidism or adrenal or pituitary insufficiency who are stable on hormone replacement will not be excluded from the study.

26. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
    Note: Lymphangitic spread of SCLC is not exclusionary.

27. Has a known history of, or active, neurologic paraneoplastic syndrome.

28. Has an active infection requiring systemic therapy.

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

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

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

31. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

Other Exclusions

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

Please refer to Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

Investigation site personnel are encouraged to assist participants with activities aimed at discontinuing smoking. All participants who smoke should be strongly advised to cease smoking.

5.3.3 Activity Restrictions

No restrictions are required

5.4 Screen Failures

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

Participants who fail screening may be rescreened one time for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management using the Sponsor Communication Form. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria are met. Participants who are rescreened will retain their original screening number.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 7.

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Table 7 Study Interventions

Arm Name	Arm Type	Intervention Name	Interven-tion Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
[redacted]											

Arm Name	Arm Type	Intervention Name	Interven-tion Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
[redacted]											
C	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W (Day 1 of each cycle for up to 35 infusions)	Test Product	IMP	Central
C	Experimental	Lenvatinib	Drug	Capsule	10 mg, 4 mg, and 1 mg	8 mg (Induction) and 20 mg (Mainte-nance)	Oral	qd, no treatment duration limit	Test Product	IMP	Central
C	Experimental	Etoposide	Drug	Solution for Infusion	100 mg (may vary if locally sourced)	100 mg/m^2	IV Infusion	Q3W (Days 1, 2, 3 of each cycle for up to 4 cycles)	Background Treatment	NIMP/ AxMP	Central or local

Arm Name	Arm Type	Intervention Name	Interven-tion Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
C	Experimental	Cisplatin	Drug	Solution for Infusion	50 mg (may vary if locally sourced)	75 mg/m^2	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment	NIMP/ AxMP	Central or local
C	Experimental	Carboplatin	Drug	Solution for Infusion	600 mg (may vary if locally sourced)	AUC 5 mg/ mL/min	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment	NIMP/ AxMP	Central or local

AUC=area under the curve; AxMP=auxiliary medicinal product; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product, Q3W=every 3 weeks; Q6W=every 6 weeks; qd=daily

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

All study interventions will be administered on an outpatient basis.

All products indicated in Table 7 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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

6.1.1 Treatment

The study intervention consists of:

- Pembrolizumab: up to 35 infusions (approximately 2 years) of study intervention
- [redacted]
- [redacted]
- Lenvatinib: has no treatment time duration limit
- Etoposide: up to 4 cycles (approximately 12 weeks) of study intervention
- Cisplatin: up to 4 cycles (approximately 12 weeks) of study intervention
- Carboplatin: up to 4 cycles (approximately 12 weeks) of study intervention

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of investigational agents are provided in the Pharmacy Manual. Concomitant chemotherapeutic agents (etoposide and cisplatin or carboplatin) will be prepared and administered as per the local approved product labels.

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 study 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

Participants who satisfy all inclusion criteria and do not meet any exclusion criteria may be randomized into any intervention group currently open to enrollment. Participants with presence of radiographic evidence of encasement or invasion of a major blood vessel (Exclusion Criterion #19) are not eligible for randomization into Intervention Group C (pembrolizumab, lenvatinib, etoposide/platinum) but may enroll and be randomized among the other intervention groups currently open to enrollment. This exclusion must be documented in the eCRF.

When there is more than 1 intervention group open for enrollment, randomization will be applied equally across all open intervention groups to which the participant is eligible. The assigned intervention group for a participant will not change during the study; there is no crossover between intervention groups. Randomization can reduce bias, even though there is no intent to compare the treatment effect among intervention groups. Randomization to intervention groups will occur centrally using an IRT system. Before randomization, the investigator's choice of platinum agent (cisplatin or carboplatin) will be documented in the IRT system.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. ECOG-PS status at Screening (0 or 1)

2. LDH at Screening (≤ULN or >ULN)

6.3.3 Blinding

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

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

6.4.1 Pembrolizumab, [redacted]

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

Refer to Section 6.6.1 for dose modifications and toxicity management for irAEs associated with pembrolizumab, [redacted] for other allowed dose interruptions.

6.4.2 Lenvatinib

Interruptions from the protocol-specified treatment for >28 days between lenvatinib doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written document of the collaborative decision on participant management.

- When participants self-administer lenvatinib at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by participant reporting and confirmed by capsule count where possible during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

- A record of the number of lenvatinib capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

Intervention start and stop dates, including dates of intervention delays and/or dose reductions will also be recorded in the CRF.

Refer to Section 6.6.2 for dose modifications and management of AEs associated with lenvatinib and for other allowed dose interruptions.

6.4.3 Etoposide/ Platinum Chemotherapeutic Agents

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

Refer to Section 6.6.3 for dose modifications and allowed drug interruptions of chemotherapeutic agents (etoposide and cisplatin/carboplatin). Administration of the full dose (specified in Table 7) is required on Cycle 1, Day 1.

6.5 Concomitant Therapy

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

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Antineoplastic systemic therapy (including chemotherapy, biological therapy, immunotherapy, and targeted therapies such as TKIs) not specified in this protocol
- Investigational agents not specified in this protocol
- Surgery for tumor control
- Radiation therapy (including prophylactic cranial irradiation or consolidative radiation therapy to the mediastinum)

  Note: Radiation therapy to a symptomatic solitary lesion or to brain metastases may be allowed after Sponsor consultation.

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. Note: Killed vaccines are allowed.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Phenytoin during therapy with cisplatin/carboplatin

- Trilaciclib administration

- For each chemotherapy agent used in the study, site staff should refer to the approved product labels for prohibited medications and drug-drug interactions.

- Systemic glucocorticoids except when used for the following purposes:

  - To modulate symptoms of an AE that is suspected to have an immunologic etiology

  - For the prevention of emesis

  - To premedicate for IV contrast allergies

  - To treat COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)

  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

- Other glucocorticoid use except when used for the following purposes:

  - For topical use or ocular use

  - Intraarticular joint use

  - For inhalation in the management of asthma or chronic obstructive pulmonary disease

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

Concomitant medications should also include medication regularly administered at intervals >28 days prior to the first dose of study intervention.

Please refer to Appendix 7 for country-specific requirements.

6.5.1 Rescue Medications and Supportive Care

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

6.5.1.1 Pembrolizumab, [redacted]

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

6.5.1.2 Etoposide/Platinum Chemotherapeutic Agents

For supportive care measures for the management of AEs that may result from treatment with chemotherapy, refer to the approved product labels for these agents.

During Induction (Cycles 1-4), the use of CSFs (G-CSF or GM-CSF) is highly recommended as primary prophylaxis to reduce the risk of febrile neutropenia, especially as many participants have multiple comorbidities and advanced disease. The ASCO guidelines for use of CSFs should be followed.

For all agents and administration, antiemetic therapy should follow MASCC guidelines (http://mascc.org/antiemetic-guidelines/) [Roila, F., et al 2016] and should include a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and/or aprepitant as per the MASCC guidelines.

In addition, all participants should receive the appropriate corticosteroid premedications as per the local approved label.

Additional premedications and pre- and post-cisplatin hydration should be administered as per local practice.

6.5.2 Drug Interactions for Lenvatinib

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

Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/Pgp substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate).

Clinical studies also showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern.

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

Lenvatinib has been reported to prolong QT/QTc interval. Avoid coadministration of lenvatinib with medicinal products with a known potential to prolong the QT/QTc interval. If QTc prolonging drugs are medically necessary and an acceptable alternative cannot be substituted, refer to Section 8.3.4 for instructions on increased frequency of ECG monitoring.

6.6 Dose Modification (Escalation/Titration/Other)

Adverse events will be graded using NCI CTCAE v5.0. Investigators will decide the probability of the event being related to one or more drugs as to whether dose modification of one or more drugs is required.

This is an open-label study with a novel combination of pembrolizumab, chemotherapy (cisplatin/carboplatin and etoposide) and one of the following investigational agents: [redacted], or lenvatinib. Because of the multiple agents included in this protocol, overlapping toxicities may occur and the determination of the contribution of agents to specific toxicities may be challenging. Dose modifications can be handled individually or in concert depending on determined relatedness. Refer to Section 6.6.1, Section 6.6.2, and Section 6.6.3 for guidance concerning dose interruption, dose modification, and overlapping toxicities. Please contact the Sponsor for additional guidance if needed.

Participants who interrupt or discontinue one of the study interventions due to toxicity may continue with the drug(s) in the assigned combination until the criteria for treatment discontinuation are met (Section 7.1).

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

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

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 8.

Table 8 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 (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations ([redacted]) 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 of infusion reaction associated with pembrolizumab monotherapy, coformulations, or IO combinations ([redacted]) are provided in Table 9.

Table 9 Pembrolizumab Monotherapy, Coformulations, or IO Combinations ([redacted])

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention 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 after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations ([redacted]) may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (for Q3W administration) or 6 weeks (for Q6W administration) of the originally scheduled dose and within 42 days (for Q3W administration) or 84 days (for Q6W administration) of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Management of AEs and Dose Modification for Lenvatinib

6.6.2.1 Lenvatinib Dose Reduction During Induction

The starting dose of lenvatinib during the Induction (Cycles 1-4 of pembrolizumab and etoposide/platinum) is 8 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level (6 mg/day, 4 mg/day, 2 mg/day) per Table 10. Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been

mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Table 10 Lenvatinib Dose Modification (Reduction) Guidelines During Induction

Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
8 mg QD	6 mg QD	4 mg QD	2 mg QD	Discontinuation

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 10, Table 11 and Table 12. An interruption of study intervention for more than 28 days will require Sponsor approval before treatment can be resumed.

Refer to the subsections below for management of hypertension (Section 6.6.2.3), proteinuria (Section 6.6.2.4), diarrhea (Section 6.6.2.5), hepatotoxicity (Section 6.6.2.6), thromboembolic events (Section 6.6.2.7), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.2.8), hypocalcemia (Section 6.6.2.9), hemorrhage (Section 6.6.2.10), gastrointestinal perforation or fistula formation (Section 6.6.2.11), QT prolongation (Section 6.6.2.12), and osteonecrosis of the jaw (Section 6.6.2.13) as appropriate, before consulting the dose modification table (Table 11). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.2.14.

Table 11 Dose Modification Guidelines for Lenvatinib-Related Adverse Events During Induction

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e, f]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 6 mg once a day
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 4 mg/day
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 2 mg/day
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discontinue lenvatinib

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 4[g]: Discontinue Study Treatment		

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

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

[a] An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

[b] Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.

[c] Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

[d] Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.

[e] For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

[f] For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.2.7.

[g] Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

6.6.2.2 Lenvatinib Dose Modification During Maintenance

A lenvatinib dose of 20 mg/day is planned for the Maintenance (Cycle 5-35 of pembrolizumab). However, the lenvatinib starting dose during Maintenance will depend on the following criteria (Figure 2):

- Participants who tolerate 8 mg lenvatinib during Induction with lenvatinib-related AE ≤Grade 1 (Grade 2 hypothyroidism is acceptable), will be eligible to escalate the dose to 20 mg at the start of Maintenance.

- Participants who tolerate 8 mg lenvatinib during Induction but do not meet the criteria for dose escalation (ie, lenvatinib-related AE ≥Grade 2 [excluding Grade 2 hypothyroidism]), may continue the 8 mg dose during Maintenance.

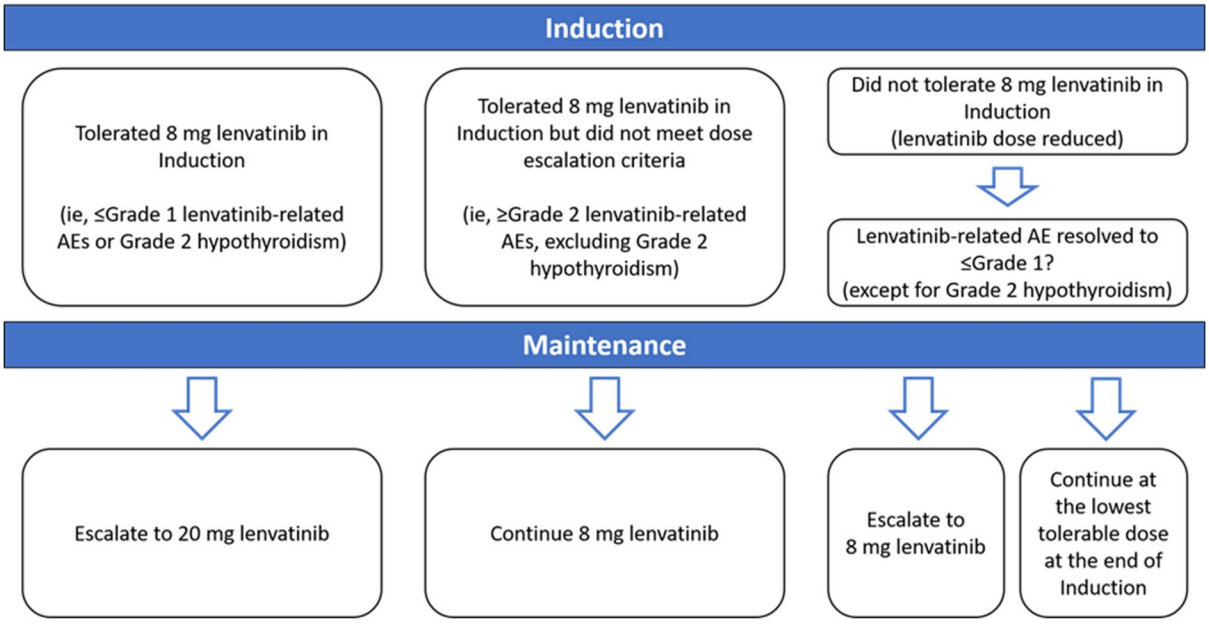
- Participants who require dose reduction during Induction, whose lenvatinib-related AE resolved to Grade 1 or less, are eligible to start Maintenance at the 8 mg dose level. Otherwise, participants may continue Maintenance at their lowest tolerable dose at the end of Induction.

Once the lenvatinib dose is determined at the beginning of Maintenance, the dose may not be further escalated.

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Figure 2 Lenvatinib Starting Dose Selection at the Beginning of Maintenance



Lenvatinib Dose Reduction

If a participant presents with toxicity that might need dose reduction, the investigator should evaluate participant's lenvatinib-related toxicity as often as needed (Table 12). Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Table 12 Dose Modification Guidelines for Lenvatinib-Related Adverse Events during Maintenance

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**		
Start dose of Maintenance		**20 mg**	**8 mg or 6 mg**	**4 mg or 2 mg**
Grade 1 or Tolerable Grade 2				
	Continue treatment	No Change	No Change	No change
Intolerable Grade 2[c, d] **or Grade 3**[e, f]				
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day	Reduce lenvatinib dose to 4 mg once a day	Discuss with Sponsor
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day	Discuss with Sponsor	

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**		
Start dose of Maintenance		**20 mg**	**8 mg or 6 mg**	**4 mg or 2 mg**
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day		
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 4 mg orally once a day		
Fifth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor		
Grade 4[g]: Discontinue Study Treatment				

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

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

[a] An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

[b] Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.

[c] Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

[d] Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.

[e] For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

[f] Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

[g] For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.2.7.

6.6.2.3 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3.1 and Section 1.3.2). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

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

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

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

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

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

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

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.

2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

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

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

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

   - Additional dose reduction should be discussed with the Sponsor.

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

- Institute appropriate medical management

- Discontinue lenvatinib

6.6.2.4 Management of Proteinuria

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

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3.1). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible

2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot UPCR test) is required in the following situations:

   - The first (initial) occurrence of ≥2+(≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participant is receiving lenvatinib

- A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level

- When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL)

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

Grading of Proteinuria

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 11 and Table 12.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles

- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician

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

6.6.2.5 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment, and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 11 and Table 12 should be followed.

6.6.2.6 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3.1 and Section 1.3.2) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 11 and Table 12 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v5.0) occurs, lenvatinib must be discontinued.

6.6.2.7 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 11 and Table 12 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

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

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

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 11 and Table 12 should be followed.

6.6.2.9 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3.1 and Section 1.3.2). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] × 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

6.6.2.10 Management of Hemorrhage

Instructions in Table 11 and Table 12 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.2.11 Management of Gastrointestinal Perforation or Fistula Formation

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

6.6.2.12 Management of QT Prolongation

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

6.6.2.13 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution (See Section 6.6.2.15).

6.6.2.14 Dose Modifications for Overlapping Toxicities

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

1. Timing of AE onset

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

- If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.

- If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

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

2 Severity of AE

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

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

   - ALT or AST >5 X ULN for more than 2 weeks.
     Pembrolizumab will have already been permanently discontinued per Table 8, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

   - ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
     Although Table 8 advises pembrolizumab to be withheld (interrupted), and Table 11 and Table 12 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.6.2.15 Other Allowed Dose Interruptions with Lenvatinib

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

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

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

- For scheduled dental surgery or invasive dental procedures: stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

6.6.3 Management of Adverse Events and Dose Modifications for Etoposide/Platinum Chemotherapeutic Agents

If a participant experiences a ≥10% weight change during Cycles 1 to 4, the doses of etoposide and cisplatin/carboplatin should be recalculated.

Study intervention-related toxicities must be resolved to baseline or Grade ≤1 (with the exception of alopecia, Grade 2 fatigue, and endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2, and creatinine clearance, for which the

guidelines provided below may be followed) before administering the next dose. Participants must not receive the next cycle of chemotherapy if any of the following apply:

- ANC <1,500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <8 g/dL
- Total bilirubin level >1.5 × ULN
- AST and ALT levels ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present

Dose modifications due to AEs will depend on the investigator's assessment of causality. and use a stepwise dose reduction according to Table 13. Recommended dose modifications for key chemotherapy toxicities (etoposide and cisplatin/carboplatin) are outlined in Table 14 and Table 15. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. A participant is allowed to switch from cisplatin to carboplatin if the participant develops unexpected toxicities with the use of cisplatin (including hearing loss), becomes ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the participant.

A maximum of 2 dose reductions per chemotherapy agent are permitted; if additional reductions are required, that particular agent must be discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or be further reduced, if necessary. There will be no dose escalations in this study.

Table 13 Dose Modifications for Chemotherapeutic Agents

	Etoposide	**Cisplatin**	**Carboplatin**
Dose Level 0 (starting dose)	100 mg/m^2/day	75 mg/m^2	AUC 5 mg/mL/min
Dose Level -1	75 mg/m^2/day	56 mg/m^2	AUC 4 mg/mL/min
Dose Level -2	50 mg/m^2/day	38 mg/m^2	AUC 3 mg/mL/min
Dose Level -3	Discontinue	Discontinue	Discontinue

Table 14 Recommended Chemotherapy Dose Modifications for Hematological Toxicity

Intervention-related Toxicity[a]	Etoposide	Cisplatin	Carboplatin
	Dose Level (DL) from Table 13		
Neutrophils (ANC) <500/mm^3 without fever	DL -1	DL -1	DL -1
Febrile neutropenia (fever ≥38.5°C and ANC <1,000/mm^3)	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 without significant bleeding or requiring packed RBC/platelet transfusion	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring packed RBC/platelet transfusion	DL -2	DL -2	DL -2
Grade 4 anemia	DL -1	DL -1	DL -1

Abbreviations: ANC=absolute neutrophil count, DL=dose level, RBC=red blood cell

Note: For grading, see CTCAE v5.0.

Note: If toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents. Investigators may decide to use supportive measures/treatment and/or secondary prophylaxis as per institutional standards (eg, filgrastim, pegfilgrastim, transfusions) instead of dose reductions for the next cycle, if considered in the best interest of the participant.

[a] Should the hematologic toxicity recur, the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

Table 15 Recommended Chemotherapy Dose Modifications for Nonhematologic Toxicity

Intervention-related Toxicity[a]	CTCAE Grade	Etoposide	Cisplatin	Carboplatin
		Dose Level (DL) from Table 13		
Nausea/vomiting	Grade ≥3[b]	DL 0	DL -1	DL -1
Mucositis	Grade ≥3[b]	DL -1	DL -1	DL -1
Diarrhea	Grade ≥3[b]	DL -1	DL -1	DL -1
Peripheral neuropathy	Grade 2	No modification	DL -1[c]	No modification
	Grade 3	No modification	Discontinue[d]	DL -1
	Grade 4	No modification	Discontinue	DL -1
Total bilirubin	Grade 2	DL -2	No modification	No modification
	Grade 3	Discontinue	No modification	No modification
	Grade 4	Discontinue	No modification	No modification
AST or ALT Elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other nonhematologic toxicity (except fatigue and transient arthralgia and myalgia)	Grade ≥3	DL -1	DL -1	DL -1

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Intervention-related Toxicity[a]	CTCAE Grade	Etoposide	Cisplatin	Carboplatin

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE= Common Terminology Criteria for Adverse Events; DL=dose level

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents.

a. Should the toxicity recur, the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

b. The first occurrence of Grade ≥3 nausea/vomiting, mucositis, and diarrhea should be managed symptomatically with optimal medical therapy, and improve to Grade ≤1 before proceeding with additional therapy. Should these events recur despite aggressive management, a dose modification can be employed once the AE improves to Grade ≤1.

c. If Grade 2 neurotoxicity recurs after DL -1, drug will be given at DL -2 or switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor. If Grade 2 neurotoxicity persists after 2 dose level reductions and 21-day hold, switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

d. If Grade 3 neurotoxicity occurs, cisplatin will be discontinued and, upon improvement, a switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

Creatinine clearance:

Creatinine clearance (CrCl) will be based on either the Cockcroft-Gault formula Section 8.1.8.1.5) or another acceptable standard formula.

For participants receiving cisplatin, the scheduled dose of cisplatin may only be administered if the calculated CrCl is ≥50 mL/min:

- If CrCl falls to <50 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥50 mL/min, decrease cisplatin to DL -1. Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the second occurrence of CrCl <50 mL/min, decrease cisplatin to DL -2 upon improvement of CrCl to ≥50 mL/min. Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the third occurrence of CrCl <50 mL/min, cisplatin should be discontinued. If in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, at the discretion of the investigator and in consultation with the Sponsor.

For participants receiving carboplatin, the scheduled dose of carboplatin may only be administered if the calculated CrCl is ≥40 mL/min:

- If CrCl falls to <40 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥40 mL/min, decrease carboplatin to DL -1.

- At the second occurrence of CrCl <40 mL/min, decrease carboplatin to DL -2 upon improvement of CrCl to ≥40 mL/min.

- At the third occurrence of CrCl <40 mL/min, carboplatin should be discontinued.

For participants receiving etoposide, the scheduled dose of etoposide may only be administered if the calculated CrCl is ≥50 mL/min. If CrCl falls between 15 mL/min and <50 mL/min, then participants should receive only 75% of the recommended dose.

6.6.3.1 Dose Modifications for Overlapping Toxicities

Participants may have chemotherapy discontinued and continue on pembrolizumab plus investigational agent. Similarly, participants may discontinue pembrolizumab plus investigational agent and continue on chemotherapy alone during the first 4 cycles, if appropriate.

Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced, interrupted, or discontinued according to recommended dose modifications. Chemotherapy may be interrupted for a maximum of 6 weeks from the last dose if due to an AE. If the toxicity is related to the combination of 4 agents, all 4 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications.

6.6.3.2 Other Allowed Dose Interruptions With Chemotherapeutic Agents

These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. During Cycles 1 through 4 of combination pembrolizumab, etoposide/platinum, and investigational agent:

- If etoposide dosing is delayed or interrupted, the platinum agent, pembrolizumab, and investigational agent should also be delayed/interrupted. If etoposide/platinum is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.

- If cisplatin/carboplatin dosing is delayed or interrupted, etoposide, pembrolizumab, and investigational agent should also be delayed/interrupted. If etoposide/platinum is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.

- If pembrolizumab and/or investigational agent is delayed or interrupted, etoposide/platinum therapy can continue as scheduled. Pembrolizumab and investigational agent administration should be attempted at the next cycle of therapy.

- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 consecutive days) despite supportive treatment (ie, chemotherapy may be interrupted for a maximum of 6 weeks from last dose). If only one of the agents is thought to be causing the specified toxicity leading to a 21-day delay of administration of the next cycle, that chemotherapeutic agent can be stopped and treatment can continue with pembrolizumab, investigational agent, and the remaining chemotherapy drug. Pembrolizumab dosing can continue with 1 agent or as a monotherapy.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study Section 7.2.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation before restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.4 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond iCRO-verified disease progression).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- Interruption of platinum-based chemotherapy for more than 6 weeks from the last dose during Induction without Sponsor consultation.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Use of prohibited medications or vaccinations as described in Section 6.5.
- The participant interrupts pembrolizumab/[redacted] administration for more than 12 consecutive weeks from last dose for an AE/toxicity or for more than 6 weeks from last dose for administrative reasons without Sponsor consultation.
- The participant interrupts [redacted] administration for more than 12 consecutive weeks from last dose for an AE/toxicity or for more than 12 weeks from last dose for administrative reasons without Sponsor consultation.

Participants receiving the combination therapy pembrolizumab and lenvatinib (Intervention Group C) must discontinue study therapy if any of the following occur:

- ALT or AST elevation meeting the following criteria:

  - ALT or AST >5 × ULN for more than 2 weeks
    Pembrolizumab will have already been permanently discontinued per Table 8, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

  - ALT or AST >3 × ULN and (TBL >2X ULN or INR > 1.5)
    Although Table 8 advises pembrolizumab to be withheld (interrupted), and Table 11 and Table 12 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

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

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the 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 not exceed the amount specified in the Laboratory Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to

the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions, tobacco use, clinically important conditions diagnosed within 10 years, any prior cancer other than ES-SCLC even if diagnosed greater than 10 years before Screening, and family history of premature cardiovascular disease. For participants having received blood transfusion within 120 days before Screening, the reason for blood transfusion (eg, bleeding, myelosuppression) must be recorded in the medical history.

Details regarding ES-SCLC will be recorded separately and not listed as medical history.

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

8.1.4.1 Tobacco Use Assessment

Definitions for cigarette use are as follows [Land, S. R., et al 2016]:

- Current smokers: persons who report smoking ≥100 cigarettes during their lifetime and who, at the time of screening, reported smoking every day or some days within the last year
- Former smokers: persons who report smoking ≥100 cigarettes during their lifetime and who, at the time of screening, had stopped smoking 1 year prior
- Never-smokers: persons who report smoking <100 cigarettes during their lifetime.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

8.1.5.3 Posttreatment Anticancer Therapy

Information about new anticancer therapies will be collected in the Posttreatment Follow-up.

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention should begin within 3 days of randomization.

On Day 1 of each cycle, intravenous study intervention will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual after all procedures and assessments have been completed.

The first dose of lenvatinib will be administered at the study site at Cycle 1, Day 1. Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately the same time each day.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab Administration

Pembrolizumab will be administered by IV infusion on Day 1 of every treatment cycle over a period of approximately 30 minutes (for up to 35 infusions).

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

[redacted]

8.1.8.1.4 Lenvatinib Administration

Lenvatinib will be taken once daily orally with water (with or without food) at approximately the same time each day. Lenvatinib should be administered on C1D1 and C2D1 approximately 2 hours before ECG assessment.

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

Lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100%

compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

8.1.8.1.5 Etoposide/Platinum Chemotherapy Administration

Etoposide Administration

Etoposide will be administered as an IV infusion on Days 1, 2, and 3 up to 4 cycles (Cycles 1-4). Days 1, 2, and 3 must be consecutive days without interruption. An infusion time of 30 to 60 minutes is recommended, but etoposide may be administered of 30 to120 minutes to accommodate local standards of care. Etoposide will be administered approximately 30 minutes after pembrolizumab [redacted] infusions (whichever is last, as applicable). Additional premedications should be administered as per standard practice.

BSA will be obtained using the Dubois and Dubois formula. The BSA calculated on Cycle 1, Day 1 can be used through the 4 chemotherapy cycles, unless there is a change in weight ≥10%.

Cisplatin Administration

Cisplatin will be administered as an IV infusion on Day 1 for up to 4 cycles (Cycles 1-4). An infusion time of 60 minutes is recommended, but cisplatin may be administered over 30 to180 minutes based on local standards of care. Cisplatin will be administered approximately 30 minutes after the completion of etoposide infusion. Additional premedications should be administered as per standard practice.

BSA will be obtained using the Dubois and Dubois formula. The BSA calculated on Cycle 1, Day 1 can be used through the 4 chemotherapy cycles, unless there is a change in weight ≥10%.

Carboplatin Administration

Carboplatin will be administered as an IV infusion over approximately 60 minutes on Day 1 for up to 4 cycles (Cycles 1-4). Carboplatin will be administered approximately 30 minutes after the completion of etoposide infusion. Additional premedications should be administered as per standard practice.

Carboplatin will be calculated using the Calvert formula to achieve an area under the plasma drug concentration time curve of 5 mg/mL/min. The dose should not exceed 750 mg.

- Total dose (mg) = (target AUC) x (CrCl + 25)
- The estimated CrCl in the Calvert formula should not exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 5 x (125 + 25)
  = 5 x 150
  = 750 mg

CrCl must be calculated using either the Cockcroft-Gault formula or another acceptable standard formula for estimating CrCl in mL/min based on serum creatinine:

- Men: [(140 – age (y)) x weight (kg)]/[72 x serum creatinine (mg/dL)]
- Women: [(140 – age (y)) x weight (kg)] x 0.85/[72 x serum creatinine (mg/dL)]

Note: Due to differences in serum creatinine units, sites may use either the standard Cockcroft-Gault formula or another acceptable standard formula at their institution.

Dose may be rounded to the nearest 50 mg at the discretion of the investigator and according to institutional standards.

Unless there is a change in weight ≥10%, the same dose of carboplatin can be used throughout the 4 cycles (provided there are no additional toxicities).

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required, if available, and is to be:

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

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

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

Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

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

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

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

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

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment include, but are not limited to, PET-CT, X-ray, etc. Other types of

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

At Screening, participant eligibility will require radiographic documentation of at least one lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1 verified by BICR, before participant randomization.

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

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

8.2.1.1 Initial Tumor Scans

The scans at screening must be submitted to the iCRO to verify that eligibility criteria (Section 5) have been met before randomization.

If brain scans are required to document the stability of existing metastases, the brain scan should be acquired during screening. The specific methods permitted for this study are described in the SIM.

All participants are required to have bone scans at Screening to assess for bone lesions. Bone scan refers to imaging methods used to assess bone metastasis. The specific methods permitted for this study are described in the SIM.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 6 weeks (42 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 48 weeks (336 days ±7 days), participants who remain on treatment will have scans performed every 9 weeks (63 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans are to be performed until disease progression is identified by the investigator and verified by the BICR, or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan

schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

Refer to the SoA (Section 1.3) for on-study brain and bone scan requirements.

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

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

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

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

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

8.2.1.4 RECIST 1.1 Assessment of Disease

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

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

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

- If participant is clinically stable, continue study intervention per protocol
  - resume imaging per protocol schedule (≥4 weeks to next scan)

- send scans to iCRO
- continue local assessment
- do not change investigator assessment of progression
- if subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification

- If the participant is not clinically stable, best medical practice is to be applied

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

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

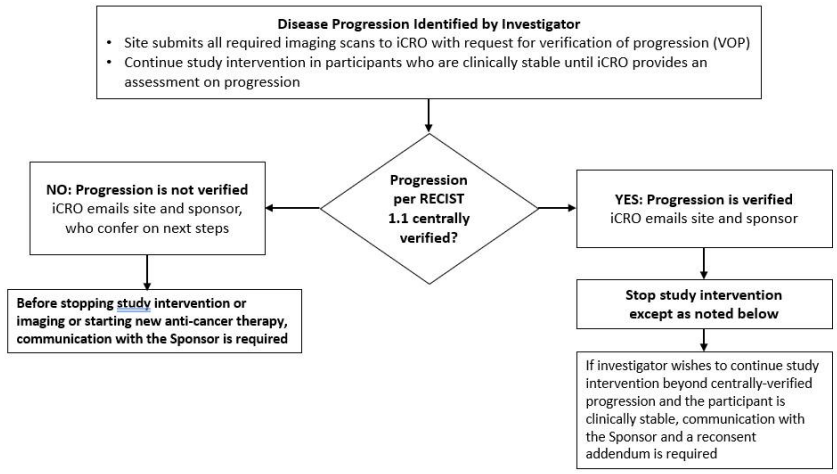
- investigator judgement will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

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

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

Figure 3 Study Intervention Decision-Making Process

Study Intervention Decision Making Process When Progression per RECIST 1.1 is Observed by Investigator (PFS endpoint)



iCRO=Imaging Contract Research Organization; VOP=verification of progression

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30 questionnaire will be administered by trained site personnel and completed electronically by participants. The questionnaire should be administered as described in Section 1.3.

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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee (consistent with local requirements) will perform a complete physical examination, including oral examination. During Screening, clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3; height and weight will also be measured and recorded as indicated. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

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

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination as defined in Section 1.3, the investigator or qualified designee (consistent with local requirements) will perform a directed physical examination (including oral examination for participants in Intervention Group C) per institutional standard before study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

Vital signs (ie, systolic and diastolic BP [mm Hg], temperature [in centigrade], heart rate [beats per minute], RR [breaths per minute], and pulse oximetry [oxygen saturation percentage]) will be assessed at the visits designated in the SoA (Section 1.3) by a validated method.

- BP and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

8.3.3 Audiometry

Participants receiving cisplatin should be monitored for audiological complications. Audiometry testing will be performed at Screening and at Safety Follow-up or per local standard, by the investigator or medically qualified designee (consistent with local requirements). Assessments may be repeated as clinically indicated. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.4 Electrocardiograms

ECG 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 before 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 in the appropriate CRF.

QTc prolongation has been seen in some lenvatinib studies. For Intervention Group C, monitor ECGs every cycle (as specified in the SoA) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Refer to the lenvatinib IB.

8.3.5 Multiple Gated Acquisition or Echocardiogram Scans

A MUGA scan (using technetium-based tracer) or an ECHO will be performed to assess LVEF as designated in the SoA (Section 1.3). MUGA or ECHO scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

8.3.6 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. CBC with differential and clinical chemistry results must be reviewed before administration of study intervention. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

Laboratory safety tests will be performed within 10 days before the first dose of study intervention. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before dosing.

8.3.7 Pregnancy Testing

- 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 every protocol cycle (D1) as per SoA.

  - Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:

    - Lenvatinib (30 days)

    - Etoposide, Cisplatin, or Carboplatin (180 days)

- Pembrolizumab, [redacted]

- 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.

8.3.8 Performance Assessments

8.3.8.1 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status as specified in the SoA (Section 1.3).

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention 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 randomization through 30 days after cessation of study intervention must be reported by the investigator.

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

- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sec. 5.1 and 8.3.7, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 16 .

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

Table 16 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in 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 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), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

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

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

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

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

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

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

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5. Lenvatinib overdose without an associated AE is not considered an ECI.

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

* Note: These criteria are based on 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: any dose of 1000 mg or greater
- [redacted]
- [redacted]
- Lenvatinib: any dose above the protocol-specified dose if associated with an AE

No specific information is available on the treatment of overdose of pembrolizumab, [redacted]. In the event of overdose, the specific investigational agent should be discontinued, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. All reports of pembrolizumab [redacted] overdose with and without an AE must be report by the investigator with 24 hours to the Sponsor either by electronic media or paper.

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in participants receiving single doses as high as 40 mg were similar to those in clinical studies at the recommended dose of differentiated thyroid cancer, RCC, and HCC. No specific information is available on the treatment of overdose of lenvatinib. All reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

8.6 [redacted]

[redacted]

8.6.1 [redacted]

[redacted]

8.6.2 [redacted]

[redacted]

[redacted]

8.10 Health Economics Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency department visits must be reported in the eCRF, from the time of treatment randomization through 90 days after cessation of study intervention, or 30 days after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

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

8.11 Visit Requirements

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

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention, unless otherwise noted in the SoA (Section 1.3).

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

8.11.2 Treatment Period

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

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue study intervention will continue to be monitored for Efficacy and Survival Follow-up as described in Section 8.11.4.

8.11.4 Posttreatment Visit

8.11.4.1 Safety Follow-up Visit

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

8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression (as defined by RECIST 1.1 verified by BICR) will begin Efficacy Follow-up and should be assessed per the protocol-defined schedule (SoA, Section 1.3) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer

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

8.11.4.3 Survival Follow-up Contacts

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

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

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

2. For participants who completed assessments in Efficacy Follow-up, the first Survival Follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.5 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the primary and secondary endpoints of this study. Exploratory and other nonconfirmatory analyses for this study will be outlined in a separate sSAP for this protocol.

If, after the study has begun, changes are made to the primary or secondary objectives of the study, or the statistical methods related to those objectives, the protocol will be amended (consistent with ICH Guideline E9). Changes to the exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the conduct of any analyses, will be documented in the sSAP as needed and referenced in the CSR for each intervention group in this study. Post hoc exploratory analyses will be clearly identified in the CSR of each intervention group.

Full details are in the SAP Section 9.6.

9.1 Statistical Analysis Plan Summary

Study Design Overview	This is a Phase 2 study to evaluate the efficacy and safety of pembrolizumab in combination with investigational agents for the treatment of patients with extensive-stage small cell lung cancer in need of first-line treatment. Investigational agents will be added to and removed from the study on a rolling basis.
Treatment Assignment	This is an open-label study. Eligible participants will be stratified by ECOG status at Screening (0 or 1) and LDH at Screening (≤ULN or >ULN). Within each stratum, participants will be equally randomized to open intervention groups to which they are eligible.
Analysis Population	Efficacy: APaT Safety: APaT
Primary Endpoint(s)	1. ORR as assessed by BICR according to RECIST 1.1 2. 6-month PFS rate as assessed by BICR according to RECIST 1.1
Key Secondary Endpoints	3. PFS as assessed by BICR based on RECIST 1.1 4. OS 5. AEs and study intervention discontinuations due to AEs
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR will be provided in each intervention group, together with 90% and 95% CIs using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]. The nonparametric Kaplan-Meier method will be used to estimate the 6-month PFS rate and PFS curve in each intervention group. The corresponding 90% and 95% CIs using Greenwood's formula will also be provided.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.

[redacted]

9.2 Responsibility for Analyses/In-house Blinding

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

ORR as evaluated by BICR per RECIST 1.1 is a primary efficacy endpoint. An objective response is a CR or PR with confirmation. 6-month PFS rate is also a primary endpoint. PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. The 6-month PFS rate is estimated by Kaplan-Meier method.

The secondary efficacy endpoints include DOR, PFS, OS, and best tumor size change. DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. OS is defined as the time from randomization to death due to any cause. Tumor size change is defined as the percent change from baseline in the sum of the diameters of the target lesions.

[redacted]

9.4.2 Safety Endpoints

The safety endpoints include AEs, SAEs, and study intervention discontinuation due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. A description of safety measures is provided in Section 8.3.

9.4.3 PRO Endpoints

The mean change from baseline at Week 19 in global health status/quality of life using the EORTC QLQ-C30 global health status/QoL scale (Items 29-30) is the secondary endpoint. All PRO analyses will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

[redacted]

9.5.2 Safety Analysis Populations

[redacted]

9.5.3 PRO Analysis Population

[redacted]

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analysis

At the end of enrollment in each intervention group and after the last participant in the intervention group receives at least 2 post baseline scans or discontinues from the study, whichever comes first, the ORR estimates obtained as the proportion of participants with CR or PR in each intervention group will be reported along with the 90% and 95% CIs using the exact method based on the binomial distribution (Clopper-Pearson).

The nonparametric Kaplan-Meier method will be used to estimate the 6-month PFS, OS and PFS curves in each intervention group, along with the corresponding 90% and 95% CIs of 6-month PFS rate using the Greenwood's formula.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event.

For the primary analysis, [redacted]

[redacted]

Descriptive summary statistics will be provided for DOR and best tumor size change.

Analysis results may be reported for one or multiple intervention groups at a time.

9.6.2 Statistical Methods for Safety Analysis

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

Descriptive summary statistics such as counts and percentages will be provided for safety analysis.

9.6.3 Statistical Methods for PRO Analysis

If the overall questionnaire completion of compliance rates at Week 19 are <60% or 80%, respectively, then the primary analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance.

Details of PRO analyses will be described in the sSAP.

9.6.4 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, and prior and concomitant therapies will be summarized.

9.7 [redacted]

[redacted]

9.8 [redacted]

[redacted]

9.9 Sample Size and Power Calculations

[redacted]

[redacted]

9.10 Subgroup Analyses

[redacted]

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during this study. Any deviation from protocol-directed administration will be reported. If there are oral medications in the respective intervention group, details of the compliance definition will be provided in the sSAP.

9.12 Extent of Exposure

The extent of exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the overall study intervention, and for each study intervention separately, for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

Not applicable.

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory.
- Results must be reviewed by the investigator or qualified designee and found to be acceptable before each dose of study intervention.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Screening laboratory safety tests will be performed within 10 days before the first dose of study intervention. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before dosing.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices[a]: MCV MCH % Reticulocytes	WBC Count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate[a]	Chloride	Phosphorous[a]
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting or nonfasting)	Calcium	Alkaline phosphatase	Magnesium
	LDH			
Urine Dipstick Testing/Routine Urinalysis[e]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Thyroid Function Tests[f]	• TSH, total or free T3, free T4			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP). A serum test is required if a urine test is positive or not evaluable. A negative pregnancy test is required within 24 hours (urine test) or 72 hours (serum test) before study intervention on Day 1 of each cycle.			
Other Screening Tests	• FSH (as needed in WONCBP only) • Serology (HIV antibody, HIV RNA[g], HBsAg, HCV antibody, and HCV RNA[h]). Only perform if required by local health authority or institutional regulation. Refer to Appendix 7 for country-specific information. • Coagulation parameters[i] (PT/INR and aPTT or PTT)			

Laboratory Assessments	Parameters
ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C1D1=Cycle 1 Day 1; CrCl=creatinine clearance; free T4=thyroxine; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; HBsAg=Hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=Hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin test; PTT=partial thromboplastin time; RBC=red blood cell; RNA=ribonucleic acid; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell count; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential Notes: a. Performed only if considered local standard of care. b. Absolute or % acceptable per institutional standard. c. Urea is acceptable if BUN is not available as per institutional standard. d. CrCl calculation is required at Screening and on Day 1 before chemotherapy dosing (Cycles 1-4). Otherwise, GFR (measured or calculated) and CrCl can be used in place of creatinine. e. Urine dipstick is the preferred method for testing urinary protein; however, urinalysis may be used if the use of urine dipsticks is not feasible. f. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending. g. Only required if immunoassay tests are equivocal. h. Only required to confirm active infection if immunoassay test is positive. i. Performed as part of the Screening assessment and as clinical indicated for participants taking anticoagulants.	

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

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." Lenvatinib overdose without an associated AE is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.2 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:

1. Results in death

2. 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.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

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

4. 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.

5. Is a congenital anomaly/birth defect

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

6. 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 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

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

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

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

  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with 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 their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a 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.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

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

Follow-up of AE and SAE

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

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

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

10.3.5 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 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).

Confidential
09-MSD-MK

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

Not applicable.

Confidential

09MSD-MK

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

    26. 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

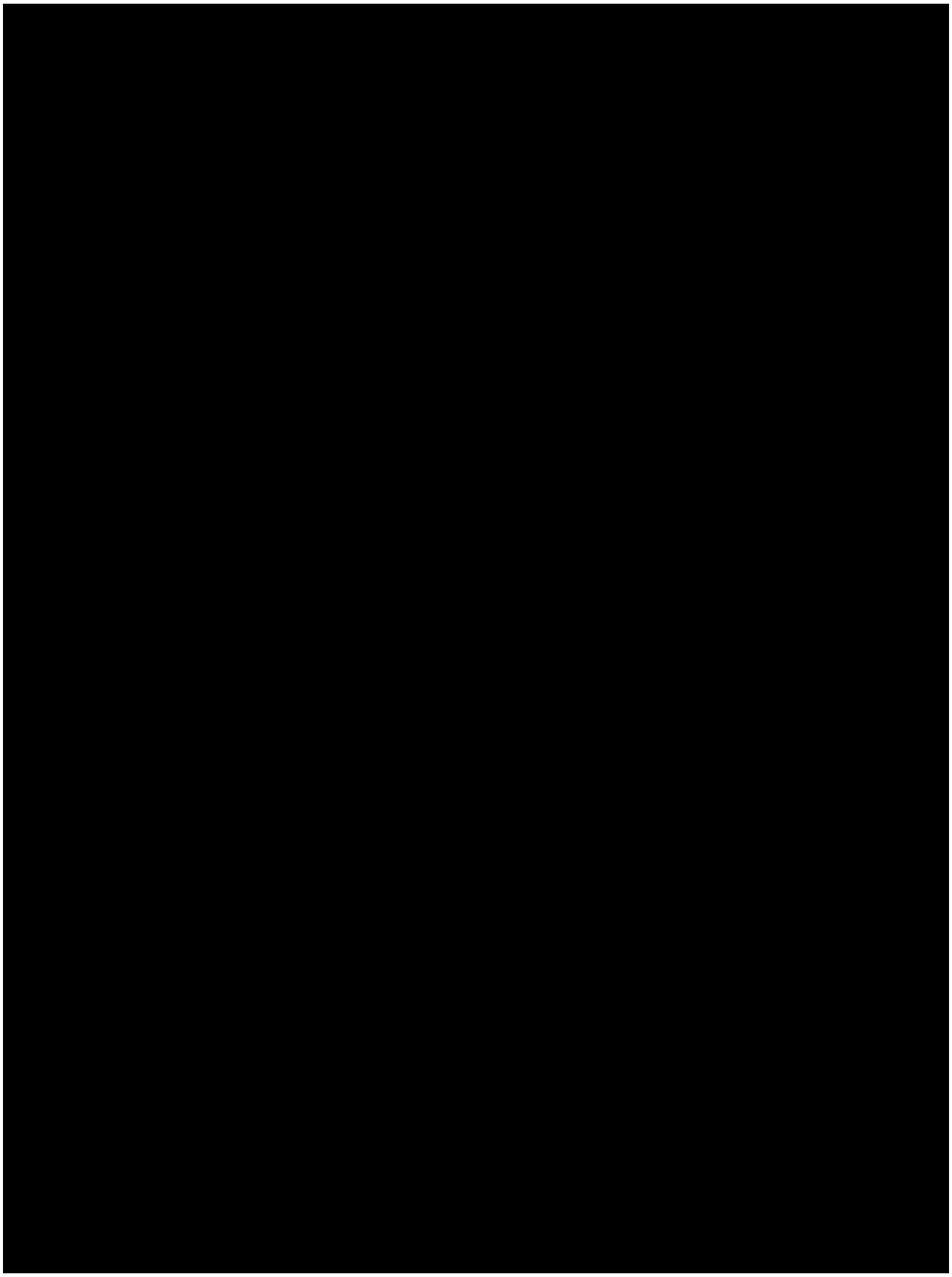
Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
•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

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

Not applicable.

Confidential

09-MSD-XX



Confidential



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10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
1L	first line
2L	second line
ADA	antidrug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BID	two times a day
BMI	body mass index
BP	blood pressure
BSA	body surface area
C	cycle
CBC	complete blood count
CD8	cluster of differentiation 8
CD26	cluster of differentiation 26
CD27	cluster of differentiation 27
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSF	colony-stimulating factor
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA
CTFG	clinical trials facilitation and coordination group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450
D	day
DBP	diastolic blood pressure
DC	discontinuation
DDI	drug-drug interaction
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis

Abbreviation	Expanded Term
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	Electronic Data Monitoring Committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
EOT	end-of-treatment
ePROs	electronic patient-reported outcomes
E-R	exposure response
ESMO	European Society for Medical Oncology
ES-SCLC	extensive-stage small cell lung cancer
EudraCT	European union drug regulating authorities clinical trials database
FAS	Full Analysis Set
FDA	Food and Drug Administration (US)
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HLA-G	human leukocyte antigen G
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
ILT4	immunoglobulin-line transcript 4
IND	Investigational New Drug

Abbreviation	Expanded Term
INR	international normalized ratio
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LLN	lower limit of normal
LS-SCLC	limited-stage small cell lung cancer
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NEAB	noneosinophilic bronchitis
NSCLC	non–small cell lung cancer
ONJ	osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell death 1 protein
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET-CT	positron emission tomography-computer tomography
PFS	progression free survival
Pgp	P-glycoprotein
PK	pharmacokinetic
po	orally
PP	per protocol
PR	partial response
PRES/RPLS	Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome
PRO	patient-reported outcome
PT	prothrombin test
PTT	partial thromboplastin time

Abbreviation	Expanded Term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
qd	daily
QoL	quality of life
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia
RAG	recombination activating genes
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	respiratory rate
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SCCHN	squamous cell cancer of the head and neck
SCLC	small cell lung cancer
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHP-1	Src homology 2 domain-containing protein tyrosine phosphatase 1
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophages
TB	tuberculosis
TIDM	Type-1 Diabetes Mellitus
TKI	tyrosine kinase inhibitor
TMDD	target-mediated drug disposition
T-reg	regulatory T-cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
URTI	upper respiratory tract infection
US	United States
VEGF	vascular epithelial growth factor
VEGFR	vascular epithelial growth factor receptor
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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