Official Protocol Title:	A Phase 3, Randomized, Double-Blind Study of MK-7684A in Combination with Etoposide and Platinum Followed by MK-7684A vs Atezolizumab in Combination with Etoposide and Platinum Followed by Atezolizumab for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer (KEYVIBE-008)
NCT number:	NCT05224141
Document Date:	22-Jan-2025

TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Double-Blind Study of MK-7684A in Combination with Etoposide and Platinum Followed by MK-7684A vs atezolizumab in Combination with Etoposide and Platinum Followed by atezolizumab for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer (KEYVIBE-008)

Protocol Number: 008-05

Compound Number: MK-7684A

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):

NCT	Not Applicable
EU CT	2023-503517-30
EudraCT	2021-005034-42
JAPIC-CT	Not Applicable
UTN/WHO	U1111-1287-4436
IND	157492

Approval Date: 22 January 2025

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	22-JAN-2025	Based on a change in strategy, text was added to state that participants who have access to approved SOC should be considered for discontinuation from the study.
Amendment 04	05-NOV-2024	Based on recommendations of the eDMC to discontinue the experimental arm (MK-7684A) following an interim review which showed that overall survival met the prespecified futility criteria.
Amendment 03	06-MAY-2024	To update the protocol to align with Regulation (EU) 536/2014.
Amendment 02	05-JUL-2022	Response to agency requests.
Amendment 01	11-JAN-2022	Clarify that dose modifications and toxicity management for immune-related adverse events pertain to both MK-7684A and atezolizumab.
Original Protocol	05-NOV-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

Based on a change in strategy, text was added to state that participants who have access to approved SOC should be considered for discontinuation from the study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1, Protocol Summary	Added text to state that participants who have access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study.	Based on a change in strategy, text was added to state that participants who have access to approved SOC should be considered for discontinuation from the study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1, Protocol Summary	Added a brief summary of new data from MK-7684A studies.	To provide context for the discontinuation of the vibostolimab/MK-7684A clinical program.
Section 1.1, Synopsis	Added atezolizumab row to the study interventions table for all participants.	As of Amendment 04, the experimental arm (Arm A: MK-7684A) was discontinued and all ongoing participants were offered an option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.
Section 4, Study Design Section 6, Study Intervention Section 7, Discontinuation of Study Intervention and Participant Withdrawal Section 8, Study Assessments and Procedures Section 9, Statistical Analysis Plan	Added text to state that: • Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit. • Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.	Refer to rationale for Section 1 (change in strategy).

Section Number and Name	Description of Change	Brief Rationale
	• There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable. • Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).	
Section 6.1, Study Intervention(s) Administered	Table 4: Added atezolizumab row to the study interventions table for all participants.	Refer to rationale for Section 1.1 (discontinuation of the experimental arm).
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

Four Phase 3 studies met prespecified futility criteria for OS or RFS: MK-7684A-003 in metastatic NSCLC with PD-L1 TPS ≥50% [redacted] MK-7684A-007 in metastatic NSCLC with PD-L1 TPS ≥1% [redacted] MK-7684A-008 in ES-SCLC (OS HR, 1.26; 95% CI, 1.00-1.59; presented at Society for Immunotherapy of Cancer 2024), and MK-7684A-010 in adjuvant melanoma (RFS HR, 1.25; 95% CI, 0.87-1.80; presented at Society for Melanoma Research 2024) (data on file). Overall, the lack of efficacy observed with MK-7684A rendered the risk-benefit balance unfavorable, so treatment with this investigational therapy was stopped in all studies.

At implementation of Amendment 05, the below changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.

- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable.
- Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).

Existing protocol content is retained for historical reference.

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind Study of MK-7684A in Combination with Etoposide and Platinum Followed by MK-7684A vs atezolizumab in Combination with Etoposide and Platinum Followed by atezolizumab for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer (KEYVIBE-008)

Short Title: Phase 3 Study of Chemotherapy with MK-7684A or atezolizumab in First-Line ES-SCLC

Acronym: MK-7684A-008/KEYVIBE-008

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with extensive-stage small cell lung cancer who are in need of first-line treatment:

Primary Objective	**Primary Endpoint**
• To compare overall survival for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab. • Hypothesis (H1): MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A is superior to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab with respect to overall survival.	• Overall survival: the time from randomization to death due to any cause
Secondary Objectives	**Secondary Endpoints**
• To compare progression-free survival per RECIST 1.1 as assessed by blinded independent central review for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Progression-free survival: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

• Hypothesis (H2): MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A is superior to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab with respect to progression-free survival per RECIST 1.1 by blinded independent central review.	
• To evaluate the objective response rate per RECIST 1.1 as assessed by blinded independent central review for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Objective response: complete response or partial response
• To evaluate duration of response per RECIST 1.1 as assessed by blinded independent central review for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Duration of response: for participants with confirmed complete response or partial response, duration of response is defined as 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 the safety and tolerability of the investigational treatment combination based on proportion of adverse events.	• Adverse events • Study intervention discontinuations due to adverse events

• To evaluate the mean change from baseline in global health status/quality of life, physical functioning, dyspnea, cough, and chest pain for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Change from baseline in the following patient-reported outcomes scales/items: - Global health status/quality of life score (EORTC QLQ-C30 items 29 and 30) - Physical functioning score (EORTC QLQ-C30 items 1-5) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) - Chest pain (EORTC QLQ-LC13 item 40)
• To evaluate the time-to-true deterioration in global health status/quality of life, physical functioning, dyspnea, cough, and chest pain for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Time-to-true deterioration: defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in the following scales/items: - Global health status/quality of life score (EORTC QLQ-C30 items 29 and 30) - Physical functioning score (EORTC QLQ-C30 items 1-5) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) - Chest pain (EORTC QLQ-LC13 item 40)

Overall Design:

Protocol Amendment 04 implementation: Based on recommendations of the eDMC following an interim efficacy and safety analysis showed that the primary endpoint of OS met the prespecified futility criteria, the study was unblinded, and the experimental arm (Arm A: MK-7684A) was discontinued. All ongoing participants on MK-7684A treatment were offered the option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study. All participants still receiving study treatment will be informed of the analysis. The study will remain open for ongoing participantsto have continued access to atezolizumab if they qualify per protocol. The final analysis will be removed and there will be no further analyses for efficacy and ePRO endpoints. Participants currently in efficacy

follow-up or in survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. Participants currently on study treatment will have tumor imaging assessed locally based on the site's standard of care imaging schedule. Scans will not be submitted to the iCRO, and VOP request and central review of imaging will no longer be applicable. PK sampling, anti-drug antibody sampling, and blood for ctDNA analysis will no longer be collected on any participants. PROs will no longer be collected on any participants. Participants on study treatment will need to have safety follow-up after treatment is discontinued (participants will no longer be treated under the study). This safety follow-up will be considered their last visit. Collection of AE and lab parameters for participants remaining in study will continue per SOA. These changes were communicated through the investigator letter dated 08-AUG-2024 and Protocol Clarification Letter dated 13-AUG-2024.

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	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	Active Control Without Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Investigator Participants or Subjects Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 450 participants will be randomized.

Intervention Groups and Duration:

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) stopped ongoing treatment with MK-7684A and were offered the option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
A (Protocol Amendment 04: Arm A discontinued)	MK-7684A	MK-7684 200 mg + pembrolizumab 200 mg/20 mL vial	200 MG/ 200 MG	IV Infusion	Q3W (Day 1 of each cycle) until discontinuation criteria are met	Test Product
A (Protocol Amendment 04: Arm A discontinued)	Saline placebo	Not applicable	Not applicable	IV Infusion	At Cycle 1 (and Q3W as needed beyond Cycle 1)	Placebo
A	Etoposide	100 mg (may vary according to supplier/ country)	100 mg/m^2	IV Infusion	Q3W (Days 1, 2, 3 of each cycle for up to 4 cycles)	Background Treatment
A	Cisplatin	50 mg (may vary according to supplier/ country)	75 mg/m^2	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment
A	Carboplatin	600 mg (may vary according to supplier/ country)	AUC 5 mg/mL/min	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment
B	Atezolizumab	1200 mg	1200 mg	IV Infusion	Q3W (Day 1 of each cycle) until discontinuation criteria are met	Comparator
B	Saline placebo	Not applicable	Not applicable	IV Infusion	At Cycle 1 (and Q3W as needed beyond Cycle 1)	Placebo
B	Etoposide	100 mg (may vary according to supplier/ country)	100 mg/m^2	IV Infusion	Q3W (Days 1, 2, 3 of each cycle for up to 4 cycles)	Background Treatment

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
B	Cisplatin	50 mg (may vary according to supplier/ country)	75 mg/m^2	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment
B	Carboplatin	600 mg (may vary according to supplier/ country)	AUC 5 mg/mL/min	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment
All participants	Atezolizumab	1200 mg	1200 mg	IV Infusion	Q3W (Day 1 of each cycle) until discontinuation criteria are met	Comparator

MK-7684A is a coformulation of vibostolimab (MK-7684) and pembrolizumab.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: atezolizumab (TECENTRIQ®); MK-7684A is a coformulation of MK-7684 (vibostolimab) and pembrolizumab (MK-3475, KEYTRUDA®).

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of 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. Protocol Amendment 04 implementation: There will be no collection of efficacy data including tumor scans, vital status, and post-treatment anticancer therapy status.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

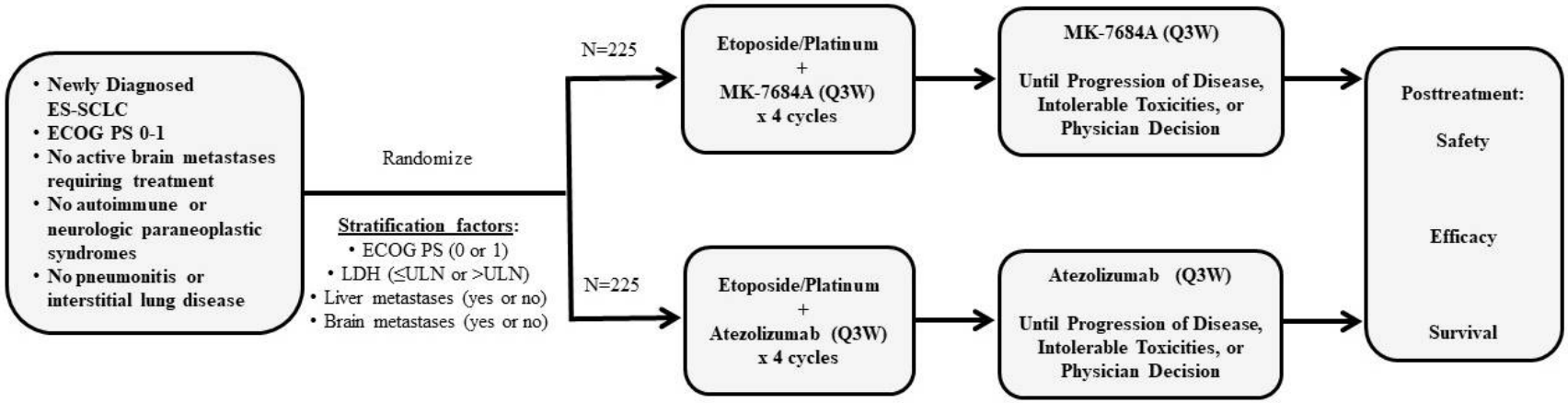
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1. Protocol Amendment 04 implementation: Following eDMC interim review of the data, the experimental arm (Arm A: MK-7684A) was discontinued and all ongoing participants were offered an option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

Figure 1 MK-7684A-008 Study Schema



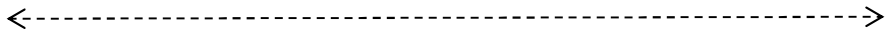
ECOG=Eastern Cooperative Oncology Group; ES-SCLC=extensive-stage small cell lung cancer; LDH=lactate dehydrogenase; PS=performance status; Q3W=every 3 weeks; ULN=upper limit of normal

1.3 Schedule of Activities

Table 1 Schedule of Assessments (Intervention Period)

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -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.
Informed Consent for Future Biomedical Research	X															This is optional for the participant. Participants can still participate in the study if they decline to provide documented informed consent for FBR.
Inclusion/Exclusion Criteria	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															
SCLC History	X															

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Prior/Concomitant Medication Review	X	X		X	X		X	X		X	X		X	X	X	
Intervention Randomization		X														Study intervention should begin within 3 days of randomization.
Posttreatment Anticancer Therapy Status															X	As of Amendment 04, posttreatment anticancer therapy status will no longer be collected for any participants.
Study Intervention Administration (atezolizumab)		X			X			X			X			X		Atezolizumab will be administered Q3W until any of the reasons for intervention discontinuation are met.
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 blinded study intervention infusions. Dose should be recalculated if there is a ≥10% weight change.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±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 platinum infusion. Dose should be recalculated if there is a ≥10% weight change.
Vital Status																After verified disease progression or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for vital status at any time during the course of the study. As of Amendment 04, vital status will no longer be collected for any participants.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Tumor Scans																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. See Section 8.2 for full details. As of Amendment 04, participants currently on study treatment will have tumor imaging assessed locally based on site's standard of care imaging schedule. VOP request and central review of imaging are no longer applicable.
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. EOT scan is not needed if tumor scans were obtained within the last 4 weeks.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Bone Scan	X														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. EOT scan is not needed if tumor scans were obtained within the last 4 weeks.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Brain Scan	X	X													X	All participants are required to have brain scans during Screening. For participants without brain metastases at Screening, on-study brain scans are required Q12W (84 days ±7 days) through Week 48 and then Q24W (168 days ±7 days) through Week 96 or more often as clinically indicated. For participants with brain metastases present at Screening, on-study brain scans are to be acquired at all scheduled post-baseline imaging timepoints, or more often as clinically indicated, and to confirm a CR. EOT scan is not needed if tumor scans were obtained within the last 4 weeks.
Safety Procedures																
Full Physical Examination	X														X	
Height	X															
Weight	X	X		X	X		X	X		X	X		X	X		If ≥10% change in body weight occurs, weight-based therapy should be readjusted.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Directed Physical Examination		X		X	X		X	X		X	X		X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	DBP, SBP, heart rate, RR, temperature, pulse oximetry
12-lead ECG	X															Additional ECG may be performed as clinically indicated.
Audiometry	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	At Screening, perform ≤7 days before randomization. Should be completed prior to dose administration.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Pregnancy Test – Urine or Serum hCG (WOCBP only; per local SOP) Please refer to Appendix 7 for country-specific requirements.	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 have elapsed before first dose of study intervention, another pregnancy test is required before starting study intervention. A negative pregnancy test is required before study intervention on Day 1 of each cycle of study intervention. Pregnancy testing should also be conducted as outlined in Section 8.3.6.
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. Please refer to Appendix 7 for country-specific requirements.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Thyroid Function Tests (TSH, T3, free T4)	X				X						X			X	X	Screening samples must be collected ≤7 days before start of study intervention. Thyroid function tests will be performed at Screening and every other cycle thereafter (ie, C2D1, C4D1, C6D1, etc).
Coagulation Tests (PT/INR and aPTT or PTT	X															Screening samples must be collected ≤7 days before start of study intervention. Hematology and chemistry tests performed at Screening must be repeated if more than 72 hours has elapsed before first dose of study intervention.
Hematology	X	X		X	X		X	X		X	X		X	X	X	
Chemistry	X	X		X	X		X	X		X	X		X	X	X	
Urinalysis	X													X		Screening samples must be collected ≤7 days before start of study intervention. To be repeated every 6 cycles beginning at Cycle 6.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -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	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.
PK/PD/Biomarkers																As of Amendment 04, PK sampling, antidrug antibody sampling, and blood for ctDNA analysis will no longer be collected for any participants.

Study Period:	**Screening**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
PK Sampling		X			X						X			X	X	Predose PK samples should be drawn within 24 hours before the start of infusion of study intervention at C1D1, C2D1, C4D1, and C8D1 and every 4 cycles thereafter. Postdose PK samples will be drawn within 10 minutes after end of infusion of blinded study intervention at C1D1 and C8D1. Samples will also be drawn at EOT.
Anti-drug Antibody Sampling		X			X						X			X	X	Predose anti-drug antibody samples should be drawn within 24 hours before start of infusion at C1D1, C2D1, C4D1, and C8D1 and every 4 cycles thereafter. Samples will also be drawn at EOT.
Archival or Newly Obtained Tissue Collection	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.

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
Blood for Genetic Analysis		X														Collect predose from randomized participants only. See Section 8.8.1.
Blood for ctDNA Analysis		X			X			X						X	X	Collect predose on C1D1, C2D1, C3D1, and then predose on D1 of every 2 cycles until C17D1, followed by predose on D1 of every 3 cycles thereafter and at EOT.
Patient-Reported Outcomes																As of Amendment 04, PROs will no longer be collected for any participants.
EORTC QLQ-C30		X			X			X			X			X	X	Completed on Day 1 of every cycle for Cycles 1-9 while the participant is receiving study intervention, then every other cycle up to Cycle 17, and then every 4 cycles onwards until EOT.
EORTC QLQ-LC13		X			X			X			X			X	X	

Study Period:	**Screen-ing**	**Treatment (3-Week Cycles)**													**End-of-Treatment**	**Notes**
Treatment Cycle:		**1**			**2**			**3**			**4**			**5+**	**Discon**	Protocol Amendment 04 implementation: Participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up and laboratory assessments, should continue as per current protocol.
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**EOT (±3 days)**	
Scheduling Window (Days)	**-28 to -1**			**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		**±1**	**±3**		
EQ-5D-5L		X			X			X			X			X	X	PROs will also be obtained at the EOT Visit. If EOT Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, ePROs do not need to be repeated. ePROs should be administered in the following order: EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L.

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CR=complete response; CT=computed tomography; D=day; DBP=diastolic blood pressure; discon=discontinuation; ECG=electrocardiogram; EORTC=European Organization for the Research and Treatment of Cancer; EOT=end-of-treatment; FBR=future biomedical research; FSH=follicle-stimulating hormone; HBV=hepatitis B virus; hCG=human chorionic hormone; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PET=positron emission tomography; PK=pharmacokinetic(s); PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q6W=every 6 weeks; Q9W=every 9 weeks; QLQ=quality of life questionnaire; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; SCLC=small cell lung cancer; SOP=standard operating procedure; TSH=thyroid-stimulating hormone; WOBCP=woman/women of childbearing potential.

Table 2 Schedule of Assessments (Posttreatment Follow-up)

Protocol Amendment 04 implementation: Efficacy Follow-up and Survival Follow-up are no longer applicable. All participants on efficacy follow-up or survival follow-up are considered to have completed all study activities. Safety Follow-up will be the last visit for participants currently on treatment.

Study Period:	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Day (in Cycle)	**30 days from last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	
Administrative Procedures				
Prior/Concomitant Medication Review	X			
Posttreatment Anticancer Therapy Status	X	X	X	
Vital Status	◄----------►		X	After verified disease progression or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for vital status at any time during the course of the study.
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. See Section 8.2 for full details.
CT/MRI of chest, abdomen, and pelvis		X		Use the same imaging modality for all evaluations.
Bone Scan		X		On-study bone scans should be acquired as clinically indicated or to confirm a CR when bone metastases were present at Screening.
Brain Scan		X		For participants without brain metastases at Screening, on-study brain scans are required at Q12W (84 days ±7 days) through Week 48 and then Q24W (168 days ±7 days) through Week 96 or more often as clinically indicated. For participants with brain metastases present at Screening, on-study brain scans are to be acquired at all scheduled post-baseline imaging timepoints, or more often as clinically indicated, and to confirm a CR.
Safety Procedures				
Directed Physical Examination	X			
Vital Signs	X			DBP, SBP, heart rate, RR, temperature, pulse oximetry

Study Period:	**Posttreatment Follow-up**			**Notes**
Treatment Cycle:	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Day (in Cycle)	**30 days from last dose (+7 days)**	**Per imaging schedule**	**Every 12 weeks (±7 days)**	
Audiometry	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			
Thyroid Function Tests (TSH, T3, free T4)	X			
Hematology	X			
Chemistry	X			
AE/SAE review	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.
Patient-Reported Outcomes				As of Amendment 04, PROs will no longer be collected on any participants.
EORTC QLQ-C30	X			
EORTC QLQ-LC13	X			
EQ-5D-5L	X			

AE=adverse event; BICR=blinded independent central review; CR=complete response; CT=computed tomography; DBP=diastolic blood pressure; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for the Research and Treatment of Cancer; EQ-5D-5L=5-level EQ-5D version; LC13=Lung Cancer 13; MRI=magnetic resonance imaging; PRO=patient-reported outcome; PS=performance status; Q12W=every 12 weeks; Q24W=every 24 weeks; QLQ=quality of life questionnaire; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure.

2 INTRODUCTION

This clinical study, MK-7684A-008 (KEYVIBE-008), will evaluate the combination of MK-7684A with etoposide/platinum chemotherapy followed by MK-7684A compared to the combination of atezolizumab with etoposide/platinum chemotherapy followed by atezolizumab in the first-line treatment of ES-SCLC.

Protocol Amendment 04 implementation: Following eDMC interim review of the data, the experimental arm (Arm A: MK-7684A) was discontinued and all ongoing participants were offered the option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

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 show 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 have synergy with anti-PD-1/PD-L1 in this patient population.

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 had not changed 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].

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 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.

2.2.1.1 Approved Immunotherapy in ES-SCLC

Recently, immunotherapy has begun to change outcomes in the first-line treatment of ES-SCLC, as shown by the IMpower133 and CASPIAN studies. In the global Phase 3 IMpower133 study, participants were randomized to receive etoposide and carboplatin with either atezolizumab or placebo for four 21-day cycles, followed by maintenance atezolizumab or placebo as assigned until they had unacceptable toxic effects, disease progression, or no additional clinical benefit [Horn, L., et al 2018]. Prophylactic cranial irradiation (PCI) was allowed based on investigators' choice during the maintenance setting, which was administered to 11% of participants in each arm. Study results showed a significant improvement in OS for the atezolizumab combination compared with chemotherapy alone (HR 0.70 [95% CI: 0.54, 0.91], p=0.007; median OS of 12.3 months compared with 10.3 months, respectively). A significant PFS benefit was shown for the atezolizumab combination (median PFS of 5.2 months compared with 4.3 months for chemotherapy only; HR 0.77 (95% CI: 0.62, 0.96); p=0.02). Importantly, ORR was not improved and DOR was only minimally longer with atezolizumab. The combination of atezolizumab with etoposide and carboplatin was approved for the first-line treatment of ES-SCLC by the US FDA on 18-MAR-2019, as it represented the first therapeutic regimen to improve survival in patients with SCLC. Recently, more mature data with median follow-up of 22.9 months were presented, which showed an OS HR of 0.76 (95% CI: 0.60, 0.95), nominal p-value of 0.0154 [Reck, M., et al 2019].

The CASPIAN study is an open-label, global Phase 3 study that randomized participants with ES-SCLC in need of first-line treatment to durvalumab in combination with etoposide and cisplatin/carboplatin, durvalumab and tremelimumab in combination with etoposide and cisplatin/carboplatin, or etoposide and cisplatin/carboplatin alone [Paz-Ares, L., et al 2019]. Participants in the immunotherapy groups received up to 4 cycles of the etoposide/platinum

doublet plus durvalumab with or without tremelimumab followed by maintenance durvalumab, while patients in the chemotherapy only group could have received an additional 2 cycles of the platinum doublet. PCI was only allowed in the chemotherapy only group and at the investigator's discretion, being administered to only 8% of the participants. At an interim analysis, durvalumab plus etoposide/platinum was associated with a significant improvement in overall survival compared with the etoposide/platinum group (HR: 0.73; 95% CI: 0·59, 0·91; *p*=0.0047; median overall survival 13.0 months [95% CI: 11.5, 14.8] vs. 10.3 months [95% CI: 9.3, 11.2]) [Paz-Ares, L., et al 2019]. Progression-free survival was not formally tested, though median PFS was 5.1 months for the durvalumab plus etoposide/platinum group and 5.4 months for the etoposide/platinum group (HR of 0.78 [95% CI: 0.65, 0.94]). A post hoc analysis showed that confirmed objective response was 68% compared with 58% in the durvalumab plus etoposide/platinum and etoposide/platinum groups, respectively (odds ratio: 1.56, 95% CI: 1.10, 2.22), with a similar median duration of response in both groups. Durvalumab in combination with etoposide and either carboplatin or cisplatin was approved for first-line treatment of ES-SCLC by the US FDA on 27-MAR-2020. The results from IMpower133 and CASPIAN provide evidence that the combination of standard chemotherapy with immunotherapy is a clinically meaningful approach in the treatment of SCLC.

2.2.1.2 Pembrolizumab

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.

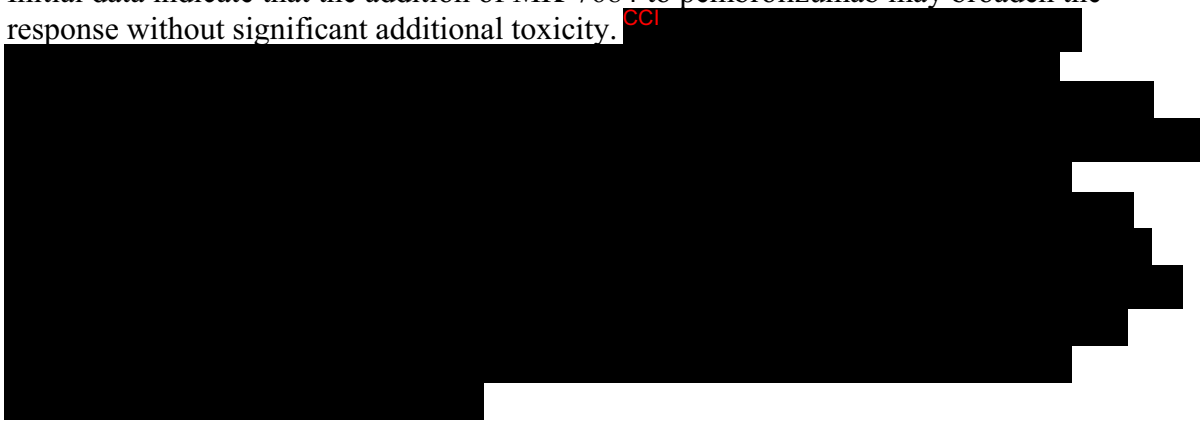
KEYNOTE-158 and KEYNOTE-028 were multicohort studies to evaluate the efficacy and safety of pembrolizumab monotherapy in multiple tumor types, including advanced or metastatic SCLC. In these studies, pembrolizumab monotherapy provided a clinically meaningful benefit in participants with locally advanced 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 [Rudin, C. M., et al 2020]. The primary efficacy results from KEYNOTE-604 showed 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 numerical improvement over the control with regard to OS, with an HR of 0.80 (95% CI: 0.64, 0.98) and p-value of 0.0164 (p-value boundary: 0.0128). 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, showing the treatment effect of pembrolizumab in the first-line setting [Horn, L., et al 2018] [Reck, M., et al 2019] [Paz-Ares, L., et al 2019] [Leal, T. A., et al 2020].

2.2.1.3 MK-7684A

Initial data indicate that the addition of MK-7684 to pembrolizumab may broaden the response without significant additional toxicity. CCI



CD155, an immune checkpoint molecule that inhibits T-cells by binding to TIGIT has recently been found to be highly expressed in various SCLC cell lines and tumor tissues [Yu, H., et al 2018] [Dora, D., et al 2020]. In addition, high CD155 expression is associated with poor prognosis and advanced tumor stage in SCLC [Yu, H., et al 2018] [Xu, Y., et al 2019]. Therefore, targeting TIGIT pathway represents a therapeutic strategy of interest in SCLC.

2.2.2 Pharmaceutical and Therapeutic Background

2.2.2.1 MK-7684A

MK-7684A is a fixed-dose coformulation of pembrolizumab (200 mg) and MK-7684 (200 mg). Combined TIGIT and PD-1 inhibition may result in synergistic tumor killing or an expansion of cancer indications responsive to anti-PD-1 containing therapy.

2.2.2.1.1 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.

2.2.2.1.2 MK-7684

MK-7684 is a humanized, antagonistic IgG1 mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. TIGIT is one of multiple immune checkpoint molecules that maintain immune homeostasis and prevent uncontrolled immune activation. TIGIT competes with the activating receptor CD226 for its ligands, CD155/PVR/Necl5/Tage4 and CD112/PVRL-2, which are expressed on antigen-presenting cells. Binding of TIGIT to its ligands negatively modulates T-cell activity.

The mechanism of TIGIT-mediated T-cell inhibition is not completely understood. Some reports showed that TIGIT knockdown increases T-cell proliferation and effector cytokine production [Zhang, T., et al 2014] and that anti-TIGIT antibodies characterized as agonists can decrease T-cell activation [Lozano, E., et al 2012]. Some reports have also showed that TIGIT may inhibit T-cell activation by opposing the CD226-mediated positive signal through ligand competition or heterodimerization with CD226 [Levin, S. D., et al 2011] [Johnston, R. J., et al 2014]. Importantly, it has been shown both in vitro and in vivo, that CD226 knockdown or blockade (with an antagonist antibody) eliminates the positive impact of TIGIT antagonism [Levin, S. D., et al 2011] [Johnston, R. J., et al 2014].

In a variety of mouse and human tumor models, TIGIT is highly expressed on CD4+ and CD8+ TIL and its expression has been correlated with CD8+ T-cell infiltration [Johnston, R. J., et al 2014] [Chauvin, J. M., et al 2015]. Coordinated TIGIT and PD-1 blockade results in increased proliferation, cytokine production, and degranulation of CD8+ human TIL from melanoma [Chauvin, J. M., et al 2015].

CCI

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the combined MK-7684/MK-7684A IB.

2.2.2.2 Atezolizumab

Atezolizumab (Tecentriq®) is a monoclonal IgG1κ antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. Tecentriq is indicated in combination with carboplatin and etoposide for the first-line treatment of adult patients with ES-SCLC. Tecentriq is also indicated as monotherapy or in combination with other therapeutics in NSCLC, alveolar soft part sarcoma, HCC, and melanoma.

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

2.2.3 Information on Other Study-related Therapy

Standard first-line 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 first-line 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 this study.

2.3 Benefit/Risk Assessment

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

As described in Section 2.2.1, anti-PD-1/L1 therapy improves the survival of patients receiving first-line 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.

CCI

CCI [redacted]

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with extensive-stage small cell lung cancer who are in need of first-line treatment:

Primary Objective	**Primary Endpoint**
• To compare overall survival for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab. • Hypothesis (H1): MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A is superior to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab with respect to overall survival.	• Overall survival: the time from randomization to death due to any cause
Secondary Objectives	**Secondary Endpoints**
• To compare progression-free survival per RECIST 1.1 as assessed by blinded independent central review for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Progression-free survival: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

• Hypothesis (H2): MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A is superior to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab with respect to progression-free survival per RECIST 1.1 by blinded independent central review.	
• To evaluate the objective response rate per RECIST 1.1 as assessed by blinded independent central review for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Objective response: complete response or partial response
• To evaluate duration of response per RECIST 1.1 as assessed by blinded independent central review for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Duration of response: for participants with confirmed complete response or partial response, duration of response is defined as 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 the safety and tolerability of the investigational treatment combination based on proportion of adverse events.	• Adverse events • Study intervention discontinuations due to adverse events

• To evaluate the mean change from baseline in global health status/quality of life, physical functioning, dyspnea, cough, and chest pain for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Change from baseline in the following patient-reported outcomes scales/items: - Global health status/quality of life score (EORTC QLQ-C30 items 29 and 30) - Physical functioning score (EORTC QLQ-C30 items 1-5) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) - Chest pain (EORTC QLQ-LC13 item 40)
• To evaluate the time-to-true deterioration in global health status/quality of life, physical functioning, dyspnea, cough, and chest pain for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.	• Time-to-true deterioration: defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in the following scales/items: - Global health status/quality of life score (EORTC QLQ-C30 items 29 and 30) - Physical functioning score (EORTC QLQ-C30 items 1-5) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) - Chest pain (EORTC QLQ-LC13 item 40)

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
• To evaluate effect of PD-L1 expression on outcomes including overall survival, as well as progression-free survival and objective response rate per RECIST as assessed by blinded independent central review	• Overall survival by PD-L1 expression (tumor proportion score <1% versus ≥1%, combined positive score <1 versus ≥1). • Progression-free survival by PD-L1 expression (tumor proportion score <1% versus ≥1%, combined positive score <1 versus ≥1). • Objective response rate by PD-L1 expression (tumor proportion score <1% versus ≥1%, combined positive score <1 versus ≥1). • Duration of response by PD-L1 expression (tumor proportion score <1% versus ≥1%, combined positive score <1 versus ≥1).
• To evaluate change from baseline in visual analog scale using the EQ-5D-5L questionnaire for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A compared to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab	• Change from baseline in EQ-5D-5L visual analog scale
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-7684A in combination with etoposide/platinum or atezolizumab in combination with etoposide/platinum	• Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue

• To evaluate objective response rate, duration of response, and progression-free survival based on RECIST 1.1 as assessed by the investigator	• Objective response rate • Duration of response • Progression-free survival
• To evaluate the pharmacokinetic profile of MK-7684 and pembrolizumab when administered as a coformulation of MK-7684A	• Pharmacokinetic parameters (C_{max}, C_{trough}) for MK-7684 • Pharmacokinetic parameters (C_{max}, C_{trough}) for pembrolizumab
• To evaluate immunogenicity of MK-7684 and pembrolizumab when administered as a coformulation of MK-7684A	• Anti-drug antibody incidence for MK-7684 • Anti-drug antibody incidence for pembrolizumab

4 STUDY DESIGN

At implementation of Amendment 05, the below changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable.
- Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).

Existing protocol content is retained for historical reference.

4.1 Overall Design

Protocol Amendment 04 implementation: Based on recommendations of the eDMC following an interim review showed that the primary endpoint of OS met the prespecified futility criteria, study was unblinded, and the experimental arm (Arm A: MK-7684A) was discontinued. All ongoing participants on treatment were offered an option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

This is a Phase 3, randomized, double-blind, active-controlled, multisite study of MK-7684A combined with etoposide/platinum chemotherapy followed by MK-7684A compared to atezolizumab combined with etoposide/platinum chemotherapy followed by atezolizumab in the first-line treatment of ES-SCLC.

Following a screening period of up to 28 days, approximately 450 eligible participants will be randomized 1:1 into 2 intervention groups:

Group A – Participants will receive 4 cycles of etoposide/platinum chemotherapy in combination with MK-7684A followed by MK-7684A until any of the conditions for discontinuation are met (Section 7.1).

Group B – Participants will receive 4 cycles of etoposide/platinum chemotherapy in combination with atezolizumab followed by atezolizumab until any of the conditions for discontinuation are met (Section 7.1).

Crossover will not be allowed between the intervention groups. A double-blinding technique will be used for atezolizumab and MK-7684A assignment. The chemotherapy agents will be open-label. The choice of platinum (cisplatin or carboplatin) in both arms is selected by the investigators before randomization.

Treatment randomization will be stratified according to ECOG performance status (0 or 1), LDH (≤ULN or >ULN), presence of liver metastases (yes or no), and presence of brain metastases (yes or no).

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.

Protocol Amendment 04 Implementation: There will be no collection of efficacy data including tumor scans, vital status and post-treatment anticancer therapy status. Participants currently on treatment will have tumor imaging assessed locally based on site's standard of care imaging schedule. Disease progression will no longer be centrally verified.

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0 (Section 10.3.4). Each participant will be monitored for AEs and SAEs (refer to Section 8.4.1 for details). If study intervention is discontinued for toxicity, neither pembrolizumab nor MK-7684 will be offered as a single agent.

Protocol Amendment 04 implementation: In participants who continue atezolizumab under the study, safety assessments and safety related data collection including safety follow-up should continue as per current protocol, including laboratory assessments.

Please refer to Appendix 7 for country-specific requirements.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Stratification Factors

Treatment randomization will be stratified according to ECOG performance status (0 or 1), LDH (≤ULN or >ULN), presence of liver metastases (yes or no), and presence of brain metastases (yes or no) to ensure a balanced allocation of participants in populations with different prognoses. Elevated LDH values, higher ECOG PS, and liver and brain metastases are each 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] [Steindl, A., et al 2019].

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

Primary Efficacy Endpoints

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

Secondary Efficacy Endpoints

This study will use PFS, ORR, and DOR per RECIST 1.1 criteria as assessed by BICR as secondary efficacy endpoints. 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.

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.

ORR is an appropriate endpoint to evaluate the antitumor activity of investigational combinations. Treatment effect measured by ORR 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.

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

4.2.2.1.1 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.

4.2.2.2 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.

4.2.2.3 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. As part of the analyses for this study, HRQoL and disease-related symptoms will be investigated among all participants via the following assessment tools: EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQol EQ-5D-5L questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.2.3.1 EORTC QLQ-C30

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

4.2.2.3.2 EORTC QLQ-LC13

The EORTC QLQ-LC13, a supplemental lung cancer-specific module, comprises multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and side effects from chemotherapy and radiation (ie, hair loss, neuropathy, sore mouth, and dysphagia). It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much) and has been translated into 64 languages and validated.

4.2.2.3.3 EQ-5D-5L

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

4.2.2.4 Planned Exploratory Biomarker Research

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

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

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

Genetic (DNA) analyses from tumor

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

Tumor and/or blood RNA analyses

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

immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood and/or tumor

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

Other blood-derived biomarkers

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

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

4.2.2.5 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.3 Rationale for the Use of Comparator

Atezolizumab was the first anti-PD-1/L1 approved for ES-SCLC and has been considered the current standard of care for the first-line treatment of ES-SCLC since its approval in 2019. In an analysis of 347 patients diagnosed with ES-SCLC between 01-OCT-2018 (after the Impower133 study publication) and 31-DEC-2019, 267 patients (76.9%) were treated with atezolizumab in combination with carboplatin and etoposide [Nadler, E., et al 2021]. As such, atezolizumab will be used as the active comparator for this study.

4.2.3.1 Justification for Dose

4.2.4 Starting Dose for This Study

4.2.4.1 Rationale for MK-7684A Dosing

MK-7684A is a single-use drug product vial containing a fixed-dose combination of 200 mg MK-7684 and 200 mg pembrolizumab in a 20.0 mL fill volume. MK-7684A is to be administered Q3W. The single coformulation vial could provide simplified preparation and reduced infusion times compared to separate formulations administered sequentially. Study PN001 is evaluating the safety and PK biocomparability of this coformulated product to that of the sequential administration of MK-7684 and pembrolizumab.

Based on the totality of available data, including preliminary clinical PK, pharmacodynamics, safety, and efficacy from Study MK-7684-001, the selected dose of MK-7684 is 200 mg Q3W.

CCI [redacted]

Available clinical safety data indicated that MK-7684 is tolerable at doses up to and including 700 mg, both when used as monotherapy and in combination with pembrolizumab. No DLTs were observed at any of the MK-7684 doses tested either as monotherapy or in combination with pembrolizumab during the dose escalation and confirmation portion of Study MK-7684-001, and the MTD was not reached.

Clinical activity was observed at the 200/210 mg and the 700 mg dose levels of MK-7684 both during the dose escalation and confirmation portion of Study MK-7684-001 in participants with advanced solid tumors of all types and during the dose expansion portion,

CCI [redacted]

CCI [redacted]

CCI [redacted]

Overall, the totality of data, CCI [redacted] support that a fixed-dose of 200 mg Q3W is the RP2D for MK-7684 in combination with 200 mg pembrolizumab. For more information, see the MK-7684/MK-7684A IB.

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 showing 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
- 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

4.2.4.2 Rationale for Atezolizumab Dosing

Atezolizumab administration is approved for the treatment of ES-SCLC with doses of 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W. This study will use fixed-dose 1200 mg atezolizumab Q3W to correspond to the dosage used in the Impower133 Study and with the MK-7684A Q3W administration in this study.

4.2.4.3 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].

4.3 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). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be approximately 5 years (~2 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

Protocol Amendment 04 implementation: The study will end when all participants discontinue from treatment and complete safety follow up.

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

4.3.1 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.

Based on recommendations of the eDMC to discontinue the experimental arm (MK-7684A) following an interim review showed that the primary endpoint of OS met the prespecified futility criteria. The study will end when all participants discontinue from treatment and complete safety follow up.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

A participant is eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. The participant must have a histologically or cytologically confirmed diagnosis of ES-SCLC in need of first-line therapy.
2. Has ES-SCLC defined as Stage IV (T any, N any, M1a/b/c) by the American Joint Committee on Cancer, Eighth Edition or T3-T4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

Demographics

3. Is an individual of any sex/gender, at least 18 years at the time of providing the 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 after the last dose of the intervention is as follows:
   - Etoposide, cisplatin, or carboplatin: 95 days
   - Blinded study intervention (MK-7684A or atezolizumab): 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 Appendix 5) as detailed below:

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

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. 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 using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 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 after the last dose of the intervention is as follows:

  - Etoposide, cisplatin, or carboplatin: 180 days

  - Blinded study intervention (MK-7684A or atezolizumab): 5 months

The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

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

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

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.

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

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

Informed Consent

6. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

7. Has measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. 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.
8. Note: for the purposes of this study, metastatic lesions situated in the brain are not considered measurable and should be considered non-target lesions.
9. Submits a pretreatment archival tumor tissue sample or newly obtained core, incisional, or excisional biopsy of a tumor lesion not previously irradiated where such sample exists. Biopsy/tissue is preferred, but cytology sample by fine needle aspiration is allowed. 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.
10. Has an ECOG performance status of 0 to 1 assessed within 7 days before allocation/randomization.
11. Has adequate organ function as defined in the following table (Table 3). Specimens must be collected within 7 days before the start of study intervention.

Table 3 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/[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 using the Cockcroft-Gault formula.

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.

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

Please refer to Appendix 7 for country-specific requirements.

5.2 Exclusion Criteria

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

Medical Conditions

1. 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 severe or life-threatening superior vena cava syndrome.

Prior/Concomitant Therapy

2. Has received prior treatment (systemic therapy including investigational agents, curative-intent radiotherapy, or curative-intent surgical resection) 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.

   Note: Specific treatment options allowed in the presence of brain metastases are not exclusionary (See exclusion criterion number 8 for details).
3. Is expected to require any other form of antineoplastic therapy for SCLC while on study.
   Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after Sponsor consultation.
4. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

Prior/Concurrent Clinical Study Experience

5. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.
   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

6. 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 medication.
7. 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,, low-risk, non-muscle-invasive bladder cancer or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.
8. 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 (preferably using the same modality) performed at least 4 weeks after treatment and within the screening period, and

- Are neurologically stable without the need for steroids 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.

9. 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).
10. 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.
11. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. Has a known history of, or active, neurologic paraneoplastic syndrome.
13. Has an active infection requiring systemic therapy.
14. History of HIV infection. HIV testing is not required unless mandated by local health authority.
15. Hepatitis B (defined as HBsAg reactive) or Hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection.
    Note: Testing for Hepatitis B or C is not required unless mandated by local health authority.
16. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or 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.
17. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

18. Has had an allogenic tissue/solid organ transplant.
19. Has had major surgery within 3 weeks before receiving the first dose of study intervention or has not recovered adequately from toxicity and/or complications from an intervention prior to receiving the first dose of study intervention.
20. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

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.

Study-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. 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 withdraws from the study will not be replaced.

6 STUDY INTERVENTION

At implementation of Amendment 05, the below changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable.
- Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).

Existing protocol content is retained for historical reference.

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 intervention(s) 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 4.

Country-specific requirements are noted in Appendix 7.

Reasonable efforts are to be made to arrange central sourcing for atezolizumab. However, in the extenuating circumstances where central sourcing is logistically difficult, local sourcing is acceptable after headquarter approval. The blinding for study interventions that are locally sourced must be maintained; blinding procedures are described in the Pharmacy Manual.

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) stopped ongoing treatment with MK-7684A and were offered the option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
A (Protocol Amendment 04: Arm A discontinued)	Experimental	MK-7684A	Drug	Solution	MK-7684 200 mg + pembrolizumab 200 mg/20 mL vial	200 MG/ 200 MG	IV Infusion	Q3W (Day 1 of each cycle) until discontinuation criteria are met	Test Product	IMP	Central
A (Protocol Amendment 04: Arm A discontinued)	Experimental	Saline placebo	Drug	Solution	Not applicable	Not applicable	IV Infusion	At Cycle 1 (and Q3W as needed beyond Cycle 1)	Placebo	NIMP/ AxMP	local
A	Experimental	Etoposide	Drug	Solution	100 mg (may vary according to supplier/ country)	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
A	Experimental	Cisplatin	Drug	Solution	50 mg (may vary according to supplier/ country)	75 mg/m^2	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment	NIMP/ AxMP	Central or local
A	Experimental	Carboplatin	Drug	Solution	600 mg (may vary according to supplier/ country)	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
B	Active Comparator	Atezolizumab	Drug	Solution	1200 mg	1200 mg	IV Infusion	Q3W (Day 1 of each cycle) until discontinuation criteria are met	Comparator	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
B	Active Comparator	Saline placebo	Drug	Solution	Not applicable	Not applicable	IV Infusion	At Cycle 1 (and Q3W as needed beyond Cycle 1)	Placebo	NIMP/AxMP	Local
B	Active Comparator	Etoposide	Drug	Solution	100 mg (may vary according to supplier/country)	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
B	Active Comparator	Cisplatin	Drug	Solution	50 mg (may vary according to supplier/country)	75 mg/m^2	IV Infusion	Q3W (Day 1 of each cycle for up to 4 cycles)	Background Treatment	NIMP/AxMP	Central or local
B	Active Comparator	Carboplatin	Drug	Solution	600 mg (may vary according to supplier/country)	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
All participants	Active Comparator	Atezolizumab	Drug	Solution	1200 mg	1200 mg	IV Infusion	Q3W (Day 1 of each cycle) until discontinuation criteria are met	Comparator	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

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.

In this protocol, placebo for MK-7684A or atezolizumab is diluent alone (normal saline); diluent is used for blinding purposes and does not contain active ingredients.

All supplies indicated in Table 4 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 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 approved product label(s).

Protocol Amendment 04 Implementation: Due to discontinuation of experimental arm (Arm A: MK-7684A), atezolizumab will be prepared and administered per approved local label.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to MK-7684A study intervention and atezolizumab study intervention, respectively.

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) stopped ongoing treatment with MK-7684A and were offered an option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. ECOG performance status at Baseline (0 or 1)
2. LDH at Baseline (≤ULN or >ULN)
3. Liver metastases at Screening (yes or no)
4. Brain metastases at Screening (yes or no)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. Atezolizumab and MK-7684A will be supplied to the sites in an open-label manner. The study site's unblinded pharmacist will obtain each participant's study identification number and study drug assignment from the IRT system. MK-7684A, atezolizumab, and placebo (when needed) will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. Blinded MK-7684A, atezolizumab, and placebo infusions are packaged identically. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments. The chemotherapy agents will be open-label.

In addition to emergency unblinding for severe or life-threatening AEs with potential immunologic etiology, non-emergency unblinding to MK-7684A versus atezolizumab administration may occur on an individual participant basis and only after consultation with the Sponsor at the time of (1) centrally verified disease progression and participant has discontinued all study treatments, (2) when the participant has discontinued all study treatments and a new anticancer treatment is going to be started or (3) Grade 2 infusion reaction to the immunotherapy/placebo agent when placebo was also required. Non-emergency unblinding, only after consultation and approval from the Sponsor, is implemented through IRT by following the instructions in the IRT site user manual.

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

Protocol Amendment 04 implementation: Following eDMC interim review of data, all participants have been unblinded.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record. Treatment intervention interruptions for greater than 21 days of the originally scheduled dose for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention require discussion between the investigator and the Sponsor.

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 site should ensure and confirm that the study intervention is administered at the correct dose to the assigned study participant.

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 and Section 6.6.2 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

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 chemotherapy (including chemotherapy, biological therapy, immunotherapy, and targeted therapies) not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy (including PCI or consolidative thoracic radiation therapy). Note: Radiation therapy to a symptomatic solitary lesion or to the brain 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: 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, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

- Phenytoin during therapy with cisplatin/carboplatin
- Trilaciclib administration
- Systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - As needed for the prevention of emesis
  - Premedication for chemotherapy
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for asthma or COPD exacerbations
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease

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

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. Please refer to Appendix 7 for country-specific requirements.

6.5.1.1 Blinded Study Intervention (MK-7684A and Atezolizumab)

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 American Society of Clinical Oncology guidelines for use of CSFs should be followed.

For all agents and administration, antiemetic therapy should follow MASCC 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.

6.6 Dose Modification

The dose modification and toxicity management guidelines for immune-related adverse events (Table 5) and the infusion reaction dose modification and treatment guidelines (Table 6) apply to both atezolizumab and MK-7684A (ie, blinded study intervention).

Protocol Amendment 04 implementation: Due to discontinuation of experimental arm (Arm A: MK-7684A) and ongoing participants being offered an option to move to the comparator arm (Arm B: atezolizumab monotherapy), the dose management and toxicity management guidelines for atezolizumab should follow approved local label.

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with MK-7684A or Atezolizumab

AEs associated with study intervention exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of 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 study intervention, 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 study intervention, study intervention must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, study intervention 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 study intervention.

Restarting Study Interventions:

Participants may restart study intervention 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, study intervention may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with MK-7684A or atezolizumab are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with MK-7684A or Atezolizumab

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. Study intervention 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 study intervention has been withheld, treatment may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Study Intervention	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 Study Intervention	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 b-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]		
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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Study Intervention	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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 (which was previously myocarditis Grade 1 using CTCAE v4.0)	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 Study Intervention	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 study intervention is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, study intervention 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 MK-7684A or Atezolizumab

Administration of study intervention may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines for the study intervention-associated infusion reaction are provided in Table 6.

Table 6 MK-7684A or Atezolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping 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 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 intervention.	No subsequent dosing
CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs= nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for MK-7684A or Atezolizumab

Study intervention 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, 21 days of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 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 before administering the next dose. Exceptions include alopecia, Grade 2 fatigue, and endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2. For creatinine clearance, ANC, platelet, hemoglobin, total bilirubin, and AST/ALT, the guidelines provided below may be followed. 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 7. Recommended dose modifications for key chemotherapy toxicities (etoposide and cisplatin/carboplatin) are outlined in Table 8 and Table 9. 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 (after consultation with the Sponsor) 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. In the absence of the agent thought to be causing toxicity, treatment can continue with blinded study intervention with or without the remaining chemotherapeutic drug.

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 7 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

Abbreviation: AUC=area under the curve

Table 8 Recommended Chemotherapy Dose Modifications for Hematologic Toxicity

Intervention-related Toxicity[a]	Etoposide	Cisplatin	Carboplatin
	Dose Level (DL) from Table 7		
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 platelet transfusion	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring packed 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

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 9 Recommended Chemotherapy Dose Modifications for Nonhematologic Toxicity

Intervention-related Toxicity[a]	CTCAE Grade	Etoposide	Cisplatin	Carboplatin
		Dose Level (DL) from Table 7		
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	Discontinue
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

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] This applies to toxicity of Grade 3 and lasting 72 hours or beyond despite aggressive supportive management, or toxicity of Grade 4.

[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 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 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 full 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.

6.6.2.1 Dose Modifications for Overlapping Toxicities

Participants may have chemotherapy discontinued and continue on blinded study intervention. Similarly, participants may discontinue blinded study intervention 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 etoposide/platinum chemotherapy and blinded study intervention, all 3 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications.

6.6.2.2 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 blinded study intervention and etoposide/platinum:

- If etoposide dosing is delayed or interrupted, the platinum agent and the blinded study intervention 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, and blinded study intervention 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 blinded study intervention is delayed or interrupted, etoposide/platinum therapy can continue as scheduled. Blinded study intervention 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 blinded study intervention, with or without the remaining chemotherapy drug.
- Etoposide/platinum administration 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, 21 days, of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

At implementation of Amendment 05, the below changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable.
- Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).

Existing protocol content is retained for historical reference.

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.

Protocol Amendment 04 implementation: Per eDMC recommendation, there will be no collection of efficacy data, and the final visit in the study will be the safety follow-up visit. Participants who discontinue study intervention and have completed safety follow up will be considered to have completed the study.

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 prior to 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 investigator assessed disease progression).
- Any progression or recurrence of 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 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 blinded study intervention 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.

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

At implementation of Amendment 05, the below changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable.
- Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).

Existing protocol content is retained for historical reference.

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the 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 or FBR. 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.

8.1.2 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.

8.1.2.1 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.3 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.

8.1.4 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.

8.1.5 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).

8.1.5.1 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

8.1.6 Prior and Concomitant Medications Review

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

8.1.6.2 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.

8.1.7 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.

8.1.8 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.

8.1.9 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

Study intervention should begin within 3 days of randomization.

8.1.9.1 Timing of Dose Administration

8.1.9.1.1 MK-7684A Administration

MK-7684A will be administered Q3W starting C1D1 until any of the reasons for intervention discontinuation are met.

To maintain the blinding, participants randomized to Intervention Group A will receive 60 minutes of saline placebo infusion during Cycle 1. After 30 minutes have passed from the beginning of the saline placebo infusion, the MK-7684A infusion, which will be administered over 30 minutes, will start (see Figure 2).

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) stopped ongoing treatment with MK-7684A and were offered an option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study.

Atezolizumab Administration

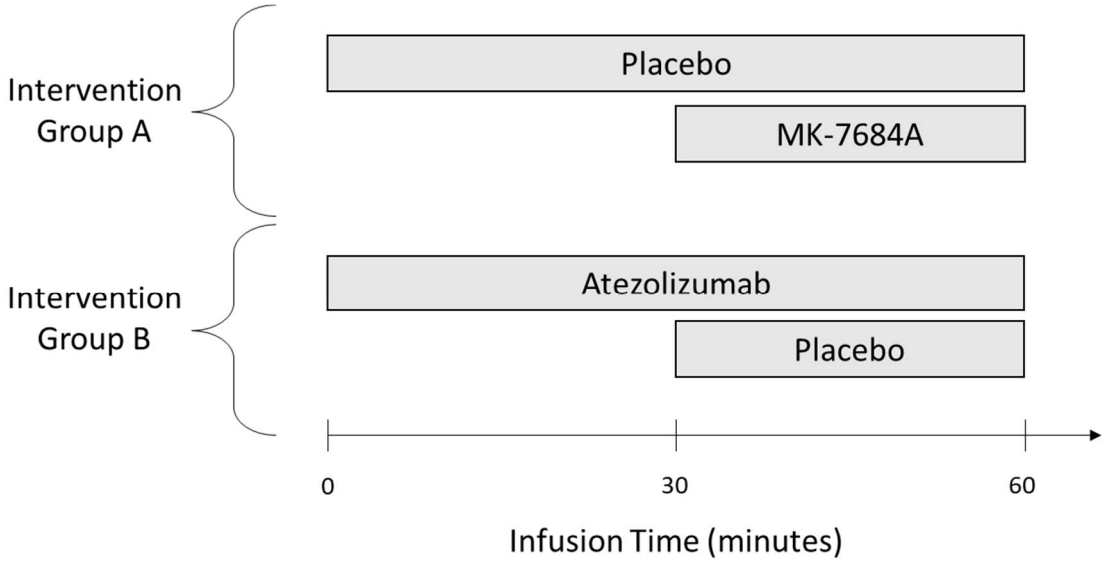
Protocol Amendment 04 implementation: For participants that have been moved from experimental arm (Arm A: MK-7684A) to the comparator arm (Arm B: atezolizumab monotherapy), the initial infusion of atezolizumab is to be administered over 60 minutes. If the first atezolizumab infusion is well tolerated, subsequent infusions can be administered over 30 minutes.

Atezolizumab will be administered Q3W starting C1D1 until any of the reasons for intervention discontinuation are met.

The initial infusion of atezolizumab is to be administered over 60 minutes. Subsequent infusions can be administered over 30 minutes.

To maintain the blinding, participants randomized to Intervention Group B will receive 60 minutes of atezolizumab infusion during Cycle 1. After 30 minutes have passed from the beginning of the atezolizumab infusion, the saline placebo, which will be administered over 30 minutes, will start (see Figure 2).

Figure 2 Intervention Blinding Schema for Initial Infusion



Additional Information for Infusions

If the IO and placebo infusions were well tolerated during Cycle 1 with no infusion reactions, placebo will no longer be required and the infusion of either atezolizumab or MK-7684A will be given over 30 minutes during Cycle 2 and beyond. If a Grade 1 infusion reaction occurred during Cycle 1, the blinding procedure should remain the same as Cycle 1. If Grade 2 infusion reaction occurred in Cycle 1 or in Cycle 2 and beyond and placebo was also needed, consultation with the Sponsor is needed to determine next step and unblinding can be considered only after Sponsor agreement and if deemed necessary for participant management. In case of Grade 3 or 4 infusion reaction, emergency unblinding is warranted.

8.1.9.1.2 Platinum/Etoposide Chemotherapy Administration

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 MK-7684A or atezolizumab infusions. Additional premedications and hydration 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 MK-7684A or atezolizumab infusions. 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 the Cockcroft-Gault formula:

- 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)]

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).

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 completion of platinum (cisplatin or carboplatin) infusions. 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%.

8.1.10 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.

Protocol Amendment 04 implementation: Per eDMC recommendation, there will be no collection of efficacy data, and the safety follow-up visit will be the final visit in this study.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

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

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

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

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study. In the event of unblinding due to a Grade 2 infusion reaction to the immunotherapy/placebo agent when placebo was also required, Sponsor consultation is required to continue on study intervention.

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

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

Protocol Amendment 04 implementation: Study has been unblinded as per the recommendation by the eDMC and discontinue the experimental arm (MK-7684A).

8.1.12 Calibration of Equipment

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

8.1.13 Tumor Tissue for Biomarker Status

A pretreatment tumor sample must be submitted before or within 4 weeks after randomization, if such sample exists, 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)

If a tumor tissue sample is not available, a cytology sample is allowed.

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

Details pertaining to tumor tissue or cytology sample 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 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 as assessed by the investigator/site.

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 e-mail 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.

Protocol Amendment 04 implementation: Participants currently on study treatment will have tumor imaging assessed locally based on site's standard of care imaging schedule. Participants currently in efficacy follow-up are considered to have completed the study and therefore should obtain imaging as per local standard of care. BICR verification of progression is no longer applicable.

8.2.1.1 Initial Tumor Scans

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

All participants are required to have brain scans 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(ses). 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 BICR, or notification by the Sponsor, or until any of these conditions are met:

- the start of new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

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.

Protocol Amendment 04 implementation: Participants currently on study treatment will have tumor imaging assessed locally based on site's standard of care imaging schedule. Participants currently in efficacy follow-up are considered to have completed the study and therefore should obtain imaging as per local standard of care. BICR verification of progression is no longer applicable.

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

Protocol Amendment 04 implementation: Participants currently on study treatment will have tumor imaging assessed locally based on site's standard of care imaging schedule. Participants currently in efficacy follow-up are considered to have completed the study and therefore should obtain imaging as per local standard of care. BICR verification of progression is no longer applicable

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 e-mail the assessment to the site and Sponsor.

Protocol Amendment 04 implementation: Participants currently on study treatment will have tumor imaging assessed locally based on site's standard of care imaging schedule. No need to submit scans to iCRO, and VOP request and central review of imaging will no longer be applicable.

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 anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

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

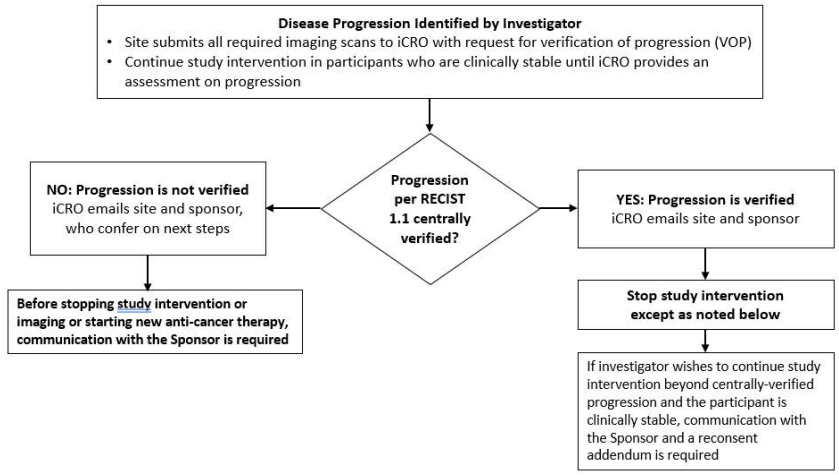
- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- Obtain scans locally per original protocol schedule
- Do not send scans to iCRO

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

- For 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, EORTC QLQ-LC13, and EuroQol EQ-5D-5L questionnaires 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.

Protocol Amendment 04 implementation: Patient-reported Outcomes Assessments will no longer be collected for any participants.

8.3 Safety Assessments

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

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

Protocol Amendment 04 implementation: Safety assessments and safety related data collection including laboratory assessments should be followed per SoA for participants who continue study therapy.

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. 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 require 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 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.

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.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 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 procedures can be conducted up to 72 hours before dosing.

Please refer to Appendix 7 for country-specific requirements.

8.3.6 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted at every protocol treatment cycle 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(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
    - Etoposide, cisplatin, or carboplatin: 180 days
    - Blinded study intervention (MK-7684A or atezolizumab): 5 months
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.7 Performance Assessments

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 PS as specified in the SoA (Section 1.3). ECOG PS should be completed prior to dose administration.

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

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

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

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

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

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

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 causes 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 Sections 5.1 and 8.3.6, 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 the investigator 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 10.

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

Table 10 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting 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

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
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. 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). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

- An overdose of Sponsor's product, as defined in Section 8.5.
- 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 MK-7684A by 3 times (ie, 300%). No specific information is available on the treatment of overdose of MK-7684A. In the event of overdose, MK-7684A should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To further evaluate immunogenicity and exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of ADA and PK are currently planned for investigational agents as shown in the SoA (Section 1.3). Blood samples will be obtained to measure PK of investigational agents in the serum. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other clinical studies with these investigational agents, it may be decided to discontinue or reduce further sample collection in this study.

Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis may be performed to characterize PK parameters (CL, V) and evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. PK

data may also be used to explore the E-R relationships for antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

Protocol Amendment 04 implementation: PK and ADA sampling will no longer be collected for any participants.

8.6.1 Blood Collection for PK

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. PK samples should be drawn according to the PK collection schedule in the SoA (Section 1.3).

8.6.2 Blood Collection for Anti-drug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. Anti-drug antibody samples should be drawn according to the ADA collection schedule in the SoA (Section 1.3). Simultaneous PK sampling is required for interpretation of ADA analysis.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for genetic analysis
- Blood for ctDNA analysis
- Tumor tissue

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the Laboratory Manual. Please refer to Appendix 7 for country-specific requirements.

Protocol Amendment 04 implementation: Biomarker samples will no longer be collected for any participants.

8.8.1 Planned Genetic Analysis Sample Collection

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

not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

Please refer to Appendix 7 for country-specific requirements.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover samples listed in Section 8.8, Biomarkers (including any extracted material from samples)

8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room 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.

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/Vaccination Visit

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.

Protocol Amendment 04 implementation: The final visit in the study will be the safety follow-up visit. No further monitoring for efficacy and survival follow-up is required.

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.

Protocol Amendment 04 implementation: Safety follow-up visit will be the final visit in the study.

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 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, withdrawal of consent, death, or 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.

Protocol Amendment 04 implementation: Efficacy follow-up visits are not required. Participants currently on study treatment will have the safety follow-up visit as the final visit. Participants currently in efficacy follow-up are considered to have completed the study and should obtain imaging and further oncological care as per local standard of care.

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.

Protocol Amendment 04 implementation: Survival follow-up contacts are not required. Participants currently on study treatment will have the safety follow-up visit as the final visit. Participants currently in survival follow-up are considered to have completed the study.

8.11.5 Vital Status

Protocol Amendment 04 implementation : There will be no collection of vital status for participants. Participants currently on study treatment will have the safety follow-up visit as the final visit.

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

9 STATISTICAL ANALYSIS PLAN

At implementation of Amendment 05, the below changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Those benefiting from atezolizumab, but unable to access it as SOC outside the study, may continue on study and receive treatment with atezolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Standard safety reporting should, however, continue, as applicable.
- Participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).

Existing protocol content is retained for historical reference.

Protocol Amendment 04 implementation: based on recommendations of the eDMC following the interim efficacy/safety analysis (data cutoff 04-JUN-2024) which showed that the primary endpoint of overall survival met the pre-specified futility criteria, the study was unblinded, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants on MK-7684A treatment will be offered the option to move to the comparator arm (Arm B: atezolizumab monotherapy) for the remainder of the study. The prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study. There will be no further analyses for efficacy and ePRO endpoints collected from participants after IA cutoff date.

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

9.1 Statistical Analysis Plan Summary

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

Protocol Amendment 04 implementation: the prespecified final analysis of the study described in the SAP will not be performed. Information regarding planned final analysis in Section 9 is being retained for historical purposes. Safety analysis will be performed at the end of the study. There will be no further analyses of efficacy and ePRO endpoints collected from participants after IA cutoff date.

Study Design Overview	This is a Phase 3, randomized, double-blind, active-controlled, multisite study of MK-7684A combined with etoposide/platinum chemotherapy followed by MK-7684A compared to atezolizumab combined with etoposide/platinum chemotherapy followed by atezolizumab in the first-line treatment of ES-SCLC.
Treatment Assignment	Approximately 450 participants will be randomized in a 1:1 ratio between 2 treatment groups: (1) the MK-7684A in combination with etoposide/platinum arm and (2) the atezolizumab in combination with etoposide/platinum arm. Stratification factors are: • ECOG performance status at Baseline (0 vs. 1) • LDH at Baseline (≤ ULN vs > ULN) • Liver metastases at Screening: Yes or No • Brain metastases at Screening: Yes or No This is a randomized double-blind study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT) PRO: Full Analysis Set (FAS)
Primary Endpoints/Hypotheses	Overall survival (OS)
Secondary Endpoints/Hypotheses	• PFS per RECIST 1.1 by BICR • ORR per RECIST 1.1 assessed by BICR • DOR per RECIST 1.1 assessed by BICR • Safety and tolerability • ePROs

Statistical Methods for Key Efficacy Analyses	The primary and secondary hypothesis will be evaluated by comparing MK-7684A in combination with etoposide/platinum to atezolizumab in combination with etoposide/platinum on OS and PFS using stratified log-rank tests. Estimation of the hazard ratio (HR) will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% confidence intervals for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.
Interim Analyses	CCI [redacted]
Multiplicity	

Sample Size and Power	The planned sample size is approximately 450 participants. CCI [redacted]

9.2 Responsibility for Analyses/In-house Blinding

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

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

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

Protocol Amendment 04 implementation: following eDMC review of data at IA, the study was unblinded.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary

- **Overall Survival (OS)**

  OS is defined as the time from randomization to death due to any cause.

Secondary

- **Progression-free survival (PFS)**

  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.

- **Objective Response Rate (ORR)**

  The ORR is defined as the percentage of participants who achieve a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 as assessed by BICR.

- **Duration of Response (DOR)**

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

9.4.2 Safety Endpoints

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

9.4.3 Patient-reported Outcome Endpoints

The following secondary PRO endpoints will be evaluated as described in Section 4.2.2.3 and analyzed as described in Section 9.6.3:

- Change from baseline in Global Health Status/QoL scale (EORTC QLQ-C30 Items 29 and 30)
- Physical functioning scale (EORTC QLQ-C30 Items 1 through 5)
- Single-item symptom scales: cough (EORTC QLQ-LC13 Item 31), chest pain (EORTC QLQ-LC13 Item 40), and dyspnea (EORTC QLQ-C30 Item 8)

Time-to-true deterioration (TTD) in

- Global Health Status/QoL scale (QLQ-C30 items 29-30)
- Single-item symptom scales: cough (QLQ-LC13 item 31), chest pain (QLQ-LC13 item 40), and dyspnea (QLQ-C30 item 8)
- Physical functioning scale (QLQ-C30 items 1-5)

Based on prior literature [Osoba, D., et al 1998] [King, M. T. 1996], a 10-point or greater worsening from baseline for each scale represents a clinically relevant deterioration. TTD is defined as the time to first onset of 10 or more (out of 100) deterioration from baseline in a given scale/subscale/item and confirmed by a second adjacent 10 or more deterioration from baseline.

CCI [redacted]

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The analyses of efficacy endpoints are based on the intention-to-treat (ITT) population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study intervention for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Populations

The PRO analyses are based on the PRO Full Analysis Set (PRO FAS) Population, defined as all randomized participants who have at least one PRO assessment available for the specific endpoint and have received at least one dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. If there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses, and events in each stratum. Details regarding the pooling strategy will be pre-specified in the sSAP, prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

9.6.1.1 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The hypotheses of treatment difference in survival will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single covariate for treatment will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.2 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (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.

CCI

Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS

9.6.1.3 Objective Response Rate (ORR)

The stratified Miettinen and Nurminen's method will be used for the comparison of ORR between 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to the analysis. Additional supportive unstratified analyses may also be provided. A sensitivity analysis will be performed for the comparison of ORR based on investigator's assessment.

The point estimate of ORR will be provided by treatment group, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

9.6.1.4 Duration of Response (DOR)

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis. Censoring rules for DOR are summarized in Table 12.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. CCI [redacted]

Table 12 Censoring Rules for DOR

CCI [redacted]

9.6.1.5 Analysis Strategy for Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 13.

Table 13 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participant last known to be alive
Key Secondary Analyses			
PFS per RECIST 1.1 by BICR	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• CCI [redacted] censoring rule • CCI [redacted] • CCI [redacted] .
Abbreviations: BICR=blinded independent central review; ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.			

CCI [redacted]

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3 based on the observed proportions of participants with an event. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Tier 1 Events

Safety parameters or adverse events of special interest (AEOSI) that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical

significance. AEOSI that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Finally, the addition of MK-7684A to etoposide/platinum treatments included in the study is not anticipated to be associated with any new safety signals. Therefore, there are no Tier 1 events expected in this study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method.

Membership in Tier 2 requires that at least 10% of participants in any treatment group show the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥1% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE that is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥1% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3-5 AE		X
	Any Serious AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity shift, vital signs)		X
Abbreviations: AE=adverse event; CI=confidence interval; SOC=system organ class.			

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

This section describes the planned analyses for the PRO endpoints.

Mean Change from Baseline

The time point for the mean change from baseline will be determined based on blinded data review prior to the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the Global Health Status/QoL scale (EORTC QLQ-C30 Items 29 and 30), Physical functioning scale (EORTC QLQ-C30 Items 1 through 5), cough (EORTC QLQ-LC13 Item 31), chest pain (EORTC QLQ-LC13 Item 40), dyspnea (EORTC QLQ-C30 Item 8) and EQ-5D-5L visual analog scale, a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger [Liang, K-Y. and Zeger, S. L. 2000] will be applied, with the PRO score as the response variable, and treatment, time, treatment by time interaction, and stratification factors used for randomization (See Section 6.3.2) as covariates. The treatment difference in terms of least square (LS) mean change from baseline will be estimated from this model

together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and post-baseline time point.

Time-to-True Deterioration (TTD)

For the TTD endpoint defined in Section 9.4.3, the Kaplan-Meier method will be used to estimate the TTD curve for each treatment group. The estimate of median time to deterioration and its 95% confidence interval will be obtained from the Kaplan-Meier estimates. The treatment difference in TTD will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling and with a single treatment covariate will be used to assess the magnitude of the treatment difference (ie, HR). The HR and its 95% CI will be reported. The same stratification factors used for randomization (See Section 6.3.2) will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

The approach for the TTD analysis will be based on the assumption of non-informative censoring. The participants who do not have deterioration on the last date of evaluation or do not have a second PRO assessment to confirm deterioration will be censored. Table 15 provides censoring rule for TTD analysis.

Table 15 Censoring Rules for Time-to-True Deterioration

Scenario	Outcome
Deterioration documented	Event observed at time of assessment (first deterioration)
Ongoing or discontinued from study without confirmed deterioration	Right censored at time of last assessment
No baseline assessments	Right censored at treatment start date

9.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age), baseline characteristics, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Protocol Amendment 04 implementation: the prespecified final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study. The subsections below are retained for reference.

The eDMC will serve as the primary reviewer of the results of the IA (analyses) and will make recommendations for discontinuation of the study or modification to the executive oversight committee of the Sponsor. If the eDMC recommends modifications to the design of

the protocol or discontinuation of the study, this executive oversight committee and potentially other limited Sponsor personnel may be unblinded to the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded study team. Additional logistic details will be provided in the eDMC Charter.

Treatment-level results of the IA will be provided by the unblinded statistician to the eDMC. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol or statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.7.1 Efficacy Interim Analyses

CCI [redacted]

CCI [redacted]

Table 16 Summary of Interim and Final Analyses Strategy

CCI [redacted]

9.7.2 Safety Interim Analyses

CCI [redacted]

CCI [redacted]

9.8 Multiplicity

The study strictly controls type I error at 0.025 1-sided CCI [redacted]

CCI [redacted]

Figure 4 Multiplicity Diagram for Type I Error Control

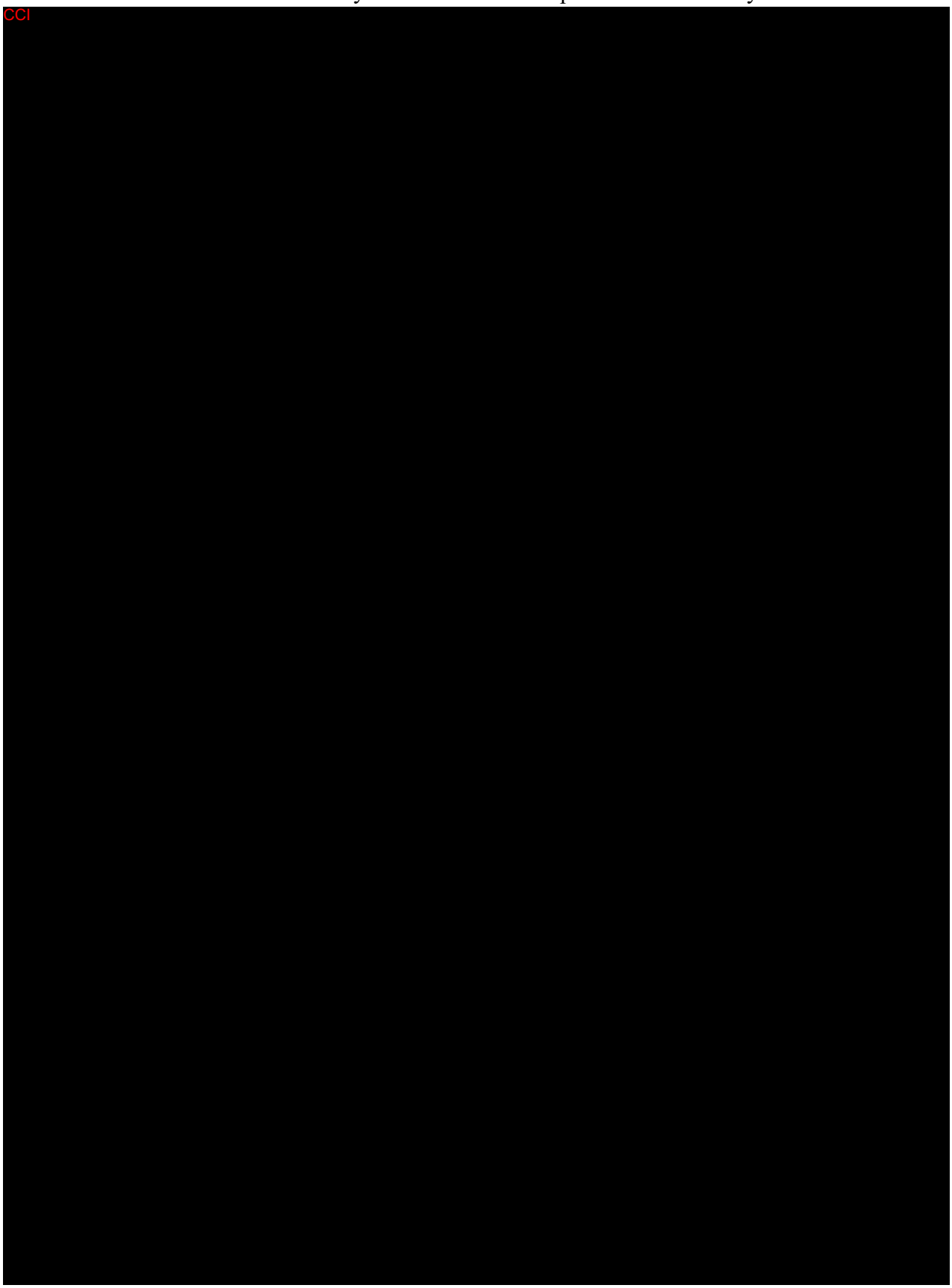
CCI [redacted]

9.8.1 Overall Survival

CCI [redacted]

Table 17 Efficacy Boundaries and Properties for OS Analyses

CCI



CCI

CCI

9.8.2 Progression-free Survival

CCI

Table 18 Efficacy Boundaries and Properties for PFS Analysis

CCI

9.8.3 Safety Analyses

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. eDMC review of efficacy data to assess the overall risk/benefit to study participants will not require a

multiplicity adjustment typically associated with a planned efficacy IA. CCI [redacted]

9.9 Sample Size and Power Calculations

The study will randomize approximately 450 subjects in a 1:1 ratio into the experimental arm of MK-7684A in combination with etoposide/platinum and the control arm of atezolizumab in combination with etoposide/platinum. OS is primary endpoint for the study, with PFS as the secondary endpoint.

CCI [redacted]

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for OS, PFS and ORR (with a nominal 95% CI) will be estimated and plotted within each category CCI

CCI

CCI

The subgroup analyses for PFS and OS will be conducted using an unstratified Cox model, and the subgroup analyses for ORR will be conducted using the unstratified M&N method.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles in which the participant receives the study medication infusion (see Section 8.6). Summary statistics will be provided on the extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

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), Regulation (EU) 536/2014, 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 their 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 their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 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 Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the

retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 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 19 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Results must be reviewed by the investigator or qualified designee and found to be acceptable before each dose of study intervention.
- Laboratory safety tests will be performed within 72 hours of dosing.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 19 Protocol-required Clinical Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices[a]: MCV MCH % Reticulocytes	WBC count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
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			
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)			

Laboratory Assessments	Parameters
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.
Other Screening Tests	• FSH (as needed in WONCBP only) • Serology (HIV antibody, HIV RNA[g], HBsAg, anti-HBc, 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)

aPTT=activated partial thromboplastin time; ALT=alanine aminotransferase; anti-HBc=Total hepatitis B core antibody; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CrCl=creatinine clearance; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; 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 time; PTT=partial prothrombin time; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; 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] 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. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Manual.

[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 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- 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.

10.3.3 Definition of SAE

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

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

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

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

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

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

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

10.3.4 Additional Events Reported 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 the cancer under study).
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/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 IRB/IEC.

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

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

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the 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 Contraceptive 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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

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3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
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10.7 Appendix 7: Country-specific Requirements

CCI

[redacted]

CCI [redacted]

10.7.3 France

Section 1.3 Schedule of Activities

Pregnancy testing must be performed at each cycle during treatment as well as at the end of study intervention.

HBV, HCV, and HIV testing at screening is mandatory.

Section 5.2 Exclusion Criteria

Exclusion Criterion: Participant has a known history of HIV infection. HIV testing is required for participants.

Exclusion Criterion: Participant has a known history of hepatitis B or hepatitis C infection. Hepatitis B and C testing is required for participants.

10.7.4 Germany

Section 5.2 Exclusion Criteria

Exclusion Criterion: Participant has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required for participants.

Exclusion Criterion: hepatitis B and C testing is required for participants.

Section 6.5.1 Rescue Medications and Supportive Care

Live vaccines must not be administered for 90 days after the last dose of study intervention.

Legally Acceptable Representative protocol sections

In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.7.5 Ireland

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.6 Italy

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.7 Japan

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[redacted]

10.7.8 Portugal

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.9 Romania

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 5.2 Exclusion Criteria

Exclusion Criterion: Participant has a known history of HIV infection. HIV testing is required for participants.

Exclusion Criterion: Participant has a known history of hepatitis B or C infection. Hepatitis B and C testing is required for participants.

10.7.10 United Kingdom

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10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All Participants as Treated
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CD112	cluster of differentiation 112
CD155	cluster of differentiation 155
CD226	cluster of differentiation 226
CI	confidence interval
CL	clearance
C_{max}	maximum serum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CSF	colony-stimulating factor

Abbreviation	Expanded Term
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
CTFG	Clinical Trial Facilitation Group
CTR	Clinical Trials Regulation
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRAE(s)	drug-related adverse event(s)
DSP	diastolic blood pressure
E-R	exposure-response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eDMC	external Data Monitoring Committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer13
EOT	end-of-treatment

Abbreviation	Expanded Term
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
ESMO	European Society for Medical Oncology
ES-SCLC	extensive-stage small cell lung cancer
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA(s)	interim analysis(ses)
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

Abbreviation	Expanded Term
iCRO	imaging CRO
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IWG	International Working Group
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LLN	lower limit of normal
M&N	Miettinen and Nurminen
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability

Abbreviation	Expanded Term
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
Necl5	nectin-like protein 5
NSCLC	non–small cell lung cancer
NDA	New Drug Application
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over-the-counter
PBPK	physiologically based PK
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
po	orally
PR	partial response
PRO	patient-reported outcome
PS	performance status
PTT	partial thromboplastin time
PVR	poliovirus receptor
PVRL-2	poliovirus receptor ligand-2
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QoL	quality of life

Abbreviation	Expanded Term
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	relapse-free survival
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SCLC	small cell lung cancer
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
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
T3	triiodothyronine
T4	thyroxine
TIGIT	T-cell immunoglobulin and immunoreceptor tyrosine based inhibitory motif
TIL	tumor-infiltration lymphocytes
TNBC	triple negative breast cancer
TPS	tumor proportion score
TTD	time-to-true deterioration
UC	urothelial carcinoma
ULN	upper limit of normal
UTN	Universal Trial Number

Abbreviation	Expanded Term
Vc	central volume of distribution
VAS	Visual Analog Scale
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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