Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-Blind Study of MK-7684 with Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab Monotherapy as First Line Treatment for Participants With PD-L1 Positive Metastatic Non-Small Cell Lung Cancer (KEYVIBE-003)
NCT number:	NCT04738487
Document Date:	29-JAN-2025

TITLE PAGE

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Protocol Title: A Phase 3, Multicenter, Randomized, Double-Blind Study of MK-7684 with Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab Monotherapy as First Line Treatment for Participants With PD-L1 Positive Metastatic Non-Small Cell Lung Cancer (KEYVIBE-003)

Protocol Number: 003-06

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	NCT04738487
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WHO	NA
UTN	U1111-1291-5552
IND	147424

Approval Date: 29 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 06	29-JAN-2025	The Sponsor has decided to discontinue treatment with MK-7684A because the study did not meet the prespecified criteria for OS and based on lack of efficacy observed in other studies.
Amendment 05	11-OCT-2024	To update the primary endpoint to OS only and to change PFS to a powered secondary endpoint based on external study data.
Amendment 04	08-NOV-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Other minor updates were also made during this amendment.
Amendment 03	21-MAR-2022	To increase the sample size and revise the statistical analysis plan to include primary hypotheses testing for OS and PFS in participants with PD-L1 TPS ≥50%.
Amendment 02	16-APR-2021	This amendment is specific to Japan to address recommendations from Japan's regulatory authority regarding inclusion and exclusion criteria.
Amendment 01	28-FEB-2021	The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated to align with the USPI as requested by the FDA.
Original Protocol	19-OCT-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendment:

The Sponsor has decided to discontinue treatment with MK-7684A because the study did not meet the prespecified criteria for OS and based on lack of efficacy observed in other studies.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1, Protocol Summary	Participants receiving MK 7684A will be transitioned to pembrolizumab.	The Sponsor has decided to discontinue treatment with MK-7684A because the study did not meet the prespecified criteria for OS and based on lack of efficacy observed in other studies.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1, Protocol Summary	A brief summary of new data from MK-7684A studies was added.	To provide context for the discontinuation of the MK-7684A clinical program.
Section 1.1, Synopsis	Added pembrolizumab row to the study interventions table for all participants.	Refer to rationale for Section 1 for the discontinuation of the MK7684A clinical program.
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, Key Statistical Considerations	• This study is closed to enrollment. This study has enrolled 1264 participants. • This study will be unblinded. • The estimated duration of study was updated from 6 years to 5 years. • Participants receiving MK-7684A will be transitioned to pembrolizumab. • Pembrolizumab can be sourced locally or centrally. • Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.	Refer to rationale for Section 1 for the discontinuation of the MK7684A clinical program.

Section Number and Name	Description of Change	Brief Rationale
	• Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally. • PK/ADA samples will no longer be collected. • Biomarker FBR samples will no longer be collected. • ePROs will no longer be collected. • Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned. • 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. • The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted. • Selected analyses of safety and endpoints will be performed at the end of the study. • There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable. • Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4). • Participants may enroll in an extension study, if available. - Participation in this study is ended when the participant is consented for an extension study.	

Section Number and Name	Description of Change	Brief Rationale
	- The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study. - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.	
Section 6.1, Study Intervention(s) Administered	Table 4: added pembrolizumab row for all participants.	Refer to rationale for Section 1 for the discontinuation of the MK7684A clinical program.

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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.

Upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- This study is closed to enrollment. This study has enrolled 1264 participants.
- This study will be unblinded.
- The estimated duration of study was updated from 6 years to 5 years.
- Participants receiving MK-7684A will be transitioned to pembrolizumab.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker FBR samples will no longer be collected.
- ePROs will no longer be collected.
- Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned.
- 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.
- The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted.

- Selected analyses of safety and endpoints will be performed at the end of the study.
- There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-Blind Study of MK-7684 with Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab Monotherapy as First Line Treatment for Participants With PD-L1 Positive Metastatic Non-Small Cell Lung Cancer (KEYVIBE-003)

Short Title: MK-7684 with Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab Monotherapy for PD-L1 Positive Metastatic NSCLC (KEYVIBE-003)

Acronym: KEYVIBE-003

Hypotheses, Objectives, and Endpoints:

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

In males and females with PD-L1 positive (TPS ≥1%) metastatic NSCLC who are 18 years of age or older and are treatment-naïve in the metastatic setting:

Primary Objective	**Primary Endpoint**
• Objective: To compare MK-7684A to pembrolizumab alone with respect to OS • Hypothesis (H1): MK-7684A is superior to pembrolizumab alone with respect to OS in participants with PD-L1 TPS ≥50%	OS: Defined as the time from randomization to the date of death due to any cause.
Secondary Objectives	**Secondary Endpoints**
• Objective: To compare MK-7684A to pembrolizumab alone with respect to OS • Hypothesis (H3): MK-7684A is superior to pembrolizumab alone with respect to OS in participants with PD-L1 TPS ≥1% • Hypothesis (H5): MK-7684A is superior to pembrolizumab alone with respect to OS in participants with PD-L1 TPS 1% to 49%	• OS
• Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR. • Hypothesis (H2): MK-7684A is superior to pembrolizumab alone with respect to PFS per RECIST 1.1 by BICR in participants with PD-L1 TPS ≥50%. • Hypothesis (H4): MK-7684A is superior to pembrolizumab alone with respect to PFS per RECIST 1.1 by BICR in participants with PD-L1 TPS ≥1%	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS 1% to 49%	• PFS

• Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR. • Hypothesis (H6): MK-7684A is superior to pembrolizumab alone with respect to ORR per RECIST 1.1 by BICR in participants with PD-L1 TPS ≥1%	• OR: Defined as a confirmed CR or PR
• Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS ≥50% and in participants with PD-L1 TPS 1% to 49%	• OR
• Objective: To evaluate DOR per RECIST 1.1 as assessed by BICR for MK-7684A compared to pembrolizumab alone in participants with PD-L1 TPS ≥50%, in participants with PD-L1 TPS 1% to 49% and in participants with PD-L1 TPS ≥1%	• DOR: For participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
• Objective: To evaluate the mean change from baseline (at randomization) in global health status/QoL, physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A compared to pembrolizumab alone in participants with PD-L1 TPS ≥50%, in participants with PD-L1 TPS 1% to 49% and in participants with PD-L1 TPS ≥1%	• Change from baseline in the following scales/items: • Global health status/QoL score (EORTC QLQ-C30 items 29 and 30) • Physical functioning score (EORTC QLQ-C30 items 1-5) • Role functioning score (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items 6 and 7) • Dyspnea score (EORTC QLQ-C30 item 8) • Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)

• Objective: To evaluate the TTD in global health status/QoL, physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A compared to pembrolizumab alone in participants with PD-L1 TPS ≥50%, in participants with PD-L1 TPS 1% to 49% and in participants with PD-L1 TPS ≥1%	• TTD: Defined as the time from baseline to the first onset of a ≥10-point decrease from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline. If the first deterioration is at the last patient-reported outcomes assessment timepoint (in the current database lock), then no confirmation is required. In the following scales/items: • Global health status/QoL score (EORTC QLQ-C30 items 29 and 30) • Physical functioning score (EORTC QLQ-C30 items 1-5) • Role functioning score (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items 6 and 7) • Dyspnea score (EORTC QLQ-C30 item 8) • Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)
• To evaluate the safety and tolerability for MK-7684A compared to pembrolizumab alone	• AEs • Discontinuations of study intervention due to an AE

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Non-small cell lung cancer
Population	Adult participants with metastatic NSCLC (TPS ≥1%) who are candidates for first-line treatment
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	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 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 1246 participants will be randomized in the study, as described in Section 9.

Intervention Groups and Duration:

Arm Name	**Intervention Name**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Regimen/ Treatment Period/ Vaccination Regimen**	**Use**
Arm 1	MK-7684A	MK-7684 200mg + pembrolizumab 200mg/ 20 mL vial	200 mg/ 200 mg	IV Infusion	q3w up to 35 cycles	Test Product
Arm 2	Pembrolizumab	25 mg/ml	200 mg	IV infusion	q3w up to 35 cycles	Comparator
All participants	Pembrolizumab	25 mg/ml	200 mg	IV infusion	q3w	Test Product

IV = Intravenous; Q3W = Every 3 weeks

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

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study for approximately 3 years from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening period of up to 28 days, each participant will be receiving assigned study intervention for approximately 2 years. After the end of treatment each participant will be followed for 1 year. After screening, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who complete study intervention after receiving 35 administrations of MK-7684A or pembrolizumab, and participants who attain a complete response and stop study intervention may be eligible for up to 17 additional administrations of MK-7684A or pembrolizumab (approximately 1 year) upon experiencing disease progression. 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. After the end of treatment, each participant will be followed for the occurrence of AEs, SAEs, and other reportable safety events. In addition, all participants will be followed for overall survival until death, withdrawal of consent, the end of the study, or enrollment into an extension study.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants: No

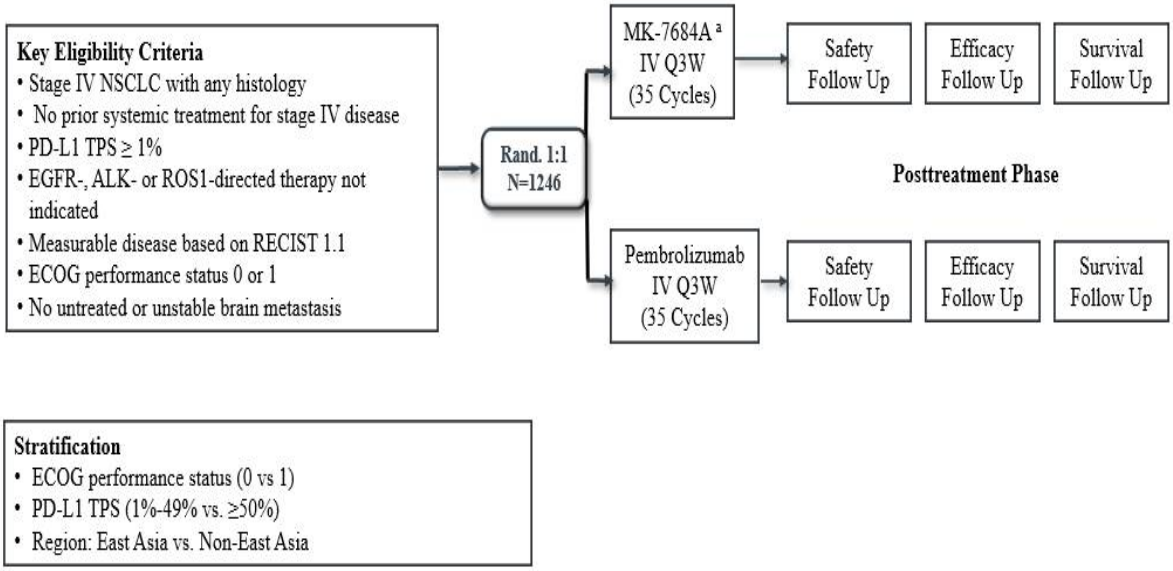
A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

1.2.1 Initial Treatment Phase

The Initial Treatment study design is depicted in Figure 1.

Figure 1 Initial Treatment Schema

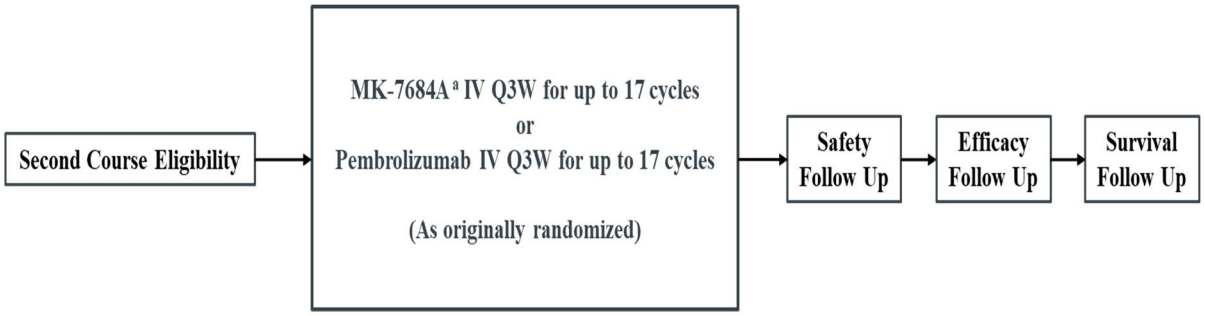


[a] MK-7684A is a coformulation of 200 mg MK-7684 and 200 mg pembrolizumab
Abbreviations: ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; IV=intravenous; NSCLC=non-small cell lung cancer; Q3W=every 3 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1; ROS=reactive oxygen species; TPS=tumor proportion score

1.2.2 Second Treatment Course

The Second Treatment Course study design is depicted in Figure 2.

Figure 2 Second Treatment Course Schema



[a] MK-7684A is a coformulation of 200 mg MK-7684 and 200 mg pembrolizumab
Abbreviation: IV=intravenous; Q3W=every 3 weeks.

1.3 Schedule of Activities

1.3.1 Initial Treatment Phase

Table 1 Study Schedule of Activities – Initial Treatment Phase

									Post-treatment			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At DC**	**30 Days post last dose**	**Every 12 weeks**	**Every 12 weeks**	
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
Administrative Procedures												
Informed consent	X											Documented informed consent must be obtained before any protocol-specific screening procedures are performed. Reconsent required to continue study intervention after PD.
Informed consent for FBR	X											This is optional for the participant.
Inclusion/exclusion criteria	X											
Participant identification card	X	X										Update with randomization number at C1D1.
Demographic and medical history	X											
Prior and concomitant medications review	X	X	X	X	X	X	X	X	X			Prior concomitant medications received within 30 days before the first dose of study intervention through 30 days after the last dose of study intervention (or 90 days if used to treat an SAE) will be recorded.
Treatment randomization		X										Dose within 3 days of randomization.
Clinical Procedures/Assessments												
Complete physical examination	X							X				To be performed within 7 days before start of study intervention.
Directed physical examination		X	X	X	X	X	X		X			
Height	X											
Vital signs, weight	X	X	X	X	X	X	X	X	X			Predose and as clinically indicated.
12-lead ECG	X											
ECOG performance status	X	X	X	X	X	X	X	X	X			Performed within 7 days of beginning of C1 and prior to each treatment administration.

									Post-treatment			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At DC**	**30 Days post last dose**	**Every 12 weeks**	**Every 12 weeks**	
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
Study Intervention Administration		X	X	X	X	X	X					
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Subsequent antineoplastic therapy status								X	X	X	X	All anticancer therapy will be recorded until time of death or termination of Survival Follow-up. If a clinic visit is not feasible, follow-up information may be obtained via documented contact.
Survival status		◄	―	―	―	―	―	―	―	►	X	Refer to Sections 8.11.5.3 & 8.11.6. Updated survival status may be requested by the Sponsor at any time during the course of the study.
Imaging												
Brain imaging	X											Required for all participants at screening. See Section 8.2.1.2 for other requirements. If MRI is contraindicated or cannot be performed, CT of the head with IV contrast is acceptable.
Bone imaging	X											Required at screening for participants with history of bone metastases. See Section 8.2.1.2 for other requirements.

									Post-treatment			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At DC**	**30 Days post last dose**	**Every 12 weeks**	**Every 12 weeks**	
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
Tumor imaging and response assessment (chest, abdomen, and pelvis)	X	X						X		X		Schedule should be followed regardless of treatment delays. Perform imaging at Screening, then Q9W (63 ±7 days) from randomization through Week 54, and Q12W (±7 days).thereafter until BICR confirmed PD or initiation of a new anticancer regimen. If imaging was obtained within 4 weeks before treatment DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule. Note: On-study brain or bone imaging should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).
Laboratory Assessments												
Pregnancy test for WOCBP	X	X	X	X	X	X	X	X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours prior to each dose of study intervention.
Hepatitis B and C and HIV serology	X											Required at baseline if mandated by local health authority.
CBC with differential	X		X	X	X	X	X	X	X			Performed locally within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C5, etc.).
Chemistry Panel	X		X	X	X	X	X	X	X			
Urinalysis	X					X	X	X	X			
PT/INR and aPTT/PTT	X											Screening samples collected within 10 days prior to first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Thyroid function (T3, T4, and TSH)	X		X		X		X	X	X			Should be performed at screening and Day 1 of every other cycle starting from C2. Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

									Post-treatment			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**At DC**	**30 Days post last dose**	**Every 12 weeks**	**Every 12 weeks**	
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
Tumor Tissue Collection												
Newly obtained/archival tissue sample for PD-L1 analysis and other biomarkers	X											May use archival tissue sample obtained before screening as part of the participant's SOC.
Patient-reported Outcomes												
CCI [redacted]												Perform every cycle through C17, then every other cycle through C35 (ie, C1-17, C19, C21, C23, C25, C27, C29, C31, C33, and C35). If the Treatment DC 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. Perform ePROs in the order listed in the SoA (CCI [redacted] first).
Pharmacokinetics												
CCI [redacted]												PK and ADA samples should be drawn within 24 hours prior to study intervention administration. Additional postdose (end-of-infusion) PK only samples will be drawn within 10 minutes after end of infusion and the flushing time at C1 and C8.
Biomarkers												
CCI [redacted]												Collect before study intervention. May be performed either on C1D1 or on the next scheduled blood draw on C2D1, only one sample needs to be collected.
												Collect at Screening, predose on Day 1 of C1, C2, C3, C4, C5, C7, C10, C13, C16, C19, then on Day 1 of every 4 cycles. Collect also at EOT and Efficacy Follow Up. During follow-up, if a clinic visit is not feasible, blood for ctDNA collection will not be collected.

AE = adverse event; ADA = antidrug antibodies; aPTT = activated partial thromboplastin time; CBC = complete blood count CT = computed tomography; CXDY= Cycle X Day Y; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; EOT = end of treatment; ePRO = electronic patient-reported outcome; FBR = future biomedical research; β-HCG = β human chorionic gonadotropin; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic(s); PT = prothrombin time; QXW = every X weeks; RNA = ribonucleic acid; SAE = serious adverse event; ; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; SoA = schedule of activities; SOC = standard of care.

[a] CCI [redacted]

1.3.2 Second Course Treatment Phase

Table 2 Study Schedule of Activities – Second Course Treatment Phase

Study Period:	**Treatment Cycle = 21 days**						**End of Treatment**	**Post-Treatment**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.**
								30 days post last dose	**Every 12 weeks post-DC**	**Every 12 weeks**	
Scheduling Window (Days):		**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
Administrative Procedures											
Eligibility Criteria	X										
Concomitant Medication Review	X	X	X	X	X	X	X	X			Concomitant medications received within 30 days before the first dose of study intervention in the Second Course through 30 days after the last dose of study intervention (or 90 days if used to treat an SAE) will be recorded.
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Complete Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X		X			
Vital Signs and Weight	X	X	X	X	X	X	X	X			Predose and if clinically indicated.

Study Period:	**Treatment Cycle = 21 days**						**End of Treatment**	**Post-Treatment**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up** **30 days post last dose**	**Efficacy Follow-up** **Every 12 weeks post-DC**	**Survival Follow-up** **Every 12 weeks**	**Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.**
Scheduling Window (Days):		**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
ECOG Performance Status	X	X	X	X	X	X	X				Performed within 7 days of beginning of C1 and prior to each treatment administration.
Study Intervention Administration	X	X	X	X	X	X					
Poststudy Anticancer Therapy Status							X	X	X	X	
Survival Status	◄	———	———	———	———	———	———	———	———	X	Refer to Sections 8.11.5.3 & 8.11.6. Updated survival status may be requested by the Sponsor at any time during the course of the study.
Laboratory Procedures/Assessments											
Pregnancy Test for WOCBP	X	X	X	X	X	X	X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours prior to each dose of study intervention.
PT/INR and aPTT/PTT	X										Required at C1. Additional testing as needed for participants on anticoagulation therapy.
CBC with Differential	X	X	X	X	X	X	X	X			Performed locally within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C1, C5, etc.).
Chemistry Panel	X	X	X	X	X	X	X	X			
Urinalysis	X				X	X	X	X			
Thyroid function (T3, T4, and TSH)	X	X		X		X		X			Should be performed at C1 and Day 1 of every other cycle starting from C2. Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

Study Period:	**Treatment Cycle = 21 days**						**End of Treatment**	**Post-Treatment**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.**
								30 days post last dose	**Every 12 weeks post-DC**	**Every 12 weeks**	
Scheduling Window (Days):		**±3**	**±3**	**±3**	**±3**	**±3**		**+14**	**±7**	**±14**	
Imaging											
Tumor Imaging (Chest, Abdomen, and Pelvis)	◄	———	———	———	———	———	———	———	———	►	Schedule should be followed regardless of treatment delays. Images are for investigator assessment of disease status only and should not be sent to the iCRO. If tumor image documenting PD is older than 28 days prior to entry into Second Course, a new image must be obtained and reviewed by the site prior to treatment. Perform Q9W through EOT and Q12W thereafter, until confirmed PD or initiation of a new anticancer regimen. The window for imaging is ±7 days. If imaging was obtained within 4 weeks before DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule. Note: On-study brain or bone imaging should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

AE = adverse event; aPTT = activated partial thromboplastin time; CXDY= Cycle X Day Y; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FT4 = free thyroxine; MRI = magnetic resonance imaging; PT/INR = prothrombin time/international normalized ratio; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

2 INTRODUCTION

MK-7684A is a coformulation of MK-7684 and pembrolizumab. MK-7684 is a humanized, antagonist mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. The coformulation of MK-7684A is being developed as a cancer immunotherapeutic with the potential to be used to increase benefit to patients with metastatic NSCLC.

2.1 Study Rationale

The global incidence of lung cancer was 2.1 million cases in 2018, resulting in an estimated 1.8 million deaths [International Agency for Research on Cancer 2018]. NSCLC represents approximately 85% of all lung cancers [National Cancer Institute 2020]. Of patients with NSCLC, tumor histology is approximately 46% adenocarcinoma, 16% squamous, and the remainder "not otherwise specified" [Sulpher, J. A., et al 2013], though histology varies somewhat by geographic region. At the time of diagnosis, approximately 80% of patients in the US with lung cancer have locally advanced or metastatic disease that is not amenable to surgical resection, and the 5-year relative survival for patients with metastatic lung cancer is only approximately 6% [National Cancer Institute 2020a].

The therapeutic landscape in metastatic NSCLC was dramatically changed with approvals of immunotherapy agents, particularly immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway (pembrolizumab, nivolumab, and atezolizumab) for both treatment-naïve and previously treated disease, irrespective of histology. KEYNOTE-024 and KEYNOTE-042 established pembrolizumab monotherapy as first-line therapy for patients with metastatic NSCLC whose tumors express PD-L1 with a TPS ≥50% or (in some countries) TPS ≥1%, respectively, with no *EGFR* or *ALK* genomic tumor aberrations [Brahmer, J. R., et al 2017] [Mok, T. S. K., et al 2019]. Likewise, the positive results from KEYNOTE-189 and KEYNOTE-407 led to the approval of pembrolizumab in combination with pemetrexed and platinum chemotherapy for first-line treatment of patients with metastatic nonsquamous NSCLC whose tumors have no *EGFR* or *ALK* genomic tumor aberrations and pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for first-line treatment of patients with metastatic squamous NSCLC [Gandhi, L., et al 2018] [Gandhi, L., et al 2018a] [Gandhi, L., et al 2018b] [Paz-Ares, L., et al 2018]. (See Section 2.2.3.2 for details on the results of these studies.)

Despite the significant progress made with the introduction of checkpoint inhibitors either as monotherapy or in combination with chemotherapy, most patients with metastatic NSCLC will still succumb to the disease within 3 years of their diagnosis [Smyth, M. J., et al 2016] [Kruger, S., et al 2019] [Martins, F., et al 2019]. Therefore, there is still substantial unmet medical need for novel therapies that can potentiate the clinical benefit of IO therapies, extend the benefit to a broader population of patients, and further improve treatment response and survival in patients with metastatic NSCLC; of particular interest to both patients and physicians is the development of chemotherapy-free options in biomarker selected patient population.

Thus far, the therapeutic benefit of immunotherapy was largely achieved by blocking the inhibitory receptors PD-1/PD-L1 or CTLA-4. However, it is believed that concurrent or sequential blockade of novel checkpoints within the intricate immune regulatory network could further improve the efficacy of immunotherapy. Recently, dual immunotherapies (IO/IO) either alone or in combination with chemotherapy have also been approved for the treatment of advanced NSCLC [Hellmann, M. D., et al 2019] [Reck, M., et al 2020]. Several other IO/IO combinations and regimens including PD-1/PD-L1 checkpoint inhibitors are under investigation or have been approved recently.

Enhancing the proven anti-PD-1 immune stimulatory mechanism through a novel mechanism of action is therefore an attractive scientific concept. One avenue for further investigation is the T-cell stimulatory/inhibitory network TIGIT (PVRIG/TACTILE)-CD226 (DNAM1) pathway. Antibody blockade of TIGIT, a T-cell inhibitory receptor within this network, has shown promising activity in preclinical cancer models, as well as in clinical studies. MK-7684 is a humanized IgG1 that blocks the inhibitory checkpoint receptor TIGIT expressed on T cells and NK cells. Preclinical data has demonstrated that anti-mTIGIT antibodies on the mIgG2a backbone (with high affinity FcγR binding) are more efficacious than anti-mTIGIT antibodies on the IgG1 D265A backbone (without FcγR binding) as single agents and in combination with mDX400 (anti-mPD-1 antibody) in multiple preclinical tumor models. Therefore, a strong rationale exists to develop anti-PD-1 and anti-TIGIT combination therapies. MK-7684 is being developed in combination with pembrolizumab in advanced solid tumors. Preliminary data for MK-7684-001, a Phase 1 study of MK-7684 as monotherapy or coformulated with pembrolizumab (known as MK-7684A) in advanced solid tumors demonstrates promising activity in PD-1 naïve and PD-1 refractory NSCLC (see Section 2.2.3.1).

Recent data from CITYSCAPE, a Phase 2 double-blind study of anti-TIGIT antibody tiragolumab plus atezolizumab versus placebo plus atezolizumab demonstrated a median PFS and OS of 5.6 months versus 3.9 months and 23.2 months versus 14.5 months, respectively in the ITT population after 2.5 years of median follow-up. The combination of tiragolumab plus atezolizumab reduced the risk of disease worsening or death (PFS) by 38% and improved overall response rates (38.8% vs. 20.6%) compared with atezolizumab alone. This improvement was driven predominantly in the participants with PD-L1 TPS ≥50% [F. Hoffmann-La Roche Ltd 2021] [Rodriguez-Abreu, D., et al 2020]. However, TIGIT and PD-1 are co-expressed, and data demonstrate improvements in outcomes in all PD-L1 expression subgroups (see Section 2.2.3.1).

In conclusion, there remains a great unmet need to develop newer, more efficacious, well tolerated therapies for the treatment of patients with metastatic NSCLC. The goal of this study is to enhance the approved anti-PD-1 immune stimulatory mechanism of pembrolizumab monotherapy in patients with TPS ≥1% NSCLC through combining it with a novel immune modulatory mechanism of action, blockade of TIGIT. This Phase 3 study is designed to assess the efficacy and safety of MK-7684A versus pembrolizumab monotherapy in participants with NSCLC who are treatment-naïve with a PD-L1 TPS ≥1% and PD-L1 TPS ≥50%. This is an attractive scientific concept and by achieving the primary endpoint of this study, an improved chemotherapy-free clinical therapeutic approach would be created that would significantly enhance presently available options.

2.2 Background

Refer to the MK-7684A IB and the pembrolizumab IB for detailed background information on MK-7684 and pembrolizumab, respectively.

2.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. TILs can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

2.2.1.1 MK-7684 Background

MK-7684 is a humanized, antagonist mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. This human IgG1 antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase benefit to patients with various tumor types.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T cells, NK cells, and NKT cells. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an immunoglobulin tail tyrosine-like phosphorylation motif, and an immunoreceptor tyrosine-based inhibitory motif.

TIGIT forms part of a co-stimulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [Levin, S. D., et al 2011]. Whereas CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T cells, Tregs, NK cells, and NKT cells [Dardalhon, V., et al 2005] [Stanietsky, N., et al 2013]. CD155/PVR (poliovirus receptor) and CD112/PVRL-2 (poliovirus receptor-related 2) are 2 nectin family members that are widely expressed both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types, and has been found to be induced by Ras activation and genotoxic stress [Carlsten, M., et al 2007] [Hirota, T., et al 2005] [Masson, D., et al 2001] [Soriani, A., et al 2009] [Stanietsky, N., et al 2009].

In addition, TIGIT is highly co-expressed with PD-1 on both CD4+ and CD8+ TILs including Tregs, in mouse and human tumors, and has been reported to be co-expressed with PD-1 and Tim-3 on the TILs with the most exhausted phenotype [Chauvin, J. M., et al 2015] [Johnston, R. J., et al 2014]. Furthermore, enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody. We

hypothesize, therefore, that combining MK-7684 with pembrolizumab will offer substantially augmented antitumor efficacy.

2.2.1.2 Pembrolizumab Background

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

2.2.2 Preclinical and Clinical Studies

2.2.2.1 MK-7684 Preclinical Studies

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

2.2.2.2 Pembrolizumab Preclinical and Clinical Trials

Refer to the IB for preclinical and clinical study data for pembrolizumab.

2.2.3 Ongoing Clinical Studies

2.2.3.1 MK-7684 Ongoing Clinical Trials

Study MK-7684-001

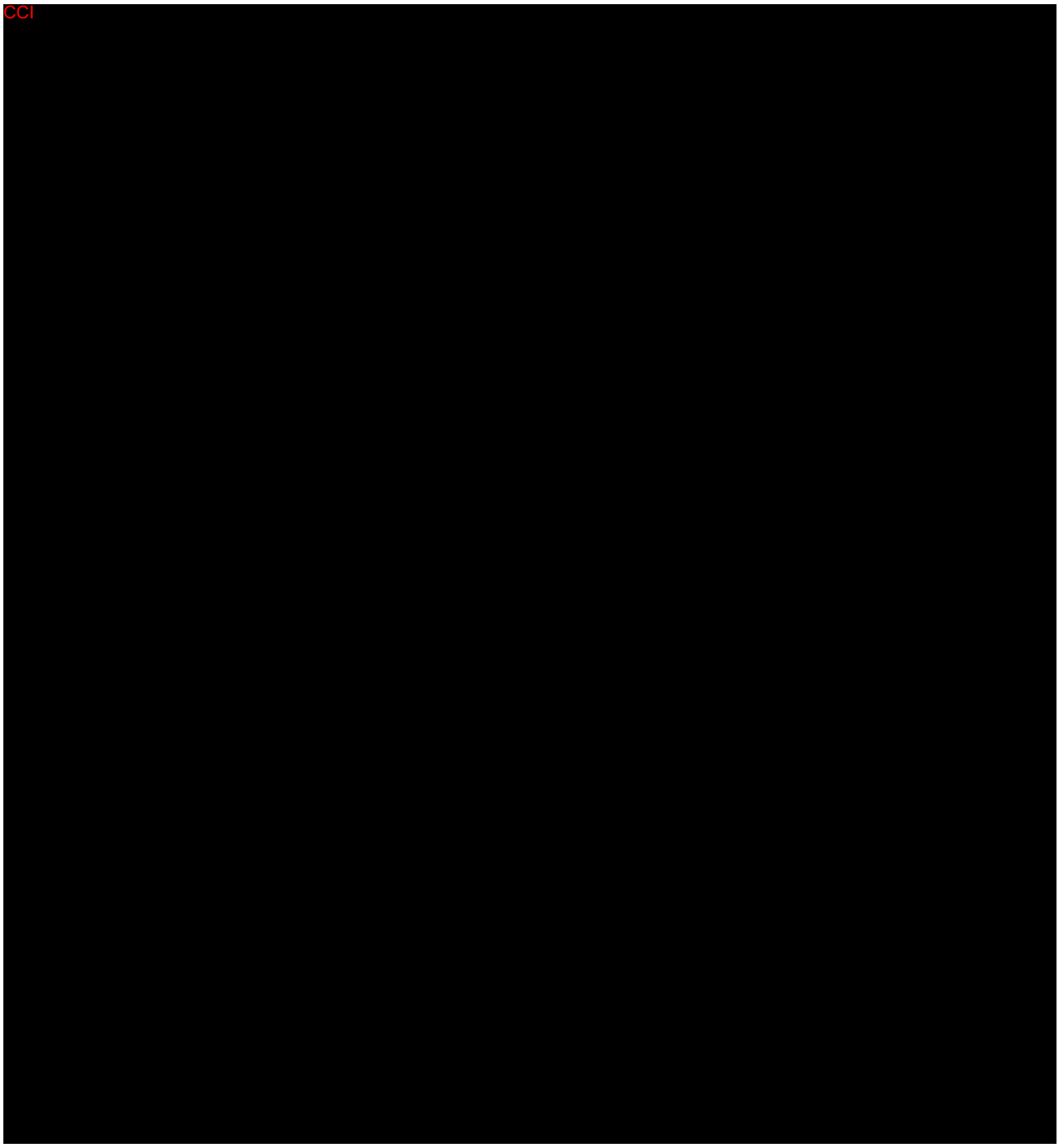
MK-7684-001 is a safety, efficacy, and PK study examining MK-7684 as monotherapy and in combination with pembrolizumab or with pembrolizumab plus chemotherapy in adults with metastatic solid tumors for which there are no available therapies expected to convey clinical benefit. This study consists of a Part A dose escalation phase and a Part B expansion phase.

Part A of this study is a dose escalation and confirmation phase to evaluate safety and estimate the RP2D for MK-7684 monotherapy or in combination with pembrolizumab plus chemotherapy.

CCI

[redacted]

CCI



A recent analysis (18-NOV-2021) of the data from this Phase 1 study also showed that MK-7684 plus pembrolizumab was well tolerated and demonstrated antitumor activity in participants with advanced solid tumors, including in participants with advanced NSCLC [Niu, J., et al 2022]. Additional details regarding other ongoing studies of MK-7684 and specific benefits and risks for participants in the MK-7684 studies may be found in the IB.

2.2.3.2 Pembrolizumab Ongoing Clinical Trials

Numerous interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications, as well as in hematological malignancies.

In the NSCLC development program, pembrolizumab monotherapy for PD-L1 positive NSCLC was approved in the first-line setting based on KEYNOTE-024 and KEYNOTE-042 and approved in the second-line setting based on KEYNOTE-001 and KEYNOTE-010. KEYNOTE-189 and KEYNOTE-407 led to the approval of pembrolizumab in combination with chemotherapy for first-line treatment of metastatic NSCLC irrespective of PD-L1 status, while KEYNOTE-021 established the benefits of the combination. For further details, refer to the IB.

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.

Despite the substantial improvement in PFS and OS observed with pembrolizumab monotherapy compared with SOC platinum-doublet chemotherapy in KEYNOTE-042 in participants with metastatic TPS ≥1% NSCLC, an unmet medical need remains for safe and efficacious treatments offering added benefit for this patient population. CCI

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

In males and females with PD-L1 positive (TPS ≥1%) metastatic NSCLC who are 18 years of age or older and are treatment-naïve in the metastatic setting:

Primary Objective	**Primary Endpoint**
• Objective: To compare MK-7684A to pembrolizumab alone with respect to OS • Hypothesis (H1): MK-7684A is superior to pembrolizumab alone with respect to OS in participants with PD-L1 TPS ≥50%	OS: Defined as the time from randomization to the date of death due to any cause.
Secondary Objectives	**Secondary Endpoints**
• Objective: To compare MK-7684A to pembrolizumab alone with respect to OS • Hypothesis (H3): MK-7684A is superior to pembrolizumab alone with respect to OS in participants with PD-L1 TPS ≥1% • Hypothesis (H5): MK-7684A is superior to pembrolizumab alone with respect to OS in participants with PD-L1 TPS 1% to 49%	• OS
• Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR. • Hypothesis (H2): MK-7684A is superior to pembrolizumab alone with respect to PFS per RECIST 1.1 by BICR in participants with PD-L1 TPS ≥50%. • Hypothesis (H4): MK-7684A is superior to pembrolizumab alone with respect to PFS per RECIST 1.1 by BICR in participants with PD-L1 TPS ≥1%	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

• Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS 1% to 49%	• PFS
• Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR. • Hypothesis (H6): MK-7684A is superior to pembrolizumab alone with respect to ORR per RECIST 1.1 by BICR in participants with PD-L1 TPS ≥1%	• OR: Defined as a confirmed CR or PR
• Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS ≥50% and in participants with PD-L1 TPS 1% to 49%	• OR
• Objective: To evaluate DOR per RECIST 1.1 as assessed by BICR for MK-7684A compared to pembrolizumab alone in participants with PD-L1 TPS ≥50%, in participants with PD-L1 TPS 1% to 49% and in participants with PD-L1 TPS ≥1%	• DOR: For participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

• Objective: To evaluate the mean change from baseline (at randomization) in global health status/QoL, physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A compared to pembrolizumab alone in participants with PD-L1 TPS ≥50%, in participants with PD-L1 TPS 1% to 49% and in participants with PD-L1 TPS ≥1%	• Change from baseline in the following scales/items: • Global health status/QoL score (EORTC QLQ-C30 items 29 and 30) • Physical functioning score (EORTC QLQ-C30 items 1-5) • Role functioning score (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items 6 and 7) • Dyspnea score (EORTC QLQ-C30 item 8) • Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)
• Objective: To evaluate the TTD in global health status/QoL, physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A compared to pembrolizumab alone in participants with PD-L1 TPS ≥50%, in participants with PD-L1 TPS 1% to 49% and in participants with PD-L1 TPS ≥1%	• TTD: Defined as the time from baseline to the first onset of a ≥10-point decrease from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline. If the first deterioration is at the last patient-reported outcomes assessment timepoint (in the current database lock), then no confirmation is required. In the following scales/items: • Global health status/QoL score (EORTC QLQ-C30 items 29 and 30) • Physical functioning score (EORTC QLQ-C30 items 1-5) • Role functioning score (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items 6 and 7) • Dyspnea score (EORTC QLQ-C30 item 8) • Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)

• To evaluate the safety and tolerability for MK-7684A compared to pembrolizumab alone	• AEs • Discontinuations of study intervention due to an AE
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

4 STUDY DESIGN

Upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- This study is closed to enrollment. This study has enrolled 1264 participants.
- This study will be unblinded.
- The estimated duration of study was updated from 6 years to 5 years.
- Participants receiving MK-7684A will be transitioned to pembrolizumab.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker FBR samples will no longer be collected.
- ePROs will no longer be collected.
- Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned.
- 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.
- The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted.
- Selected analyses of safety and endpoints will be performed at the end of the study.
- There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.

- Participation in this study is ended when the participant is consented for an extension study.
- The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
- For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multisite, double-blind study of MK-7684A versus pembrolizumab. Participants with metastatic Stage IV NSCLC with no previous treatment for Stage IV disease and PD-L1 positive tumors (TPS ≥1%) will be enrolled in the study. This study will be conducted in participants with measurable disease in whom *EGFR*-, *ALK*-, or *ROS1*-targeted therapy is not indicated.

Participants will be stratified by:

- ECOG performance status (0 versus 1)
- PD-L1 TPS (1% to 49% versus ≥50%)
- Geographic Region: East Asia versus Non-East Asia

Initial Treatment Phase

Overall, approximately 1246 participants will be randomized 1:1 to:

- MK-7684A (Arm 1)
- Pembrolizumab (Arm 2)

No treatment crossover is planned for the study. The study design is shown in Figure 1 (Initial Treatment) and Figure 2 (Second Course).

Participants will be evaluated with radiographic imaging to assess response to study intervention every 9 weeks from randomization through 54 weeks, then every 12 weeks until confirmed PD or initiation of a new anticancer regimen. All imaging obtained during the initial treatment phase of the study will be submitted to the iCRO for BICR, which will assess the images using RECIST 1.1 for determination of PFS, OR, and DOR. Tumor imaging showing site-assessed PD should be submitted immediately for verification by BICR

before study intervention discontinuation. Once disease progression is verified centrally, subsequent imaging (if acquired) should not be submitted to the iCRO.

Participants receiving MK-7684A or pembrolizumab may be permitted to continue study intervention beyond PD verified by BICR per RECIST 1.1 if the treating investigator considers that the participant may experience clinical benefit with continued treatment and the participant is clinically stable and tolerating study intervention; however, this decision must be approved by the Sponsor. If the investigator recommends continuation of study intervention beyond disease progression, the participant or legally acceptable representative will be asked to provide a new documented informed consent.

Survival follow-up will continue after PD, discontinuation of study intervention, and the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.

AE monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the NCI CTCAE, version 5.0.

Treatment with MK-7684A or pembrolizumab will continue for up to 35 treatment cycles, or until a discontinuation criterion is met (see Section 7.1). Treatment may be discontinued for participants with a confirmed CR (see Section 6.6.2).

CCI [redacted] for this study. Details regarding interim analyses are provided in Section 9.7.

Second Course Treatment Phase

Participants who stop MK-7684A or pembrolizumab after receiving 35 treatment cycles of MK-7684A or pembrolizumab or participants who stop study intervention after attaining a confirmed CR may be eligible for the Second Course. See Section 6.6.3 for details.

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

4.2 Scientific Rationale for Study Design

This study is being conducted to compare the efficacy and safety of MK-7684A to pembrolizumab monotherapy in participants with metastatic NSCLC in a randomized, double-blinded fashion.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study has OS as the primary endpoint. PFS, OR and DOR will be secondary efficacy endpoints.

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

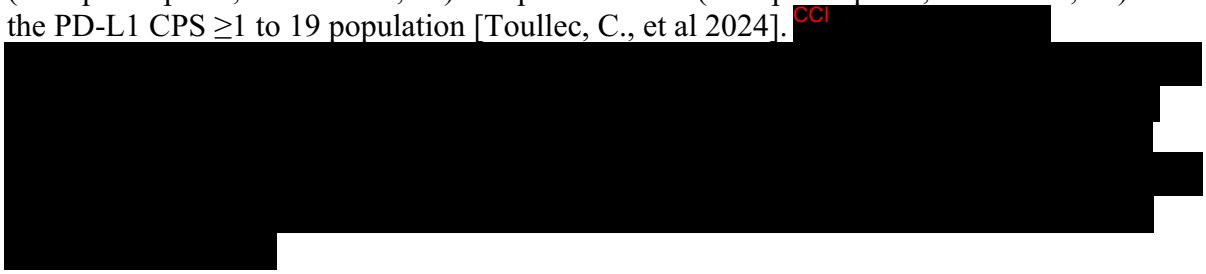
PFS and OR are secondary endpoints and acceptable measures of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable benefit/risk profile. The use of BICR and RECIST 1.1 to assess PFS and OR is considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to study intervention assignment to minimize bias in response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression as determined by central review will be communicated to the site.

As of Amendment 5, OS in the PD-L1 TPS ≥50% population is the only primary endpoint. PFS and OS in the TPS ≥1% population were moved to secondary endpoints.

PFS was moved from a primary to a secondary endpoint based on external data from SKYSCRAPER-01, a Phase 3 study evaluating patients with newly diagnosed metastatic NSCLC and PD-L1 TPS ≥50% and treated with atezolizumab + placebo compared to atezolizumab + tiragolumab (TIGIT mAb). Recent data from the study demonstrated that the PFS endpoint was not met at the final prespecified analysis and delayed survival benefit was observed though not statistically significant (HR=0.81, 95% CI: 0.63, 1.03) [F. Hoffmann-La Roche Ltd. 2023].

OS in the PD-L1 TPS ≥50% population was selected based on these NSCLC results from SKYSCRAPER-01 and data from the Phase 2 study KEYVIBE-005 in participants with advanced solid tumors treated with vibostolimab and pembrolizumab. The KV-005 study demonstrates potential benefit in the most IO sensitive tumor populations, such as dMMR endometrial cancer [Toullec, C., et al 2024] and in tumors with higher PD-L1, including in the HNSCC and cervical cancer cohorts [Leary, A., et al 2024] [Toullec, C., et al 2024].

In participants with HNSCC and PD-L1 CPS ≥20, the ORR by investigator review was 41% (7/17 participants; 95% CI: 18, 67) compared to 21% (5/24 participants; 95% CI: 7, 42) in the PD-L1 CPS ≥1 to 19 population [Toullec, C., et al 2024]. CCI



Altogether, the NSCLC Phase 3 data and advanced solid tumor Phase 2 data indicate potential greater benefit with anti-TIGIT antibodies in tumors with higher PD-L1 and provide the rationale for the primary endpoint change to OS in the PD-L1 TPS ≥50% population.

The secondary efficacy endpoint of DOR based on RECIST 1.1 and assessed by BICR is accepted by regulatory authorities and the oncology community.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

4.2.1.2 Safety Endpoints

Safety parameters 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.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

4.3 Justification for Dose

4.3.1 MK-7684A

Based on the totality of available data, including preliminary clinical PK, pharmacodynamics, safety, and efficacy from the dose escalation and confirmation portion of Study MK-7684-001, the selected dose of MK-7684 is 200 mg, to be administered as MK-7684A (a coformulation with 200 mg pembrolizumab) as a 30-minute IV infusion Q3W.

CCI

[redacted]

4.3.2 Pembrolizumab

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including OS 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.

For more information, please refer to the pembrolizumab IB.

4.3.3 Maximum Dose Exposure for This Study

The maximum dose/exposure of MK-7684A allowed in this study is 200 mg MK-7684/ 200 mg pembrolizumab for up to 2 years (35 treatment cycles) of initial treatment (Section 6.6.2) and an additional 1 year (17 cycles) for Second Course (Section 6.6.3).

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg IV Q3W for up to 2 years (35 treatment cycles) of initial treatment (Section 6.6.2) and an additional 1 year (17 cycles) for Second Course (Section 6.6.3).

4.4 Beginning and End-of-Study Definition

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

If the study includes countries in the 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 6 years (~3 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.

4.4.1 Clinical Criteria for Early Study Termination

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.

Early study termination will be the result of the criteria specified below:

1. Incidence or severity of emerging effects/clinical endpoints is such that the risk/benefit ratio for the study population as a whole is unacceptable.

2. Plans to modify or discontinue the development of the study drug

Ample notification will be provided in the event of Sponsor’s decision to no longer supply MK-7684A or pembrolizumab.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has a histologically or cytologically confirmed diagnosis of NSCLC (Stage IV: M1a, M1b, M1c, AJCC Staging Manual, version 8).

   Note: Mixed tumors will be characterized by the predominant cell type; if small cell elements are present, the participant is ineligible.

2. Has measurable disease based on RECIST 1.1, as determined by the local site assessment.

   Note: Measurable disease is defined as having at least 1 measurable lesion by CT or MRI per RECIST 1.1. Lesions that appear measurable but are situated in a previously irradiated area can be considered measurable (eligible for selection as target lesions) if they have shown documented growth since the completion of radiation.

3. Has confirmation that EGFR-, ALK-, or ROS1-directed therapy is not indicated as primary therapy (documentation of the absence of tumor-activating *EGFR* mutations [eg, DEL19 or L858R], AND absence of *ALK* and *ROS1* gene rearrangements).

   Note: If participant's tumor is known to have a predominantly squamous histology, molecular testing for *EGFR* mutation and *ALK* and *ROS1* translocations will not be required, as this is not part of current diagnostic guidelines.

4. Has provided tumor tissue that demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1%) as assessed by IHC at a central laboratory.

   Note: Assessment of PD-L1 expression must be made from provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Details pertaining to tumor tissue submission can be found in the procedures manual.

Demographics

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

6. Has an ECOG PS of 0 or 1 assessed within 7 days prior to randomization.

7. Has a life expectancy of at least 3 months.

Female Participants

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

◦ Is not a WOCBP

OR

◦ Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention.

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

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.

- 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 females 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 drugs is more stringent than the requirements above, the local label requirements should be followed.

Informed Consent

9. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

10. Has adequate organ function as defined in Table 3. Specimens must be collected within 10 days before the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

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

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal.

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

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

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.

See Appendix 7 for country specific requirements.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has a known history of an additional malignancy, except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for at least 3 years since initiation of that therapy.

   Note: The time requirement for no evidence of disease for at least 3 years does not apply to the NSCLC for which a participant is enrolled in the study. The time requirement also does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

Prior/Concomitant Therapy

2. Has received prior systemic chemotherapy or other targeted or biological antineoplastic therapy for their metastatic NSCLC.

   Note: Prior treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant or chemoradiation therapy for nonmetastatic NSCLC is allowed as long as therapy was completed at least 6 months before the diagnosis of metastatic NSCLC.

   Note: Participants must have recovered from all AEs due to previous therapies to Grade ≤1 or baseline. Participants with Grade ≤2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

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

4. Has received previous treatment with another agent targeting the TIGIT receptor pathway.

5. Has received radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

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

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

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

9. Has severe hypersensitivity (≥Grade 3) to MK-7684A or pembrolizumab and/or any of its 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 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 to the first dose of study intervention.

12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

13. Has a known history of interstitial lung disease. Lymphangitic spread of the NSCLC is not exclusionary.

14. Has an active infection requiring systemic therapy.

15. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority. See Section 10.7.1 for South Africa-specific requirements.

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

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

17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that prevents the participant from receiving platinum-doublet chemotherapy for first line NSCLC, or that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

Other Exclusions

19. If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.

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

See 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.

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 for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

Upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- This study is closed to enrollment. This study has enrolled 1264 participants.
- This study will be unblinded.
- The estimated duration of study was updated from 6 years to 5 years.
- Participants receiving MK-7684A will be transitioned to pembrolizumab.
- Pembrolizumab can be sourced locally or centrally
- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker FBR samples will no longer be collected.
- ePROs will no longer be collected.
- Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned.
- 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.
- The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted.
- Selected analyses of safety and endpoints will be performed at the end of the study.
- There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4).

- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

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 (MK-7684A and pembrolizumab) 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 intervention(s) are in Table 4.

Country-specific requirements are noted in Appendix 7.

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
Arm 1	Experimental	MK-7684A	Biological/Vaccine	Solution	MK-7684 200mg + pembrolizumab 200mg/ 20 mL vial	200 mg/ 200 mg	IV Infusion	q3w up to 35 cycles	Test Product	IMP	Central
Arm 2	Active comparator	Pembrolizumab	Biological/vaccine	Solution	25 mg/ml	200 mg	IV infusion	q3w up to 35 cycles	Comparator	IMP	Central
All participants	Experimental	Pembrolizumab	Biological/vaccine	Solution	25 mg/ml	200 mg	IV infusion	q3w	Test Product	IMP	Central

IMP = investigational medicinal product; MK-7684A = Coformulated as 200 mg MK-7684 and 200 mg pembrolizumab; 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 European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-7684A and pembrolizumab are provided in the Pharmacy Manual.

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 or pembrolizumab alone, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. ECOG performance score (0 versus 1)
2. PD-L1 TPS (1% to 49% versus ≥50%)
3. Geographic Region: East Asia versus Non-East Asia

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-7684A and pembrolizumab will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Access to the randomization schedule and unblinded results for presentation of summaries and analyses to the eDMC will be restricted to an unblinded statistician and as needed, an unblinded scientific programmer performing the analysis, who will have no other responsibilities associated with the study. Participant level PD-L1 results will be masked to the site.

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

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.

Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with MK-7684A or pembrolizumab and for other allowed dose interruptions of MK-7684A or pembrolizumab.

When participants will be 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.

6.5 Concomitant Therapy

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

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

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab or MK-7684A.
- Radiation therapy for disease control.
- Note: Palliative radiotherapy is permitted for nontarget lesions if considered medically necessary by the treating physician and upon discussion with the Sponsor.
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study, and for after the last dose of study intervention.
  Note: Killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology.
  - As needed for the prevention of emesis.
  - Premedication for IV contrast allergies.
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for COPD exacerbations.

  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent.
- In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention must be discontinued:

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 30 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.

6.5.1 Rescue Medications and Supportive Care

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

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.1.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or MK-7684A, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

6.6 Dose Modification (Escalation/Titration/Other)

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

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

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce

complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

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

Holding Study Interventions:

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

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

Restarting Study Interventions:

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to MK-7684A or Pembrolizumab

MK-7684A or pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on MK-7684A or pembrolizumab associated infusion reaction are provided Table 6.

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

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

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

MK-7684A or pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 6 weeks 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 Initial Treatment or First Course

The initial treatment or first course of MK-7684A Q3W or pembrolizumab Q3W consists of 35 treatments (approximately 2 years). Note: The number of treatments is calculated starting with the first dose.

For participants who have attained a confirmed CR and have received at least 8 doses of MK-7684A or pembrolizumab, including at least 2 doses of MK-7684A or pembrolizumab beyond the initial CR confirmation date, treatment may be stopped.

These participants may be eligible for Second Course, as described in Section 6.6.3.

6.6.3 Second Course

All participants who have SD, PR, or CR may be eligible for up to an additional 17 cycles of MK-7684A or pembrolizumab treatment based on original randomization assignment if there is BICR verification of radiographic disease progression by RECIST 1.1 after initial treatment or first course has been completed or stopped for confirmed CR, as specified in Section 6.6.2. This retreatment is the Second Course of this study.

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

1. No new anticancer treatment was administered after the last dose of study intervention
2. The participant meets all of the inclusion criteria and none of the exclusion criteria
3. The study is ongoing

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

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). In the event that 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

Upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- This study is closed to enrollment. This study has enrolled 1264 participants.
- This study will be unblinded.
- The estimated duration of study was updated from 6 years to 5 years.
- Participants receiving MK-7684A will be transitioned to pembrolizumab.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker FBR samples will no longer be collected.
- ePROs will no longer be collected.
- Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned.
- 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.
- The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted.
- Selected analyses of safety and endpoints will be performed at the end of the study.
- There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4).

- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

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 the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.4 unless the participant has withdrawn from the study (see Section 7.2).

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation 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.
- Taking any prohibited medications noted in Section 6.5.
- Radiographic disease progression outlined in Section 8.2.1.5 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond iCRO-verified disease progression).
- Any progression or recurrence of 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 6.6.1.

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.

7.2 Participant Withdrawal From the Study

If a participant fails to return for scheduled visits and/or if the study site is unable to contact the participant after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 7.3.

If a participant decides not to continue receiving study intervention, the participant is to be encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

Participants who withdraw consent during the study.

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

Section 8.1.9 delineates the specific procedures performed at the time of withdrawal and withdrawal from future biomedical research. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

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

Upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- This study is closed to enrollment. This study has enrolled 1264 participants.
- This study will be unblinded.
- The estimated duration of study was updated from 6 years to 5 years.
- Participants receiving MK-7684A will be transitioned to pembrolizumab.
- Pembrolizumab can be sourced locally or centrally
- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker FBR samples will no longer be collected.
- ePROs will no longer be collected.
- Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned.
- 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.
- The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted.
- Selected analyses of safety and endpoints will be performed at the end of the study.
- There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.

- Participation in this study is ended when the participant is consented for an extension study.
- The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study
- For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

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 decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study can be found in the procedures 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

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

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research 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 future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant

within 30 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. (30 days after the last dose of study intervention or 90 days if used to treat an SAE). Any new anticancer therapy started after the participant's discontinuation from initial treatment will be recorded separately. Additional information collected on this treatment will include, but is not limited to, best response and date of progression.

In addition, medications taken within 30 days of the first dose of Second Course treatment through the Second Course Safety Follow-up Visit (30 days after the last dose of study intervention or 90 days if used to treat an SAE) should be recorded.

8.1.6 Assignment of Screening Number

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

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

8.1.6.1 Treatment Eligibility Assessment Survey

A Treatment Eligibility Assessment survey will be included in this study to document the rationale for the investigator's choice for each individual participant to participate in the study rather than receive other licensed therapies. These data may be required to support reimbursement efforts for MK-7684A.

The survey will be administered using a survey software platform after participant enrollment is completed, with one survey sent to the investigator per participant enrolled in the trial.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study interventions 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.

8.1.8.1 Timing of Dose Administration

MK-7684A or pembrolizumab will be administered using 30-minute IV infusion every 3 weeks. The Pharmacy Manual contains specific instructions for MK-7684A and pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

All study treatment will be dosed on Day 1 of each 21-day cycle. After Cycle 1 Day 1, study medication may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle for administrative reasons.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Table 1 and Table 2) and Section 8.11.4.

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

8.1.9.1 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.

8.1.10 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. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

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

Once an emergency unblinding or a nonemergency unblinding that is part of the study design has taken place, the 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 should continue to be monitored in the study.

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

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

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue for Biomarker Status

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

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

  Or

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

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

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

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx kit except it is labeled IUO.

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 scans to evaluate changes in tumor burden over time, until the participant is discontinued from the study or enters the survival follow-up. The process for scan collection and transmission to the iCRO can be found in the Site Imaging Manual.

Chest, abdomen, and pelvis scans are required for all participants. CT scans are preferred over other tumor imaging methods. 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 type of scan 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. 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, MRI is preferred; however, CT scans are 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.

Additional imaging (including via other modalities, such as PET-CT, X-ray) that are obtained at an unscheduled time point to determine disease progression, and scans obtained for other reasons that capture radiologic progression based on investigator assessment, should be submitted to the iCRO. Other types of scans (eg, ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

Participant eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1. When the investigator identifies radiographic progression per RECIST 1.1, the iCRO will perform expedited verification of radiologic disease progression and communicate the results to the study site and Sponsor via email. In clinically stable participants, imaging should continue until disease progression has been verified by BICR (if initial site-assessed disease progression was not verified by BICR, each subsequent scan must be submitted to iCRO with verification of disease progression request until disease progression has been verified by BICR). Once disease progression is verified centrally, subsequent imaging (if acquired) should not be submitted to the iCRO.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to randomization. The screening images must be submitted to the iCRO for retrospective review.

Brain imaging is required for all participants at Screening. Bone imaging is required at Screening for participants with a history of bone metastases and/or for those participants with clinical indication, such as bone pain or elevated alkaline phosphatase.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days), or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), imaging should be performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator and verified by BICR, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the iCRO.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for

confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by BICR.

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

Treatment beyond BICR-verified PD per RECIST 1.1 may be permitted at the discretion of the investigator after consulting with the Sponsor and after the participant provides a new documented informed consent (see Figure 5). Participants who continue treatment beyond BICR-verified PD must continue tumor imaging assessments as described in the SoA (Section 1.3.1). Investigator assessments are to be documented on the eCRF, but scans are not to be submitted to the iCRO. Further progression and discontinuation of study intervention are to be determined by the investigator.

For participants who have unconfirmed disease progression (investigator assessment of disease progression, but BICR assessment of disease progression per RECIST 1.1 = "No"), treatment can continue at the investigator's discretion for clinically stable participants (see Section 8.2.1.5). Imaging should continue to be performed as per imaging schedule and must be submitted to the iCRO along with a VOP request until central confirmation of progression is received.

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

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

For participants who complete all 35 cycles of initial treatment or discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment, calculated from the date of randomization (see Section 8.2.1.2) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Before a participant may enter the Second Course Phase, BICR verification of radiographic disease progression must have occurred. Tumor imaging must be performed within 28 days prior to restarting treatment with MK-7684A or pembrolizumab in the Second Course. The disease progression imaging may also be used as the Second Course baseline imaging if it is within 28 days before restarting treatment and otherwise meets the baseline standards outlined in the Site Imaging Manual.

Response assessments and progressive disease in the Second Course are determined by site assessment only. No imaging from the Second Course Phase should be provided to the

central vendor, except for the Second Course Phase baseline scan if this scan is also the final imaging for the Initial Treatment Phase.

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) through the end of treatment and every 12 weeks (84 days ±7 days) thereafter, or more frequently if clinically indicated. Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. The schedule should be followed regardless of treatment delays.

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

For participants who complete all 17 cycles of Second Course treatment or discontinue Second Course treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±7 days) until the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR 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(s) are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

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

- If participant is clinically stable, continue study intervention per protocol
    - 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
  Note: the reconsent addendum may be signed any time after investigator-assessed progression is identified, but must be signed prior to starting study intervention after verification of disease progression is provided by the iCRO

- Obtain scans locally per original protocol schedule

- Do not send scans to iCRO

Figure 5 illustrates the decision process involving verification of disease progression for participants.

For the purpose of this decision process, lack of clinical stability is defined as:

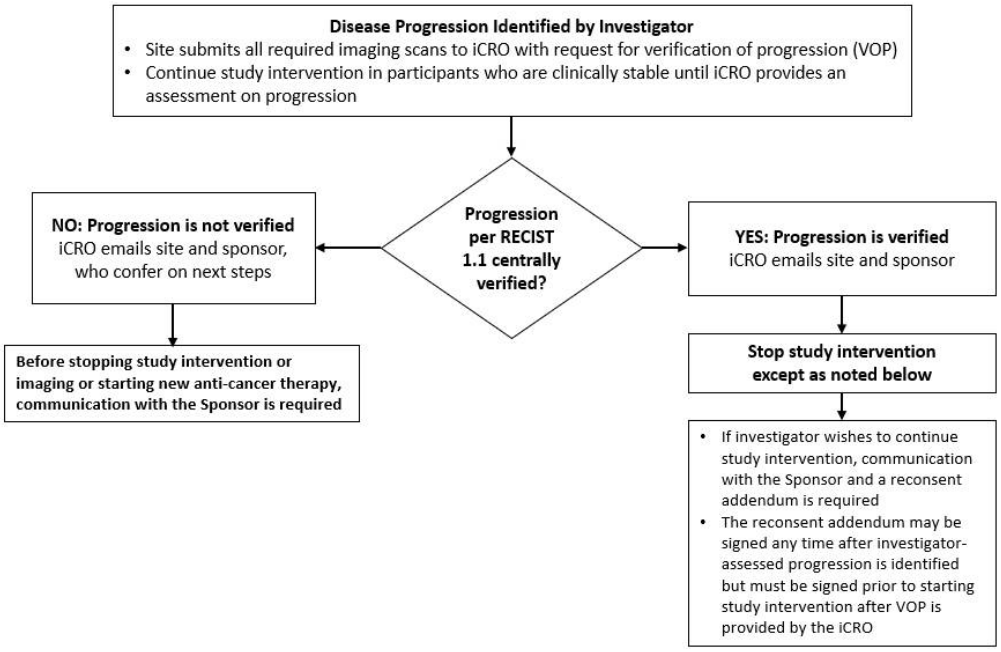
- Unacceptable toxicity

- Clinical signs or symptoms indicating clinically significant disease progression

- Decline in performance status

- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 5 Decision Making Process When Progression Observed by Investigator



iCRO = imaging CRO; RECIST = Response Evaluation Criteria in Solid Tumors.

8.2.2 Quality-of-Life Assessments

8.2.2.1 Patient-reported Outcomes

The CCI [redacted], and CCI [redacted] questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: CCI [redacted] and lastly CCI [redacted]. The questionnaires should be administered prior to dosing every cycle through Cycle 17, then every other cycle through Cycle 35, at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit. If the treatment discontinuation visit occurs 30 days from the last dose of study intervention, at the time of the mandatory safety follow-up visit, the ePROs do not need to be repeated.

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

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided in the Central Laboratory Manual.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

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

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

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

- Temperature (oral, tympanic, rectal, axillary, skin, or temporal artery); pulse rate; respiratory rate; and BP will be assessed.

- Weight will also be measured and recorded.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2 and the schedule is provided in the SoA (Section 1.3).

8.3.5 Pregnancy Testing

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

Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.

Pregnancy testing (urine or serum as required by local regulations) should be conducted 120 days after the last dose of MK-7684A or pembrolizumab.

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.

8.3.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG PS at screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3). See Appendix 8 for details.

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

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

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

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

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

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

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

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

- All AEs from the time of intervention randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/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 8.3.5, 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 7.

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

Table 7 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: -participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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) 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 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 lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less

than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

For the purpose of this study, an overdose of MK-7684A will be defined as any dose exceeding 3 times or 300% the prescribed dose. For pembrolizumab, an overdose will be defined as any dose ≥1000 mg. No specific information is available on the treatment of overdose of pembrolizumab or MK 7684A. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Serum MK-7684 and Pembrolizumab

CCI [redacted]

8.6.1.1 Blood Collection for PK

CCI [redacted]

8.6.1.2 Blood Collection for Antidrug Antibodies

CCI [redacted]

8.7 Pharmacodynamics

CCI [redacted].

8.8 Biomarkers

8.8.1 Planned Genetic Analysis Sample Collection

8.9 Future Biomedical Research Sample Collection

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 allocation/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.

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

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

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of study intervention.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
- For WOCBP, a serum pregnancy test will be performed within 72 hours or a urine pregnancy test within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Additional pregnancy testing can be conducted if required by local regulations or clinically indicated.
- Archival tumor sample collection is not required to be obtained within 28 days before the first dose of study intervention. Newly obtained tumor tissue may be obtained according to the Procedures Manual.

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 Initial Treatment Period

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

8.11.3 Second Course Treatment Phase

See Section 6.6.3 for details concerning Second Course Treatment.

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

Participants who discontinue study treatment due to disease recurrence or start of a new anticancer therapy will have Safety Follow-up and then proceed directly to Survival Follow-up Phase as described in Section 8.11.5.

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory safety follow-up visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed.

8.11.5 Posttreatment Visit

8.11.5.1 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.

Participants who are eligible for retreatment with pembrolizumab or MK-7684A may have up to 2 safety follow-up visits: 1 after the Initial Treatment or First Course and 1 after the Second Course.

8.11.5.2 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 every 12 weeks to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab or MK-7684A according to the criteria in Section 6.6.3 will move from the Efficacy Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab.

8.11.5.3 Survival Follow-up Contacts

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

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

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

8.11.6 Survival Status

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

9 KEY STATISTICAL CONSIDERATIONS

Upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

- This study is closed to enrollment. This study has enrolled 1264 participants.
- This study will be unblinded.
- The estimated duration of study was updated from 6 years to 5 years.
- Participants receiving MK-7684A will be transitioned to pembrolizumab.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy, as monotherapy or in combination) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- Imaging scans should no longer be submitted to iCRO nor read by BICR. However, for participants who are still on study treatment and deriving clinical benefit and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker FBR samples will no longer be collected.
- ePROs will no longer be collected.
- Treatment beyond progression will no longer be offered. Any participant already receiving treatment beyond progression will be able to complete treatment as planned.
- 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.
- The futility interim analysis (IA1) was conducted. The pre-specified efficacy interim analysis (IA2) and final analysis outlined in the SAP will not be conducted.
- Selected analyses of safety and endpoints will be performed at the end of the study.
- There will be no follow-up for survival status. Participants currently in imaging follow up should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4).

- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

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 E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail PK and biomarker analyses. The ePRO analysis plan will be included in the sSAP.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, multicenter, randomized, double-blind study of MK-7684 with pembrolizumab as a coformulation (MK-7684A) versus pembrolizumab monotherapy as first line treatment for participants with PD-L1 positive (TPS ≥1%) metastatic NSCLC (KEYVIBE-003)
Treatment Assignment	Approximately 1246 participants will be randomized in a 1:1 ratio between treatment groups: (1) MK-7684A (2) pembrolizumab. Stratification factors are: • ECOG PS (0 versus 1) • PD-L1 TPS (1% to 49% versus ≥50%) • Region: East Asia vs Non-East Asia
Analysis Populations	Efficacy: ITT Safety: APaT PRO: PRO FAS
Primary Endpoints	• OS in participants with PD-L1 TPS ≥50%

Secondary Endpoints	• OS in participants with PD-L1 TPS ≥1% and PD-L1 TPS 1% to 49% • PFS per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS ≥50%, PD-L1 TPS ≥1% and PD-L1 TPS 1% to 49% • OR per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS ≥50%, PD-L1 TPS ≥1% and PD-L1 TPS 1% to 49% • DOR per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS ≥50%, PD-L1 TPS ≥1% and PD-L1 TPS 1% to 49% • ePROs: global health status/QoL score, physical functioning score, role functioning score, and dyspnea score using EORTC QLQ C30 and cough and chest pain scores using EORTC QLQ-LC13 in participants with PD-L1 TPS ≥50%, PD-L1 TPS ≥1% and PD-L1 TPS 1% to 49% • Safety and tolerability
Statistical Methods for Key Efficacy Analyses	The primary hypotheses testing for OS and the secondary hypotheses testing for PFS and OS will be evaluated by comparing the MK-7684A group to the pembrolizumab group using CCI. The HR will be estimated using a CCI Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. CCI
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events CCI
Interim Analyses	CCI

Multiplicity	CCI [redacted]
Sample Size and Power	

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 Sponsor will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an IRT.

Key aspects of blinding during interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

  OR is defined as a confirmed CR or PR per RECIST 1.1 based on BICR.

- **Duration of Response (DOR)**

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

9.4.2 Safety Endpoints

Key safety endpoints are AEs and study treatment discontinuations due to AEs. In addition, safety parameters commonly used for evaluating investigational systemic anticancer treatments, including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes, will be evaluated by clinical review. AEs will be assessed as defined by NCI CTCAE, Version 5.0. A description of safety measures is provided in Section 8.3.

9.4.3 PRO Endpoints

Key PRO endpoints include the following:

- Change from baseline in EORTC QLQ-C30 global health status/QoL score, physical functioning score, role functioning score, dyspnea score, and EORTC QLQ-LC13 cough and chest pain scores.

- TTD as measured by EORTC QLQ-C30 global health status/QoL score, physical functioning score, role functioning score, dyspnea score, and EORTC QLQ-LC13 cough and chest pain scores.

Based on prior literature [Bjordal, K., et al 2000] [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 (of 100) deterioration

from baseline in a given scale/subscale/item and confirmed by a second adjacent 10 or more deterioration from baseline. If the first deterioration is at the last PRO assessment timepoint (in the current database lock), then no confirmation is required.

CCI [redacted]

Details regarding PRO endpoints will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The analyses of the efficacy endpoints are based on the ITT population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 9.6.1.5.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be analyzed in the treatment group corresponding to the study treatment they actually received. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

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

9.5.3 Patient-reported Outcome Analysis Population

The PRO analyses are based on the 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

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

Participants will be categorized into PD-L1 TPS groups based on stratification level at randomization.

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, CCI [redacted] In the event that 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 prespecified in the sSAP prior to the database lock for the first efficacy interim analysis, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

The efficacy analyses for PFS, OR, and DOR will include documented progression events and responses that occur prior to Second Course treatment.

9.6.1.1 Overall Survival (OS)

The nonparametric Kaplan-Meier method will be used to estimate the overall survival curves in each treatment group. CCI [redacted] The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive. Additional supportive unstratified analyses may also be provided.

9.6.1.2 Progression-free Survival (PFS)

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. CCI [redacted]

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

CCI

[redacted]

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 CCI [redacted] will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to the analysis. The point estimate of ORR will be provided by treatment group, together with 95% CI using CCI [redacted]

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. CCI [redacted]

CCI [redacted]

9.6.1.5 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 10.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
OS	CCI	ITT (participants with PD-L1 TPS ≥50%)	Censored at the date participant last known to be alive
Key Secondary Analyses			
OS	CCI		Censored at the date participant last known to be alive
PFS per RECIST 1.1 by BICR			Censored according to rules in Table 8
ORR per RECIST 1.1 by BICR			Participants with missing data are considered nonresponders

BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.

9.6.2 Statistical Methods for Safety Analyses

The primary safety analyses will include only events that occur prior to Second Course Treatment.

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, discontinuation from study intervention due to an AE, and an AE resulting in death. Only point estimates by treatment group are provided.

CCI

CCI [redacted]

CIs for between treatment group differences will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. 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 (Table 11).

CCI [redacted]

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

This section describes the planned analyses for the PRO endpoints.

Change from baseline

The time point for the 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, physical functioning, role functioning, dyspnea, cough, chest pain, and, EQ-5D-5L VAS outcome a constrained longitudinal data analysis 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, the treatment by time interaction, and stratification

factors used for randomization (see Section 6.3.2) as covariates. The treatment difference in terms of 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 postbaseline time point.

Time-to-Deterioration (TTD)

The Kaplan-Meier method will be used to estimate the TTD curve for each treatment group. The estimate of median TTD 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.

9.6.4 Demographic and Baseline Characteristics

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

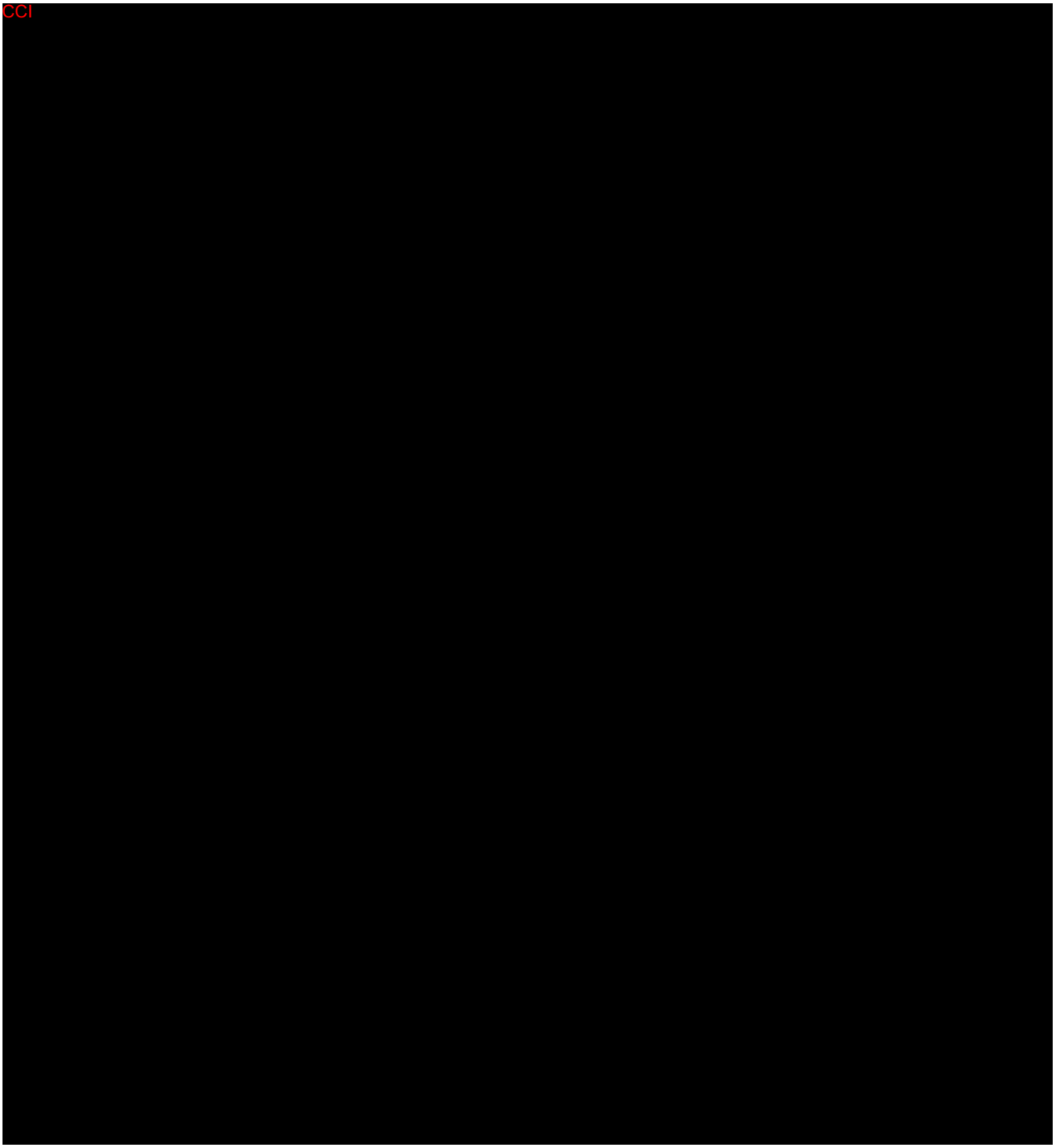
9.7 Interim Analyses

The eDMC will serve as the primary reviewer of the results of the interim analyses and will make recommendations for discontinuation of the study or modification to the EOC of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC and potentially other limited Sponsor personnel may be unblinded to the treatment-level results 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 team. Additional logistic details will be provided in the eDMC Charter.

Treatment-level results of the interim analyses 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



9.7.2 Safety Interim Analyses

The eDMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the eDMC charter. eDMC monitoring for safety will be conducted at a minimum every 6 months until such time that the eDMC determines that monitoring at a different frequency is appropriate.

9.8 Multiplicity

CCI

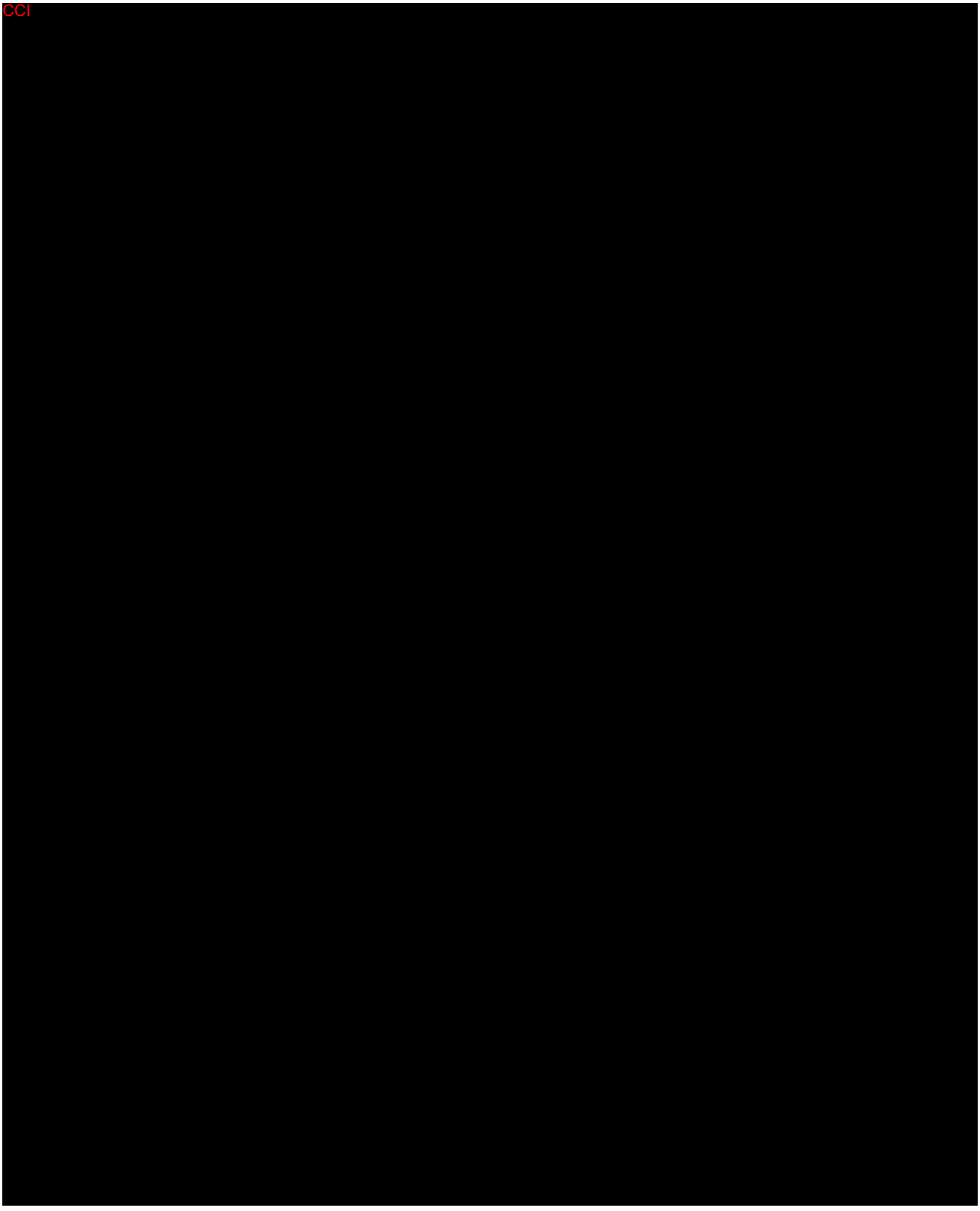
[redacted]

9.8.1 Overall Survival

CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.8.2 Progression-free Survival

CCI

[redacted]

CCI

[redacted]

9.8.3 Objective Response Rate

No initial alpha is allocated to test ORR. If superiority for all PFS and OS hypotheses (H1, H2, H3, H4 and H5) are declared, CCI

[redacted]

CCI

[redacted]

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. CCI

[redacted]

9.9 Sample Size and Power Calculations

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.10 Subgroup Analyses

CCI

[redacted]

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 intervention. 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)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee

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

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) 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 trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[a] MCH[a] %Reticulocytes[a]	WBC count with Differential[b] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)[c]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[a]	Chloride	Phosphorous[a]
	Creatinine[d]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
	TSH[e]	Free thyroxine (FT4)[e]	Lactate dehydrogenase (LDH)	Amylase
	Lipase	Triiodothyronine (Total T3)[e]		
Routine Urinalysis	• 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
Other Screening Tests	• PT/INR and aPTT/PTT[f] • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) NOTE: certain ex-US sites require testing for HIV and hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable. • Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • TB Testing (South Africa only) • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP).

FT4 = free thyroxine; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV, mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell; WOCBP = women of childbearing potential.

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. Glomerular filtration rate (GFR) (measured or calculated) or creatinine clearance can be used in place of creatinine.
e. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.
f. Performed as part of the screening assessment and as clinically 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."

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 a condition of the study).
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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

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

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

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

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

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

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

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

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

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

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

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

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

Follow-up of AE and SAE

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

10.3.6 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 nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • 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.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. d IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 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 8.9 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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10.7 Appendix 7: Country-specific Requirements

10.7.1 South Africa-specific Requirements

- Section 5.2 Exclusion Criteria

Exclusion Criterion: HIV testing is required for participants.

Exclusion Criterion: TB testing is required for participants.

10.7.2 Japan-specific Requirements

- 1.3 Schedule of Activities

Note: For the assistance to early diagnosis of pneumonitis/interstitial lung disease in study participants, the following items, such as SpO_2, CRP, KL-6, and SP-D, will be measured in this study. These items should be measured as follows:

- SpO_2 at the timing of vital sign assessment.

- CRP, KL-6, and SP-D at screening*, predose on Day 1 of every cycle, EOT, and the Safety Follow-up visit (30 days after last dose).

- *Should be measured at the timing of clinical laboratory tests (such as hematology/chemistry).

If pneumonitis/ILD occurs, regardless of causality with study intervention, an independent ILD evaluation committee will conduct adjudication of cases of the pneumonitis/ILD. For this purpose, relevant data, such as chest imaging (from the baseline to the recovery of pneumonitis/ILD) will be submitted to the Sponsor.

- Section 1.3, Section 5.2, Section 8.11.1, and Section 10.2 Appendix 2

Hepatitis B testing (HBsAg, HBsAb, HBcAb) and Hepatitis C testing (HCV RNA [qualitative]) at screening is mandatory in Japan.

- 5.1 Inclusion Criteria

    - In addition to inclusion criterion 8, to be eligible for enrollment into this study, participants in Japan must also satisfy the following requirement:

        - Female participants who stop breastfeeding at the start of the study but wish to resume breastfeeding thereafter are not eligible for enrollment in the study.

- 5.2 Exclusion Criteria

  - For participants in Japan, exclusion criterion 16 is as follows:

    - Has an active hepatitis B infection (HBsAg positive) or known history of hepatitis B infection (defined as HBsAg is negative, and HBsAb and/or HBcAb is positive) or known active hepatitis C virus infection (defined as HCV RNA [qualitative] is detected). Note: Patients who are hepatitis B surface antibody (anti-HBs) positive by vaccine are eligible.

10.7.3 Vietnam-specific Requirements

Table 19 Study Intervention Information for Vietnam

No.	Study Drug Details	Arm 1	Arm 2
1	Drug name, Dosage form, Packaging	Drug name: MK-7684A (MK-3475 and MK-7684) Dosage form: Sterile solution for IV infusion. Packaging: Each box contains one vial of 20 mL.	Drug name: MK-3475 Dosage form: Sterile solution for IV infusion. Packaging: Each box contains 2 vials; each vial contains 4 mL.
2	Active Ingredient, Unit dose strength(s)/Concentration	MK-7684A at 10/10 mg/mL (MK-3475 10 mg/mL and MK-7684 10 mg/mL).	MK-3475 at 100 mg/mL (25 mg/mL) 1 vial of 4 mL.
3	Unit	Box	Box
4	Amount	2496	2496
5	Shelf life	36 months	24 months
6	Specification	Manufacturer's specification.	Manufacturer's specification.
7	Indication	For the treatment of patients with PD-L1 positive metastatic NSCLC.	For the treatment of patients with PD-L1 positive metastatic NSCLC.
8	Manufacturer and manufactured country	MSD international GmbH t/a MSD Ireland (Carlow), Ireland Or: Patheon biologics LLC, US Or: Boehringer Ingelheim pharma GmbH & Co.KG, Germany.	MSD international GmbH t/a MSD Ireland (Carlow), Ireland OR: Patheon biologics LLC, US Or: Boehringer Ingelheim pharma GmbH & Co.KG, Germany.
9	Company owned marketed license on certification of pharmaceutical products	Not applicable as the drugs are in clinical trials in Vietnam.	

IV= intravenous; PD-L1=programmed cell death ligand 1; NSCLC= non-small cell lung cancer; US=United States.

10.8 Appendix 8: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

[ECOG ACRIN Cancer Research Group 2016]

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
1L	first line
ACCP	American College of Chest Physicians
ADA	antidrug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BICR	blinded independent central review
BP	blood pressure
CAC	Clinical Adjudication Committee
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CL	clearance
COPD	chronic obstructive pulmonary disease
CPS	combined positive score
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA

Abbreviation	Expanded Term
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	discontinuation
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	defective DNA mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eDMC	Data Monitoring Committee
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for the Research and Treatment of Cancer
EOT	end-of-treatment
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
ES-SCLC	Extensive stage small-cell lung cancer
FA	final analysis
FAS	Full Analysis Set
FBR	future biomedical research
FcγR	Fc gamma receptor
FDA (AA)	Food and Drug Administration (Amendments Act)

Abbreviation	Expanded Term
FFPE	Formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
FSR	first subject randomized
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging Clinical Research Organization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG	immunoglobulin G
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
IO	Immune-oncology
irAEs	immune-related AEs

Abbreviation	Expanded Term
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intention to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
IVD	in vitro diagnostic
LAM	lactational amenorrhea method
LS	least square
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NKT	natural killer T
NSCLC	non-small cell lung cancer
NDA	New Drug Application
NSAID	nonsteroidal anti-inflammatory drug
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell-death 1
PD-L1	programmed cell death ligand 1

Abbreviation	Expanded Term
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
PT	prothrombin time
PTT	partial thromboplastin time
PVRL-2	poliovirus receptor-related 2
QXW	every X week(s)
QoL	quality of life
QP2	department of quantitative pharmacology and pharmacometrics
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-free survival
RNA	ribonucleic acid
ROS	c-ROS oncogene 1
RP2D	recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
siDMC	standing internal Data Monitoring Committee
SIM	Site Imaging Manual
SJS	Stevens-Johnson Syndrome
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
Teff	effector T cell
TEN	toxic epidermal necrolysis
TIGIT	T cell immunoreceptor with Ig and ITIM domains
Tim-3	T cell immunoglobulin and mucin domain containing-3
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
TPS	tumor proportion score
TRAE	Treatment-related adverse events
TTD	time to deterioration
Vc	(central) volume of distribution
VAS	Visual Analog Scale
VOP	verification of progression
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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