Official Protocol Title:	A Randomized, Double-Blind, Phase 3 Study of Pembrolizumab/Vibostolimab Coformulation (MK-7684A) in Combination with Chemotherapy Versus Pembrolizumab Plus Chemotherapy as First Line Treatment for Participants with Metastatic Non-Small Cell Lung Cancer (MK-7684A-007/KEYVIBE-007)
NCT number:	NCT05226598
Document Date:	22 January 2025

TITLE PAGE

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Protocol Title: A Randomized, Double-Blind, Phase 3 Study of Pembrolizumab/Vibostolimab Coformulation (MK-7684A) in Combination with Chemotherapy Versus Pembrolizumab Plus Chemotherapy as First Line Treatment for Participants with Metastatic Non-Small Cell Lung Cancer (MK-7684A-007/KEYVIBE-007)

Protocol Number: 007-05

Compound Number: MK-7684A

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

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

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WHO	U1111-1293-2114
UTN	U1111-1293-2114
IND	147424

Approval Date: 22 January 2025

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	22-JAN-2025	The Sponsor has decided to discontinue treatment with MK-7684A based on lack of efficacy observed in other studies.
Amendment 4	03-JUN-2024	CCI [redacted] the objectives, hypotheses, and statistical analysis plan were updated to evaluate participants with PD-L1 TPS≥1% in addition to all participants.
Amendment 3	16-APR-2024	Revisions to align with Regulation (EU) 536/2014
Amendment 2	17-NOV-2023	CCI [redacted] Additionally, interim data recently became available from the external Phase 3 SKYSCRAPER-01 study. CCI [redacted]

Document	Date of Issue	Overall Rationale
Amendment 1	23-JUN-2022	Clarified the contraception requirements for male participants in UK to meet the requirements of UK Regulatory Agency.
Original Protocol	11-NOV-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

The Sponsor has decided to discontinue treatment with MK-7684A 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 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	Updated the pembrolizumab row(s) in the study interventions table to apply to all participants.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.
Section 4, Study Design Section 6, Study Intervention Section 7, Discontinuation of Study Intervention and Participant Withdrawal	• This study will be unblinded. • Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy. • Pembrolizumab can be sourced locally or centrally.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.

Section Number and Name	Description of Change	Brief Rationale
Section 8, Study Assessments and Procedures Section 9, Statistical Analysis Plan	• Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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. • Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned. • 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. • There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.	

Section Number and Name	Description of Change	Brief Rationale
	• Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4). • Assessments listed in the SoA will be done per local SOC. • 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.	
Section 6.1, Study Intervention(s) Administered	Table 5: updated the pembrolizumab row to apply to all participants.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.
	Pembrolizumab can be sourced locally or centrally.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A 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.

At implementation of Amendment 05 or 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 will be unblinded.
- Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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.
- Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned.
- 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.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.

- Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Assessments listed in the SoA will be done per local SOC.
- 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 Randomized, Double-Blind, Phase 3 Study of Pembrolizumab/Vibostolimab Coformulation (MK-7684A) in Combination with Chemotherapy Versus Pembrolizumab Plus Chemotherapy as First Line Treatment for Participants with Metastatic Non-Small Cell Lung Cancer (MK-7684A-007/KEYVIBE-007)

Short Title: A Phase 3 study of MK-7684A in combination with chemotherapy in metastatic NSCLC

Acronym: MK-7684A-007-05

Hypotheses, Objectives, and Endpoints:

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

In males and females with treatment-naïve metastatic NSCLC (squamous or nonsquamous):

Primary Objective	**Primary Endpoint**
Objective: To compare MK-7684A in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to Overall Survival (OS) in participants with PD-L1 TPS ≥1% Hypothesis (H1): MK-7684A in combination with chemotherapy is superior to pembrolizumab combination with chemotherapy with respect to OS in participants with PD-L1 TPS ≥1%	• 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 in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to OS in all participants • Hypothesis (H2): MK-7684A in combination with chemotherapy is superior to pembrolizumab combination with chemotherapy with respect to OS in all participants	• OS, defined as the time from randomization to the date of death due to any cause
• Objective: To compare MK-7684A in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to progression-free survival (PFS) in participants with PD-L1 TPS≥1% and in all participants per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR) • Hypothesis (H3): MK-7684A in combination with chemotherapy is superior to pembrolizumab in combination with chemotherapy with respect to PFS in all participants per RECIST 1.1 as assessed by BICR	• PFS, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

• Objective: To evaluate MK-7684A in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to Objective Response Rate (ORR) in participants with PD-L1 TPS≥1% and in all participants per RECIST 1.1 as assessed by BICR	• Objective response, defined as a confirmed Complete Response (CR) or Partial Response (PR) • •
• Objective: To evaluate the mean change from baseline in global health status/quality of life (QoL), physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A in combination with chemotherapy compared to pembrolizumab in combination with chemotherapy in participants with PD-L1 TPS≥1% and in all participants	• Change from baseline in the following patient-reported outcomes (PROs) 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 (EORTC QLQ-C30 items 6-7) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)
• Objective: To evaluate the time to deterioration in global health status/QoL, physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A in combination with chemotherapy compared to pembrolizumab in combination with chemotherapy in participants with PD-L1 TPS≥1% and in all participants	• Time to deterioration: time from baseline to the first onset of a ≥10-point (out of 100 points) deterioration from baseline in a given scale/subscale/item with confirmation at a subsequent visit of a ≥10-point deterioration from baseline. If the first deterioration is at the last patient-reported outcomes assessment timepoint, then no confirmation is required. Time to deterioration 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 (EORTC QLQ-C30 item 6-7)

	- Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)
• Objective: To evaluate the safety and tolerability of MK-7684A in combination with chemotherapy compared to pembrolizumab in combination with chemotherapy	• Adverse Events (AEs) • Discontinuations of study intervention due to an AE
• Objective: To evaluate DOR per RECIST 1.1 as assessed by BICR for MK-7684A plus chemotherapy compared to pembrolizumab plus chemotherapy in participants with PD-L1 TPS≥1% and in all participants	• 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

Note: This study will be considered to have met its success criteria if MK-7684A plus chemotherapy is superior to pembrolizumab plus chemotherapy with respect to OS.

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Non-small cell lung cancer metastatic
Population	Adult participants with metastatic NSCLC 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	Sponsor Investigator Participants or Subjects

Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 700 participants may be enrolled.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Arm 1	MK-7684A	MK-7684 200 mg +pembrolizumab 200 mg/20 mL vial	200 mg/200 mg	IV Infusion	Q3W for up to 35 cycles	Test Product
Arm 1	Carboplatin	10 mg/mL	Squamous: AUC 6 mg/ml/min Non squamous: AUC 5 mg/mL/min	IV Infusion	Q3W for 4 cycles	Background Treatment
Arm 1	Cisplatin	1 mg/mL	75 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment
Arm 1	Paclitaxel	6 mg/mL	200 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment
Arm 1	Nab-paclitaxel	100 mg/vial	100 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 21 day cycle for 4 cycles	Background Treatment
Arm 1	Pemetrexed	500 mg/vial	500 mg/m^2	IV Infusion	Q3W until progression, intolerable AE, or participant or physician decision	Background Treatment
All participants	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Q3W for up to 35 cycles	Test Product

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Arm 2	Carboplatin	10 mg/mL	Squamous AUC 6 mg/mL/min Non-squamous: AUC 5 mg/mL//min	IV Infusion	Q3W for 4 cycles	Background Treatment
Arm 2	Cisplatin	1 mg/mL	75 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment
Arm 2	Paclitaxel	6 mg/mL	200 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment
Arm 2	Nab-paclitaxel	100 mg/vial	100 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 21 day cycle for 4 cycles	Background Treatment
Arm 2	Pemetrexed	500 mg/vial	500 mg/m^2	IV Infusion	Q3W until progression, intolerable AE, or participant or physician decision	Background Treatment

Abbreviations: AE=adverse event; AUC=area under the curve; IV=intravenous; Q3W=every 3 weeks.

[a.] MK-7684A = coformulated as 200 mg MK-7684 and 200 mg pembrolizumab.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who complete study intervention after receiving 35 administrations of MK-7684A or pembrolizumab (4 cycles in combination with chemotherapy and up to 31 cycles of MK-7684A or pembrolizumab treatment [including pemetrexed for participants with nonsquamous NSCLC]), may be eligible for up to 17 additional administrations of MK-7684A or pembrolizumab (approximately 1 year). There is no treatment duration limit for pemetrexed in nonsquamous NSCLC. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who discontinue for reasons other than BICR-verified radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants:

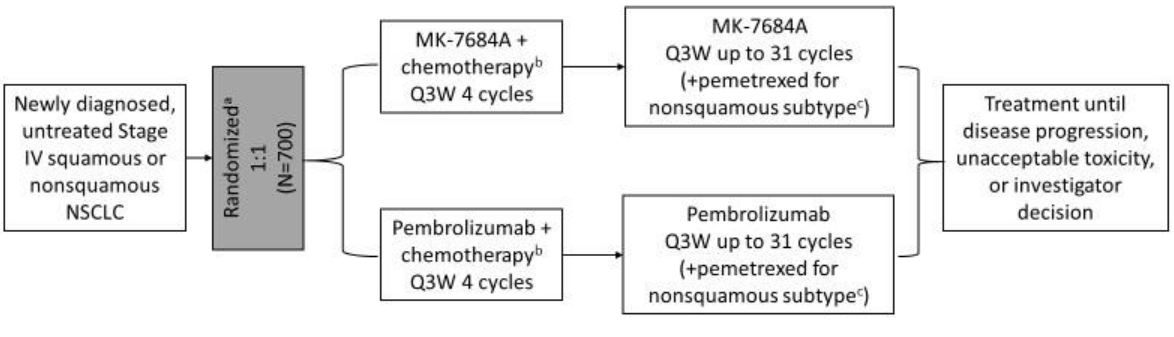
No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1 and Figure 2.

Figure 1 Initial Treatment Period



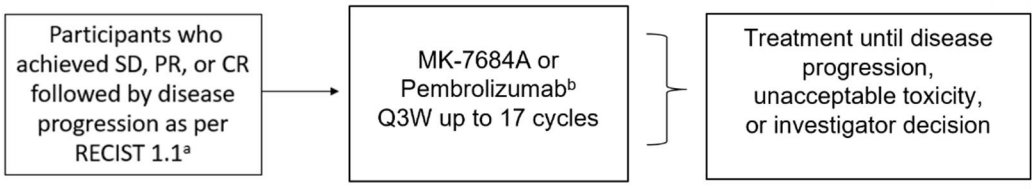
CCI

b. Chemotherapy consists of:
   - Squamous: Carboplatin with taxane (paclitaxel or nab-paclitaxel)
   - Nonsquamous: Pemetrexed with platinum (cisplatin or carboplatin)

c. There is no treatment duration limit for pemetrexed in nonsquamous NSCLC

Abbreviations: ECOG=Eastern Cooperative Oncology Group; N=sample size; NSCLC=non-small cell lung cancer; PD-L1=programmed cell death ligand 1; PS=performance status; Q3W=every 3 weeks; TPS=tumor proportion score; vs=versus.

Figure 2 Second Course Treatment



a. Participants may enter the Second Course if all of the following criteria are met:
   - The participant received MK-7684A/pembrolizumab
   - No new anticancer treatment was administered after the last dose of study intervention
   - The participant meets all of the inclusion criteria and none of the exclusion criteria
   - The study is ongoing

b. Second course treatment should be the assigned treatment in the initial treatment course

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

1.3 Schedule of Activities

1.3.1 Initial Treatment Period

Table 1 Initial Treatment Period Schedule of Activities

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures													
Informed Consent	X												Documented informed consent must be obtained before any protocol-specific screening procedures are performed. Additional consent is required to continue study intervention beyond PD.
Informed Consent for Future Biomedical Research	X												This is optional for the participant.
Inclusion/Exclusion Criteria	X												
Participant Identification Card	X												Update with randomization number at C1D1.
Demographics and Medical History	X												Data collection will follow local regulations where applicable. See Section 8.1.4 for specific requirements.
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.5 for specific requirements.
NSCLC Disease Details and Prior Treatment	X												See Section 8.1.4.1 for specific requirements.
Randomization		X											Obtain allocation number using IRT. Study intervention is required to begin within 3 days of randomization.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Study Intervention Administration													See Section 8.1.8.1 for details regarding order of study intervention administration.
MK-7684A or Pembrolizumab		X	X	X	X	X	X	X	X	X	X		
Platinum Doublet for Nonsquamous Histology (Carboplatin or Cisplatin) Administration		X	X	X	X								Investigator choice of carboplatin or cisplatin. See Appendix 7 for country-specific requirements.
Pemetrexed Administration (Nonsquamous only)		X	X	X	X	X	X	X	X	X	X	X	Pemetrexed administration is to be completed at least 30 minutes before the initiation of carboplatin or cisplatin during Cycles 1 to 4. Premedication is to be dosed per the approved product labels. Pemetrexed treatment will continue as per standard care beyond C35 for participants who remain progression-free and tolerate treatment. See Table 5 for premedication requirements.
Platinum Doublet for Squamous Histology (Carboplatin/Taxane Administration)		X	X	X	X								Investigator choice of paclitaxel or nab-paclitaxel as taxane. Participants receiving nab-paclitaxel are dosed on Days 1, 8 (±1 day), and 15 (±1 day) of each 21-day cycle. Carboplatin is to be administered immediately after taxane.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Efficacy Assessments													See Section 8.2.1 for further details.
Brain Scan	X			X									Brain scans are required for all participants at Screening. For participants with brain metastases at Screening (treated or untreated), on-study brain scans are to be acquired at Week 6 and as clinically indicated. Participants with brain metastases at Screening require brain scans to confirm CR. For those with no brain metastases at Screening, on-study brain scans are to be acquired only if clinically indicated.
Bone Scan	X												Bone scans are required at screening for participants with history of bone metastases or signs/symptoms suggestive of bone metastases. On-study bone scans are to be acquired as clinically indicated or to confirm a CR when bone metastases were present at Screening.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Tumor Scans (chest, abdomen, and pelvis)	X	←								→	X	X	Screening scans are to be captured within 28 days before randomization. All time points are calculated from the date of randomization. Scans will be captured at Week 6 (42 days ±7 days), Week 12 (84 days ±7 days), Week 18 (126 days ±7 days), and subsequently every 9 weeks (63 days ±7 days). After 63 weeks (441 days ±7 days), participants who remain on treatment will have scans performed every 12 weeks (84 days ±7 days). Scan timing will follow calendar days and should not be adjusted for delays in study intervention. Imaging will continue to be performed until progressive disease is documented by the investigator and verified by BICR, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Patient-reported Outcomes													
EORTC QLQ-C30		X	X	X	X	X	X	X	X	X	X		PROs are assessed before dosing at every cycle through C17, then every other cycle through C35 (ie, Cycles 1-17, 19, 21, 23, 25, 27, 29, 31, 33, and 35). PROs should be performed at the scheduled study visit until treatment discontinuation. PROs are to be administered by trained study personnel and completed electronically by participants. [redacted]
EORTC QLQ-LC13		X	X	X	X	X	X	X	X	X	X		
[redacted]		X	X	X	X	X	X	X	X	X	X		
[redacted]		X	X	X	X	X	X	X	X	X	X		
[redacted]		X	X	X	X	X	X	X	X	X	X		
Safety Assessments													All assessments should be performed predose.
Full Physical Examination	X												Other system-based examinations should be included if clinically indicated.
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	Review of new clinically significant abnormal findings.
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	If >10% change in body weight occurs, weight-based therapy should be readjusted.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	Measure temperature, RR, pulse, and BP after 5 minutes rest.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
12-lead ECG	X												After Screening Visit, repeat if clinically indicated.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	Performed within 7 days before randomization.
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	Record all AEs occurring from time of consent to within 30 days after last dose of study intervention. After 30 days, record all SAEs occurring up to 90 days after last dose of study intervention or 30 days after last dose if the participant initiates new anticancer therapy, whichever comes first. See Sections 1.3.2 and 8.4.3 for FU details.
Laboratory Assessments													Analysis performed by local laboratory.
Archival or Newly Obtained Tissue Collection	X												Absence of EGFR, ALK and ROS1 sensitizing genetic aberrations are required for inclusion in the study. See Section 8.1.12 for details. Sample must be submitted to Central Laboratory and results obtained for determination of PD-L1 status before randomization. The sample will also be utilized for EGFR, ALK, and ROS1 testing prior to randomization if this testing cannot be performed locally for subjects with predominantly nonsquamous histology.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Hematology, Serum Chemistry	X		X	X	X	X	X	X	X	X	X	X	See Appendix 2 for parameters. Screening samples to be collected and results reviewed within 10 days before the first dose of study intervention. After C1, collect within 3 days before dosing. Urinalysis is to be performed at Cycles 5, 9, and every 4 cycles thereafter.
Urinalysis	X					X				X	X	X	
INR or PT and aPTT/PTT	X												Screening samples to be collected within 10 days before first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. Pregnancy testing will also be conducted at the end of relevant systemic exposure as outlined in Section 8.3.5. Refer to Appendix 7 for country-specific requirements.
FSH (WONCBP)	X												To confirm WONCBP status if applicable. See Appendix 5.

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Thyroid function (T3, T4, and TSH)	X		X		X		X		X		X		Screening samples to be collected within 10 days before the first dose of study intervention. Performed D1 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.
Infection Testing (HBV / HCV / HIV)	X												Required at Screening if mandated by local health authority Refer to Appendix 2 for details and Appendix 7 for country-specific requirements.
CCI [redacted]													

Study Period:	**Screening**	**Treatment (21-Day Cycles)**											**Notes**
Visit Timing / Cycle Number	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 to 35**	**>36**	**Each cycle consists of 3 weeks (21 calendar days)**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
CCI [redacted]													

Abbreviations: ADA=antidrug antibodies; AE=adverse event; ALK=anaplastic lymphoma kinase; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; C=Cycle; CR=complete response: ctDNA=circulating tumor deoxyribonucleic acid; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=endothelial growth factor receptor; EORTC QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FSH=follicle-stimulating hormone; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR= international normalized ratio; IRT=intervention randomization system; NSCLC=non-small cell lung cancer; PD=progressive disease; PD-L1=programmed cell death ligand 1; PK=pharmacokinetic; PROs=patient-reported outcomes; PT=prothrombin time; PTT=partial thromboplastin time; ROS1=c-ros oncogene 1; RR=respiratory rate; SAE=serious adverse event; SAQ=Symptom Assessment Questionnaire; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

1.3.2 Follow-up Assessments

Table 2 Follow-up Schedule of Activities

Study Period:	**Follow-up**				**Notes**
	End of Treatment	**Safety FU**	**Efficacy FU**	**Survival FU**	Follow-up visits are required for participants who complete 35 cycles of treatment without disease progression. Efficacy FU visits are required for participants who withdraw from treatment without BICR-verified radiographic disease progression and have not received new anticancer therapy. Survival FU visits are required for participants that withdraw from treatment for BICR-verified radiographic disease progression or have started other anticancer therapy.
Visit:	**At treatment Discontinuation**	**30 Days Post Discontinuation**	**See Notes**	**Every 12 weeks**	
Window (days):		**±14**	**±7**	**±14**	
Efficacy Assessments					For participants who discontinued study intervention without disease progression.
Tumor Scans (chest, abdomen, and pelvis)	X		X		EOT scans are not required if obtained within 4 weeks before the EOT visit. Follow-up visits may be scheduled to coincide with the scan schedule. If discontinuation is not due to BICR-verified disease progression, then tumor scans are to continue on the initial treatment period schedule. See Section 8.2 for details.
Vital Status				X	On Sponsor request, participants may be contacted for survival information at any time during the study.
Patient-reported Outcomes					Not applicable to participants receiving Second Course Treatment.
EORTC QLQ-C30	X	X			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, PROs do not need to be repeated PROs are to be administered by trained study personnel and completed electronically by participants. CCI [redacted]
EORTC QLQ-LC13	X	X			
CCI [redacted]	X	X			
CCI [redacted]	X	X			
Safety Assessments					
ECOG Performance Status	X	X			
Vital signs and Weight	X	X			Temperature, RR, pulse, and BP are to be measured after 5 minutes rest.
Complete Physical Examination	X				
Directed Physical Examination		X			

Study Period:	**Follow-up**				**Notes**
	End of Treatment	**Safety FU**	**Efficacy FU**	**Survival FU**	Follow-up visits are required for participants who complete 35 cycles of treatment without disease progression. Efficacy FU visits are required for participants who withdraw from treatment without BICR-verified radiographic disease progression and have not received new anticancer therapy. Survival FU visits are required for participants that withdraw from treatment for BICR-verified radiographic disease progression or have started other anticancer therapy.
Visit:	**At treatment Discontinuation**	**30 Days Post Discontinuation**	**See Notes**	**Every 12 weeks**	
Window (days):		**±14**	**±7**	**±14**	
AE/SAE Review	X	X			Record all AEs occurring within 30 days after last dose of study intervention. After 30 days, record all SAEs occurring up to 90 days after last dose of study intervention or 30 days after last dose if the participant initiates new anticancer therapy, whichever comes first. Any treatment-related SAEs must be reported regardless of time they occur.
Anticancer Therapy Status	X	X	X	X	
Concomitant Medication	X	X			See Section 6.5 for specific requirements.
Laboratory Assessments					
Pregnancy Test (WOCBP only)	X	X			Refer to Appendix 7 for country-specific requirements.
Hematology, Serum Chemistry	X	X			
Urinalysis	X	X			
Thyroid Function (T3, T4, and TSH)	X	X			Free T3 and free T4 are acceptable.
CCI [redacted]					
Biomarker					
CCI [redacted]					

Abbreviations: ADA=antidrug antibodies; AE=adverse event; BICR=blinded independent central review; BP=blood pressure; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end of treatment; FU=follow-up; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; PRO=patient-reported outcomes; RR=respiratory rate; SAQ=Symptom Assessment Questionnaire; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.3 Second Course Treatment

Table 3 Second Course Schedule of Activities

Study Period:	**Second Course Treatment**							**Follow-up**				**Notes**
Visit Timing / Cycle number	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 17**	**End of Treatment**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1 Every Cycle**	**At Treatment Discontinuation**	**30 Days Post Discontinuation**	**Every 12 Weeks**	**Every 12 Weeks**	Each cycle consists of 3 weeks (21 calendar days).
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±14**	**±7**	**±14**	
Administrative Procedures												
Eligibility Criteria	X											Only participants who achieved SD, PR, or CR followed by disease progression as assessed by the investigator and verified by BICR as per RECIST 1.1 will be eligible for a Second Course of treatment.
Concomitant Medication	X	X	X	X	X	X	X	X	X			See Section 6.5 for specific requirements.
Study Intervention Administration (MK-7684A or Pembrolizumab)	X	X	X	X	X	X	X					Participants will receive the same study intervention allocated in the initial treatment phase.
Anticancer Therapy Status								X	X	X	X	

Study Period:	**Second Course Treatment**							**Follow-up**				**Notes**
Visit Timing / Cycle number	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 17**	**End of Treatment**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1 Every Cycle**	**At Treatment Discontinuation**	**30 Days Post Discontinuation**	**Every 12 Weeks**	**Every 12 Weeks**	Each cycle consists of 3 weeks (21 calendar days).
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±14**	**±7**	**±14**	
Efficacy Assessments												
Tumor scans (chest, abdomen, and pelvis)	X				X		X	X		X*		Second Course Screening scans are to be captured within 28 days before Second Course C1. Scans will be captured Q12W (±7 days) from Second Course C1 (Weeks 12, 24, 36, and 48). Scan timing will follow calendar days and should not be adjusted for delays in study intervention. Images are for investigator assessment of disease status only and are not to be sent to the iCRO, Refer to Section 8.2.1.4. If scans were obtained within 4 weeks before DC, scans at DC are not mandatory. *For participants discontinuing Second Course for reasons other than PD, follow-up visits and scans continue until PD is documented by the investigator, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.
Brain Scans	X											Second Course Screening scans need to be captured within 28 days before planned C1D1 for participants who had brain metastases at Screening or before entering Second Course, or those where it is clinically indicated. Brain scans during the Second Course are to be performed as clinically indicated.

Study Period:	**Second Course Treatment**							**Follow-up**				**Notes**
Visit Timing / Cycle number	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 17**	**End of Treatment**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1 Every Cycle**	**At Treatment Discontinuation**	**30 Days Post Discontinuation**	**Every 12 Weeks**	**Every 12 Weeks**	Each cycle consists of 3 weeks (21 calendar days).
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±14**	**±7**	**±14**	
Safety Assessments												All assessments are to be collected predose.
Complete Physical Examination	X							X				
Directed Physical Examination		X	X	X	X	X	X		X			Review of new clinically significant abnormal findings.
Weight	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X			
Vital Signs	X	X	X	X	X	X	X	X	X			Measure temperature, RR, pulse, and BP after 5 minutes rest.
12-lead ECG												12-lead ECG is only required where clinically indicated.
AE/SAE review	X	X	X	X	X	X	X	X	X			Record all AEs occurring within 30 days after last dose of study intervention. After 30 days, record all SAEs occurring up to 90 days after last dose of study intervention or 30 days after last dose if the participant initiates new anticancer therapy, whichever comes first.
Laboratory Procedures												Analysis Performed by Local laboratory.
Hematology, Serum Chemistry	X	X	X	X	X	X	X	X	X			Performed within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis is to be performed every 4 cycles thereafter (C5, C9, etc.). See Appendix 2 for parameters.
Urinalysis	X				X		X	X	X			
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. See Appendix 7 for country-specific requirements.

Study Period:	**Second Course Treatment**							**Follow-up**				**Notes**
Visit Timing / Cycle number	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 17**	**End of Treatment**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1 Every Cycle**	**At Treatment Discontinuation**	**30 Days Post Discontinuation**	**Every 12 Weeks**	**Every 12 Weeks**	Each cycle consists of 3 weeks (21 calendar days).
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±14**	**±7**	**±14**	
INR or PT and aPTT/PTT	X											Required at C1. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Thyroid Function (T3, T4, and TSH)	X		X		X		X		X			Perform within 10 days before Second Course C1. To be performed D1 of every other cycle starting from C3. Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.
Biomarker												
CCI [redacted]												

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; C=Cycle; CR=complete response; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FU=follow-up; iCRO=imaging contract research organization; INR= international normalized ratio; PD=progressive disease; PR=partial response; PT=prothrombin time; PTT=partial thromboplastin time; Q12W=every 12 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; RR=respiratory rate; SAE=serious adverse event; SD=stable disease; 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. Effective antitumor immunity depends on presentation of a tumor antigen, activation of protective T-cell responses, and the ability to overcome tumor-based blockade of antitumor responses, and therefore rationale exists to develop anti-PD-1 and anti-TIGIT combination therapies. 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 2.2 million cases in 2020, resulting in an estimated 1.8 million deaths, representing the second most frequently diagnosed cancer and the leading cause of cancer death in 2020 [Sung, H., et al 2021]. NSCLC represents approximately 84% 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, 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 and TPS ≥1% (in some countries), respectively, with no EGFR or ALK genomic tumor aberrations [Brahmer, J. R., et al 2017] [Mok, T. S. K., et al 2019]. Following this, 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] [Paz-Ares, L., et al 2018].

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 [Goldstraw, P., et al 2016]. 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.

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.

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 shown that anti-TIGIT antibodies on the mIgG2a backbone (with high affinity FcγR binding) are more efficacious than anti-TIGIT 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 of MK-7684 as monotherapy or coformulated with pembrolizumab (MK-7684A) in advanced solid tumors shows promising activity in PD-1/PD-L1 naïve NSCLC (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. Given the substantial clinical benefit that pembrolizumab has brought to patients with NSCLC, the concept of extending this benefit to a broader population by combining pembrolizumab with an anti-TIGIT agent is a promising avenue to investigate. Promising efficacy and safety data observed in participants with metastatic NSCLC in Study MK-7684-001 show a potential opportunity to improve upon the current standard of care in NSCLC (see Section 2.2.3.1 for further details). Therefore, the present study is designed to further evaluate the safety and efficacy of MK-7684A (a fixed dose coformulation of MK-7684 with pembrolizumab) when administered in combination with chemotherapy for the treatment of metastatic NSCLC.

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several indications. Refer to the MK-7684/ MK-7684A IB and the pembrolizumab IB for detailed background information on MK-7684A 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 tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

TIGIT forms part of a costimulatory 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, T-regs, NK cells, and NKT cells [Dardalhon, V., et al 2005] [Stanietsky, N., et al 2013]. CD155/PVR and CD112/PVRL-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 coexpressed with PD-1 on both CD4+ and CD8+ TILs including T-regs, in mouse and human tumors, and has been reported to be coexpressed 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 to decrease inhibitory signaling in T cells. We hypothesize, therefore, that combining MK-7684 with pembrolizumab will offer substantially augmented antitumor efficacy.

Interim data recently became available from the external Phase 3 SKYSCRAPER-01 study evaluating the investigational anti-TIGIT mAb tiragolumab plus atezolizumab versus atezolizumab alone as an initial (first-line) treatment for people with PD-L1-high locally advanced or metastatic NSCLC. This study showed minimal benefit to PFS, and the median overall survival estimates were 22.9 months (95% CI: 17.5, NE) in the anti-TIGIT mAb

tiragolumab plus atezolizumab arm, and 16.7 months (95% CI: 14.6, 20.2) in the atezolizumab monotherapy arm, yielding an HR of 0.81 (95% CI: 0.63, 1.03).

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, T-regs, 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.

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 and clinical safety profile as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several 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

Refer to the MK-7684/MK-7684A IB for detailed background information on MK-7684A.

Although preclinical studies with anti-TIGIT as monotherapy or in combination with anti-PD-1 are limited, preliminary efficacy has been shown for the combination. Using A20 lymphoma cells in Balb/c mice as B-cell NHL model, the study showed prolonged survival with anti-TIGIT and anti-PD-1 combination therapy compared with either anti-TIGIT or anti-PD-1 monotherapy [Sunseri, N., et al 2019]. In MM mouse models, Vk12653 and Vk12598 cell lines, TIGIT blockage prolonged survival in preclinical studies [Guillerey, C., et al 2018] [Minnie, S. A., et al 2018].

2.2.2.2 Pembrolizumab Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

2.2.3.1 MK-7684A Ongoing Clinical Studies

Numerous interventional clinical studies involving MK-7684/MK-7684A are currently ongoing in a number of advanced solid tumor indications, as well as hematological malignancies. Sponsored clinical studies are ongoing which include participants with NSCLC; ie, MK-7684-001, MK-3475-U01, MK-7684A-002, and MK-7684A-003. Preliminary data are available for MK-7684-001 and MK-3475-U01 studies.

Study MK-7684-001

MK-7684-001 is a first-in-human, safety, tolerability, PK, pharmacodynamic, and efficacy 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]

Study MK-3475-U01

MK-3475-U01 is a Phase 2, umbrella study with rolling arms of investigational agents with either pembrolizumab in combination with chemotherapy or with pembrolizumab alone in participants with advanced NSCLC. In Substudy 01A, treatment-naïve participants with advanced or metastatic (squamous or nonsquamous) NSCLC will receive pembrolizumab plus chemotherapy in combination with MK-7684 followed by treatment with pembrolizumab and MK-7684.

CCI

[redacted]

CCI [redacted]

Study MK-7684A-002

MK-7684A-002 is a Phase 2, multicenter, randomized study to compare the efficacy and safety of MK-7684A or MK-7684A plus docetaxel versus docetaxel monotherapy in the treatment of participants with metastatic NSCLC with progressive disease after treatment with a platinum doublet chemotherapy and immunotherapy. The study is ongoing.

Study MK-7684A-003

MK-7684A-003 is a Phase 3, multicenter, randomized, double-blind study of MK-7684A versus pembrolizumab monotherapy as first-line treatment for participants with PD-L1 positive metastatic NSCLC. No results are currently available.

Additional details regarding other ongoing studies of MK-7684A may be found in the MK-7684/MK-7684A IB.

2.2.3.2 Pembrolizumab Ongoing Clinical Studies

Numerous interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications, as well as in hematological malignancies. Additional details regarding other ongoing studies of pembrolizumab and specific benefits and risks for participants treated with pembrolizumab may be found in the pembrolizumab 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 in combination with chemotherapy in KEYNOTE-189 and KEYNOTE-407 in participants with metastatic NSCLC, an unmet medical need remains for safe and efficacious treatments offering added benefit for this patient population.

CCI [redacted]

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

In males and females with treatment-naïve metastatic NSCLC (squamous or nonsquamous):

Primary Objective	**Primary Endpoint**
Objective: To compare MK-7684A in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to Overall Survival (OS) in participants with PD-L1 TPS ≥1% Hypothesis (H1): MK-7684A in combination with chemotherapy is superior to pembrolizumab combination with chemotherapy with respect to OS in participants with PD-L1 TPS ≥1%	• 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 in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to OS in all participants • Hypothesis (H2): MK-7684A in combination with chemotherapy is superior to pembrolizumab combination with chemotherapy with respect to OS in all participants	• OS, defined as the time from randomization to the date of death due to any cause

• Objective: To compare MK-7684A in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to progression-free survival (PFS) in participants with PD-L1 TPS≥1% and in all participants per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR) • Hypothesis (H3): MK-7684A in combination with chemotherapy is superior to pembrolizumab in combination with chemotherapy with respect to PFS in all participants per RECIST 1.1 as assessed by BICR	• PFS, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
• Objective: To evaluate MK-7684A in combination with chemotherapy to pembrolizumab in combination with chemotherapy with respect to Objective Response Rate (ORR) in participants with PD-L1 TPS≥1% and in all participants per RECIST 1.1 as assessed by BICR	• Objective response, defined as a confirmed Complete Response (CR) or Partial Response (PR) • •
• Objective: To evaluate the mean change from baseline in global health status/quality of life (QoL), physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A in combination with chemotherapy compared to pembrolizumab in combination with chemotherapy in participants with PD-L1 TPS≥1% and in all participants	• Change from baseline in the following patient-reported outcomes (PROs) 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 (EORTC QLQ-C30 items 6-7) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)

• Objective: To evaluate the time to deterioration in global health status/QoL, physical functioning, role functioning, dyspnea, cough, and chest pain for MK-7684A in combination with chemotherapy compared to pembrolizumab in combination with chemotherapy in participants with PD-L1 TPS≥1% and in all participants	• Time to deterioration: time from baseline to the first onset of a ≥10-point (out of 100 points) deterioration from baseline in a given scale/subscale/item with confirmation at a subsequent visit of a ≥10-point deterioration from baseline. If the first deterioration is at the last patient-reported outcomes assessment timepoint, then no confirmation is required. Time to deterioration 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 (EORTC QLQ-C30 item 6-7) - Dyspnea score (EORTC QLQ-C30 item 8) - Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ-LC13 item 40)
• Objective: To evaluate the safety and tolerability of MK-7684A in combination with chemotherapy compared to pembrolizumab in combination with chemotherapy	• Adverse Events (AEs) • Discontinuations of study intervention due to an AE
• Objective: To evaluate DOR per RECIST 1.1 as assessed by BICR for MK-7684A plus chemotherapy compared to pembrolizumab plus chemotherapy in participants with PD-L1 TPS≥1% and in all participants	• 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

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
CCI [redacted]	

Note: This study will be considered to have met its success criteria if MK-7684A plus chemotherapy is superior to pembrolizumab plus chemotherapy with respect to OS in participants with PD-L1 TPS≥1%.

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

4 STUDY DESIGN

At implementation of Amendment 05 or 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 will be unblinded.
- Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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.
- Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned.
- 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.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Assessments listed in the SoA will be done per local SOC.
- 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 plus chemotherapy versus pembrolizumab plus chemotherapy in participants with metastatic NSCLC. Participants must have newly diagnosed, untreated Stage IV NSCLC, an ECOG PS of 0 to 1, and no current pneumonitis or interstitial lung disease at enrollment.

Overall, approximately 700 participants will be randomized 1:1 to receive either:

- MK-7684A in combination with chemotherapy (Arm 1), or
- Pembrolizumab in combination with chemotherapy (Arm 2)

Participants will be stratified by ECOG PS, histology, PD-L1 status, and geographic region, as described in Section 6.3.2.

Treatment with MK-7684A or pembrolizumab in combination with chemotherapy will be administered for 4 cycles followed by up to 31 cycles of MK-7684A or pembrolizumab treatment (including pemetrexed for participants with nonsquamous histology), until a discontinuation criterion is met (see Section 7.1).

The investigator will select the platinum chemotherapy regimen before randomization (see Table 5).

Participants who have completed the first course (achieve SD, PR, or CR) and who go on to progress may be eligible for up to an additional 17 cycles of the assigned treatment (MK-7684A or pembrolizumab) if there is BICR-verified progressive disease by RECIST 1.1 after initial treatment (see Section 6.1.2).

Participants will be evaluated with radiographic imaging to assess response to study intervention at Week 6, Week 12, and Week 18 from randomization, then every 9 weeks through 63 weeks, and subsequently every 12 weeks until BICR-verified radiographic PD, initiation of a new anticancer regimen, withdrawal of consent, pregnancy, or death. All scans 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, ORR, and

DOR. Tumor imaging showing site-assessed PD is to be submitted immediately for verification by BICR before study intervention discontinuation. Once disease progression is verified centrally, subsequent imaging (if acquired) is not to 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.

Participants who discontinue study intervention for reasons other than BICR-verified PD will have long-term follow-up for disease status (including imaging), until BICR-verified PD, initiation of a new anticancer therapy, withdrawal of informed consent, or becoming lost to follow-up. After BICR-verified PD, each participant will be contacted approximately every 12 weeks (± 14 days) to assess for survival status until withdrawal of consent, becoming lost to follow-up, death, or the end of the study, whichever occurs first.

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

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

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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. See Appendix 7 for country-specific requirements.

4.2 Scientific Rationale for Study Design

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

4.2.1 Rationale for Endpoints

Endpoint definitions are provided in Section 9.4.

4.2.1.1 Efficacy Endpoint

The primary endpoint for this study is OS.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in

total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

Overall Survival

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

Progression-free Survival

This study will use PFS based on RECIST 1.1 criteria as assessed by BICR as a secondary endpoint. PFS is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. 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.

Objective Response Rate and Duration of Response

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

4.2.1.2 Safety Endpoints

The safety and tolerability of MK-7684A will be assessed by clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examination, and laboratory safety tests at time points specified in the SoA. AEs will be assessed as defined by NCI CTCAE 5.0 and recorded according to Section 8.4 and Appendix 3.

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

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. CCI [redacted]

CCI [redacted]

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EORTC QLQ-LC13

The EORTC QLQ-LC13, a supplemental lung cancer-specific module used in combination with QLQ-C30, is composed of multi-item and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia) [Bergman, B., et al 1994]. It is scored on a 4-point scale (l = not at all, 2 = a little, 3 = quite a bit, and 4 = very much) and has been translated and validated into more than 60 languages.

The EORTC QLQ-C30 and QLQ-LC13 are the most frequently used and reported PRO measures in lung cancer clinical studies. The reliability, validity, and practicality of these instruments have been reported [Bergman, B., et al 1994] [Aaronson, N. K., et al 1993].

CCI [redacted]

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[redacted]

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[redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

The comparator arm for this study will include pembrolizumab in combination with chemotherapy. The type of chemotherapy will depend on the histology type.

Pembrolizumab in combination with chemotherapy is approved as first-line treatment for patients with metastatic NSCLC regardless of tumor PD-L1 expression and is considered the standard of care for patients who are not candidates for targeted therapies. The chemotherapy regimens used in this study are well-established standards for first-line treatment of squamous (carboplatin with paclitaxel or nab-paclitaxel) or nonsquamous (pemetrexed and carboplatin or cisplatin) NSCLC. These regimens are also identical to the regimens used in KEYNOTE-189 and KEYNOTE-407.

4.3 Justification for Dose

4.3.1 MK-7684A

Based on the totality of available data, including 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]

CCI [redacted]

Further information is provided in the MK-7684/MK-7684A IB.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. CCI [redacted] As outlined below, this dose is justified by:

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

4.3.3 Justification of Chemotherapy Dose

The chemotherapy treatments used in this study are well-established regimens for squamous (carboplatin with paclitaxel or nab-paclitaxel) or nonsquamous (pemetrexed and carboplatin or cisplatin) NSCLC, as described above. See Section 6.1 for information on the order in which study interventions are to be administered.

4.3.4 Biocomparability of MK-7684 and Pembrolizumab as Sequential Infusions Versus Coformulated Product MK-7684A in Solid Tumors

CCI [redacted]

CCI [redacted]

Further details are provided in the MK-7684/MK-7684A IB.

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 5 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

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

- Incidence or severity of emerging effects/clinical endpoints is such that the risk/benefit ratio for the study population as a whole is unacceptable.
- Plans to modify or discontinue the development of the study drug.

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

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Section 10.1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are to follow all local laws and guidelines in keeping with the needs for participant confidentiality 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 Stage IV (T any, N any, M1a, M1b, M1c - AJCC eighth Edition) squamous or nonsquamous NSCLC.
2. Note: Mixed tumors will be characterized by the predominant cell type; if small cell elements are present, the participant is ineligible.
3. Has measurable disease based on RECIST 1.1, as determined by the local site assessment.
4. 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.
5. Has provided tumor tissue (post diagnosis of metastatic disease is preferred) for determination of PD-L1 status before randomization.
6. Note: Assessment of PD-L1 expression must be made from provided archival tumor tissue sample or newly obtained core or incisional or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Details pertaining to tumor tissue submission can be found in the laboratory manual.
7. 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 OR presence of a KRAS mutation).
8. 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.
9. Has not received prior systemic treatment for metastatic NSCLC.

Demographics

10. Is male or female, from ≥18 years of age inclusive, at the time of signing the informed consent.
11. Has an ECOG PS of 0 or 1 assessed within 7 days before randomization.
12. Has a life expectancy of at least 3 months.

Male Participants

13. If male, agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

Chemotherapy: at least 95 days from the last dose

Refrain from donating sperm

a. PLUS either:

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

OR

Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause), documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview as detailed below:

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

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

Female Participants

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

Not a WOCBP

OR

Is a WOCBP and:

Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate

each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

MK-7684A/pembrolizumab: 120 days

Chemotherapy: 180 days

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

Has a negative highly sensitive pregnancy test (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 in Section 8.3.5.

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

Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

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

Additional Categories

16. Has adequate organ function as defined in Table 4. Specimens must be collected within 10 days before the start of study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Estimated creatinine clearance using the Cockcroft-Gault equation[b]	To initiate treatment with carboplatin or cisplatin, CrCl must be ≥60 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=absolute neutrophil count; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase);Crcl= creatinine clearance ULN=upper limit of normal.

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

[b] Estimated creatinine clearance using Cockcroft-Gault:

(140-age [years] × weight (kg) (×F)*

Serum creatinine (mg/dL) × 72

*where F = 0.85 for females and F = 1 for males

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

See Appendix 7 for country-specific requirements for inclusion criteria.

5.2 Exclusion Criteria

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

Medical Conditions

1. Known additional malignancy that is progressing or has required active treatment within the past 3 years.
2. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.
3. Known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks as confirmed by repeat imaging performed during study screening, are clinically stable and have not required steroid treatment for at least 14 days before the first dose of study intervention. Participants with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate.
4. Severe hypersensitivity (≥Grade 3) to MK-7684, MK-7684A, pembrolizumab, chemotherapy components, and/or any of its excipients.
5. 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 before the first dose of study medication.
6. Active autoimmune disease that has required systemic treatment in past 2 years, except replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).
7. History of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
8. Note: Lymphangitic spread of the NSCLC is not exclusionary.
9. Active infection requiring systemic therapy.
10. Known history of HIV infection. No HIV testing is required unless mandated by local health authority.
11. 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.
12. Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
13. History or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
14. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Prior/Concomitant Therapy

15. Received prior therapy with an anti-TIGIT, anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
16. Received prior systemic anticancer therapy for metastatic disease.

    Note: Participants who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months before the development of metastatic disease.
17. If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the operation before starting study intervention.
18. Received prior radiotherapy within 2 weeks of start of study intervention or have had a history of radiation pneumonitis.
    Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
19. Received radiation therapy to the lung that is >30 Gray within 6 months of the first dose of study intervention.
20. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

Pemetrexed-Specific Concomitant Therapy

21. Is unable to interrupt aspirin or other NSAIDs, other than an aspirin dose ≤1.3 g/day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).
22. Is unable or unwilling to take folic acid or vitamin B12 supplementation.

Prior/Concurrent Clinical Study Experience

23. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.
24. 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.

Other Exclusions

25. History of allogeneic tissue/solid organ transplant.

See Appendix 7 for country-specific requirements for exclusion criteria.

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 one time for eligibility.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

At implementation of Amendment 05 or 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 will be unblinded.
- Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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.
- Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned.
- 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.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Assessments listed in the SoA will be done per local SOC.
- 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 (study treatments provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 5. Country-specific differences are noted in Appendix 7.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	MK-7684A	Biological/ Vaccine	Solution	MK-7684 200 mg +pembrolizumab 200 mg/20 mL vial	200 mg/200 mg	IV Infusion	Q3W for up to 35 cycles	Test Product	IMP	Central
Arm 1	Experimental	Carboplatin	Drug	Solution	10 mg/mL	Squamous: AUC 6 mg/ml/ min Non squamous: AUC 5 mg/mL/ min	IV Infusion	Q3W for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central
Arm 1	Experimental	Cisplatin	Drug	Solution	1 mg/mL	75 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central
Arm 1	Experimental	Paclitaxel	Drug	Solution	6 mg/mL	200 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central
Arm 1	Experimental	Nab-paclitaxel	Drug	Powder, For Solution	100 mg/vial	100 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 21 day cycle for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pemetrexed	Drug	Powder, For Solution	500 mg/vial	500 mg/m^2	IV Infusion	Q3W until progression, intolerable AE, or participant or physician decision	Background Treatment	NIMP/AxMP	Local or Central
All participants	Active Comparator	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Q3W for up to 35 cycles	Test Product	IMP	Local or Central
Arm 2	Active Comparator	Carboplatin	Drug	Solution	10 mg/mL	Squamous AUC 6 mg/mL/min Non-squamous: AUC 5 mg/mL//min	IV Infusion	Q3W for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central
Arm 2	Active Comparator	Cisplatin	Drug	Solution	1 mg/mL	75 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central
Arm 2	Active Comparator	Paclitaxel	Drug	Solution	6 mg/mL	200 mg/m^2	IV Infusion	Q3W for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central
Arm 2	Active Comparator	Nab-paclitaxel	Drug	Powder, For Solution	100 mg/vial	100 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 21 day cycle for 4 cycles	Background Treatment	NIMP/AxMP	Local or Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Active Comparator	Pemetrexed	Drug	Powder, For Solution	500 mg/vial	500 mg/m^2	IV Infusion	Q3W until progression, intolerable AE, or participant or physician decision	Background Treatment	NIMP/AxMP	Local or Central

Abbreviations: AE=adverse event; AUC=area under the curve; BID=bis in die (twice daily); EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; MASCC=Multinational Association of Supportive Care in Cancer; NIMP/AxMP=noninvestigational medicinal product/auxiliary medicinal product; PO=per oral.

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

MK-7684A = coformulated as 200 mg MK-7684 and 200 mg pembrolizumab

For commercially available supplies, the unit dose strength or formulation may vary, depending on market availability.

All participants taking pemetrexed are to receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis, as listed below (or as per local label):

- Folic acid 350-1000 µg PO: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4, but not to exceed the doses in the MASCC guidelines.

All study interventions will be administered on an outpatient basis.

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

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

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

6.1.1 Treatment

The Initial Treatment or First Course of MK-7684A plus chemotherapy or pembrolizumab plus chemotherapy consists of 4 cycles (Q3W) of treatment followed by up to 31 cycles (Q3W) of MK-7684A or pembrolizumab treatment, including pemetrexed for participants with nonsquamous NSCLC. Note: The number of treatments is calculated starting with the first dose.

The investigator will select the platinum chemotherapy regimen before randomization.

The platinum chemotherapy regimen will be selected based on histological subtype:

- Squamous: carboplatin with taxane (investigators choice of paclitaxel/nab-paclitaxel)
- Nonsquamous: pemetrexed with platinum (cisplatin/carboplatin) followed by pemetrexed maintenance until progression, intolerable AE, participant or investigator decision. There is no treatment duration limit for pemetrexed in nonsquamous histology.

These participants may be eligible for Second Course described in Section 6.1.2.

6.1.2 Second Course

All participants who have completed the first course may be eligible for up to an additional 17 cycles of MK-7684A or pembrolizumab if there is BICR-verified progressive disease by RECIST 1.1 after initial treatment. This retreatment is the Second Course of this study.

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

1. The participant received MK-7684A or pembrolizumab, determined on unblinding if applicable
2. No new anticancer treatment was administered after the last dose of study intervention
3. The participant meets all of the inclusion criteria and none of the exclusion criteria
4. The study is ongoing

Participants will receive the same study intervention that was allocated in the initial treatment phase (MK-7684A or pembrolizumab).

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. Carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and pemetrexed will be prepared and administered as per the approved product labels.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized 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.

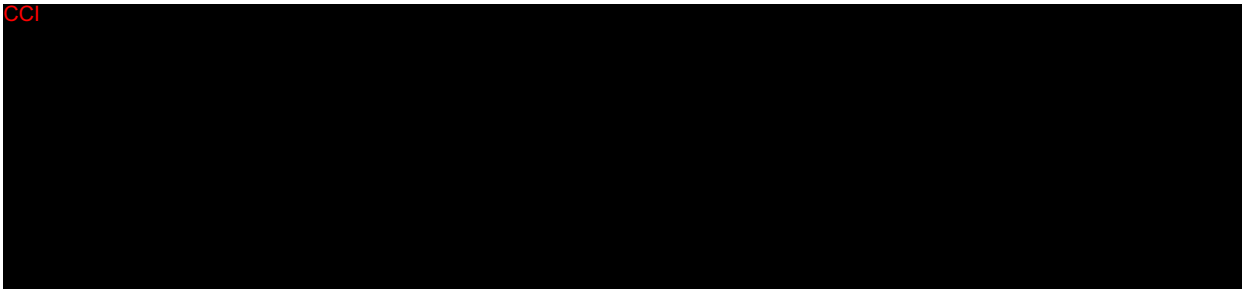
The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

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 plus chemotherapy or pembrolizumab plus chemotherapy.

6.3.2 Stratification



6.3.3 Blinding

A double-blinding technique 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. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments. The chemotherapy agents will be open-label.

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

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

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

6.5 Concomitant Therapy

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

participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

The following medications and vaccinations are prohibited during the study: (See Appendix 7 for country-specific requirements):

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-7684A or pembrolizumab
- 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.
- Surgery for tumor control
- Anticancer hormonal therapy (eg, androgen deprivation, androgen receptor blockade, anti-estrogens)
  Note: Hormonal replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
- Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.
  Note: Killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, 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
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD
- Phenytoin during therapy with cisplatin/carboplatin.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention (all combination treatments) 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 medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

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

If a participant receives additional anticancer therapies, this will be judged to represent evidence of PD, and study intervention will be discontinued. These participants are required to complete all end-of-treatment assessments and continue to be followed for survival in the follow-up period.

Investigators must always refer to the up-to-date label of chemotherapeutics agents used in this study (ie, paclitaxel, nab-paclitaxel, pemetrexed, cisplatin and carboplatin) regarding the use of concomitant medications to address adequately the drug interaction potential.

- Caution must be exercised when administering pemetrexed together with ibuprofen in patients with mild to moderate renal impairment. Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

- Caution and increased monitoring must be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the CYP2C8 and CYP3A4.
- Caution must be exercised when administering cisplatin or carboplatin together with other nephrotoxic agents (eg, aminoglycosides, diuretics, antihypertensives, other chemotherapy specified in the study).
- Caution and increased monitoring must be exercised when administering cisplatin with other ototoxic agents (eg, aminoglycosides, loop diuretics).

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.

Refer to Appendix 7 for country-specific requirements.

6.5.1.1 Pembrolizumab

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.

6.5.1.2 Chemotherapy

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

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

Prior to paclitaxel infusion, all participants should be premedicated with oral or IV corticosteroids, diphenhydramine, and H2 antagonists according to the approved product label and/or standard practice, see Section 8.1.8.1.2.2.

Prior to pemetrexed infusion, all participants should receive the appropriate supplementation of vitamin B12, folic acid, and dexamethasone; see Section 8.1.8.1.2.3.

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

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

6.6 Dose Modification (Escalation/Titration/Other)

Dose modifications for chemotherapy components are to follow the recommendation detailed in the prescribing information for the relevant product.

Toxicity events may be attributed to MK-7684A, pembrolizumab, individual chemotherapy agents, or to the combination of MK-7684A plus chemotherapy or pembrolizumab plus chemotherapy.

Refer to Appendix 7 for country-specific dose modification requirements.

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 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations (MK-7684A) or IO Combinations

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

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

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

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

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

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations (MK-7684A) or IO Combinations

Pembrolizumab monotherapy, coformulations (MK-7684A) or IO combinations may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations (MK-7684A) or IO combinations associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Monotherapy, Coformulations (MK-7684A) or IO Combinations Infusion Reaction Dose Modification and Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing
h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSAIDs= nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

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

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Dose Modifications for Chemotherapy

If a participant experiences a >10% weight change from baseline, the doses of paclitaxel/nab-paclitaxel, pemetrexed, cisplatin, or carboplatin are to be recalculated.

Dose modifications due to AEs will depend on the investigator's assessment of causality. If appropriate, the investigator may attribute each toxicity event to paclitaxel, nab-paclitaxel, pemetrexed, cisplatin, carboplatin, MK-7684A or pembrolizumab alone, or to the combination, and use a stepwise dose modification (Table 8, Table 9, Table 10). Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both agents are to be reduced according to recommended dose modifications.

If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of chemotherapy throughout the course of the study for toxicities. Participants who require a third dose modification to any particular component will have that intervention discontinued. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative recommended dose adjustment is to be followed (ie, the dose reduction appropriate to the most severe toxicity). Once the dose has been decreased, it should remain reduced for all subsequent administrations or be further reduced, if necessary. There will be no dose escalations in this study.

If the toxicity is related to the combination of 3 agents (MK-7684A/pembrolizumab, taxane, and platinum agents), all 3 agents are to be reduced (chemotherapy only), interrupted, or discontinued according to the recommended dose modifications. If all 3 agents are discontinued due to a toxicity, the participant must be discontinued from the study. MK-7684A and pembrolizumab dose reductions are not permitted. MK-7684A and pembrolizumab treatment may be delayed/interrupted for a maximum of 12 weeks for an AE (see Section 6.6.1).

Study intervention-related toxicities must be resolved to baseline or Grade ≤1 (with the exception of alopecia, Grade 2 fatigue, Grade 2 peripheral neuropathy, Grade 2 anemia, endocrine-related AEs (Grade ≤2) requiring treatment or hormone replacement and creatinine clearance, for which the guidelines provided below may be followed) before administering the subsequent cycle. Participants must not receive the next cycle of chemotherapy if any of the following apply:

- Absolute neutrophil count <1500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <8 g/dL
- Total bilirubin level >1.5 × ULN
- AST and ALT levels ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present
- CrCl will be based on the Cockcroft-Gault formula.
    - For participants receiving cisplatin, the scheduled dose of cisplatin may only be administered if the calculated CrCl is ≥50 mL/min.

If CrCl falls to <50 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥50mL/min,

decrease cisplatin to DL-1 (Table 8). Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the second occurrence of CrCl <50 mL/min, decrease cisplatin to DL-2 upon improvement of CrCl to ≥50 mL/min. Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.
- At the third occurrence of CrCl <50 mL/min, cisplatin is to be discontinued. If in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, at the discretion of the investigator and in consultation with the Sponsor.
  - For participants receiving carboplatin, the scheduled dose of carboplatin may only be administered if the calculated CrCl is ≥40 mL/min.

If CrCl falls to <40 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥40 mL/min, decrease carboplatin to DL-1 (Table 8).

- At the second occurrence of CrCl <40 mL/min, decrease carboplatin to DL-2 (Table 8) upon improvement of CrCl to ≥40mL/min.
- At the third occurrence of CrCl <40 mL/min, carboplatin is to be discontinued.

During concurrent chemotherapy treatment:

- If paclitaxel/nab-paclitaxel or pemetrexed dosing is delayed or interrupted on Day 1, the platinum agent and MK-7684A/pembrolizumab will also be delayed/interrupted. If paclitaxel/nab-paclitaxel or pemetrexed is delayed or interrupted during Cycles 1 through 4, participants are to be seen weekly until toxicity resolves.
- If platinum dosing is delayed or interrupted on Day 1, MK-7684A/pembrolizumab and pemetrexed/paclitaxel/nab-paclitaxel will also be delayed/interrupted. If platinum agent is delayed or interrupted during Cycles 1 through 4, participants are to be seen weekly until toxicity resolves.
- If MK-7684A/pembrolizumab dosing is delayed or interrupted, platinum agent, pemetrexed/paclitaxel/nab-paclitaxel can continue as scheduled. MK-7684A/pembrolizumab administration is to be attempted at the next cycle of therapy.
- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 days) despite supportive treatment. If only one of the agents is thought to be causing the specified toxicity leading to a 21-day delay of administration of the next cycle, that chemotherapeutic agent can be withheld and treatment can continue with MK-7684A/pembrolizumab and the remaining chemotherapy drug. MK-7684A/pembrolizumab dosing can continue with 1 agent or as monotherapy.

The reason for the dose interruption or reduction is to be captured on the appropriate eCRF.

A participant is allowed to switch from cisplatin to carboplatin if the participant develops unexpected toxicities with the use of cisplatin (including hearing loss), becomes ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the participant. This switch from cisplatin to carboplatin requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

A participant may be allowed to switch from paclitaxel to nab-paclitaxel if the participant experiences an infusion reaction to paclitaxel and the investigator considers switching to be in the best interest of the participant. This switch from paclitaxel to nab-paclitaxel requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

The CTCAE 5.0 must be used to grade the severity of AEs. All dose modifications are to be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 8, Table 9, and Table 10. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent.

Table 8 Dose-level Modifications for Chemotherapeutic Agents

	Nonsquamous: Pemetrexed Plus Platinum-based Chemotherapy			**Squamous: Carboplatin Plus Taxane (Paclitaxel or Nab-paclitaxel)**		
	Pemetrexed	Carboplatin	Cisplatin	Carboplatin	Paclitaxel	Nab-paclitaxel
Dose Level 0 (starting dose)	500 mg/m^2	AUC 5 mg/mL/min	75 mg/m^2	AUC 6 mg/mL/min	200 mg/m^2	100 mg/m^2
Dose Level -1	375 mg/m^2	AUC 3.75 mg/mL/min	56 mg/m^2	AUC 4.5 mg/mL/min	150 mg/m^2	75 mg/m^2
Dose Level -2	250 mg/m^2	AUC 2.5 mg/mL/min	38 mg/m^2	AUC 3 mg/mL/min	100 mg/m^2	50 mg/m^2
Dose Level -3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Abbreviation: AUC=area under the curve.						

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 9 and Table 10. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. These data are based on Day 1 cell counts.

Table 9 Recommended Chemotherapy Dose Modifications for Hematological Toxicity

Drug-related Toxicitya	Cisplatin	Carboplatin	Paclitaxel	Nab-paclitaxel	Pemetrexed
	Dose Level from Table 8				
Neutrophils (ANC) <500/mm^3 without fever	DL-1	DL-1	DL-1	DL-1	DL-1
Febrile neutropenia (fever ≥38.5°C and ANC <1,000/mm^3)	DL-1	DL-1	DL-1	DL-1	DL-1
Platelets <50,000/mm^3 without significant bleeding or requiring blood transfusion	DL-1	DL-1	DL-1	DL-1	DL-1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring blood transfusion	DL-2	DL-2	DL-2	DL-2	DL-2
Grade 4 hemoglobin	DL-1	DL-1	DL-1	DL-1	DL-1

Abbreviations: ANC=absolute neutrophil count; DL=dose level

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

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

Table 10 Recommended Chemotherapy Dose Modifications for Nonhematological Toxicity

Drug-Related Toxicitya	CTCAE Grade	Cisplatin	Carboplatin	Paclitaxel	Nab-paclitaxel	Pemetrexed
		Dose Level from Table 8				
Nausea/vomiting	Grade ≥3[b]	DL-1	DL-1	DL-1	DL-1	No modification
Mucositis	Grade ≥3[b]	DL-1	DL-1	DL-1	DL-1	DL-2
Diarrhea	Grade ≥3[b]	DL-1	DL-1	DL-1	DL-1	DL-1

Drug-Related Toxicity[a]	CTCAE Grade	Cisplatin	Carboplatin	Paclitaxel	Nab-paclitaxel	Pemetrexed
Peripheral neuropathy	Grade 2	DL-1[c]	No modification	DL-1	DL-1	No modification
	Grade 3	Discontinue[d]	DL-1	Discontinue	Discontinue	DL-1
	Grade 4	Discontinue	DL-1	Discontinue	Discontinue	DL-1
Total bilirubin	Grade 2	No modification	No modification	DL-2	DL-2	No modification
	Grade 3	No modification	No modification	Discontinue	Discontinue	No modification
	Grade 4	No modification	No modification	Discontinue	Discontinue	No modification
AST or ALT Elevation	Grade 3	DL-1	DL-1	Discontinue	Discontinue	DL-1
	Grade 4	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Other nonhematologic toxicity (except fatigue and transient arthralgia and myalgia)	Grade≥ 3	DL-1	DL-1	DL-1	DL-1	DL-1

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=common terminology criteria for adverse events; DL=dose level.

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

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

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

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

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

6.6.3 Other Allowed Dose Interruption for Study Intervention

Pembrolizumab, MK-7684A, or chemotherapy may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously

administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is blinded, but supplies are provided open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

At implementation of Amendment 05 or 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 will be unblinded.
- Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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.
- Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned.
- 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.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Assessments listed in the SoA will be done per local SOC.
- 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 regimen will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.5 unless the participant has withdrawn from the study Section 7.2.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Interruption of chemotherapy (carboplatin and/or taxane [paclitaxel/nab-paclitaxel] for squamous NSCLC; pemetrexed and/or carboplatin/cisplatin for nonsquamous NSCLC) for more than 6 weeks. Participants may continue on study upon consultation with Sponsor.
- 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.
- The participant is 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 BICR-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.

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

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

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

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

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

At implementation of Amendment 05 or 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 will be unblinded.
- Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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.
- Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned.
- 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.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Assessments listed in the SoA will be done per local SOC.
- 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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent, 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

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

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

8.1.2 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.

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

8.1.4.1 Non-small Cell Lung Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's NSCLC. This information will include, but is not limited to, date of diagnosis, stage, histology, location(s) of primary lesions, location(s) of metastases and prior treatment.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. 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. In addition, new medications started during the Second Course through the Second Course Safety Follow-up Visit are to 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.

Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

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

Study intervention should begin within 3 days of intervention randomization.

8.1.8.1 Timing of Dose Administration

For in-clinic dosing, study intervention will be administered after all procedures and assessments have been performed. When administering MK-7684A or pembrolizumab in combination with chemotherapy, administer treatments in the following order:

- MK-7684A or pembrolizumab
- Chemotherapy

8.1.8.1.1 MK-7684A and Pembrolizumab

MK-7684A and pembrolizumab will be administered using a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of 5 minutes and +10 minutes is permitted (ie, infusion time is 25 to 40 minutes). The Pharmacy

Manual contains specific instructions for MK-7684A and pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

After Cycle 1 Day 1, MK-7684A or pembrolizumab will be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle for administrative reasons.

8.1.8.1.2 Chemotherapy

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

8.1.8.1.2.1 Carboplatin (AUC 6 [Squamous] or AUC 5 [Nonsquamous])

Carboplatin (AUC 6 [mg/mL/min] squamous; AUC 5 [mg/mL/min] nonsquamous) will be administered as an IV infusion over approximately 60 minutes Q3W on Day 1 for each of the 4 cycles (Intervention Phase) and after MK-7684A or pembrolizumab as per local practice and labels. The carboplatin dose is to be calculated using the Calvert Formula (see below) and is not to exceed 900 mg (squamous) or 750 mg (nonsquamous).

Calvert Formula (Squamous dose):

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert Formula is not to exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 6 × (125 + 25)
  = 6 × 150

  = 900 mg

Calvert Formula (Nonsquamous dose):

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert Formula is not to exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 5 × (125 + 25)
  = 5 × 150

  = 750 mg

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

- Male: [(140 - age (y)) × weight (kg)]/[72 × serum creatinine (mg/dL)]
- Female: [(140 - age (y)) × weight (kg)] × 0.85/[72 × serum creatinine (mg/dL)]

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

Additional premedications are to be administered as per standard practice.

8.1.8.1.2.2 Paclitaxel or Nab-paclitaxel (Squamous)

Paclitaxel or nab-paclitaxel will be administered immediately after MK-7684A or pembrolizumab and is to be completely administered before initiating the carboplatin dose.

- Paclitaxel (200 mg/m^2 Q3W) will be administered as an IV infusion over 3 hours for 4 cycles as per local practice and labels. All participants are to be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications are to be administered as per standard practice.
- Nab-paclitaxel (100 mg/m^2) will be administered at as an IV infusion over 30 minutes for 4 cycles as per local practice and labels. Participants will be dosed on Day 1, 8 (±1 day), and 15 (±1 day) of each 3-week cycle.

A participant may be allowed to switch from paclitaxel to nab-paclitaxel if the participant experiences an infusion reaction to paclitaxel and the investigator considers switching to be in the best interest of the participant. This switch from paclitaxel to nab-paclitaxel requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

8.1.8.1.2.3 Pemetrexed (Nonsquamous)

Pemetrexed (500 mg/m^2 Q3W) will be administered as an IV infusion over 10 minutes. Pemetrexed administration is to be completed at least 30 minutes before the initiation of carboplatin or cisplatin. All participants are to receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis as listed below (or as per local label):

- Folic acid 350 to 1000 µg PO: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1-4 but not to exceed doses in MASCC guidelines (Section 8.1.8.1.3).

8.1.8.1.2.4 Cisplatin (Nonsquamous)

Cisplatin (75 mg/m^2 Q3W) will be administered as an IV infusion over 30 to 180 minutes on Day 1 for up to 4 cycles (Intervention Phase) and after MK-7684A or pembrolizumab as per local practice and labels.

Participants are allowed to switch from cisplatin to carboplatin if the participant becomes ineligible for further cisplatin therapy according to local guidelines and the investigator considers switching to carboplatin to be in the best interest of the participant. This switch

from cisplatin to carboplatin requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

8.1.8.1.3 Antiemetic Therapy

Antiemetic therapy should follow the MASCC guidelines. In each cycle of treatment during the Intervention Phase, antiemetic therapy should include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and/or aprepitant [Roila, F., et al 2016].

8.1.8.1.4 Colony-stimulating Factors

The use of CSFs when administering chemotherapy is highly recommended as primary prophylaxis to reduce the risk of febrile neutropenia in this patient population, especially as many participants have multiple comorbidities and advanced disease. Granulocyte-CSF should not be used within 14 days before randomization.

8.1.9 Discontinuation and Withdrawal

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

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

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

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

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician 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. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

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

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue for Biomarker Status

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

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

Or

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

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

Details pertaining to tumor tissue submission can be found in the 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 diagnostic kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status in participants with NSCLC for treatment with pembrolizumab.

The PD-L1 result will be masked to the site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

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

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

Magnetic resonance imaging is preferred for brain scans; however, CT imaging with IV contrast will be acceptable, if MRI is medically contraindicated.

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

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment include PET-CT. Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

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

Further details are provided in the SIM.

8.2.1.1 Initial Tumor Scans

The screening scans must be submitted to the iCRO for retrospective review.

Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days of randomization and can be assessed by the iCRO.

Bone scans are required at Screening for participants with history of bone metastases or signs/symptoms suggestive of bone metastases. Bone scan refers to imaging methods used to assess bone metastasis. The specific methods permitted for this study are described in the SIM.

Brain scans are required for all participants at Screening. Participants with treated brain metastases (eg, whole brain radiation treatment, stereotactic radiosurgery, or equivalent) may participate only if they satisfy all of the following:

- Have no evidence of new or enlarging brain metastases confirmed by posttreatment repeat brain imaging (using the same modality) performed at least 4 weeks after pretreatment brain imaging, and
- Are neurologically stable without the need for steroids for at least 14 days before first dose of study treatment as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.
- Have asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm).

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 6 weeks (42 days ±7 days) from the date of randomization followed by Week 12 (84 days ±7 days) and Week 18 (126 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 63 weeks (441 days ±7 days), participants who remain on treatment will have scans performed every 12 weeks (84 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans are to be performed until disease progression is identified by the investigator and verified by the BICR, or until the start of new anticancer treatment, pregnancy, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

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

For participants with brain metastases at Screening (whether treated or untreated), on-study brain scans are to be acquired at Week 6 and as clinically indicated. For participants with no brain metastases at Screening, on-study brain scans are to be acquired only if clinically indicated. All participants with brain metastases at Screening require brain scans to confirm CR.

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

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

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

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

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

- the end of the study

Follow-up visits may be scheduled to coincide with the scan schedule. If discontinuation is not due to BICR-verified disease progression, then tumor scans should continue on the initial treatment period schedule.

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days before restarting study intervention with MK-7684A or pembrolizumab.

If disease progression has been verified by BICR for the First Course, the Second Course may be initiated. The disease progression scan may be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets scan standards.

The first scan should be performed at 12 weeks (84 day ±7 days) after restarting study intervention. Subsequent tumor scans are to be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Scans are to be performed until:

- disease progression,
- the start of a new anticancer treatment,
- pregnancy,
- withdrawal of consent,
- death,
- completion of Second Course,
- or notification by the Sponsor, whichever occurs first

Response assessments and PD in the Second Course are determined by site assessment only. No scans from the Second Course Phase should be provided to the central vendor, except for the Second Course Phase Screening scan if this scan is also the final scan for the initial treatment phase.

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

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

8.2.1.5 RECIST 1.1 Assessment of Disease

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

Upon investigator-assessed disease progression, the indicative scans 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.

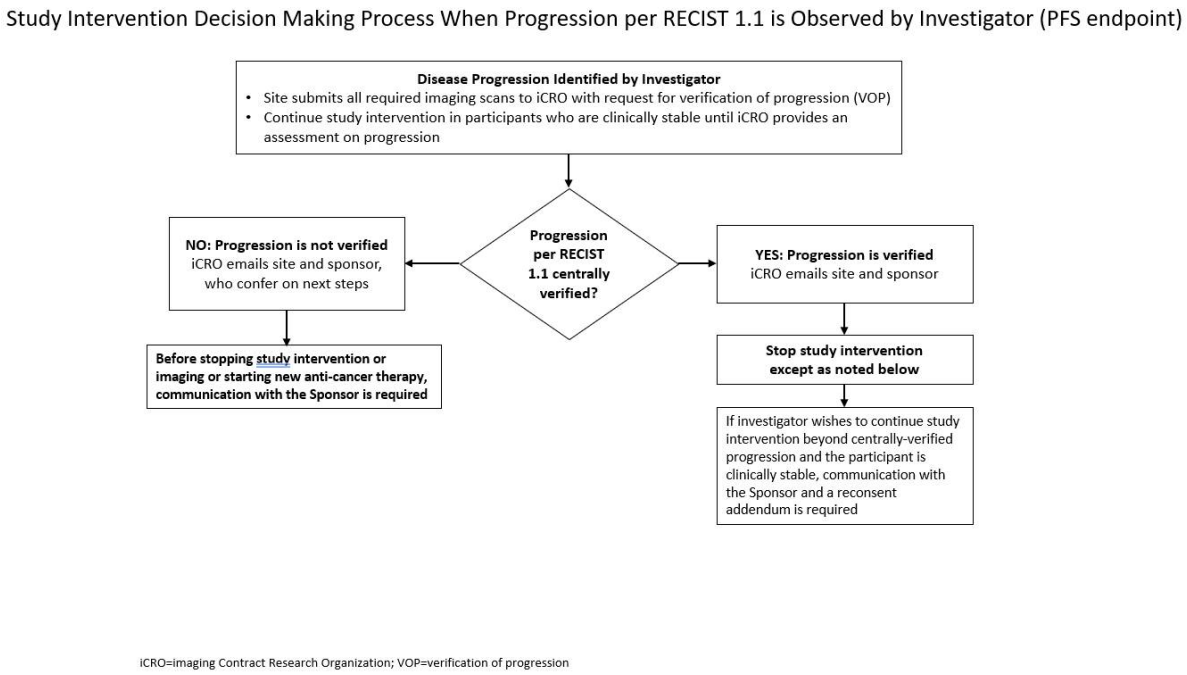
If disease progression is verified, the process continues as follows:

- 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
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

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

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

Figure 3 Imaging and Treatment for Clinically Stable Participants Treated With MK-7684A or Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator



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

8.2.2 Patient-reported Outcomes

CCI [redacted] The questionnaires are to be administered before dosing at every cycle through Cycle 17, then every other cycle through Cycle 35 (eg, Cycles 1-17, 19, 21, 23, 25, 27, 29, 31, 33, and 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.

8.2.3 PD-L1 Status

The results of PD-L1 status are required before randomization.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.1.1 Full Physical Examination

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

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

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

Vital signs will be recorded after 5 minutes of rest and include systolic and diastolic blood pressure, temperature, pulse, and respiration rate. Vital signs will be assessed at the visits designated in the SoA (Section 1.3) by a validated method.

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 pulse rate, QRS, and QT intervals. Refer to Appendix 3 for evaluation and potentially significant findings.

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 Laboratory or Study Procedures Manual. Refer to the Schedule of Activities (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.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1. Refer to Appendix 7 for country-specific requirements.

- 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 for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
  - MK-7684A/pembrolizumab: 120 days
  - Chemotherapy: 180 days
- 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 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group Performance Status

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

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

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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 causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, 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 11.

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

Table 11 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

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

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

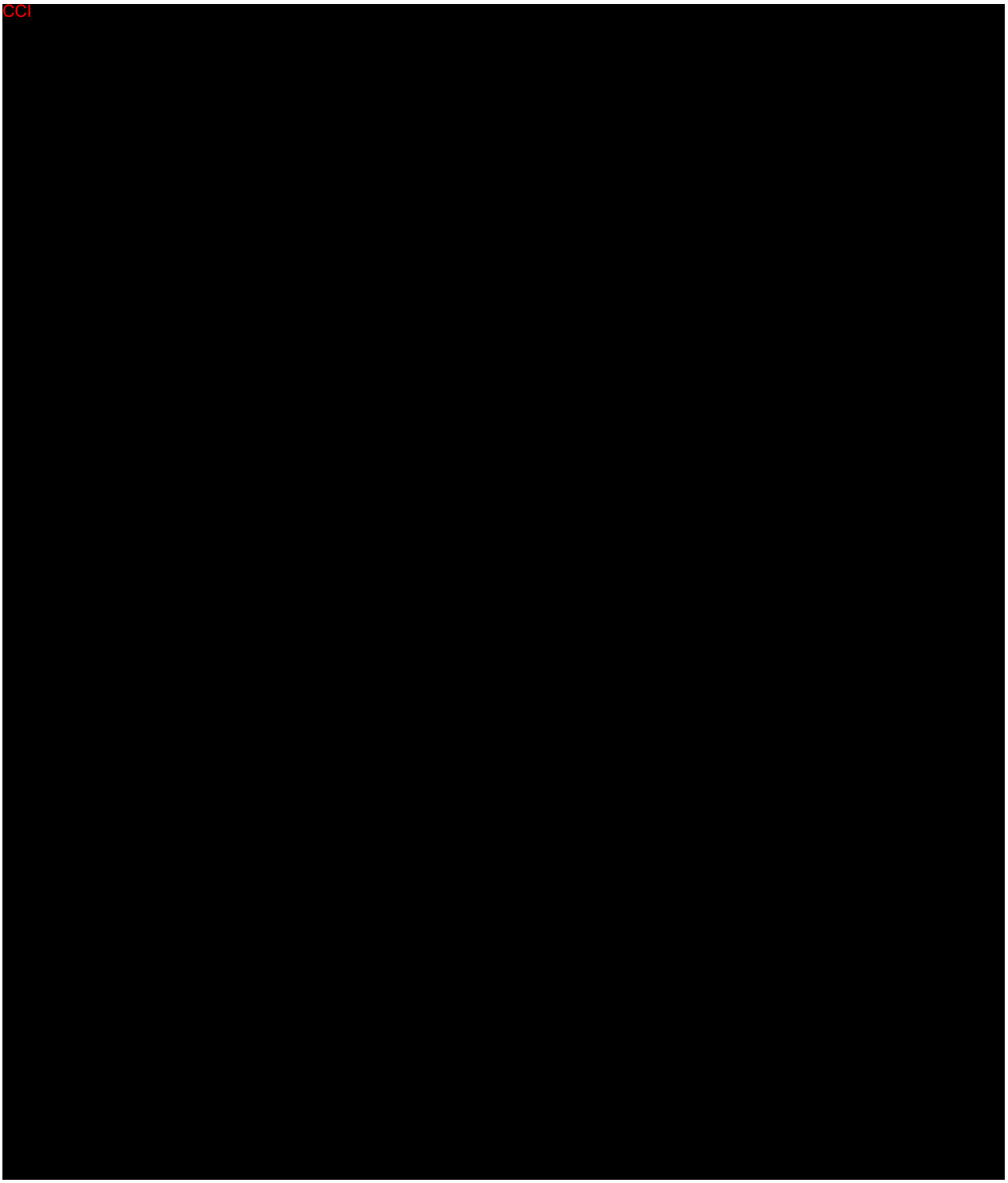
1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

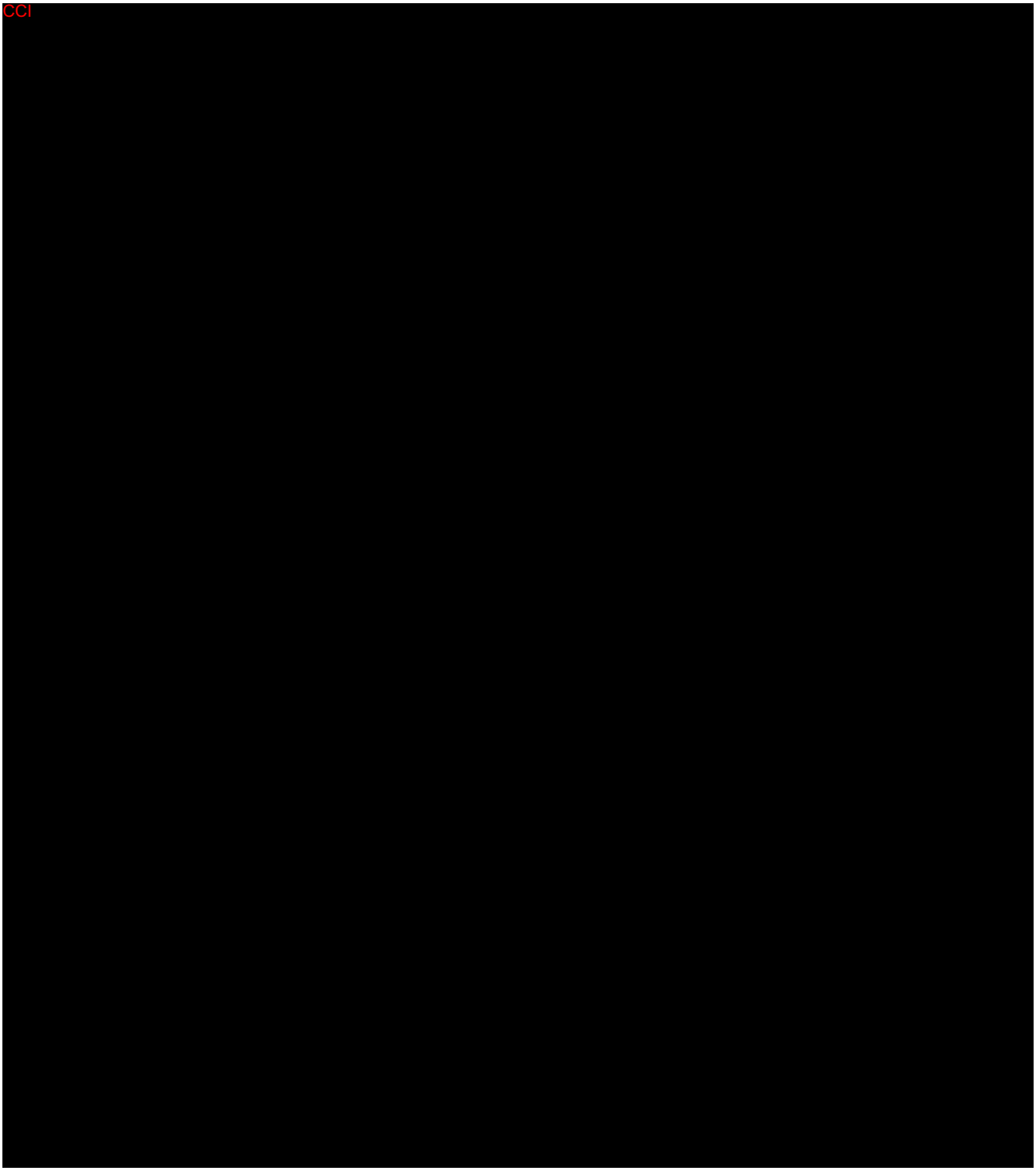
8.5 Treatment of Overdose

For 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.

CCI





8.10 Medical Resource Utilization and Health Economics

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

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

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency department visits, tests and procedures, and medications).

8.11 Visit Requirements

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

8.11.1 Screening

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

Screening procedures are to be completed within 28 days before the first dose of study intervention or sooner as indicated in the SoA (Section 1.3).

Participants may be rescreened one time 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 Sections 8.1, 8.2, and 8.3.

8.11.3 Second Course Treatment Period

See Sections 1.3.3 and 6.1.2 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 intervention due to BICR-verified disease progression 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 End of Treatment Visit is to 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 are to be performed.

8.11.5 Posttreatment Visit

At the end of study intervention, each participant will be followed for a minimum of 30 days for AE monitoring. Serious AEs occurring within 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, will be collected.

Participants will have posttreatment follow-up for disease status, including radiographic imaging, until initiating a nonstudy anticancer treatment, experiencing BICR-verified disease progression, death, withdrawing consent, becoming lost to follow-up, or end of study.

All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

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 MK-7684A or pembrolizumab 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 BICR-verified disease progression will begin Efficacy Follow-up and are to be assessed using the same schedule calculated from the date of randomization. Imaging will continue to be collected in the Efficacy Follow-up Phase (see Section 8.2.1.3). Every effort should be made to collect information regarding disease status until BICR-verified disease progression, the start of new anticancer therapy, pregnancy, death, withdrawal of consent, or the end of the study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who complete all efficacy assessments and/or will not have further efficacy assessments must enter survival follow-up.

Participants who are eligible to receive retreatment with MK-7684A or pembrolizumab according to the criteria in Section 6 will move from Efficacy Follow-up to the Second

Course when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with MK-7684A or 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 are to 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 complete 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 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

At implementation of Amendment 05 or 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 will be unblinded.
- Participants receiving MK-7684A plus chemotherapy will be transitioned to pembrolizumab plus chemotherapy.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab plus chemotherapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab with chemotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab plus chemotherapy 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 on 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.
- Second course treatment of pembrolizumab for participants currently not on second course treatment will be offered. Any participant already receiving Second Course treatment will be able to complete treatment as planned.
- 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.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Assessments listed in the SoA will be done per local SOC.
- 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. Changes to analyses made after the protocol has been finalized will be documented in a sSAP and referenced in the CSR for the study.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Randomized, Double-Blind, Phase 3 Study of Pembrolizumab/Vibostolimab Coformulation (MK-7684A) in Combination with Chemotherapy Versus Pembrolizumab Plus Chemotherapy in Participants with Metastatic Non-Small Cell Lung Cancer (MK-7684A-007/KEYVIBE-007)
Treatment Assignment	Approximately 700 participants will be randomized in a 1:1 ratio between 2 treatment arms: (1) MK-7684A plus chemotherapy and (2) pembrolizumab plus chemotherapy. CCI [redacted]
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoints	• OS in participants with PD-L1 TPS≥1%

Secondary Endpoints	• OS in all participants • PFS per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS≥1% and all participants • ORR per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS≥1% and all participants • DOR per RECIST 1.1 as assessed by BICR in participants with PD-L1 TPS≥1% and all participants • Change from baseline in global health status/QoL, cough, chest pain, dyspnea, role functioning, and physical functioning scores in participants with PD-L1 TPS≥1% and all participants • TTD in global health status/QoL, cough, chest pain, dyspnea, role functioning, and physical functioning in participants with PD-L1 TPS≥1% and all participants • Safety and tolerability
Statistical Methods for Key Efficacy Analyses	The primary and key secondary hypotheses testing of OS in participants with PD-L1 TPS≥1% and all participants, and PFS in all participants will be evaluated by comparing the MK-7684A plus chemotherapy treatment arm with the pembrolizumab plus chemotherapy treatment arm using a stratified log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
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, these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	CCI [redacted]

Multiplicity	The overall Type I error over the primary and key secondary hypotheses is strongly controlled at 2.5% (1-sided), CCI [redacted] [Lan, K. K. G. and DeMets, D. L. 1983] [O'Brien, P. C. and Fleming, T. R. 1979].
Sample Size and Power	CCI [redacted] articipants per treatment arm will be used for study planning purposes. CCI [redacted]

9.2 Responsibility for Analyses/In-house Blinding

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

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

An eDMC will serve as the primary reviewer of the results of the interim analysis of the study and will make recommendations for discontinuation of the study or protocol modifications to the study EOC. Treatment-level results of the interim analyses will be provided by the unblinded statistician to the eDMC. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level 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 logistical details will be provided in the eDMC charter. Key aspects of the interim analyses are described in Section 9.7.

Before 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.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoints

- **Overall Survival**

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

Secondary Efficacy Endpoints

- **Progression-free survival**

  PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

- **Objective Response Rate**

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

- **Duration of Response**

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

9.4.2 Safety Endpoints

Safety and tolerability of study treatment will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. AEs will be assessed as defined by NCI CTCAE 5.0. A description of safety measures is provided in Section 8.3.

9.4.3 Patient-reported Outcomes

The following secondary PRO endpoints will be evaluated as described in Section 4.2.1.3 and analyzed as described in Section 9.6.3:

Change from baseline in

1. Global health status/QoL score (QLQ-C30 items 29-30)
2. Single-item symptom scores: cough (QLQ-LC13 item 31), chest pain (QLQ-LC13 item 40), and dyspnea (QLQ-C30 item 8)
3. Functioning scores: physical functioning (QLQ-C30 items 1-5) and role functioning (QLQ-C30 items 6-7)

Time to deterioration in

4. Global health status/QoL score (QLQ-C30 items 29-30)
5. Single-item symptom scores: cough (QLQ-LC13 item 31), chest pain (QLQ-LC13 item 40), and dyspnea (QLQ-C30 item 8)
6. Functioning scores: physical functioning (QLQ-C30 items 1-5) and role functioning (QLQ-C30 items 6-7)

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

These analyses and other supportive PRO analyses will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for primary efficacy analysis. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

The analysis population for DOR consists of participants in the analysis population of OR who demonstrate confirmed CR or PR.

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 included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. 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. Any participants who receive the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the participant's randomized treatment group and a narrative will be provided for any events that occur during the cycle for which the participant was incorrectly dosed.

At least one laboratory or vital sign 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

9.6.1 Statistical Methods for Efficacy Analyses

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.6.2 Statistical Methods for Safety Analyses

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

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, a drug-related AE, a serious AE, a serious drug-related AE, a Grade 3-5 AE, a drug-related Grade 3-5 AE, a discontinuation from study intervention due to an AE, and an AE resulting in death. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with the event will be provided based on the criteria described below.

Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided for AEs that occur in at least 10% of participants in any treatment group. The threshold of at least 10% of participants was chosen because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in

the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will also be summarized by point estimate and 95% CIs.

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.

9.6.2.2 Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated will be evaluated separately. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI.

Table 15 summarizes the analysis strategy for safety endpoints in this study.

Table 15 Analysis Strategy for Safety Endpoints

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI (Graphical Display)
Overall Safety Assessment	Specific AEs (incidence 10% of participants in one of the treatment groups)	X	X
	Specific Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Any AE	X	
	Any Grade 3-5 AE	X	
	Any serious AE	X	
	Any drug-related AE	X	
	Any serious and drug-related AE	X	
	Any Grade 3-5 and drug-related AE	X	
	Discontinuation study treatment due to AE	X	
	AE that resulted in death	X	

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI (Graphical Display)
	AE that led to dose interruption	X	
	AE that led to dose reduction	X	
	Specific AEs, system organ classes (incidence <10% of participants in all of the treatment groups)	X	
	Change from Baseline Results (laboratory toxicity shift, vital signs)	X	
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	
Abbreviations: AE=adverse event; AEOSI=adverse event of special interest; CI=confidence interval.			

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 PRO endpoint (global health status/QoL, physical functioning, role functioning, dyspnea, cough, chest pain) defined in Section 9.4.3, 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

For the TTD endpoint defined in Section 9.4.3, the Kaplan-Meier method will be used to estimate the TTD curve for each treatment group. The estimate of median TTD and its 95% CI 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. Table 16 provides censoring rule for TTD analysis.

Table 16 Censoring Rules for Time-to-Deterioration

Scenario	Outcome
Deterioration confirmed	Event observed at time of assessment (first deterioration)
Ongoing or discontinued from study without confirmed deterioration	If the first deterioration is at the last assessment timepoint, then event observed at time of assessment (first deterioration); otherwise, right censored at time of last assessment
No baseline assessments	Right censored at treatment start date

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 analysis 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 [redacted]

CCI [redacted]

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. CCI [redacted]

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W., et al 2011] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. CCI [redacted]

CCI

[redacted]

9.8.1 Progression-free Survival

CCI

[redacted]

CCI

[redacted]

9.8.2 Overall Survival

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.8.3 Safety Analyses

The DMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. DMC review of efficacy data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy interim analysis. However, to account for any multiplicity concerns raised by the DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for ORR, PFS, and OS adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

CCI

[redacted]

CCI

[redacted]

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 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 prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

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

III. Participant Protection

A. 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 their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this

process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 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) 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.

10.1.4.2 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.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 22 will be performed by the local laboratory.
- All on-treatment samples will be collected before administration of study intervention.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 22 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	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate[a]	Chloride	Phosphorous[a]
	Creatinine or creatinine clearance[d]	Sodium	ALT/SGPT	Total Protein
	Glucose (nonfasting)	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[f] by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	FSH (as needed in women of nonchildbearing potential only) Serum or urine β-hCG pregnancy test (as needed for WOCBP) Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) as required by local health authority or institutional regulations. Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

Laboratory Assessments	Parameters
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; SOC=standard of care; ULN=upper limit of normal; WBC=white blood count; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential Notes: a. Performed only if considered local SOC. b. Absolute or % acceptable per institutional standard. c. If BUN is not available, urea may be tested. d. 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. Leukocyte esterase testing is optional if it is not the local SOC	

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

Refer to Appendix 7 for country-specific requirements.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

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

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- 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 (diary, etc.), seroconversion or identification of vaccine virus 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?

  - **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 the 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, AND IF REQUIRED, THE IRB/IEC.

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

10.3.6 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 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

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

See Appendix 7 for country-specific requirements.

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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

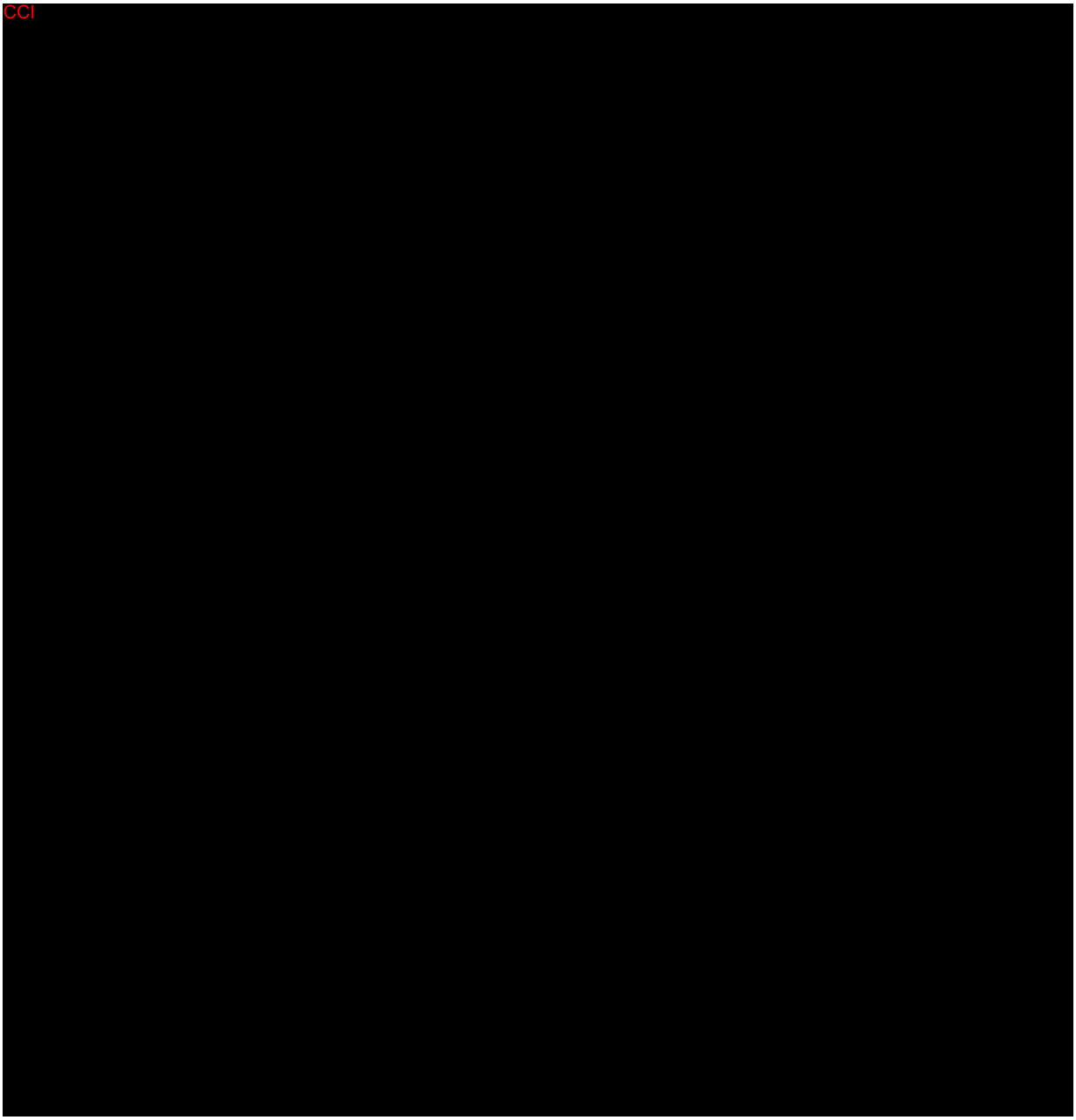
10.7 Appendix 7: Country-specific Requirements

10.7.1 Argentina-specific Requirements

Section 1.3 Schedule of Activities

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

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



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[redacted]

10.7.3 France-specific Requirements

Section 1.3.1 Screening and Intervention Phase

Audiogram to be completed at screening and at the beginning of each cycle for participants taking cisplatin.

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

Section 1.3.3 End-of-intervention and Long-term Follow-up

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

Section 5.2 Exclusion Criteria

- Participants who have a known history of HIV infection. HIV testing is required for participants.
- Participants who have a known history of hepatitis B or C infection. Hepatitis B and C testing is required for participants.

Carboplatin / Paclitaxel only:

a. Participants who experience hemorrhage from tumor

b. Participants who use phenytoin or fosphenytoin

Cisplatin / Pemetrexed only:

a. Participants with a hearing impairment

b. Participants with pathologies that are a contraindication to hyperhydration before chemotherapy administration

c. Participants who are unable to tolerate use of phenytoin

Section 6.5 Concomitant Therapy

Investigators must refer to the up-to-date SmPC of registered products used in this study, regarding forbidden medications or medications to be used with precaution.

Section 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 (MK-7684A) or IO Combinations

Participants are to be discontinued from study intervention if any of the following AEs occur:

- Grade 4 skin rash
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Section 8.3.5 Pregnancy Testing

- Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

Section 10.5 Appendix 5: Contraceptive Guidance

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

10.7.4 Germany-specific Requirements

Section 1.3 Schedule of Activities

Monthly urine pregnancy testing is required during study intervention as well as at the end of study intervention.

Section 5.2 Exclusion Criteria

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

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

Section 6.5.1 Rescue Medications and Supportive Care

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

Legally Acceptable Representative Protocol Sections

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

10.7.5 Japan-specific Requirements

Section 1.3 Schedule of Activities

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 MSD K.K.

Section 6.1 Study Intervention(s) Administered

Table 5 Study Interventions

Pembrolizumab used in this study is categorized as “product(s) used in the clinical trial other than test product(s)” in Japan local regulation.

10.7.6 Spain-specific Requirements

Section 1.3.1 Screening and Intervention Phase

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

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

Tuberculosis (TB; *Bacillus tuberculosis*) testing at screening is a required evaluation for study entry and needs to be performed to evaluate eligibility. This testing can be performed at any time during the screening period.

Section 1.3.3 End-of-intervention and Long-term Follow-up

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

Section 5.2 Exclusion Criteria

Has a known history of HIV infection. HIV testing is required at screening as mandated by local regulation.

Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for Hepatitis B and Hepatitis C is required at screening.

Has known active tuberculosis (TB; *Bacillus tuberculosis*). Testing for tuberculosis is required at screening.

Section 6.5 Concomitant Therapy

Investigators must refer to the up-to-date SmPC of registered products used in this study, regarding forbidden medications or medications to be used with precaution.

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

Section 8.3.5 Pregnancy Testing

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

Section 10.2 Appendix 2: Clinical Laboratory Tests

Other screening tests: serology (HIV-RNA, hepatitis B surface antigen, hepatitis C virus antibody, and tuberculosis), amylase, lipase.

Section 10.5 Appendix 5: Contraceptive Guidance

Monthly and end-of-treatment pregnancy testing must be conducted as per local regulations.

10.7.7 United Kingdom-specific Requirements

Section 5.1 Inclusion Criteria – Demographics

Males are to be advised to seek counseling on sperm storage before starting treatment with pemetrexed, taxane (paclitaxel/nab-paclitaxel), and/or platinum-based therapy as per respective SmPCs.

If male, agrees to the following during the intervention period and for at least the time required to continue contraception for each study intervention is as follows:

- Chemotherapy: at least 6 months from the last dose
- Refrain from donating sperm

PLUS:

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

Section 6.5 Concomitant Therapy

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

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

10.8 Appendix 8: ECOG Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry 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
5-HT3	5-hydroxytryptamine type 3
ADA	antidrug antibodies
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BID	twice daily
CD	cluster of differentiation
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSF	colony-stimulating factor
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group

Abbreviation	Expanded Term
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	minimum concentration
CYP	cytochrome P450
DCR	disease control rate
DL	dose level
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EGFR	endothelial growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EOT	end of treatment
ePROs	electronic patient-reported outcomes
EU CTR	European Union Clinical Trial Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FA	final analysis

Abbreviation	Expanded Term
FAS	Full Analysis Set
FBR	future biomedical research
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FoxP3	forkhead box P3
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
H	hypothesis
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGRAC	Human Genetic resources Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICSR	individual Case Safety Report
iCRO	imaging Clinical Research Organization
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry

Abbreviation	Expanded Term
ILD	interstitial lung disease
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	intervention randomization system
ITT	Intent-to-Treat
IUD	intrauterine device
IUO	Investigational Use Only
IUS	intrauterine hormone-releasing system
IV	intravenous
JAPIC-CT	Japan Pharmaceutical Information Center – Clinical Trials
KRAS	Kirsten rat sarcoma viral oncogene homolog
LAM	lactational amenorrhea method
LS	least squares
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
M&N	Miettinen and Nurminen
MM	multiple myeloma
mPD-1	murine programmed cell death 1 protein
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
NHL	non-Hodgkin lymphoma
NK	natural killer

Abbreviation	Expanded Term
NKT	natural killer T
N/n	number
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NSCLC-SAQ	Non-small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically-based PK
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Device Agency
PK	pharmacokinetic
PO	orally
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVR	poliovirus receptor
PVRIG	poliovirus receptor-related immunoglobulin
PVRL-2	poliovirus receptor-related 2
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ	quality of life questionnaire
QoL	quality of life

Abbreviation	Expanded Term
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RMST	restricted mean survival time
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIL	tumor-infiltrating lymphocyte(s)
Tim-3	T-cell immunoglobulin and mucin domain-containing-3
TPS	tumor proportion score
T-regs	regulatory T cells
TTD	time to deterioration
ULN	upper limit of normal
US	United States
VAS	Visual Analog Scale

Abbreviation	Expanded Term
vs	versus
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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