Official Protocol Title:	A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant EGFR-mutated Tumors in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants (KEYNOTE-789)
NCT number:	NCT03515837
Document Date:	24-July-2023

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant EGFR-mutated Tumors in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants (KEYNOTE-789)

Protocol Number: 789-08

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

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

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND NUMBER: 116,833

EudraCT NUMBER: 2017-004188-11

Approval Date: 24 July 2023

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-789-08	24-JUL-2023	Global amendment. To allow participants to rollover to the extension study (MK-3475-587).
MK-3475-789-07	20-SEP-2022	Global amendment. To provide additional text to specify that IA3 will become the final analysis if the observed number of events at IA3 is too close to the target number of events at FA.
MK-3475-789-06	17-JUN-2021	Global amendment. To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
MK-3475-789-05	25-JAN-2021	Global amendment. The overall survival (OS) assumption of this protocol was based on the IMPRESS study, which comprised patients who failed only first-line gefitinib. In this population, the median OS was 19.5 months; however, a recent small retrospective study showed a much lower median OS of 7.8 months in patients who failed osimertinib and switched to another therapy (primarily chemotherapy). Since KEYNOTE-789 includes a more heterogenous population, including those who failed first-line or second-line osimertinib or other first-line TKIs (if T790M-), the original assumption of OS will likely overestimate the survival in this study. Therefore, this amendment updates the OS design based on the characteristics of the population that was actually enrolled, changing the control assumption of median OS from 19.5 months to 15 months. The number and timing of analyses has also been updated based on actual enrollment timing.

Document	Date of Issue	Overall Rationale
MK-3475-789-04	23-MAR-2020	Global amendment. Based on better understanding of survival outcomes for this population, the initial hazard ratio (HR) assumption is likely to be too aggressive. To relax the HR for both OS and progression-free survival (PFS), and to maintain the same sample size, alpha allocation from objective response rate (ORR) needed to be redistributed. This amendment removes alpha from ORR and redistributes equally between PFS and OS, changes the assumption of the HR for PFS and OS from 0.65 to 0.7, and from 0.7 to 0.72, respectively, and removes ORR-only interim analysis (IA) reducing the number of IAs from 5 to 4.
MK-3475-789-03	30-AUG-2018	Global amendment. To update the inclusion criteria regarding creatinine clearance in order to align with regulatory safety labeling for pemetrexed.
MK-3475-789-02	10-JUL-2018	Germany-specific amendment. Per the German Health Authority request, pregnancy testing must be conducted monthly, and testing for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and tuberculosis (TB) at screening is required for residents of Germany.
MK-3475-789-01	16-MAY-2018	Sweden-specific amendment. Per the Swedish Health Authority request, the Health Authority must be notified in addition to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) when the protocol is amended or terminated.
MK-3475-789-00	23-FEB-2018	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.1	Synopsis	Added text related to extension study enrollment.	To allow participants to rollover to the extension study (MK-3475-587).
'4.4	Beginning and End of the Trial	Added text related to extension study enrollment.	To allow participants to rollover to the extension study (MK-3475-587) .

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Throughout Document		Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant EGFR-mutated Tumors in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants (KEYNOTE-789)

Short Title:

Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant *EGFR*-mutated Tumors in Metastatic Non-Squamous NSCLC

Objectives/Hypotheses and Endpoints:

In adult participants with TKI-resistant epidermal growth factor receptor (*EGFR*)-mutated tumors in metastatic non-squamous NSCLC:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To compare PFS per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) based on blinded independent central review (BICR) of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. • Hypothesis (H1): The combination of pembrolizumab + chemotherapy has superior PFS per RECIST 1.1 based on BICR compared to saline placebo + chemotherapy	• Progression-free survival (PFS) is the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first.
• Objective: To compare overall survival (OS) of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. • Hypothesis (H2): The combination of pembrolizumab + chemotherapy has superior OS compared to saline placebo + chemotherapy.	• OS is defined as the time from randomization to death due to any cause.

This study will be considered to have met its success criteria if the combination of pembrolizumab + chemotherapy is superior to saline placebo + chemotherapy in PFS or OS.	
Secondary	
• Objective: To compare objective response rate (ORR) per RECIST 1.1 based on BICR of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. • Hypothesis (H3): The combination of pembrolizumab + chemotherapy has superior ORR per RECIST 1.1 based on BICR compared to saline placebo + chemotherapy.	• Objective response is a confirmed complete response (CR) or partial response (PR).
• Objective: To evaluate duration of response (DOR) of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• DOR is defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST 1.1 based on BICR.
• Objective: To evaluate the patient reported outcomes (PROs) mean score changes from baseline in global health status and quality of life scale between pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 items (QLQ-C30) global health status (item 29) and quality of life scale (item 30).
• Objective: To evaluate the PROs time to true deterioration (TTD) in the composite endpoint of cough, chest pain or dyspnea between pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• TTD is the time from baseline to first onset of 10 points or more deterioration from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline of the composite endpoint of cough [EORTC QLQ-Lung Cancer Module 13 (LC13) item 1], chest pain [EORTC QLQ-LC13 item 10], or dyspnea [EORTC QLQ-LC30 item 8].
• Objective: To evaluate the safety and tolerability of the combination of pembrolizumab + chemotherapy and saline placebo + chemotherapy.	• Adverse events (AEs) and study drug discontinuation due to AEs.

Overall Design:

Study Phase	Phase 3
Clinical Indication	Treatment of Metastatic Non-squamous Non-small Cell Lung Cancer
Population	Adult participants with TKI-resistant *EGFR*-mutated tumors in metastatic non-squamous NSCLC including: • TKI-failures (including osimertinib failure) with T790M-negative mutation tumors • T790M-positive mutation tumors with prior exposure to osimertinib • First-line osimertinib failure regardless of T790M mutation status
Study Type	Interventional
Type of Design	Randomized, active-control with placebo, parallel-group, multi-site, double-blind
Type of Control	Active control with placebo
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 7 years from the time the first participant provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 492 participants will be randomized.

Treatment Groups and Duration:

Treatment Groups	There are 2 treatment arms: • Arm 1: Pembrolizumab (MK-3475) plus pemetrexed plus carboplatin or cisplatin • Arm 2: Saline placebo plus pemetrexed plus carboplatin or cisplatin
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 42 days, each eligible participant will be assigned to receive study treatment until reaching a discontinuation criterion (Section 7.1), examples of which include: disease progression is radiographically documented and verified by blinded independent central review (BICR), when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab/saline placebo (approximately 2 years). Maintenance pemetrexed may continue for participants past 35 cycles until reaching a discontinuation criterion (Section 7.1), as long as the participant is receiving benefit and per local regulations, whereas pembrolizumab/saline placebo are limited to 35 cycles. At the time of documented disease progression as confirmed by BICR using RECIST 1.1 (Section 8.2.1), participants may have treatment assignment unblinded (Figure 3). Participants who received saline placebo in combination with chemotherapy per their randomized treatment assignment may be eligible to receive pembrolizumab monotherapy for a total of 35 administrations in the Crossover Treatment Phase (Section 8.11.3). Tumor imaging is to be re-baselined and RECIST 1.1 criteria used for participant assessments (Sections 8.2.1.4 and 8.2.1.5).

	Participants who received pembrolizumab in combination with chemotherapy, but are deemed to be benefiting clinically despite disease progression, may continue study treatment beyond progression and receive pembrolizumab monotherapy in the Crossover Treatment Phase (Section 8.11.3) to complete a total of up to 35 pembrolizumab administrations. Repeat imaging should occur at appropriate intervals per iRECIST criteria (Sections 8.2.1 and 10.10) until iRECIST confirmed PD (iCPD) is established. Study treatment may continue until reaching a discontinuation criterion (Section 7.1). Alternatively, participants may have treatment assignment remain blinded at the time of BICR-verified progression and may continue receiving the study treatment per their randomized treatment assignment as long as they continue to be clinically stable (Figure 3). Blinded study treatment can continue beyond verified progression at the Investigator's discretion. Repeat imaging should occur at appropriate intervals per iRECIST criteria (Sections 8.2.1 and 10.10) until iCPD is established. Once iCPD is established, the participant may then have treatment assignment unblinded, but may not continue study treatment in the Crossover Treatment Phase (Section 8.11.3) as described above. Participants on the pembrolizumab plus chemotherapy arm who have been on study treatment for ≥ 6 months and who attain a complete response (CR) may consider stopping study treatment. These participants, as well as those who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, may be eligible for up to 17 additional administrations of open-label pembrolizumab monotherapy (approximately 1 year) in the Second Course Retreatment Phase upon experiencing subsequent disease progression (Section 8.2.1). Second Course Retreatment Phase is at the discretion of the investigator according to the criteria in Section 8.11.4. After the end of study treatment, each participant will be followed for a minimum of 30 days for the occurrence of AEs and for 120 days for spontaneously reported pregnancy, as described in Section 8.4. Serious adverse events will be collected for up to 90 days following cessation of the study treatment or 30 days following the cessation of treatment if the participant initiates new anti-cancer therapy.

	Participants who complete the protocol-required cycles of study intervention or who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR, the start of new anti-cancer treatment, pregnancy, participant withdraws consent, participant becomes lost to follow-up, participant death, or the end of the study. The Sponsor may request survival status to be assessed at additional time points and entered into the database during the course of the study. For example, survival status may be requested prior to, but not limited to, an external Data Monitoring Committee (eDMC) review. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. Survival status can be done in a variety of ways including phone, email, chart review, or review of public records. Survival status information (whether by telephone, review of public records, etc.) should be officially documented by the site. Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Study Governance:

Study Governance Committees

Committee	**Included in this study?**
Steering Committee	N
Executive Oversight Committee	Y
Data Monitoring Committee	Y
Clinical Adjudication Committee	N

Study governance considerations are outlined in Section 10.1.

A list of abbreviations used in this document can be found in Section 10.9.

1.2 Schema

The Study Eligibility Diagram is depicted in Figure 1, Initial and Crossover Treatment Phases is depicted in Figure 2, Initial Treatment Phase – Progressive Disease Decision Flow Diagram is depicted in Figure 3. Completion/Attainment of CR Decision Flow Diagram is depicted in Figure 4.

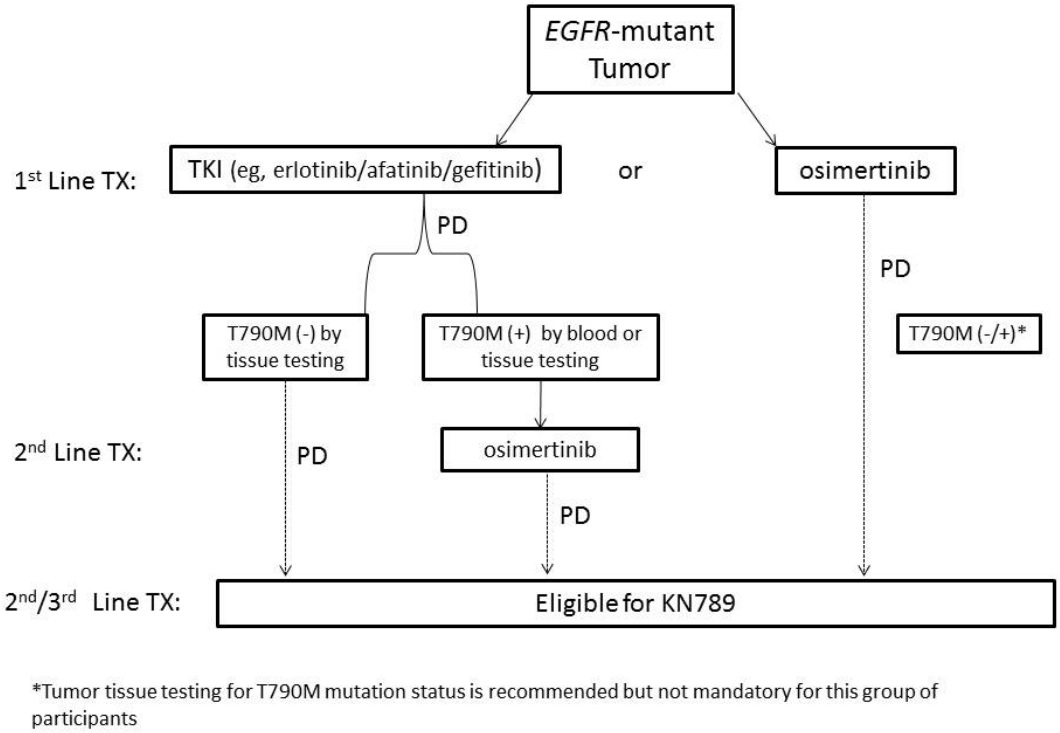


Figure 1 Eligibility Diagram

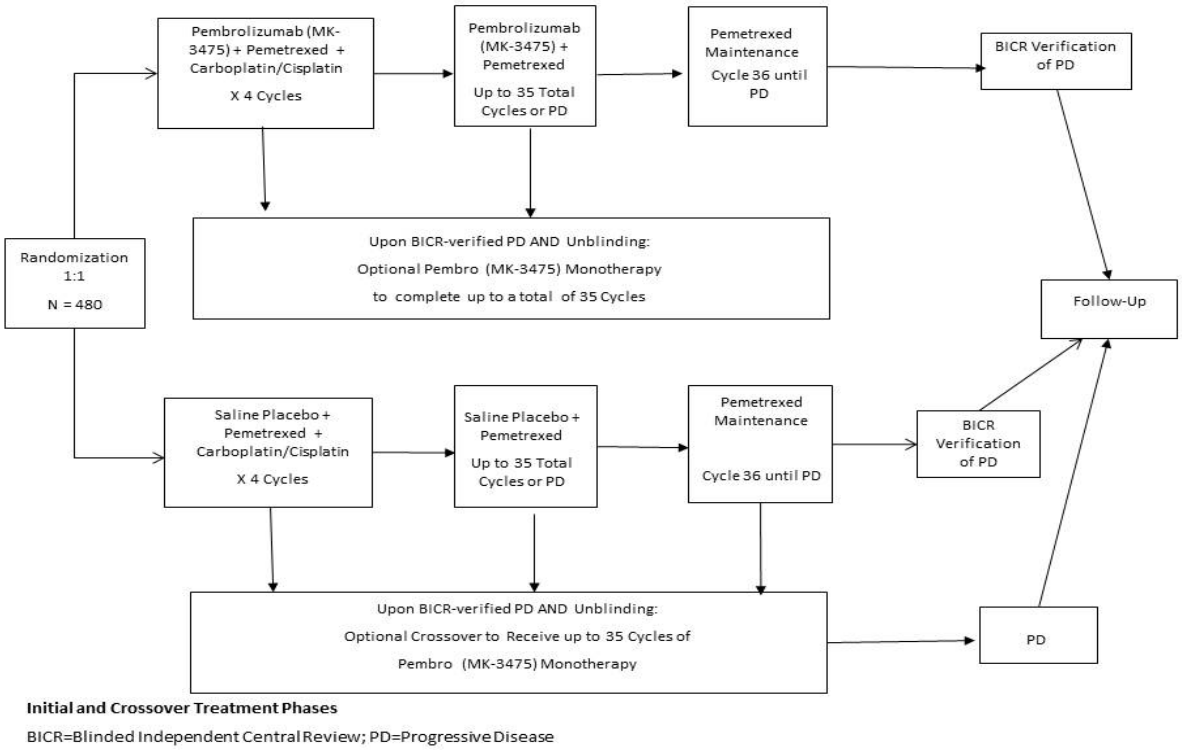


Figure 2 Initial and Crossover Treatment Phases

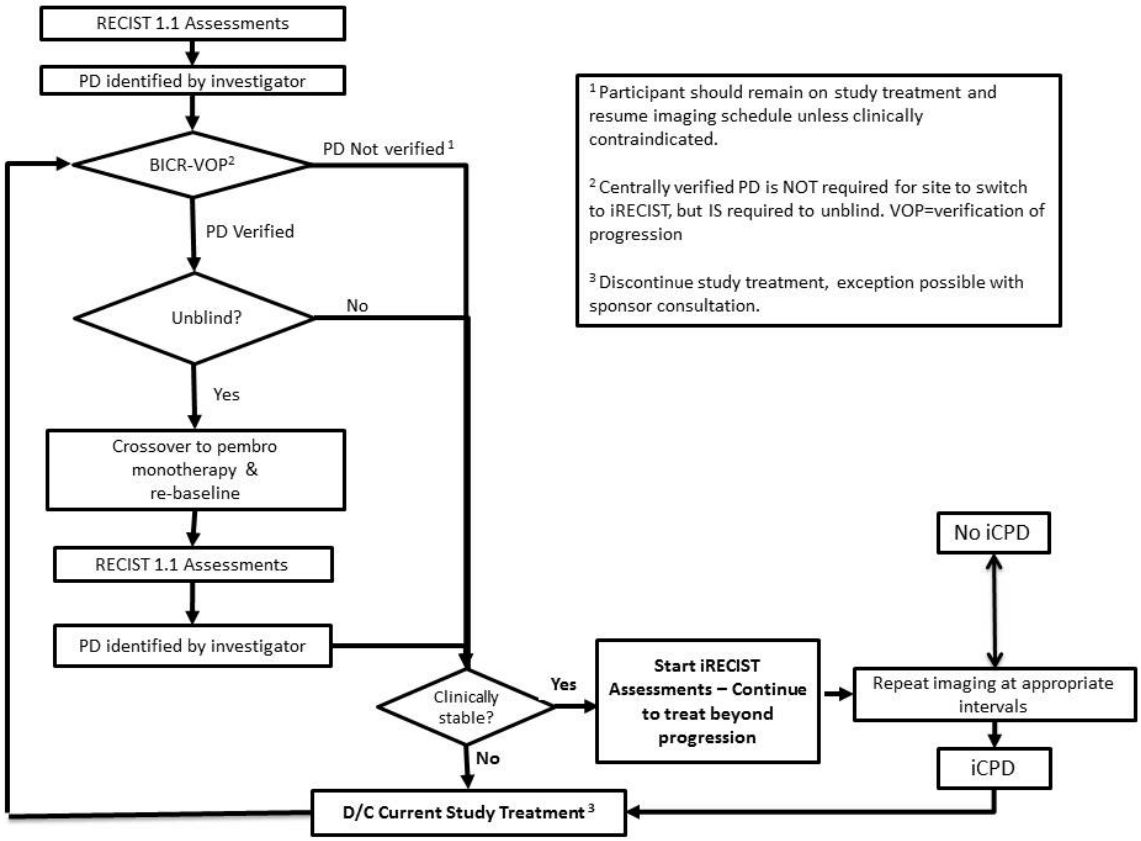


Figure 3 Initial/Crossover Treatment Phase – Progressive Disease Decision Flow Diagram

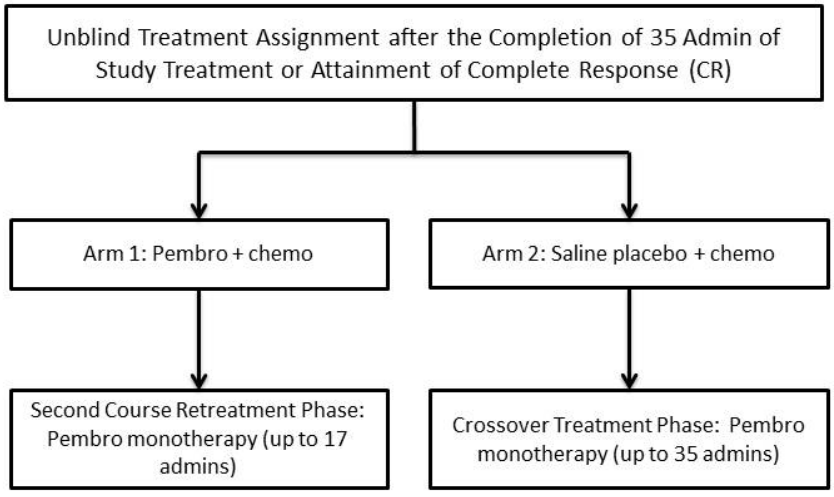


Figure 4 Completion/Attainment of CR Decision Flow Diagram

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities for Initial Treatment Phase

Details regarding the procedures listed in this table are outlined in Section 8.

Study Period	**Screening Phase**		**Treatment Cycles (3-Week Cycles)**								**End of Treatment (EOT)**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Administrative Procedures															
Informed Consent Form (ICF) [3]	X														
ICF for Future Biomedical Research (FRB) (optional)	X														Documented informed consent for FBR is optional and is not required to participate in the study
Inclusion/Exclusion Criteria		X													
Participant ID Card	X														
Demographics and Medical History		X													
Prior/Concomitant Meds		X	X	X	X	X	X	X	X	X	X	X	X[4]		Record all concomitant medications received within 28 days before the first dose of study treatment

Study Period	**Screening Phase**		**Treatment Cycles (3-Week Cycles)**								**End of Treatment (EOT)**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
NSCLC Disease Details and Prior Treatment		X													
Treatment Eligibility Assessment (TEA)		X													The investigator must complete this form to document the rationale for the choice of carboplatin or cisplatin prior to randomization.
Obtain randomization number using IRT			X												
Subsequent Anti-neoplastic Therapy Status											X	X	X	X	If participant discontinues study treatment for any reason other than PD, imaging should continue to be collected and sent to the central imaging vendor for possible retrospective review

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Survival Status			←	—	—	—	—	—	—	→				X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures / Assessments															
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X		Report non-serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anti-cancer therapy is initiated.
Full Physical Examination		X									X				

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Directed Physical Examination			X	X	X	X	X	X	X	X		X			
Vital Signs, Height, and Weight		X	X	X	X	X	X	X	X	X	X	X			Height at Screening only. BSA calculations required for chemo dosing.
12-Lead ECG		X									X				
ECOG Performance Status		X	X[5]	X	X	X	X	X	X	X	X	X			At Screening, perform within 7 days prior to first dose of study treatment but before randomization. To be assessed prior to dosing at each cycle (Section 10.6)
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory															
Pregnancy Test – Highly Sensitive Urine or Serum HCG		X									X				WOCBP require negative test within 72 hours prior to Cycle 1. Test monthly if required by local regulations.

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Hepatitis B & C Serology		X													Testing for Hepatitis B and Hepatitis C is not required unless mandated by local health authority. Refer to Section 10.12 for country-specific requirements. Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SOC).

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
HIV testing		X													Testing for HIV is not required unless mandated by local health authority. Refer to Section 10.12 for country-specific requirements.
PT/INR and aPTT/PTT		X													Perform eligibility labs within 10 days prior to Cycle 1. PT/INR and aPTT/PTT to be tested at Screening for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

Study Period	**Screening Phase**		**Treatment Cycles (3-Week Cycles)**								**End of Treatment (EOT)**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Hematology: CBC with Differential		X		X	X	X	X	X	X	X	X	X			Perform eligibility labs within 10 days prior to Cycle 1. After Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel		X		X	X	X	X	X	X	X	X	X			
Creatinine Clearance Calculation		X		X	X	X									
Urinalysis		X		X		X		X	X	X	X	X			Perform within 10 days prior to Cycle 1, then every 2nd cycle through Cycle 6, then every 6th cycle thereafter (Cycles 2, 4, 6, 12, 18, etc.). After Cycle 1, may collect up to 3 days prior to dosing.

Study Period	**Screening Phase**		**Treatment Cycles (3-Week Cycles)**								**End of Treatment (EOT)**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
T3/FT3, FT4, and TSH		X		X		X		X	X	X	X	X			Perform within 10 days prior to Cycle 1, then every 2nd cycle (Cycles 2, 4, 6, 8, etc.). May use central lab only if local lab is not capable. After Cycle 1, may collect up to 3 days prior to dosing.
Analysis Performed by Central Laboratory															
Blood for Genetics Analysis			X												Collect pre-dose. Do not collect if a documented law or regulation prohibits or local IRB/IEC does not approve.

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Blood for RNA Analysis			X	X							X				Collect pre-dose
Blood for ctDNA Analysis			X												
Blood for Serum/Plasma Biomarker Analysis			X												
Tumor Tissue Collection															
Newly Obtained or Archival Tissue for PD-L1 Analysis	X														May use an archival tissue sample that was obtained prior to screening period as part of the participant's standard care.

Study Period	**Screening Phase**		**Treatment Cycles (3-Week Cycles)**								**End of Treatment (EOT)**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Tissue/Plasma Collection after 1st disease progression for T790M Molecular Status	X														May send tumor tissue to central lab for T790M testing if status is unknown and cannot be determined locally. Participants with negative T790M mutation using plasma specimens will be required to have tissue biopsy confirmation of negative T790M mutation prior to enrollment. Participants with osimertinib treatment as 1st line therapy are not required to have T790M status.

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Efficacy Measurements															
Submission of Pre-trial Tumor Imaging	X														The site's study team must have reviewed pre-trial images that are of diagnostic quality from at least 2 dates to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the *EGFR* TKI. The central imaging vendor must have received these scans and have confirmed that they are of acceptable diagnostic quality prior to randomization in this trial for a possible retrospective analysis of this eligibility criterion. The central vendor will not be confirming eligibility prior to randomization.

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Tumor Imaging		X			X			X	X	X	X	X[6]	X[6]		Perform imaging at Baseline, and 6 weeks after randomization, then Q9W through 51 weeks, and Q12W after randomization subsequently (all imaging after baseline has a ±7 day window). Schedule should be followed regardless of treatment delays. If participant discontinues study treatment for any reason other than PD, imaging should continue to be collected and sent to the central imaging vendor for possible retro-spective review If participant discontinues study treatment for PD, and imaging was obtained within 4 weeks prior to DC, then a new scan at DC is not mandatory.

Study Period	**Screening Phase**		**Treatment Cycles (3-Week Cycles)**								**End of Treatment (EOT)**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Brain MRI	X														
Study Drug Administration – ***Per Randomized Assignment***															
Pembrolizumab (MK-3475) or Saline Placebo			X	X	X	X	X	X	X						
Pemetrexed			X	X	X	X	X	X	X	X					Premedication should also be dosed per the approved product labels and as described in Section 6.5.3.
Carboplatin or Cisplatin			X	X	X	X									

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Patient Reported Outcomes (PROs)															
EQ-5D-5L			X	X	X	X	X	X	X		X	X			Perform every cycle through Cycle 7, then every 3rd cycle through Cycle 19, then every 4th cycle through Cycle 35 (eg, Cycles 1-7, 10, 13, 16, 19, 23, 27, 31 and 35.). PROs will also be obtained at the Treatment Discontinuation visit and 30-day Safety Follow-up visit. If the Treatment Discontinuation visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up visit, PROs do not need to be repeated. Perform ePROs in the order listed in the SoA (EQ-5D-5L first).
EORTC QLQ-C30			X	X	X	X	X	X	X		X	X			
EORTC QLQ-LC13			X	X	X	X	X	X	X		X	X			

Study Period	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment (EOT)	Post Treatment Visits			Notes
Treatment Cycle	**Screening (Visit 1)**		**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36+**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**-42 to -1**	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	

Notes:
1. If Discontinuation visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.
2. Follow-Up visits may be scheduled to coincide with Follow-Up imaging (eg, 12 weeks from last imaging time point).
3. Informed consent must be obtained prior to sending any of the following: (a) plasma/tumor tissue samples to the central lab for PD-L1/*EGFR* T790M testing; (b) pretrial tumor imaging to the central imaging vendor for confirmation of diagnostic quality
4. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 10.4.
5. Does not have to be done if Screening ECOG was performed within 3 days prior to first dose of study treatment in Cycle 1.
6. For participants discontinuing for reasons other than BICR-verified PD, follow-up visits and imaging continue until BICR-verified PD (these images should continue to be sent to the central imaging vendor), the start of new anti-cancer treatment, withdrawing consent, or becoming lost to follow-up. Participants discontinuing treatment with BICR-verified PD proceed directly to survival follow-up or Crossover Treatment Phase, if applicable. Follow-up Visits may be scheduled to coincide with Follow-up imaging (eg, 9 weeks from last imaging time point through Week 51 or 12 weeks from last imaging if after Week 51).

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central (imaging) review; BSA=body surface area; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; CXDX=Cycle X Day X; d=days; DC/Discon=discontinuation; DNA = deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EOT=end of treatment; ePRO=electronic patient reported outcome; EQ-5D-5L=EuroQol 5-dimension, 5-level Questionnaire; FRB=future biomedical research; FT4= free thyroxine; H/hr=hours; HBV/HCV=hepatitis B/C virus; HCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; ICF=informed consent form; ID=identification; INR=international normalized ratio; IRB/IEC= Institutional Review Board/Independent Ethics Committee; min=minutes; IRT=interactive response technology; MRI=magnetic resonance imaging; NSCLC=non-small cell lung cancer; PD=progressive disease; PD-L1=programmed cell death ligand 1; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q=every; QLQ-C30=Quality of Life Questionnaire Core 30; QLQ-LC13=Quality of Life Questionnaire and Lung Cancer Module 13; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; T3/FT3= free or total triiodothyronine; TSH= thyroid stimulating hormone; V=visit; W=weeks; WOCBP=woman of child-bearing potential.

1.3.2 Schedule of Activities for Crossover Treatment Phase

Only applicable for participants that have BICR-verified progressive disease and are qualified for the Crossover Phase. Details regarding the procedures listed in this table are outlined in Section 8.

Study Period	**Treatment Cycles (3-Week Cycles)**														**EOT**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**±3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Administrative Procedures																			
Eligibility Criteria	X																		
Prior/Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[3]		
Subsequent Anti-neoplastic Therapy Status															X	X	X	X	
Survival Status	←													→				X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period	Treatment Cycles (3-Week Cycles)														EOT	Post Treatment Visits			Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**±3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Clinical Procedures/Assessments																			
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Report non-serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anti-cancer therapy is initiated.
Full Physical Examination	X														X				
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG	X														X				

Study Period	Treatment Cycles (3-Week Cycles)														EOT	Post Treatment Visits			Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			To be assessed prior to dosing at each cycle (Section 10.6).
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory																			
Pregnancy Test – Highly Sensitive Urine or Serum HCG	X														X				WOCBP require negative test within 72 hours prior to Cycle 1. Test monthly if required by local regulations. Refer to Section 10.12 for country-specific requirements.
Hematology: CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Period	Treatment Cycles (3-Week Cycles)														EOT	Post Treatment Visits			Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
PT/INR and aPTT/PTT	X																		PT/INR and aPTT/PTT to be tested at Cycle 1 for all Crossover participants. Any Crossover participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X	X		X		X						X		X	X	X			Perform prior to Cycle 1 and Cycle 2, then every 2nd cycle through Cycle 6, then every 6th cycle thereafter (Cycles 2, 4, 6, 12, 18, etc.). After Cycle 1, may collect up to 3 days prior to dosing.

Study Period	Treatment Cycles (3-Week Cycles)														EOT	Post Treatment Visits			Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
T3/FT3, FT4, and TSH	X	X		X		X		X		X		X		X	X	X			Perform prior to Cycle 1 and Cycle 2, then every 2nd cycle (Cycles 2, 4, 6, 8, etc.). May use central lab only if local lab is not capable. After Cycle 1, may collect up to 3 days prior to dosing.
Efficacy Measurements																			
Brain MRI	X																		Perform at time of crossover if participant has history of brain metastases.
Tumor Imaging	X				X				X				X	X	X	X	X		Blinded central review verifying progressive disease is required for crossover, without exception

Study Period	Treatment Cycles (3-Week Cycles)														EOT	Post Treatment Visits			Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**±3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	
Study Drug Administration																			
Pembrolizumab (MK-3475)	X	X	X	X	X	X	X	X	X	X	X	X	X	X					Treatment with Pembro should not initiate until at least 21 days after the last dose of chemo regardless of the time of progression. Participants originally assigned to pembro + chemo arm will complete up to a total of 35 admin of pembro and participants from the saline placebo + chemo arm will receive up to 35 admin of pembro

Study Period	Treatment Cycles (3-Week Cycles)														EOT	Post Treatment Visits			Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 thru 35**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon (+3)**	**30 Days Post Discon (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (±14)**	

Notes:
1. If Discontinuation visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.
2. Follow-Up visits may be scheduled to coincide with Follow-Up imaging (eg, 12 weeks from last imaging time point).
3. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 10.4

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CBC=complete blood count; CXDX=Cycle X Day X; d=days; DC/Discon=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FT4= free thyroxine; H/hr=hours; HCG=human chorionic gonadotropin; INR=international normalized ratio; min=minutes; MRI=magnetic resonance imaging; PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q=every; SAE=serious adverse event; SoA=schedule of activities; T3/FT3= free or total triiodothyronine; TSH= thyroid stimulating hormone; V=visit; WOCBP=woman of child-bearing potential.

1.3.3 Schedule of Activities for Second Course Retreatment Phase

Details regarding the procedures listed in this table are outlined in Section 8. Second course retreatment participants may receive up to 17 cycles (approximately 1 year) of open-label pembrolizumab monotherapy.

Study Period	Treatment Cycles (3-Week Cycles)						EOT	Post-Treatment Visits			Notes
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC (+3)**	**30 Days Post-DC (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (± 14)**	
Administrative Procedures											
Eligibility Criteria	X										
Concomitant Medication Review	X	X	X	X	X	X	X	X			
Subsequent Anti-neoplastic Therapy Status							X	X	X	X	
Survival Status	←								→	X	Participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X		Report non-serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anti-cancer therapy is initiated.
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X		X			
Vital Signs and Weight	X	X	X	X	X	X	X	X			
12-Lead ECG	X						X				
ECOG Performance Status	X	X	X	X	X	X	X	X			Perform within 7 days prior to SC Cycle 1. To be assessed prior to dosing at each cycle.

Study Period	Treatment Cycles (3-Week Cycles)						EOT	Post-Treatment Visits			Notes
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC (+3)**	**30 Days Post-DC (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (± 14)**	
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory											
Pregnancy Test – Highly Sensitive Urine or Serum HCG	X						X				WOCBP require negative test within 72 hours prior to Second Course (SC) Cycle 1. Test monthly if required by local regulations. Refer to Section 10.12 for country-specific requirements.
PT/INR and aPTT/PTT	X										PT/INR and aPTT/PTT to be tested at Cycle 1 for all Second Course participants. Any Second Course participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
Hematology: CBC with Differential	X	X	X	X	X	X	X	X			Perform within 10 days prior to SC Cycle 1. After SC Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel	X	X	X	X	X	X	X	X			
Urinalysis	X		X		X	X	X	X			Every 2 cycles through SC Cycle 5, then every 6 cycles (SC Cycles 1, 3, 5, 11, 17). After SC Cycle 1, may collect up to 3 days prior to dosing.
T3/FT3, FT4, TSH	X		X		X	X	X	X			Perform within 10 days prior to SC Cycle 1. Repeat every 2 cycles (SC Cycles 1, 3, 5, 7, etc.). May use central lab if local lab is not capable. After SC Cycle 1, may collect up to 3 days prior to dosing.
Efficacy Measurements											
Tumor Imaging	X				X	X	X	X	X[3]		SC baseline imaging within 28 days prior to SC Cycle 1. Perform imaging Q12W (±7 days) from SC Cycle 1 (after weeks 12, 24, 36, 48). Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks prior to DC, imaging at DC is not mandatory.
Brain MRI	X										Perform within 28 days prior to SC Cycle 1 if participant has history of brain metastases.

Study Period	Treatment Cycles (3-Week Cycles)						EOT	Post-Treatment Visits			
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**Discon**	**Safety Follow-up[1]**	**Follow-up[2]**	**Survival Follow-up**	**Notes**
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC (+3)**	**30 Days Post-DC (+14)**	**Every 12 Weeks (±7)**	**Every 12 Weeks (± 14)**	
Study Drug Administration											
Pembrolizumab (MK-3475)	X	X	X	X	X	X					Pembro can be administered for up to 17 administrations (approximately 1 year).

Notes:
1. If Discontinuation visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.
2. For participants discontinuing second course for reasons other than PD, follow-up visits and imaging continue until the start of new anti-cancer treatment, PD, withdrawal of consent, death or end of the study Participants discontinuing second course treatment with PD proceed directly to survival follow-up.

Abbreviations: AE=adverse events; aPTT=activated partial thromboplastin time; CBC=complete blood count; CXDX= Cycle X Day X; DC/Discon=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FT4= free thyroxine; H/hr=hours; HCG=human chorionic gonadotropin; INR=international normalized ratio; PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q=every; SAE=serious adverse event; SC=Second Course; SC C1D1=Second Course Cycle 1 Day 1; T3/FT3=free or total triiodothyronine; TSH=thyroid stimulating hormone; W=weeks; WOCBP=woman of child-bearing potential.

2. Introduction

2.1 Study Rationale

The global incidence of lung cancer was 1.8 million in 2012, resulting in an estimated 1.6 million deaths [World Health Organization 2012]. In the United States, the 2016 estimated incidence of new diagnoses was 224,400 and estimated number of deaths was 158,100 [National Cancer Institute 2016]. Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Of the patients with NSCLC, tumor histology is approximately 40% to 60% adenocarcinoma, 10% to 15% squamous, 5% neuroendocrine, and the rest "not otherwise specified" [Sulpher, J. A., et al 2013].

Approximately 70% of patients with NSCLC have advanced disease not amenable to surgical resection at the time of diagnosis. The 5-year relative survival for patients with any lung cancer overall and metastatic lung cancer specifically has been reported to be 17.7% and 4.3%, respectively [National Cancer Institute 2016].

The standard of care (SOC) for metastatic NSCLC has changed in recent years with the development of immunotherapy agents. In the Phase 3 study KEYNOTE-024, pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, showed statistically significant increases in overall survival (OS) and progression-free survival (PFS) compared to SOC platinum-based chemotherapy for treatment-naïve participants with metastatic NSCLC whose tumors expressed high levels of the programmed cell death ligand 1 (PD-L1) (tumor proportion score [TPS] ≥50%) with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, leading to regulatory approval for this indication in the US and other countries around the world. Approximately 30% of patients with newly diagnosed, advanced NSCLC highly express PD-L1 to a TPS ≥50% [Reck, M., et al 2016].

In the Phase 2 study KEYNOTE-021 Cohort G, pembrolizumab plus pemetrexed and carboplatin showed statistically significant increases in objective response rate (ORR) and PFS compared to pemetrexed and carboplatin alone in participants with non-squamous advanced NSCLC, regardless of PD-L1 status. These results established pembrolizumab plus chemotherapy as an efficacious option for first-line (1L) therapy in patients with NSCLC; these findings are being further evaluated in the ongoing Phase 3 studies KEYNOTE-189 (non-squamous) and KEYNOTE-407 (squamous) (see the Investigator's Brochure [IB]).

The *EGFR* is a transmembrane receptor with tyrosine kinase activity (TK) involved in the regulation of cell proliferation, survival, differentiation and other crucial processes through activation of multiple downstream signaling cascades, including PI3K/AKT, RAS/RAF/mitogen-activated protein kinase (MAPK) and STAT pathways. *EGFR* pathway is often deregulated in NSCLC. The overall prevalence for *EGFR* mutations in patients with NSCLC is 30%, ranging from 38% in China to 14% in Europe. The most common mutations are the in-frame exon 19 deletion and the exon 21 point mutation L858R (substitution from leucine to arginine at amino acid 858) accounting for about 90% of all mutations. Somatic activating mutations of *EGFR* are predominant in adenocarcinoma; the prevalence of *EGFR* mutations is higher in never-smokers, females and patients of East Asian ethnicity [Zhang, Y. L., et al 2016].

The first-generation, reversible *EGFR* tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, are orally bioavailable synthetic anilinoquinazolines designed to compete for adenosine triphosphate (ATP) binding to the catalytic site of the receptor, switch off survival signals, leading to tumor cell death, whereas the second-generation inhibitors, including afatinib and dacomitinib, are irreversible inhibitors with greater affinity for the *EGFR* kinase domain and can also inhibit and block signaling from other members of the ErbB family, thus providing enhanced *EGFR* blockade.

Iressa Pan-Asia Study (IPASS) was the first study demonstrating the superiority of gefitinib with a significantly longer PFS and ORR compared with chemotherapy in subgroup of patients with *EGFR* mutations NSCLC (hazard ratio [HR] for PFS, 0.48; 95% confidence interval (CI): 0.36, 0.64; p<0.001) thus leading to its approval [Mok, T. S., et al 2009]. Subsequent multiple, randomized Phase 3 trials, exclusively enrolling patients with *EGFR*-mutated NSCLC, explored the use of gefitinib, erlotinib or afatinib as first-line treatment in comparison with standard platinum-based chemotherapy showed that *EGFR* TKIs improved ORRs ranging between 62% to 83%, and PFS (median PFS ranging between 9 to 13 months), leading to approval of gefitinib, erlotinib, and afatinib, as upfront therapies in advanced NSCLC patients with *EGFR* mutations. Unfortunately, the vast majority of patients will later develop progressive disease, generally within 1 year of treatment, due to development of acquired resistance, limiting the long-term efficacy of these agents, multiple mechanisms are responsible for the acquired resistance have been identified such as: 1) secondary mutation of the *EGFR* target gene, such as T790M mutation, which occurs in about 50% to 60% of *EGFR* TKI-resistant tumors, 2) bypass pathway activation such as amplification, overexpression of MET, HER2, and molecular alterations of downstream molecules of the PI3K/AKT/mammalian target of rapamycin (mTOR) or the RAS/RAF/MAPK pathways, and 3) histologic transformation, such as small cell lung cancer (SCLC) transformation and epithelial–mesenchymal transition [Morgillo, F., et al 2016].

The identification of *EGFR* T790M prompted the development of second-generation *EGFR* TKIs such as afatinib and dacomitinib to overcome resistance; however, available clinical data have indicated a rather limited activity of these drugs in the setting of acquired resistance to first-generation TKIs. Subsequently, third-generation, mutant *EGFR*-selective TKIs have been developed, including rociletinib and osimertinib. Osimertinib was granted US FDA approval for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC who have progressed on or after *EGFR* TKI therapy based on the AURA3 study, which demonstrated improvement in PFS in patients treated with osimertinib versus chemotherapy, with an HR of 0.30 (95% CI: 0.23, 0.41; p<0.001) and median PFS of 10.1 months versus 4.4 months [Mok, T. S., et al 2017]. Recently, the AURA3 study has been updated to report a median OS of 26.8 months in the osimertinib arm versus 22.5 months in the chemotherapy arm [Papadimitrakopoulou, V. A., et al 2020]. While these results are encouraging, most patients eventually progressed and will die of their disease. There is very little data on the survival of patients with T790M+ NSCLC who were treated with chemotherapy after failed osimertinib in the second-line setting. In a small retrospective study of 91 subjects with T790M+ NSCLC treated with osimertinib beyond progression or switched to other therapies (primarily chemotherapy), the PFS and OS for those who switched therapies after progression on osimertinib were 4.7 months and 7.8 months, respectively [Cortellini, A., et al 2020].

The benefit of third-generation *EGFR* TKI is also evolving in the first-line setting. In the Phase 3 FLAURA study of osimertinib versus gefitinib/erlotinib, the PFS HR was 0.46 (95% CI: 0.37, 0.57, p <0.001) and the medians were 18.9 months versus 10.2 months, respectively, with comparable safety profiles of osimertinib to erlotinib/gefitinib, but with lower rates of Grade ≥3 AEs and a lower discontinuation rate [Ramalingam, S., et al 2017]. Recently, the FLAURA study was updated to report a longer median OS of 38.6 months for patients receiving first-line osimertinib versus 31.8 months in the erlotinib/gefitinib group, in which 47% of patients received osimertinib as the first subsequent therapy [Ramalingam, S. S., et al 2020].

Despite these developments in the treatment of *EGFR* mutant NSCLC, most patients still ultimately progress. Prolonged survival rates remain very low with median OS between 1 to 2 years [Yu, H. A., et al 2013]. Systemic chemotherapy treatment generally represented by platinum-based doublet is currently considered the standard of care with only modest benefit of 20% to 30% response rate. Furthermore, the Phase 3 IMPRESS study failed to demonstrate long-term benefit combining gefitinib with chemotherapy (cisplatin and pemetrexed) compared with chemotherapy and placebo in patients who progressed on first-line gefitinib. There was no difference in PFS between groups, with median PFS of 5.4 months in both groups (95% CI: 4.5, 5.7 in the gefitinib group and 95% CI: 4.6, 5.5 in the placebo group), and the combination of gefitinib plus chemotherapy was detrimental to OS compared with chemotherapy alone, with median OS of 13.4 months versus 19.5 months (HR 1.44, 95% CI: 1.07, 1.94; p=0.016) [Soria, J. C., et al 2015] [Mok, T. S. K., et al 2017].

Alternative treatment strategies, including investigational drugs or novel combinations have been explored in clinical trials, but none of these has been approved as standard treatment in this setting, confirming the unmet medical need that exists in this patient population. Thus, further development of new regimen and novel treatment strategies are urgently warranted. Recently, immune checkpoint inhibitors and anti-PD-1 (programmed death-1) and anti-PD-L1 (programmed death-ligand) antibodies demonstrated quite promising and durable response across broad range of solid tumors including NSCLC.

2.1.1 PD1/PD-L1 Inhibitors in *EGFR*-mutant NSCLC

Pembrolizumab monotherapy is one of the current standards of care (SOC) for the treatment of patients with good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0 or 1) and previously treated, advanced, or metastatic NSCLC with a programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) ≥1%, including patients with *EGFR* mutation who have failed both prior *EGFR* TKI and platinum doublet chemotherapy. This is based on data from KEYNOTE-010 [IB Edition 15 2017]. KEYNOTE-010 was an open-label Phase 3, randomized, controlled study, compared pembrolizumab monotherapy to standard second-line docetaxel therapy in 1034 previously treated participants with advanced NSCLC and a PD-L1 TPS ≥1%, including patients with *EGFR* mutation who have failed both TKI and platinum doublet chemotherapy. Results from KEYNOTE-010 indicated a significant overall survival (OS) benefit for pembrolizumab over docetaxel therapy with an HR of 0.71 (p=0.00076) and 0.61 (p<0.00001) for pembrolizumab 2 mg/kg every 3 weeks (Q3W) and 10 mg/kg Q3W, respectively, compared to docetaxel. Pembrolizumab was superior to docetaxel in the strongly positive TPS ≥50% stratum with regard to PFS, with an HR of 0.58 (p=0.00009) and 0.59 (p=0.00007) for pembrolizumab 2 mg/kg Q3W and

10 mg/kg Q3W, respectively, compared to docetaxel. Although KEYNOTE-010 was not a study powered for distinguishing the effectiveness of pembrolizumab by *EGFR* mutational status from another, but was instead powered to demonstrate that selection of a group of subjects based on expression of the PD-L1 biomarker, irrespective of *EGFR* status, in a subgroup analysis of 54 patients with *EGFR* mutation, there was a trend toward improved OS favoring pembrolizumab 2mg /kg over standard of care docetaxel, with OS [HR] was 0.78 (95% CI: 0.39, 1.60).

In addition, the Phase 3 study IMpower150, has shown that chemotherapy in combination with checkpoint inhibitor anti-PD-L1 (atezolizumab) with the addition of bevacizumab, reduces the risk of disease progression in advanced non-squamous NSCLC with an investigator assessed PFS [HR]=0.62; p<0.0001; 95 % CI: 0.52, 0.74 (patients with ALK and *EGFR* tumor mutations were excluded from the primary intent-to-treat [ITT] analysis). When the analysis was performed on the ITT population that included patients with mutant *EGFR* [108/800 (14%)] or ALK, the PFS [HR] was 0.59 (95 % CI: 0.37, 0.94), confirming the trend in improvement in PFS when a checkpoint inhibitors is added to chemotherapy in patients with *EGFR* mutations who has failed prior *EGFR* TKIs therapy [Reck, M., et al 2017] [Reck, M., et al 2017].

Based on the potential beneficial role of pembrolizumab in previously treated (with *EGFR* TKIs treatment followed by chemotherapy) patients with *EGFR* mutant metastatic NSCLC, and since chemotherapy combination with pembrolizumab or atezolizumab demonstrated promising ORR and/or PFS in the first-line setting in non-squamous NSCLC as seen in KEYNOTE-021G and IMpower150, the combination of chemotherapy with pembrolizumab in patients who have failed *EGFR* TKIs previously warrants further exploration.

2.2 Background

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

Refer to the IB/approved labeling for detailed background information on pembrolizumab.

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

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

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 efficacy of an investigational medicine.

The beneficial effects of pembrolizumab have been observed in several NSCLC studies to date. A significantly positive benefit/risk ratio has been demonstrated for pembrolizumab in multiple randomized studies for NSCLC, both as a monotherapy (KEYNOTE-010, KEYNOTE-024) and in combination with chemotherapy (KEYNOTE-021G, KEYNOTE-189).

KEYNOTE-010 included patients with PD-L1 TPS ≥1% and an *EGFR* mutation, who have failed both a TKI and platinum doublet chemotherapy. Although KEYNOTE-010 was not a study powered for distinguishing the effectiveness of pembrolizumab in participants with an *EGFR* mutation, in a subgroup analysis of 54 patients with an *EGFR* mutation, there was a trend toward improved OS favoring pembrolizumab 2 mg/kg over standard of care docetaxel (HR=0.78; 95% CI: 0.39, 1.60). In addition, the Phase 3 study IMpower150 has shown that chemotherapy in combination with atezolizumab (a PD-L1 inhibitor) and bevacizumab reduced the risk of disease progression or death in advanced non-squamous NSCLC [Reck, M., et al 2017] [Reck, M., et al 2017]. When the analysis was performed to include

patients with mutant *EGFR* (108/800 [14%)]) or rearranged ALK, an improved PFS was observed (HR=0.59; 95% CI: 0.37, 0.94). These data suggested that checkpoint inhibitors, either alone or in combination with chemotherapy, have clinical activity in patients with *EGFR* mutation after TKI failure. The most frequently reported AEs for patients treated with pembrolizumab (reported in ≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia and diarrhea. These were predominantly Grade 1 to 2, with fatigue being the only AE that occurred with a severity of Grade 3 or above in 5% of patients. Immune-related pneumonitis, colitis, hepatitis, hypophysitis, nephritis and thyroid abnormalities were seen at low frequency and were managed by holding or discontinuing the drug as described.

Based on data from KEYNOTE-021G and KEYNOTE-189, the addition of pembrolizumab did not increase the frequency of AEs beyond what was expected with regimens involving pemetrexed and platinum doublet chemotherapy. Moreover, the incidence of most immune-mediated AEs was not higher with pembrolizumab combination therapy than that previously observed with pembrolizumab monotherapy.

Despite the substantial improvement in ORR and PFS observed with different generation of *EGFR* TKIs treatment, most patients eventually have progressive disease. The current SOC chemotherapy does not improve outcomes. There remains a need to investigate new treatments which offer the prospect of added benefit for this patient population. The preliminary data showing potential benefits for patients with an *EGFR* mutation who progressed on a TKI, argues strongly for a comparison of the addition of pembrolizumab with chemotherapy to the currently accepted standard of care, platinum doublet chemotherapy. 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. Objectives/Hypotheses and Endpoints

In adult participants with TKI-resistant *EGFR*-mutated tumors in metastatic non-squamous NSCLC:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To compare PFS per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) based on blinded independent central review (BICR) of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. • Hypothesis (H1): The combination of pembrolizumab + chemotherapy has superior PFS per RECIST 1.1 based on BICR compared to saline placebo + chemotherapy	• Progression-free survival (PFS) is the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first.
• Objective: To compare OS of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. • Hypothesis (H2): The combination of pembrolizumab + chemotherapy has superior OS compared to saline placebo + chemotherapy.	• OS is defined as the time from randomization to death due to any cause.
This study will be considered to have met its success criteria if the combination of pembrolizumab + chemotherapy is superior to saline placebo + chemotherapy in PFS or OS.	

Objective/Hypothesis	Endpoint
Secondary	
• Objective: To compare objective response rate (ORR) per RECIST 1.1 based on BICR of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. • Hypothesis (H3): The combination of pembrolizumab + chemotherapy has superior ORR per RECIST 1.1 based on BICR compared to saline placebo + chemotherapy.	• Objective response is a confirmed complete response (CR) or partial response (PR).
• Objective: To evaluate DOR of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• DOR is defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST 1.1 based on BICR.
• Objective: To evaluate the patient reported outcomes (PROs) mean score changes from baseline in global health status and quality of life scale between pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 items (QLQ-C30) global health status (item 29) and quality of life scale (item 30).
• Objective: To evaluate the PROs time to true deterioration (TTD) in the composite endpoint of cough, chest pain or dyspnea between pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• TTD is the time from baseline to first onset of 10 points or more deterioration from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline of the composite endpoint of cough [EORTC QLQ-Lung Cancer Module 13 (LC13) item 1], chest pain [EORTC QLQ-LC13 item 10], or dyspnea [EORTC QLQ-C30 item 8].
• Objective: To evaluate the safety and tolerability of the combination of pembrolizumab + chemotherapy and saline placebo + chemotherapy.	• Adverse events (AEs) and study drug discontinuation due to AEs.

Objective/Hypothesis	Endpoint
Tertiary/Exploratory	
• Objective: To compare the PFS and ORR per Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST) of the combinations of pembrolizumab + chemotherapy versus saline placebo + chemotherapy.	• PFS is defined as the time from randomization to the first documented PD per iRECIST as assessed by the Investigator or death due to any cause, whichever occurs first. • ORR is defined as the proportion of participants who have a confirmed CR or PR per iRECIST as assessed by the Investigator.
• Objective: To evaluate changes in health-related quality of life assessments from baseline in the overall study population using the EORTC QLQ-C30 and EORTC QLQ-LC13	• Change from baseline in health-related quality of life evaluated using the multi-item and single-item scales of EORTC QLQ-C30 and EORTC QLQ-LC13.
• Objective: To characterize utilities using the European Quality of Life Five-dimension Five-level Scale Questionnaire (EQ-5D-5L).	• Health utilities assessed using the EQ-5D-5L.
CCI [redacted]	

4. Study Design

4.1 Overall Design

This is a worldwide, randomized, active-control with placebo, parallel-group, multi-site, double-blind study of IV pembrolizumab (also known as MK-3475) combined with pemetrexed plus platinum chemotherapy versus saline placebo combined with pemetrexed plus platinum chemotherapy in participants with TKI-resistant *EGFR*-mutated tumors in metastatic non-squamous NSCLC. Approximately 492 participants will be enrolled in this trial to examine the efficacy of pembrolizumab combined with chemotherapy compared to chemotherapy alone. Participants will be randomized 1:1 to either receive pembrolizumab 200 mg combined with pemetrexed and platinum chemotherapy (investigator's choice of carboplatin or cisplatin), or saline placebo plus pemetrexed and platinum chemotherapy (investigator's choice of carboplatin or cisplatin) as indicated below:

- **Arm 1**: Pembrolizumab 200 mg + pemetrexed 500 mg/m^2 (with vitamin supplementation) + carboplatin AUC 5 mg/mL•min OR cisplatin 75 mg/m^2, all on Day 1 every 3 weeks (Q3W) for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2 Q3W for up to an additional 31 cycles (up to 35 total cycles), followed by pemetrexed 500 mg/m^2 Q3W maintenance until progression or unacceptable toxicity.
- **Arm 2**: Saline placebo + pemetrexed 500 mg/m^2 (with vitamin supplementation) + carboplatin AUC 5 mg/mL•min OR cisplatin 75 mg/m^2, all on Day 1 Q3W for 4 cycles followed by saline placebo + pemetrexed 500 mg/m^2 Q3W for up to an additional 31 cycles (up to 35 total cycles), followed by pemetrexed 500 mg/m^2 Q3W maintenance until progression or unacceptable toxicity.

Participants who received adjuvant or neoadjuvant therapy are permitted onto the study if the therapy was completed at least 6 months prior to the development of metastatic disease.

Participants will be stratified by PD-L1 expression: TPS ≥50% versus <50%; treatment history: osimertinib versus no osimertinib; and geographic region of the enrolling site: East Asia versus Non-East Asia, prior to randomization.

Treatment with pembrolizumab or saline placebo will continue until reaching a discontinuation criterion (Section 7.1), examples of which include: administration of 35 study treatments, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, or administrative reasons.

Maintenance pemetrexed may continue for participants past 35 cycles until reaching a discontinuation criterion (Section 7.1), as long as the participant is receiving benefit and per local regulations, whereas pembrolizumab/saline placebo are limited to 35 cycles.

Participants will be evaluated at 6 weeks (42 + 7 days) and then every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment for the first 51 weeks and every 12 weeks (84 ± 7 days) subsequently; treatment-based decisions should be based on the iRECIST criteria. All imaging obtained on study during the initial treatment phase will be submitted without indication of treatment assignment to a central imaging review vendor, ie, blinded independent central review (BICR), who will assess the images using RECIST 1.1 for determination of PFS and ORR (Section 8.2.1).

AE monitoring will be ongoing throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Section 10.11).

At the time of documented disease progression as confirmed by BICR using RECIST 1.1 (Section 8.2.1), participants may have treatment assignment unblinded (Figure 3). Participants who received saline placebo in combination with chemotherapy may be eligible to receive pembrolizumab monotherapy for a total of 35 administrations in the Crossover Treatment Phase (Section 8.11.3). Tumor imaging is to be re-baselined and RECIST 1.1 criteria used for participant assessments (Sections 8.2.1.4 and 8.2.1.5).

Participants who received pembrolizumab in combination with chemotherapy, but are deemed to be benefiting clinically despite disease progression, may continue study treatment beyond progression and receive pembrolizumab monotherapy in the Crossover Treatment Phase (Section 8.11.3) to complete a total of up to 35 pembrolizumab administrations. Repeat imaging should occur at appropriate intervals per iRECIST criteria (Sections 8.2.1 and 10.10) until iCPD is established.

Study treatment may continue until participant reaches a discontinuation criterion (Section 7.1), examples of which include subsequent documented progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, or for administrative reasons.

Alternatively, participants may have treatment assignment remain blinded at the time of BICR-verified progression and may continue receiving the study treatment per their randomized treatment assignment as long as they continue to be clinically stable (Figure 3). Clinical Stability is defined in Section 7.1.

Blinded study treatment can continue beyond verified progression at the Investigator's discretion. Repeat imaging should occur at appropriate intervals per iRECIST criteria (Sections 8.2.1 and 10.10) until iCPD is established. Once iCPD is established, the participant may then have treatment assignment unblinded, but may not continue study treatment in the Crossover Treatment Phase (Section 8.11.3) as described above.

Participants who attain a confirmed complete response (CR) per RECIST 1.1 criteria may consider stopping study treatment. These participants, as well as participants randomized to the pembrolizumab plus chemotherapy arm that stop study treatment after 35 treatment administrations may be eligible for the Second Course Phase (Figure 4).

Participants randomized to the saline placebo plus chemotherapy arm who complete 35 treatment administrations and subsequently experience progressive disease will not be eligible for Second Course Phase but may continue into the Crossover Treatment Phase instead (Section 8.11.3).

The Second Course Phase is re-treatment with open-label pembrolizumab monotherapy after Initial Treatment Phase completion or the attainment of a CR and upon subsequent radiographic disease progression. Second Course Phase is only available to participants randomized to the pembrolizumab plus chemotherapy arm. Participation is at the discretion of the investigator according to defined criteria in Section 8.11.4. Response or progression in the Second Course Phase will not count toward the PFS and ORR endpoints in this trial.

After the end of treatment, each participant will be followed for a minimum of 30 days for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4. Serious adverse events will be collected for up to 90 days following cessation of the study treatment, or 30 days following the cessation of treatment if the participant initiates new anti-cancer therapy.

Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is

documented radiographically per RECIST 1.1 and verified by BICR, the start of new anti-cancer treatment, pregnancy, participant withdraws consent, participant becomes lost to follow-up, participant death, or the end of the study.

The Sponsor may request survival status to be assessed at additional time points and entered into the database during the course of the study. For example, survival status may be requested prior to, but not limited to, an external Data Monitoring Committee (eDMC) review.

All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. Survival status can be done in a variety of ways including phone, email, chart review, or review of public records. Survival status information (whether by telephone, review of public records, etc.) should be officially documented by the site.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities (SoA), Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use PFS based on RECIST 1.1 criteria as assessed by BICR and overall survival (OS) as the co-primary endpoints.

Progression-free survival 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 read by a central imaging vendor 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. Real time verification of radiologic progression when requested by the local site investigator/radiology assessment as assessed by BICR will be communicated to the site and sponsor.

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

ORR by RECIST 1.1 criteria as assessed by BICR is considered preliminary evidence of efficacy and is a secondary endpoint for this study.

DOR by RECIST 1.1 criteria and assessed by BICR is a commonly accepted endpoint by both regulatory authorities and the oncology community.

The BICR consists of a group of highly qualified radiologists contracted by the central imaging vendor who are otherwise not involved in the study. The methodology of the BICR is described in the imaging review charter.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility. Although traditional RECIST 1.1 references 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. This will be termed as RECIST 1.1 throughout the protocol. Further details are found in Section 8.2.1.5.

4.2.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.1.6). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and participants treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by Investigators to assess tumor response and progression and make treatment decisions as well as for exploratory efficacy analyses where specified.

4.2.1.2 Safety Endpoints

The incidence of AE/serious AEs (SAEs) (including fatal SAEs), immune-related AEs, laboratory abnormalities, and rates of dose interruption and discontinuation due to AEs are important endpoints for safety and tolerability evaluations.

Refer to Section 10.12 for country-specific requirements.

4.2.1.3 Rationale for Patient Reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their health-related quality of life (HRQoL) via the following assessment tools: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires.

4.2.1.3.1 EORTC QLQ-C30 and EORTC QLQ-LC13

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

The EORTC Quality of Life Questionnaire and Lung Cancer Module 13 (QLQ-LC13), a supplemental lung cancer-specific module used in combination with QLQ-C30, comprises 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 (1=not at all, 2=a little, 3=quite a bit, 4=very much) and has been translated and validated into more than 60 languages.

4.2.1.3.2 EQ-5D-5L

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

4.2.1.4 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers,

biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

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

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

Genetic (DNA) analyses from tumor

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

Tumor and/or blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with immunotherapies and/or other treatments administered. Immunotherapies induce a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to immunotherapy in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with immunotherapy in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to immunotherapy. Therefore, tumor tissue may be subjected to

proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for immunotherapy and/or treatments.

Other biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunosorbent assay (ELISA) that measure proteins may also be evaluated from blood samples. Correlation of these biomarkers with response to immunotherapy and/or treatments may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

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

4.2.1.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Section 10.2.

4.2.2 Rationale for the Use of Comparator/Placebo

Platinum doublet chemotherapy remains the most widely accepted approach, and currently considered the standard of care for treating Stage IV NSCLC in patients with *EGFR* mutation who has failed either 1st or 2nd generation *EGFR* TKI (eg, erlotinib/afatinib/gefitinib), and has not develop T790M mutation as a TKIs-resistant mechanism. Platinum doublet chemotherapy is also considered the standard of care for patient who has developed T790M mutation and has failed 3rd generation *EGFR* TKI osimertinib. The most commonly used platinum doublet is pemetrexed in combination with cisplatin or carboplatin. In a non-inferiority, Phase 3 trial, overall survival in 1725 subjects with previously untreated NSCLC was found to be non-inferior after treatment with cisplatin and pemetrexed compared to cisplatin combined with gemcitabine (median survival 10.3 months versus 10.3 months; HR, 0.94; 95% CI: 0.84%, 1.05%) [Scagliotti, G. V., et al 2008]. However, in a planned subgroup

analysis, cisplatin and pemetrexed was found to be superior in subjects with non-squamous NSCLC (n=1000; HR 0.81; 95% CI: 0.7, 0.94; p = 0.005). Pemetrexed and platinum therapy has become a significant treatment of choice for advanced non-squamous NSCLC. Continuation of pemetrexed after initial 4 cycles of pemetrexed cisplatin demonstrated a survival benefit in a randomized double-blind, placebo-controlled study: median overall survival 13.9 months (95% CI: 12.8, 16.0) for pemetrexed compared to 11.0 months (95% CI: 10.0, 12.5) for placebo and a HR of 0.78 (95% CI: 0.64, 0.96) [Paz-Ares, L. G., et al 2013]. Pemetrexed in combination with either cisplatin or carboplatin is therefore an appropriate control arm treatment in this Phase 3 trial.

The use of pembrolizumab matching placebo in combination with platinum doublet chemotherapy will ensure the objectivity of the local investigators' treatment decision and AE causality assessments, while still providing participants the SOC treatment.

4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dosing Regimen

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [Physiological Based Pharmacokinetics (PBPK)] analysis) at 200 mg Q3W

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

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

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

4.3.2 Rationale for Chemotherapy Dosing Regimens

The dosing regimens of chemotherapy represent the SOC per the approved product labels. Chemotherapy may be reduced, interrupted, or discontinued at the Investigator's discretion using the guidance provided in Section 6.6. (Note: Guidance in Section 6.6 should serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.)

4.4 Beginning and End of Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

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

5. Study Population

As stated in the Code of Conduct for Clinical Trials (Appendix 1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the Investigational Medical Product (IMP) under investigation.

Male/female participants with TKI-resistant *EGFR*-mutated tumors in metastatic NSCLC who are at least 18 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Have histologically or cytologically confirmed diagnosis of Stage IV (AJCC Version 8 or current version as applicable) non-squamous NSCLC.
2. Have documentation of tumor activating *EGFR* mutation, specifically either *DEL19* or *L858R*.
3. Have investigator determined radiographic disease progression per RECIST 1.1 after treatment with an *EGFR* TKI therapy:
    a) Participants previously treated with 1st or 2nd generation *EGFR* TKI (eg, erlotinib/afatinib/gefitinib) are required to have confirmed documented absence of *EGFR T790M* mutation. **Note:** Participants with negative *EGFR* T790M mutation using plasma specimens will be required to have tissue biopsy confirmation of negative T790M mutation prior to enrollment/confirmation of eligibility.
    b) Participants with confirmed acquired T790M mutation after 1st or 2nd generation *EGFR* TKI (eg, erlotinib/afatinib/gefitinib) are required to have osimertinib TKI treatment failure prior to enrollment. **Note:** Participants must have documentation of acquired T790M mutation (using plasma or tissue biopsy specimens) after 1st disease progression prior to osimertinib treatment.
    c) Participants previously failed osimertinib TKI treatment as 1st line therapy are eligible regardless of their *EGFR* T790M mutation status.

    Note: TKI washout period for all participants is 1 week or 2 half-lives after last treatment dose, whichever is longer. TKI washout should be completed prior to the first dose of study medication.

    Note: The site's study team must have reviewed pre-trial images that are of diagnostic quality from at least 2 dates to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the *EGFR* TKI. The central imaging vendor must have received these scans and have confirmed that they are of acceptable diagnostic quality prior to randomization in this trial for a possible retrospective analysis of this eligibility criterion. The central vendor will not be confirming eligibility prior to randomization.
4. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

5. Have provided archival tumor tissue sample or newly obtained (no anti-neoplastic therapy since biopsy) core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archival tissue.

   Note: If site is sending unstained slides, we strongly recommend that sites freshly cut sections and send out to the pathology laboratory within 7 days from sectioning in order for samples to be received within 14 days of site slide-cutting date.

Demographics

6. Be ≥18 years of age on the day of signing informed consent.
7. Have a life expectancy of at least 3 months.
8. Have an ECOG performance status of 0 or 1 within 7 days prior to the first dose of study treatment but before randomization.

Male participants:

9. A male participant must agree to use contraception as detailed in Section 10.3 of this protocol during the treatment period and for at least 120 days after the last dose of pembrolizumab and up to 180 days after last dose of chemotherapeutic agents.

Female participants:

10. A female participant is eligible to participate if she is not pregnant (see Section 10.3), not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

    OR

    b. A WOCBP who agrees to follow the contraceptive guidance in Section 10.3 during the treatment period and for at least 120 days after the last dose of pembrolizumab and up to 180 days after the last dose of chemotherapeutic agents.

Informed Consent

11. The participant provides written informed consent for the study.
12. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to the start of study treatment.

Table 1 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[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥50 mL/min for participant with creatinine levels >1.5 × institutional ULN
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
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 aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

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

[2] Creatinine Clearance should be calculated using the Cockcroft-Gault Method: Refer to Section 10.8 for the appropriate calculation.

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

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has predominantly squamous cell histology NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible.

2. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
3. A WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization (see Section 10.3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication

Prior/Concomitant Therapy

4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
5. Has received prior systemic cytotoxic chemotherapy or investigational agent(s), excluding *EGFR* TKIs, for metastatic NSCLC.

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

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

   Note: Prior exposure to traditional medicine(s) is allowed as long as therapy was discontinued at least 4 weeks prior to the first dose of study treatment.
6. Has received prior radiotherapy within 2 weeks of start of study treatment or has received lung radiation therapy of >30 Gy within 6 months before the first dose of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
7. Has received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment.
10. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
11. Has known active untreated CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
12. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
13. Has a known sensitivity to any component of cisplatin, carboplatin, or pemetrexed.
14. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
16. Has an active infection requiring systemic therapy.
17. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
18. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive or HBV-DNA detected) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected or HCV antibody reactive, if HCV-RNA is not the local SOC) infection.
    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
19. Has a known history of active tuberculosis (TB; Bacillus tuberculosis)

20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
21. Has known psychiatric or substance abuse disorder that would interfere with cooperating with the requirements of the study.

Other Exclusions

22. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab and up to 180 days after the last dose of chemotherapeutic agents.

Refer to Section 10.12 for country-specific requirements regarding 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 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Section 10.3 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Section 10.3) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab and up to 180 days after the last dose of chemotherapeutic agents. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant’s status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the

Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 10.3.

5.3.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws consent will not be replaced.

6. Treatments

Study treatment is defined as any investigational treatment(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 treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

The treatments to be used in this study are outlined below in Table 2.

Table 2 Study Treatment(s)

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi-mental	Pembrolizumab (MK-3475)	Biological/ Vaccine	Solution for Infusion	100 mg/ vial	200 mg	IV Infusion	Q3W	Test Product	IMP	Provided centrally by the Sponsor
Arm 1	Experi-mental	Pemetrexed	Drug	Lyophilized Powder	500 mg / vial	500 mg/m^2	IV Infusion	Q3W	Background Treatment	NIMP/ AxMP	Provided locally by the study site, subsidiary, or designee. OR Provided centrally by the Sponsor
Arm 1	Experi-mental	Carboplatin	Drug	Solution for Infusion	10 mg/mL vial	AUC 5 mg/mL• min	IV Infusion	Q3W for 4 cycles (Cycles 1-4)	Background Treatment	NIMP/ AxMP	Provided locally by the study site, subsidiary, or designee. OR Provided centrally by the Sponsor
Arm 1	Experi-mental	Cisplatin	Drug	Solution for Infusion	1 mg/mL vial	75 mg/m^2	IV Infusion	Q3W for 4 cycles (Cycles 1-4)	Background Treatment	NIMP/ AxMP	Provided locally by the study site, subsidiary, or designee. OR Provided centrally by the Sponsor
Arm 2	Placebo Com-parator	Saline Placebo	Drug	Solution for Infusion	NA	NA	IV Infusion	Q3W	Placebo	IMP	Provided locally by the study site, subsidiary, or designee
Arm 2	Placebo Com-parator	Pemetrexed	Drug	Lyophilized Powder	500 mg / vial	500 mg/m^2	IV Infusion	Q3W	Background Treatment	NIMP/ AxMP	Provided locally by the study site, subsidiary, or designee. OR Provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Placebo Com-parator	Carboplatin	Drug	Solution for Infusion	10 mg/mL vial	AUC 5 mg/mL• min	IV Infusion	Q3W for 4 cycles (Cycles 1-4)	Background Treatment	NIMP/ AxMP	Provided locally by the study site, subsidiary, or designee. OR Provided centrally by the Sponsor
Arm 2	Placebo Com-parator	Cisplatin	Drug	Solution for Infusion	1 mg/mL vial	75 mg/m^2	IV Infusion	Q3W for 4 cycles (Cycles 1-4)	Background Treatment	NIMP/ AxMP	Provided locally by the study site, subsidiary, or designee. OR Provided centrally by the Sponsor

AUC=area under the curve; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NA=not applicable; NIMP/AxMP=noninvestigational/ auxiliary medicinal product; Q3W=every 3 weeks.

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

In this protocol, placebo for pembrolizumab is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients.

For pemetrexed plus platinum chemotherapy, the investigator will select one of the following regimens prior to randomization:

- Pemetrexed 500 mg/m^2 + carboplatin AUC 5 mg/mL•min Q3W for 4 cycles followed by pemetrexed 500 mg/m^2 Q3W
- Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 for 4 cycles followed by pemetrexed 500 mg/m^2 Q3W

Maintenance pemetrexed may continue for participants past 35 administrations until reaching a discontinuation criterion (Section 7.1), as long as the participant is receiving benefit and per local regulations, whereas pembrolizumab/saline placebo are limited to 35 administrations.

All study treatments will be administered on an out-patient basis.

All products indicated in Table 2 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements with the exception of saline placebo, which will be provided locally by the study site, subsidiary or designee.

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.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Pembrolizumab: the dose amount required to prepare the pembrolizumab infusion solution will be based on a fixed dose of 200 mg. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

Chemotherapeutic agents will be prepared and administered as per the approved product label at the doses indicated below:

- **Pemetrexed:** 500 mg/m^2
- **Cisplatin:** 75 mg/m^2

- **Carboplatin:** AUC 5 mg/mL•min (using Calvert formula). Carboplatin dose not to exceed 750 mg

  Calvert Formula

  Total Dose (mg) = (target AUC) x (CrCl*+25)

  The estimated GFR used in the Calvert formula should not exceed 125 mL/min

  Maximum carboplatin dose (mg) = target AUC 5 (mg/mL•min) x (125+25) = 5x150 mL/min = 750 mg

*CrCl should be calculated using the Cockcroft-Gault Method: Refer to Section 10.8 for the appropriate calculation.

6.2.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment 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 treatments in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab plus pemetrexed plus platinum chemotherapy or saline placebo plus pemetrexed plus platinum chemotherapy, respectively.

6.3.1.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. PD-L1 expression: Tumor Proportion Score (TPS) ≥50% or TPS <50%;
2. Treatment history: osimertinib or no osimertinib;
3. Geographic region of the enrolling site: East Asia versus Non-East Asia

6.3.2 Blinding

This is a double-blinded trial; therefore, the participant, the Investigator and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the participants are unaware of the group assignments. The chemotherapy agents will be open-label. The Sponsor, investigator and participant will not know whether the treatment administered contains pembrolizumab or saline placebo. The study site's unblinded pharmacist will obtain each participant's study identification number and study treatment assignment from the interactive voice response system (IVRS)/interactive web response system (IWRS) and prepare the solutions for infusion. The unblinded pharmacist will provide the investigative staff with ready-to-use blinded pembrolizumab/saline placebo infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion. The unblinded pharmacist should have no involvement in study assessments.

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 Treatment Compliance

Administration of study medication(s) will be monitored by the Investigator and/or study staff. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol-specified treatment plan for more than 12 weeks between study treatment doses for nondrug-related or administrative reasons require consultation between the Investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

6.5.1 Acceptable Concomitant Medications

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control is not permitted during the study. Palliative radiotherapy is permitted to a limited number of lesions if considered medically necessary by the treating physician as long as the lesions are NOT a RECIST 1.1-defined target lesion. Study therapy should be held during the course of palliative radiotherapy, and study therapy should be resumed no earlier than the next scheduled administration of study therapy. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 28 days before the first dose of study treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 10.4.

If a participant enters into second course therapy, all concomitant medications received within 28 days before the first dose of second course treatment should be recorded. Following second course therapy Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 10.4.

6.5.2 Prohibited Concomitant Medications

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 treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab/saline placebo
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

  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 for any purpose other than those described in Section 6.5.3.1 are prohibited. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study, as is the use of local steroid injections and topical steroids.

- Phenytoin during therapy with cisplatin/carboplatin.

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study treatment.

All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (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 treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 10.4.

If a participant enters into second course therapy, all concomitant medications received within 28 days before the first dose of second course treatment should be recorded. Following second course therapy Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 10.4.

6.5.3 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.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 6.6 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

For supportive care guidelines for chemotherapy agents, please refer to current version of the SmPC for cisplatin, carboplatin, and pemetrexed for details.

6.5.3.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- To modulate symptoms of an AE that is suspected to have an immunologic etiology as guided in Table 4.
- For the prevention of emesis and other chemotherapy-related AEs.
- To premedicate for IV contrast allergies.
- To treat asthma or chronic obstructive pulmonary disease (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.

In addition, the following corticosteroid use is allowed:

- Topical use or ocular use
- Intraarticular joint use
- Inhalation in the management of asthma or COPD

6.5.3.2 Antiemetic Use

For participants receiving chemotherapy, antiemetic therapy should follow Multinational Association of Supportive Care in Cancer (MASCC) or appropriate local guidelines (Section 10.7) and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and aprepitant (or equivalent NK-1 receptor antagonist) as per the guideline followed.

6.5.3.3 Colony-Stimulating Factors

For participants receiving chemotherapy, the American Society of Clinical Oncology (ASCO) guidelines for use of colony-stimulating factors (CSFs), or local equivalent, should be used for patient management [Smith, T. J., et al 2015].

6.5.3.4 Pemetrexed Premedication

All participants must receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below or as per local label:

- Folic acid 350 to 1000 μg oral: 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, orally twice per day (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 doses in MASCC guidelines (or local equivalent).

6.5.3.5 Cisplatin Premedication

Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. All participants should receive adequate hydration from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin per the local label.

6.6 Dose Modification (Escalation/Titration/Other)

If appropriate, the investigator may attribute each toxicity event to cisplatin/carboplatin, pemetrexed or pembrolizumab alone or to the combination and use a stepwise dose reduction according to Table 3 to Table 7. Dose modifications must be based on the maximum toxicity experienced during a cycle. Toxicity needs to resolve to Grade ≤1 or baseline prior to resuming subsequent cycle. For individual participants requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the participant.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. 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 study therapy throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Participants who require a 3rd dose modification to any particular component will have that agent discontinued.

Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications.

Participants may have chemotherapy discontinued and continue on pembrolizumab/saline placebo alone. Similarly participants may discontinue pembrolizumab/saline placebo and continue on chemotherapy alone if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks from last dose; pembrolizumab may be interrupted for a maximum of 12 weeks from last dose.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 3 through Table 7.

Table 3 Dose Modifications for Study Medications

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	Area under curve (AUC) 5 Maximum dose 750mg	AUC 3.75 Maximum dose 562.5mg	AUC 2.5 Maximum dose 375mg	Discontinue
Pemetrexed	500mg/m2	375 mg/m2	250 mg/m2	Discontinue
Pembrolizumab/ Saline placebo	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

6.6.1 Dose Modification for Pembrolizumab

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

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

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

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 12 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.2 Dose Modification for Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 6 and Table 7. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Table 6 Recommended Dose Modifications for Chemotherapy Hematological Toxicity

		Pemetrexed	Cisplatin/Carboplatin
Platelets	**ANC**	**Dose level (DL) from Table 3**	
≥50,000/mcL AND	≥ 500/mcL	DL 0	DL 0
≥50,000/mcL AND	< 500/mcL	DL -1	DL -1
<50,000/mcL without bleeding AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥ 2 bleeding AND	ANY	DL -2	DL -2
ANY AND	< 1,000/mcL + fever ≥ 38.5°C (101°F)	DL -1	DL -1

Table 7 Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

		Pemetrexed	Cisplatin	Carboplatin
Event	**CTC Grade**	**Dose level (DL) from Table 3**		
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1	DL -1

Creatinine clearance (CrCl):

CrCl will be based original weight-based Cockcroft and Gault formula in Section 10.8. CrCl must be ≥45 mL/min prior to the administration on the day of chemotherapy. Pemetrexed and/or platinum may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If a participant's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, platinum and/or pemetrexed must be discontinued.

6.7 Treatment After the End of the Study

There is no study-specified treatment following 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 treatment 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 treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.5 unless the participant has withdrawn from the study (Section 7.2).

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

A participant must be discontinued from study treatment 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 treatment.
- The participant's treatment assignment has been unblinded by the investigator for reasons other than BICR-verified radiographic disease progression, by MSD subsidiary or through the emergency unblinding call center.
- 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 treatment.
- The participant has a confirmed positive serum pregnancy test.
- BICR-verified disease progression as outlined in Section 8.2.1 AND the participant is clinically unstable.

  Clinical Stability is defined as:

  1. Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) indicating disease progression.
  2. No decline in ECOG performance status.
  3. Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment
- Noncompliance with study treatment or procedure requirements
- Unacceptable adverse experiences.

Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 8.11.4.

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

Participants may be allowed to begin study treatment again if deemed medically appropriate for Second Course Retreatment Phase if the participant meets all eligibility criteria in Section 8.11.4.

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

Participants who withdraw consent during the study

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

Section 8.1.9 delineates the specific procedures performed at the time of withdrawal and withdrawal from future biomedical research. Survival Follow-up Procedures are outlined in Section 8.11.6.3. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4. 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

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), 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 total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant 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 future biomedical research. 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 trial protocol number, trial 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 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.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized 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 treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study medication.

Prior anti-cancer treatment for NSCLC will be recorded separately and not listed as a prior medication. The investigator or qualified designee will review and record all prior anti-cancer treatments including systemic treatments, radiation, and surgeries, regardless of the time prior to first dose of study treatment.

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 Crossover Phase and Second Course through the Crossover Safety Follow-up Visit and Second Course Safety Follow-up Visit should be recorded.

All medications related to reportable SAEs and ECIs should be recoded as defined in Sections 8.4 and 10.4.

8.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of study treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of study treatment, the 30 day Safety Follow-up visit must occur before the first new dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

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

8.1.6.1 Treatment Eligibility Assessment (TEA) Form

A TEA form is included in this study to document the investigators' choice of carboplatin or cisplatin and the rationale. These data may be required to support reimbursement efforts for pembrolizumab.

The investigator must complete this form to document the rationale for the choice of carboplatin or cisplatin prior to randomization.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Treatment Administration

Administration of study medication will be monitored by the investigator and/or study staff.

Study interventions will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance to each dose of pembrolizumab administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. Premedication should also be dosed per the approved product labels and as described in Section 6.5.3.

Study treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

8.1.8.1 Timing of Dose Administration

Participants will receive blinded pembrolizumab 200 mg or saline placebo together with pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5 mg/mL•min all on Day 1 Q3W for 4 cycles followed by blinded pembrolizumab 200 mg or saline placebo together with pemetrexed 500 mg/m^2 Q3W on Day 1 of each subsequent cycle until BICR-verified disease progression, study completion, or any discontinuation criteria are met per Sections 7.1 and 8.1.9.

Study treatment should be administered on Day 1 of each cycle after all procedures / assessments have been completed (Section 1.3). Study treatment can be administered 3 days before or after of the targeted Day 1 for each cycle, except Cycle 1 Day 1 (C1D1), where study treatment can only be administered + 3 days from randomization.

All study treatments will be administered on an outpatient basis.

8.1.8.1.1 Timing of Dose Administration of Pembrolizumab/Saline Placebo

Pembrolizumab/saline placebo will be administered as a dose of 200 mg using a 30-minute IV infusion prior to administration of chemotherapy agents. 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 30 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

For participants who experience disease progression, investigators may elect to interrupt treatment by deferring the decision to continue/discontinue treatment in the trial until confirmation of disease progression per RECIST 1.1 at least 28 days from the date of imaging demonstrating disease progression confirmed through blinded central imaging vendor review. Participants for whom disease progression is not confirmed on subsequent imaging may resume treatment. Please see Section 7 for other exceptions.

8.1.8.1.2 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity. All participants should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as described in Section 6.5 and/or according to local practice and labels.

8.1.8.1.3 Cisplatin

Cisplatin 75 mg/m^2 will be administered as an IV infusion over a recommended time of 60 minutes. However, cisplatin may be administered over 30 to 150 minutes to accommodate local SOC. Treatment will be administered after pemetrexed on Day 1 of the 21 day cycle, for a maximum of 4 administrations.

Cisplatin administration should be immediately preceded and followed by hydration procedures described in Section 6.6 and administered according to local practice and labels.

8.1.8.1.4 Carboplatin

Carboplatin AUC 5 mg/mL•min will be administered as an IV infusion over 30 to 60 minutes. Treatment will be administered after pemetrexed on Day 1 of the 21 day cycle, for a maximum of 4 administrations. The dose of carboplatin will be calculated using the Calvert Formula as described in Section 6.2.

For additional details, refer to approved product labels for details regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration for each of the standard of care chemotherapies.

8.1.9 Discontinuation and Withdrawal

Participants who withdraw consent from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal.

Once the participant moves to survival follow-up, he/she shall not be allowed to restart study treatment, but overall survival information will still be collected.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main 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 future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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 TREATMENT 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 drug 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 medical qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment 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 drug, the reason thereof, etc., in the medical chart etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

For studies that require non-emergency unblinding as part of the study design (BICR-verified radiographic disease progression) to support treatment decisions, instructions in Section 8.11 should be followed. The emergency unblinding center should not be used for this purpose.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

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

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably

calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. CT scans are preferred over other tumor imaging methods. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same type of scan, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment. Note: for the purposes of assessing tumor imaging, the term “Investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Brain MRI will be done for all participants at screening. If MRI is medically contraindicated, then CT with contrast is an acceptable alternative.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be submitted to the central imaging vendor.

When the Investigator identifies radiographic progression per RECIST 1.1, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor (See Section 8.2.1.5 and Figure 3). Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement iRECIST, the Investigator will assess for confirmation of progression by iRECIST at subsequent time points (Section 1.2, Figure 3). Images should continue to be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

The site’s study team must have reviewed pre-trial images from at least 2 dates to confirm that radiographic progression has occurred per RECIST 1.1 confirming disease progression after TKI treatment failure. The central imaging vendor must have received these scans prior to randomization in this trial for a possible retrospective analysis of this eligibility criterion. The central imaging vendor must also confirm that pre-trial scans are of diagnostic quality prior to randomization.

Initial tumor imaging at Screening must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

The screening images must be submitted to the central imaging vendor for retrospective review.

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

When brain imaging is performed, MRI should be used if possible. If MRI is medically contraindicated, then CT with contrast is an acceptable alternative.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 51 weeks, participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator and verified by the central imaging vendor (unless the Investigator elects to continue treatment and follow iRECIST), the start of a new anti-cancer treatment, pregnancy, withdrawal of consent, death, or the end of the study. All imaging must be submitted to the central imaging vendor.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the central imaging vendor.

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

Per iRECIST (Section 8.2.1.6), disease progression should be confirmed by the site 4 to 8 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable participants. Participants, who have unconfirmed disease progression may continue on their assigned study treatment at the discretion of the Investigator until progression is confirmed by the site (Section 1.2, Figure 3) and provided they have met the conditions detailed in Section 8.2.1.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants, who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.2.1.6.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation

is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the Investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 12 weeks after Year 1) or according to local standard of care imaging intervals should be used to monitor disease status until the start of new anti-cancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 Second Course (Retreatment) and Crossover Tumor Imaging

Tumor imaging must be performed within 28 days prior to starting/restarting treatment with pembrolizumab. The Investigator, working with local radiology will be used to determine eligibility. Imaging should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review.

The first on-study imaging assessment should be performed at 12 weeks (±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (±7 days) or more frequently, if clinically indicated.

Per iRECIST (Section 8.2.1.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anti-cancer treatment, pregnancy, withdrawal of consent, death, or the end of the study, whichever occurs first. In clinically stable participants, disease progression may be confirmed by the investigator using iRECIST 4 to 8 weeks after the first tumor imaging indicating PD.

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

For participants who discontinue Second Course study treatment without documented disease progression, radiologic tumor imaging using the same imaging schedule used while on treatment (ie, every 12 weeks ±7 days) or according to local standard of care imaging intervals should be used to monitor disease status until the start of new anti-cancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of

5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using RECIST 1.1. Figure 5 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator, working with local radiology to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Section 10. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined in Section 7.1.

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

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Section 10, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Section 10, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 8 and illustrated as a flowchart in Figure 5.

Table 8 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

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

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression

Note: If progressive disease (PD) has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no real-time review will occur. If RECIST 1.1 disease progression has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.

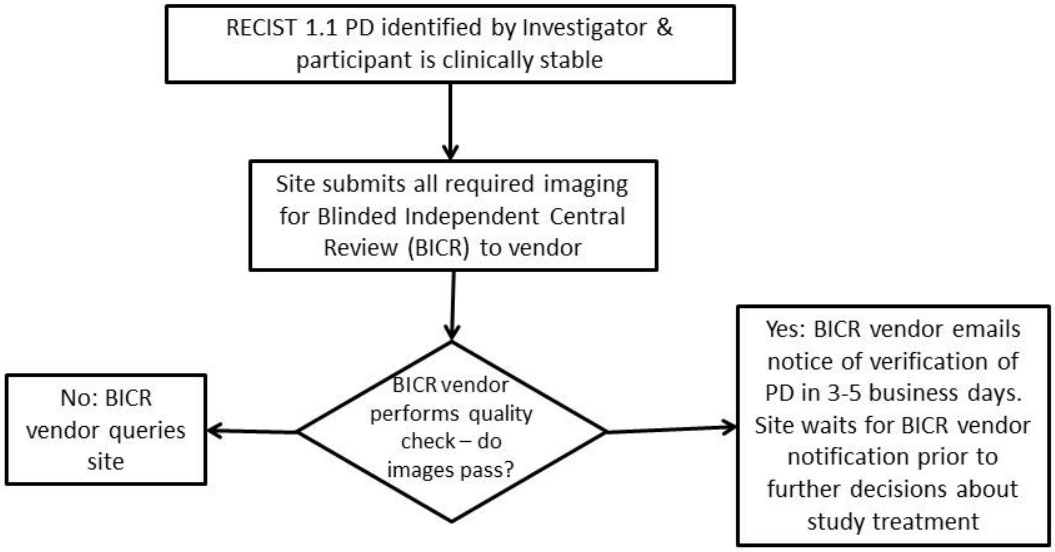


Figure 5 Imaging and Treatment for Clinically Stable Participants After First Radiologic Evidence of PD Assessed by the Investigator

8.2.2 Patient Reported Outcomes

The EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EQ-5D-5L first, then EORTC QLQ-C30, then EORTC QLQ-LC13. The questionnaires should be administered prior to dosing at every cycle through Cycle 7, then every 3rd cycle through Cycle 19, then every 4th cycles through Cycle 35 (eg, Cycles 1-7, 10, 13, 16, 19, 23, 27, 31, 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 treatment, at the time of the mandatory Safety Follow-up visit, PROs do not need to be repeated.

It is best practice and strongly recommended that electronic patient reported outcomes (ePROs) are administered to randomized participants prior to drug administration, adverse event evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

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

8.3.1 Physical Examinations

A complete (full) physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard during the Screening period and at Discontinuation.

For cycles that do not require a full physical examination, a brief directed physical examination will be conducted as per institutional standard.

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

8.3.2 Vital Signs

Vital signs will be collected at Screening, prior to the administration of each dose of study treatment, EOT/Discontinuation and/or 30 days after the last dose of study treatment (follow-up) as outlined in the SoA in Section 1.3. Vital signs measurements include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at Screening only. Refer to Section 10.12 for country-specific requirements.

8.3.3 Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at Screening and at EOT/Discontinuation using local standard procedures as outlined in the SoA in Section 1.3.

Clinically significant abnormal findings at Screening should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Section 10.5 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 case report form (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 Section 10.5, must be conducted in accordance with the laboratory manual and the SoA Section 1.3.
- If laboratory values from non-protocol 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 treatment, 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 pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Procedures Manual. Refer to the SoA in 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 Section 10.5.

8.3.4.2 Pregnancy Test

- All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of the first dose of study treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated Pregnancy test (such as monthly testing) may be conducted if required by local regulations.

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

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Section 10.4, Appendix 4.

Progression of the cancer under study is not considered an AE as described in Section 8.4.5 and Section 10.4.

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before treatment allocation/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 treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment 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 treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment 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 of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE 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 treatment 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 9.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, ECIs, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Section 10.4.

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 treatment 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 treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 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.

8.4.6 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events 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, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

ECIs that occur after the participant provides documented informed consent, but before treatment randomization, must be reported by the investigator to Sponsor if the event caused the participant to be excluded from the study or is the result of a protocol-specified intervention.

All ECIs that occur from the time of treatment randomization through 30 days following cessation of study treatment must be reported by the investigator to Sponsor in accordance with the reporting time period described in Table 9.

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the electronic data collection (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for ctDNA, Genetics, and RNA Analyses
- Blood for Serum and Plasma Analyses
- Archival tumor specimen

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

The sample for genetic analysis should be drawn for planned exploratory biomarker research. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for

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

8.9 Future Biomedical Research Sample Collection

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

- *Leftover DNA for future research*
- *Leftover main study tumor stored for future research*
- *Leftover main study serum/plasma from biomarker analyses stored for future research*
- *Leftover main study RNA stored for future research*
- *Leftover plasma or derivative for ctDNA*

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 allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment, if the participant initiates new anti-cancer therapy, whichever is earlier.

8.11 Visit Requirements

8.11.1 Screening

Within 42 days prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing documented informed 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 42 days prior to the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study treatment. An exception is hepatitis and/or HIV (if required by local SOC) testing which may be done up to 28 days prior to the first dose of study treatment.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study treatment but before randomization (see Section 10.6).
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study treatment. If urine

pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Archival tumor sample collection is not required to be obtained within 42 days prior to the first dose of study treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

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

8.11.2 Initial Treatment Phase

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

8.11.3 Crossover Treatment Phase

Participants who experience BICR-verified disease progression and are unblinded (Section 1.2, Figure 3) will have the opportunity to crossover to receive pembrolizumab monotherapy.

At the time of documented disease progression as confirmed by BICR using RECIST 1.1 (Section 8.2.1), participants may have treatment assignment unblinded (Figure 3). Participants who received saline placebo in combination with chemotherapy may be eligible to receive pembrolizumab monotherapy for a total of 35 administrations in the Crossover Treatment Phase.

Participants who received pembrolizumab in combination with chemotherapy, but are deemed to be benefiting clinically despite disease progression, may continue study treatment beyond progression and receive pembrolizumab monotherapy in the Crossover Treatment Phase to complete a total of up to 35 pembrolizumab administrations.

Study treatment may continue until participant reaches a discontinuation criterion (Section 7.1), examples of which include subsequent documented progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, or for administrative reasons.

Crossover Qualifications:

Participants will be considered for crossover to pembrolizumab monotherapy after documented, progressive disease assessed based on RECIST 1.1 verified by central imaging vendor BICR. Participants who permanently discontinue chemotherapy due to an adverse event, withdraw consent, or for any reason other than progressive disease, will not be eligible for crossover. Crossover participants must not initiate treatment with pembrolizumab any earlier than 21 days after their last dose of chemotherapy regardless of the time of progression.

Crossover is optional and is at the discretion of the Investigator and with Sponsor consultation. Participants who meet the following criteria are eligible for crossover:

- Documented verification of progressive disease by BICR;
- Adverse events (except alopecia) due to therapy must have improved to CTCAE (Version 4.0) ≤Grade 1;
- ECOG Performance Status 0-1
- Participant has not received any other cytotoxic anticancer therapies other than the chemotherapy administered during the initial treatment phase;
- If required, completed palliative radiotherapy (30 Gy or less) ≥ 7 days before the first dose of crossover study treatment.
- Participant has adequate organ function as indicated by the laboratory values in Section 5.1 (Inclusion Criteria).

If progressive disease is centrally verified but participant does not qualify for Crossover per the above listed criteria, unblinding may be considered after consulting with Sponsor.

NOTE: If a participant is clinically unstable as a result of a new or progressing CNS metastasis(es) the participant will not be eligible for crossover.

8.11.3.1 Crossover Assessments and Procedures

Crossover participants must not initiate treatment with pembrolizumab any earlier than 21 days after their last dose of chemotherapy regardless of the time of progression. The participant will then start the Crossover Phase as outlined in Crossover Treatment Phase SoA in Section 1.3.2. Crossover entry procedures need to be completed within 28 days of confirmed progressive disease (or up to 42 days from last dose if recovering from adverse event). All procedures and assessments completed at the time of withdrawal from the Initial Treatment Phase may be used as appropriate for the start of the Crossover Treatment Phase of the study. The tumor image used to determine progressive disease can be used as the new baseline image for the Crossover Phase if: 1) 28 days prior to receiving the first dose of pembrolizumab monotherapy and 2) No study treatment between the image and first dose of pembrolizumab monotherapy, otherwise a new baseline image must be performed prior to pembrolizumab monotherapy treatment.

Participants entering the Crossover Treatment Phase will be treated with pembrolizumab monotherapy. Chemotherapy will not be dosed in the Crossover Treatment Phase.

Pembrolizumab monotherapy will be dosed every 21 days ± 3 days (1 cycle). Treatment may continue until a discontinuation criterion is met (Section 7.1).

8.11.4 Second Course Retreatment Phase

Second Course Phase visit requirements are outlined in the SoA (Section 1.3.3). Specific procedure-related details are provided in Section 8.1.

Participants who stop study treatment with a SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab monotherapy treatment if they progress after stopping study treatment from the Initial Treatment Phase. This retreatment is

termed Second Course Phase and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - o Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - o Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND, regardless of what is true above

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
    - o Upon unblinding at the time of centrally verified disease progression were found to have been treated on the pembrolizumab plus chemotherapy arm, and
    - o No new anti-cancer treatment was administered after the last dose of study treatment, and
    - o The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - o The study is ongoing.

Participants who enter the Second Course Phase will be retreated with open-label pembrolizumab monotherapy. Chemotherapy will not be dosed in Second Course Phase.

Pembrolizumab will be dosed every 21 days (1 cycle) for up to 17 administrations (approximately 1 year). Treatment may continue until a discontinuation criterion is met (Section 7.1).

An objective response or progression of disease that occurs during the Second Course Phase for a participant will not be counted as an event in the primary analyses in this trial.

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

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

Descriptions of the study follow-up visits including required procedures are provided in Section 8.11.6.

8.11.6 Post-Study

8.11.6.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment and before the initiation of a new anti-cancer treatment.

Participants who are eligible for crossover and/or retreatment with pembrolizumab monotherapy may have up to 2 safety follow-up visits; 1 after the Initial Treatment Period, and 1 after either the Crossover Phase or after the Second Course Treatment.

8.11.6.2 Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study treatment for a reason other than BICR-verified disease progression will move into the Follow-Up Phase and should be assessed at least every 12 weeks ± 7 days to monitor disease status, including tumor imaging. Follow-up Visits may be scheduled to coincide with Follow-up imaging (eg, 9 weeks from last imaging time point through Week 51 or 12 weeks from last imaging if after Week 51). Follow-up visits and imaging continue until BICR-verified PD, the start of new anti-cancer treatment, pregnancy, participant withdraws consent, participant becomes lost to follow-up, participant death, or end of the study. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Participants discontinuing treatment with BICR-verified PD proceed directly to survival follow-up or Crossover Treatment Phase, if applicable.

The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until disease progression, death, end of study or if the participant begins Second Course Retreatment Phase with pembrolizumab as detailed in Section 8.11.4. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 8.11.4 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in the Study Flow Chart (Section 1.2) for retreatment with pembrolizumab.

8.11.6.3 Survival Follow-up Assessments

Participants who experience BICR-verified disease progression will move into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. Survival status can be done in a variety of ways including phone, email, chart review, or review of public records. Survival status information (whether by telephone, review of public records, etc.) should be officially documented by the site.

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

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

For participants who discontinue treatment intervention and who will not enter the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

For participants who completed assessments in the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.7 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool). Survival status can be done in a variety of ways including phone, email, chart review, or review of public records. Survival status information (whether by telephone, review of public records, etc.) should be officially documented by the site.

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) may be developed to detail other planned analyses (ie, those specific to the analysis of patient-reported outcomes and future biomedical research).

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.11.

Study Design Overview	A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant *EGFR*-mutated Tumors in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants (KEYNOTE-789)
Treatment Assignment	Participants will be randomized in a 1:1 ratio to receive pembrolizumab or saline placebo in combination with pemetrexed plus platinum chemotherapy, with pemetrexed maintenance. Stratification factors are in Section 6.3.1.1. This is a randomized double-blinded study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	1) Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR 2) Overall survival (OS)
Key Secondary Endpoints	1) Objective response rate (ORR) per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS will be evaluated by comparing pembrolizumab to saline placebo in combination with platinum and pemetrexed 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. The stratified M&N method with sample size weights will be used for analysis of ORR.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There are no Tier 1 safety parameters in this trial. All safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference will be analyzed using the Miettinen and Nurminen method. In the primary safety comparison, participants who crossover to pembrolizumab monotherapy are censored at time of crossover (ie, AEs occurring during treatment with pembrolizumab are excluded for control-arm participants). Additional safety summary may be conducted for the crossover population including all safety events starting from the date of the first dose of pembrolizumab. Safety data from the Second Course Treatment Phase will be summarized separately and will not be included in the primary safety comparison.

Interim Analyses	Three interim analyses will be performed in this study. Results will be reviewed by an external data monitoring committee. The primary purpose of the interim analyses is to demonstrate superior efficacy. Safety data will also be reviewed at each planned interim analysis to assess the overall risk: benefit. These interim analyses and the FA are summarized below. Details are provided in Section 9.7. • IA 1: o Timing: To be performed at approximately 6 months after the last participant has been randomized (estimated ~30 months after the first participant randomized) o Testing: 1) To demonstrate superiority of pembrolizumab in combination with platinum and pemetrexed in PFS; 2) To demonstrate superiority of pembrolizumab in combination with platinum and pemetrexed in OS. • IA 2 (Final PFS analysis): o Timing: To be performed ~16 months after the last participant has been randomized AND approximately 414 PFS events have been observed (estimated ~40 months after the first participant randomized). o Testing: 1) To demonstrate superiority of pembrolizumab in combination with platinum and pemetrexed in PFS; 2) To demonstrate superiority of pembrolizumab in combination with platinum and pemetrexed in OS. • IA 3: o Timing: To be performed at ~29 months after the last participant has been randomized (estimated ~53 months after the first participant randomized). o Testing: To demonstrate superiority of pembrolizumab in combination with platinum and pemetrexed in OS. • FA: o Timing: To be performed at ~42 months after the last participant has been randomized AND approximately 423 deaths have occurred (estimated ~66 months after the first participant randomized). o Testing: To demonstrate superiority of pembrolizumab in combination with platinum and pemetrexed in OS. • Note that for the FA, if the OS events accrue slower than expected such that the targeted number of events cannot be reached in the anticipated timeframe, the Sponsor may conduct the analysis with approximately 2 additional months of follow-up, or when the specified number of events is observed, whichever occurs first. If the observed number of OS events at the time of IA3 is very close to the target number of events at FA (if more than ~98% information fraction, ie, ~415 OS events), then IA3 will become the FA using the remaining alpha that has not been spent at the earlier analyses, and will be performed at ~29 months after the last participant has been randomized and approximately 423 deaths have occurred.

Multiplicity	The study uses an extension of the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to control multiplicity 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 alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The overall type I error is controlled at 0.025 (one-sided) for the hypothesis testing of ORR, PFS and OS. The pre-allocated alpha is 0, 0.0125 and 0.0125 for ORR, PFS, and OS, respectively.
Sample Size and Power	The planned sample size is 492 participants assuming 24 months of enrollment. The FA will occur after approximately 423 deaths have been observed. With 492 participants, the study has ~86% power to detect a HR of 0.72 on OS at 0.0125 (one-sided) alpha-level, and ~91% power to detect a HR of 0.7 on PFS at 0.0125 (one-sided) alpha-level.

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.

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

This trial is double blinded with a Crossover Phase. At the time of documented progression, participants may have treatment assignment unblinded and be able to continue therapy in the Crossover Phase (please refer to Section 4, Study Design for details). In addition, the BICR will be performed by the central imaging vendor without knowledge of treatment assignment.

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Efficacy Endpoints

Dual Primary

Progression-free survival (PFS) – RECIST 1.1 assessed by BICR

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent central imaging vendor review or death due to any cause, whichever occurs first. See Section 9.6.1 for the censoring rules.

Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known contact.

Secondary

Objective response rate (ORR) – RECIST 1.1 assessed by BICR

Objective response rate (ORR) is defined as the proportion of participants who have a CR or a partial response (PR). Responses are based on confirmed assessments by the BICR by the central imaging vendor per RECIST 1.1.

Duration of Response (DOR) – RECIST 1.1 assessed by BICR

For participants who demonstrated CR or PR, duration of response (DOR) is defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for participants who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Response duration will be calculated for RECIST 1.1 based on BICR by the imaging vendor.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2.

9.4.3 PRO Endpoints

The secondary patient-reported outcome (PRO) endpoints include the global health status/quality of life scale of the QLQ-C30 (items 29 and 30) and TTD in the composite endpoint of cough (LC13 Q1), chest pain (LC13 Q10) or dyspnea (C30 Q8). The TTD is defined as the time from baseline to first onset of 10 points or more deterioration from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline in any of the 3 items.

Additional scales of EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L are exploratory PRO endpoints as described in Section 3 and will also be evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The Intention-to-Treat (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.

9.5.2 Safety Analysis Populations

The All Participants as Treated (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 participant who receives 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 PRO Analysis Populations

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as participants who have at least one PRO assessment available and have received at least one dose of study medication.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

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

All statistical tests, unless otherwise specified, will be stratified for the stratification factors.

9.6.1.1 Progression-free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.1.1). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 via BICR by the imaging vendor. Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease

assessment. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 via BICR by the imaging vendor, one primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The first sensitivity analysis follows intention-to-treat principles. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. For the second sensitivity analysis, it considers discontinuation of treatment or initiation of an anti-cancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 10.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
Progressive disease (PD) or death documented after ≤ 1 missed disease assessment; and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anti-cancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study treatment
No PD and no death; new anti-cancer treatment is initiated	Censored at last disease assessment before new anti-cancer treatment	Censored at last disease assessment	Progressed at date of new anti-cancer treatment

In case the proportional hazards assumption is not valid, supportive analyses using Restricted Mean Survival Time (RMST) method may be conducted for PFS to account for the possible non-proportional hazards effect.

Further details of sensitivity analyses will be described in sSAP as needed.

9.6.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factor defined in Section 6.3.1.1). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model. The Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect and to estimate the absolute benefit of experimental treatment. A cure rate model may be applied to estimate the long-term effect.

Since participants in the control arm are allowed to switch to the pembrolizumab treatment after progressive disease, adjustment for the effect of crossover on OS may be performed based on recognized methods, eg, a two-stage method or the Rank Preserving Structural Failure Time (RPSFT) model, based on an examination of the appropriateness of the data to the assumptions required by the methods.

Further details of sensitivity analyses will be described in sSAP as needed.

9.6.1.3 Objective Response Rate (ORR) and Duration of Response (DOR)

The stratified Miettinen and Nurminen method will be used for the comparison of the ORR between the 2 treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.1.1) will be applied to the analysis.

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed complete response or partial response will be included in this analysis. Censoring rules for DOR are summarized in Table 11.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 11 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

The primary analysis approach for the primary and key secondary efficacy endpoints are summarized in Table 12. Sensitivity analysis methods are described above for each endpoint as applicable.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, and interim analyses is described in Section 9.7, Interim Analyses and in Section 9.8, Multiplicity.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Dual Primary Endpoints			
PFS per RECIST 1.1 by blinded independent central review (BICR) by the imaging vendor	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at the last date the participant was known to be alive)

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Key Secondary Endpoints			
ORR per RECIST 1.1 by blinded independent central review (BICR) by the imaging vendor	Test and Estimation: Stratified M&N method with sample size weights††	ITT	Participants without assessments are considered non-responders and conservatively included in denominator
DOR per RECIST 1.1 by blinded independent central review (BICR) by the imaging vendor	Descriptive statistics for range and Kaplan-Meier estimate of median	Participants in ITT population with an objective response	

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.1.1) will be applied to the analysis.

†† Miettinen and Nurminen method

Abbreviations: DOR=duration of response; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors 1.1;

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs. In the primary safety comparison, participants who crossover to pembrolizumab monotherapy are censored at time of crossover (ie, AEs occurring during treatment with pembrolizumab are excluded for control-arm participants). Additional safety summary may be conducted for the crossover population including all safety events starting from the date of the first dose of pembrolizumab. Safety data from the Second Course Treatment Phase will be summarized separately and not be included in the primary safety comparison.

Adverse Events

Adverse events will be coded using the standard MedDRA and grouped system organ class. Adverse events will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. Adverse experiences (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs parameters are either pre-specified as Tier-1 endpoints, or will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed.

Tier 1 Events

Safety parameters or adverse experiences of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be participant to inferential testing for statistical significance with p values and 95% confidence intervals to be provided for between-treatment comparisons. For this protocol, there are no Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-treatment differences in the proportion of participants with events.

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event. The threshold of at least 10% participants was chosen because patient population enrolled in this study are in critical conditions and usually experience various adverse events of similar types regardless of treatment, events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and safety parameters that meet predefined limits of change.

In addition to individual events that occur in ≥10% or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with Grade 3 to 5 AEs (≥2% of participants in 1 of the treatment groups) and SAEs (≥2% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. The 95% confidence intervals will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3 to 5 AE (incidence ≥2% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥2% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3 to 5 AE		X
	Any Serious AE		X
	Any Drug-related AE		X
	Any Serious and Drug-related AE		X
	Any Grade 3 to 5 and Drug-related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)		X
	Change from baseline results (lab toxicity shift)		X

AE=adverse event; CI=confidence interval; SOC=system organ class.

9.6.3 Statistical Methods for PRO Analyses

To assess change from baseline in the EORTC QLQ-C30 global health status/QoL scale score (items 29 and 30), the constrained longitudinal data analysis (cLDA) model will be applied for treatment comparison of pembrolizumab + chemotherapy versus saline placebo + chemotherapy. The response variable consists of baseline values and the values observed at each pre specified post-baseline time point for primary analysis. The model will be adjusted for treatment by time interaction and stratification factors as covariates. Least square mean change from baseline will be summarized.

The Kaplan-Meier method will be used to estimate the TTD survival curve for the composite endpoint of cough (LC13 Q1), chest pain (LC13 Q10) or dyspnea (QC30 Q8) in each treatment group. The TTD is defined as the time to the first onset of 10 points or more deterioration in cough, chest pain, or dyspnea from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline in any of these 3 symptoms. A stratified Cox PH model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference for the pembrolizumab + chemotherapy and saline placebo + chemotherapy regimen. Stratification factors used for randomization will be used in the stratified Cox PH model.

Details of additional PRO analyses will be included in the sSAP.

9.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.4.1 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, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

An external data monitoring committee (eDMC) will be convened to review the unblinded efficacy results and accumulating safety at the planned interim analyses. An external unblinded statistician and programmer will be responsible for conducting and presenting the interim analyses results to the eDMC. The eDMC responsibilities and review schedules will be outlined in the eDMC charter. The recommendation of the eDMC will be communicated to an executive oversight committee of the Sponsor. In the event of a recommendation to halt the trial early due to safety concerns, the Sponsor will communicate this to the appropriate regulatory agencies. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations.

A limited number of additional Sponsor personnel may be unblinded, if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded to the results will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

9.7.1 Efficacy Interim Analyses

Three IAs are planned in addition to the FA for this study. For the interim and final analyses, all randomized participants will be included. The primary purpose of the IAs is to demonstrate superior efficacy. Safety data will also be reviewed at each planned IA to assess the overall risk: benefit. Details on the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 9.8. The trial will continue until the number of deaths (see Section 9.9) is approximately equal to the targeted number for the FA, irrespective of the outcome from the IAs.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 14.

Table 14 Summary of Interim and Final Analyses Strategies

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	PFS OS	~6 months after the last participant has been randomized.	~30 months	• Demonstrate PFS superiority • Demonstrate OS superiority
IA2 (Final PFS Analysis)	PFS OS	~16 months after the last participant has been randomized AND approximately 414 PFS events have been observed.	~40 months	• Demonstrate PFS superiority • Demonstrate OS superiority
IA3	OS	~29 months after the last participant has been randomized.	~53 months	• Demonstrate OS superiority
FA	OS	~42 months after the last participant has been randomized AND approximately 423 deaths have occurred for the final OS analysis.	~66 months	• Demonstrate OS superiority

Note: For the final analysis, if the events accrue slower than expected such that the targeted number of events cannot be reached in the anticipated timeframe, the Sponsor may conduct the analysis with approximately 2 additional months of follow-up, or when the specified number of events is observed, whichever occurs first. If the observed number of OS events at the time of IA3 is very close to the target number of events at final analysis (if more than ~98% information fraction, ie, ~415 OS events), then IA3 will become the final analysis using the remaining alpha that has not been spent at the earlier analyses, and will be performed at ~29 months after the last participant has been randomized and approximately 423 deaths have occurred.
FA=final analysis; IA=interim analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

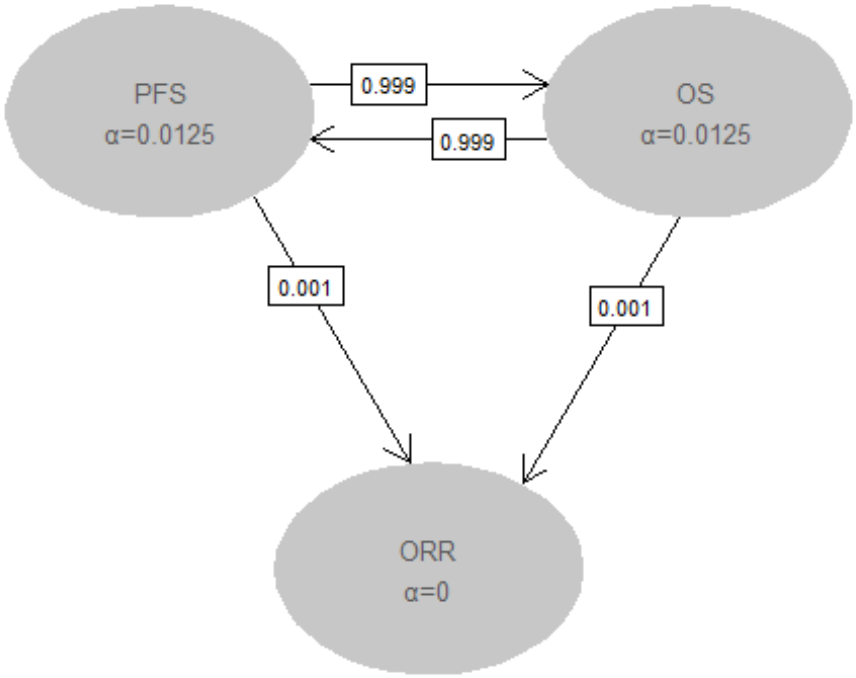
9.7.2 Safety Interim Analyses

Accumulating safety data will be reviewed approximately every 6 months after the first participant is randomized. Interim safety analyses will also be performed at each planned IA described in Section 9.7.1 to assess the overall risk: benefit. Further details on the timing of safety monitoring will be specified in the eDMC charter.

9.8 Multiplicity

The trial uses an extension of the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses while making the interim and final analysis timing be more flexible [Anderson and Gause, manuscript submitted]. According to Maurer and Bretz approach, study hypotheses may be tested in a group sequential fashion, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The extended graphical method spends alpha as a function of the minimum of the actual event information fraction and the expected event information fraction. This ensures that spending will be no more aggressive than the information fraction method, while at the same time ensuring not

all alpha is spent prior to final planned analysis calendar time. Figure 6 shows the initial one-sided alpha allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.



Note: If both PFS and OS null hypotheses are rejected, the reallocation strategy allows re-testing of ORR at alpha=0.025 based on the p-value at IA1
ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Figure 6 Type I Error Reallocation Strategy

9.8.1 Objective Response Rate

The study does not allocate initial alpha to ORR. ORR will be formally tested only if the hypotheses for PFS and/or OS is significant. The testing of ORR will be based on all randomized subjects. If the null hypotheses for OS and PFS are rejected at IA1 or at a time later than IA1, the p-value of ORR from the IA1 analysis will be compared to the α level passed to ORR from PFS and/or OS. Power at the possible alpha-levels as well as the approximate treatment difference required to reach the bound (ORR difference) are shown in Table 15 assuming underlying 34% and 54% response rates in the control and experimental groups, respectively.

Table 15 Possible Alpha-levels and Approximate Objective Response Rate (ORR) Difference Required to Demonstrate Efficacy for ORR at Interim Analysis 1

Alpha	ORR difference	Power
0.0000125	~0.19	0.60
0.025	~0.09	0.99

9.8.2 Progression-Free Survival

The PFS hypothesis may be tested at alpha=0.0125 (initially allocated alpha), or alpha=0.0249875 (if OS null hypothesis is rejected), or alpha=0.025 (if both OS and ORR null hypothesis are rejected). Table 16 shows the boundary properties for each of these alpha-levels, which were derived using a Lan-DeMets O'Brien-Fleming spending function based on predicted number of events at the planned time of interim analysis. Note that the final row indicates the total power to reject the null hypothesis for PFS at each alpha-level. Also note that if the OS null hypothesis is rejected at an interim or final analysis, each PFS interim and final analysis test may be compared to its updated bounds considering the alpha reallocation from the OS hypothesis.

Table 16 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	**Value**	**α=0.0125**	**α=0.0249875**	**α=0.025**
IA1: 88%* N: 492 Events: 367 Month: 30	Z	2.4121	2.1158	2.1155
	p (1-sided) [§]	0.0079	0.0172	0.0172
	HR at bound[%]	0.7772	0.8017	0.8017
	P(Cross) if HR=1[†]	0.0079	0.0172	0.0172
	P(Cross) if HR=0.7[#]	0.8435	0.9038	0.9038
IA2: 100%* N: 492 Events: 414 Month: 40	Z	2.3169	2.0491	2.0489
	p (1-sided) [§]	0.0103	0.0202	0.0202
	HR at bound[%]	0.7963	0.8176	0.8176
	P(Cross) if HR=1[†]	0.0125	0.0250	0.025
	P(Cross) if HR=0.7[#]	0.9135	0.9492	0.9492

*Percentage of expected number of events at FA
[§]p (1-sided) is the nominal alpha for testing.
[%]HR at bound is the approximate HR required to reach an efficacy bound
[†]P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
[#]P(Cross if HR=0.7) is the cumulative probability of crossing a bound under the alternative hypothesis
Abbreviations: FA=final analysis; HR=hazard ratio; IA=interim analysis.

The bounds provided in the table above are based on the assumption that the expected number of events at IA1 and IA2 are 367 and 414, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an IA and leave reasonable alpha for the FA, the minimum alpha spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending

function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically:

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information fraction will be calculated as the observed number of events at the IA over the target number of events at FA.

- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information fraction will be calculated as the expected number of events at the IA over the target number of events at FA.

The FA will use the remaining Type I error that has not been spent at the earlier analyses. The event counts for all analyses will be used to compute correlations.

Of note, while the information fraction used for alpha spending calculation will be the minimum of the actual information fraction and the expected information fraction, the correlations required for deriving the bounds will still be computed using the actual information fraction based on the observed number of events at each analysis over the target number of events at FA.

The minimum spending approach assumes timing is not based on any observed Z-value and thus the Z test statistics used for testing conditioned on timing are multivariate normal. Given the probabilities derived with the proposed spending method, the correlations based on actual event counts are used to compute bounds that control the Type I error at the specified alpha level for a given hypothesis conditioned on the IA timing. Since this is true regardless of what is conditioned on, the overall Type I error for a given hypothesis is unconditionally controlled at the specified level. By using more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.

9.8.3 Overall Survival

The OS hypothesis may be tested at alpha=0.0125 (initially allocated alpha), or alpha=0.0249875 (if the PFS null hypothesis is rejected) or alpha=0.025 (if both the PFS and ORR null hypothesis are rejected). Table 17 demonstrates the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets O'Brien-Fleming spending function based on predicted number of events at the planned time of interim analysis. Note that if the PFS null hypothesis is rejected at an interim or final analysis, each OS interim and final analysis test may be compared to its updated bounds considering the alpha reallocation from the PFS hypothesis.

Table 17 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α=0.0125	α=0.0249875	α=0.025
IA1: 57%* N: 492 Events: 242 Month: 30	Z	3.1029	2.7437	2.7434
	p (1-sided) §	0.0010	0.0030	0.0030
	HR at bound %	0.6710	0.7027	0.7027
	P(Cross) if HR=1†	0.0010	0.0030	0.0030
	P(Cross) if HR=0.72#	0.2938	0.4269	0.4270
IA2: 76%* N: 492 Events: 321 Month: 40	Z	2.6699	2.3635	2.3632
	p (1-sided) §	0.0038	0.0091	0.0091
	HR at bound %	0.7420	0.7678	0.7678
	P(Cross) if HR=1†	0.0041	0.0100	0.0100
	P(Cross) if HR=0.72#	0.6135	0.7254	0.7254
IA 3: 91%* N: 492 Events: 385 Month: 53	Z	2.4311	2.1545	2.1542
	p (1-sided) §	0.0075	0.0156	0.0156
	HR at bound %	0.7804	0.8028	0.8028
	P(Cross) if HR=1†	0.0088	0.0187	0.0188
	P(Cross) if HR=0.72#	0.7959	0.8666	0.8666
FA: 100%* N: 492 Events: 423 Month: 66	Z	2.3405	2.0788	2.0786
	p (1-sided) §	0.0096	0.0188	0.0188
	HR at bound %	0.7964	0.8170	0.8170
	P(Cross) if HR=1†	0.0125	0.0250	0.0250
	P(Cross) if HR=0.72#	0.8644	0.9147	0.9147

* Percentage of expected number of events at FA
§p (1-sided) is the nominal α for testing.
%HR at bound is the approximate HR required to reach an efficacy bound
†P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
#P(Cross if HR=0.72) is the cumulative probability of crossing a bound under the alternative hypothesis
Abbreviations: FA=final analysis; HR=hazard ratio; IA=interim analysis.

The bounds provided in the table above are based on the assumption that the expected number of events at IA1, IA2, IA3, and FA are 242, 321, 385, and 423, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an IA and leave reasonable alpha for the FA, the minimum alpha spending strategy will be implemented for OS in the same manner as PFS (Section 9.8.2).

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk: benefit. At each planned interim analysis, eDMC will review the accumulating safety data in addition to the unblinded efficacy results. No separate safety interim analysis is planned; therefore, it will not require a

separate multiplicity adjustment as they are associated with the planned efficacy interim analysis.

9.9 Sample Size and Power Calculations

With 414 PFS events, the study has ~91% power for detecting a HR of 0.7 at initially assigned 0.0125 (one-sided) significance level, ~95% power for detecting a HR of 0.7 at 0.025 (one-sided) significance level.

With 423 deaths, the study has ~86% power for detecting a HR of 0.72 at 0.0125 (one-sided) significance level and ~91% power for detecting a HR of 0.72 at 0.025 (one-sided) significance level. The assumption of HR of 0.72 does not take into account the crossover treatment in this study. The actual power could be lower than 91% if the HR for OS is larger than 0.72 due to crossover effect.

With ~492 participants at IA1, the study has ~60% power for detecting a 20% difference in ORR (54% vs 34%) at 0.0000125 (one-sided) significance level if one of PFS or OS hypothesis is rejected. The study has ~99% power for detecting a 20% difference in ORR (54% versus 34%) at 0.025 (one-sided) significance level if both PFS and OS hypotheses are rejected.

The planned sample size is approximately 492 participants assuming: (1) the enrollment period of approximately 24 months; (2) the duration of PFS and OS follow exponential distribution; (3) median PFS is 5.4 months in the control group and the true HR is 0.7; (4) median OS is 15 months in the control group and the true HR is 0.72, as estimated approximately from Cortellini, IMPRESS, FLAURA, and AURA3 studies based on prior treatment history of osimertinib [Papadimitrakopoulou, V. A., et al 2020] [Cortellini, A., et al 2020] [Ramalingam, S. S., et al 2020] [Soria, J. C., et al 2015] [Mok, T. S. K., et al 2017]; (5) the annual dropout rate is 15% for PFS (as estimated approximately from KEYNOTE-189) and 1% for OS; (6) the number of events and alpha levels of IAs and FA are as specified in Section 9.7 and Section 9.8.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of each subgroup. The following are examples of classification variables:

- Age category (<65 vs ≥65 years)
- Sex (female, male)
- Race (white, non-white)
- Geographic region (East Asia vs Non-East Asia)
- Smoking history (never, current/former)
- Treatment history (osimertinib, no osimertinib)
- T790M mutation (positive, negative, unknown)

- *EGFR* mutation (L858R, DEL19)
- PD-L1 expression (TPS ≥50% vs TPS <50%; TPS ≥1% vs TPS <1%; TPS <1% vs 1%≤TPS≤49% vs TPS ≥50%)
- Platinum chemotherapy (cisplatin, carboplatin)

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is <10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

9.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Summary statistics will be provided on extent of exposure for All Subjects As Treated (ASaT) population.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and 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 (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial 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 using 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 (eg, to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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 which would make the participant identifiable will not be transferred.

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

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

10.1.4 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.

10.1.5 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 in order to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.6 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.

10.1.7 Committees Structure

10.1.7.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.7.2 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 (see 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.

10.1.8 Publication Policy

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

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

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

10.1.9 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.10 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council for Harmonisation of Technical Requirements for Pharmaceuticals

for Human Use of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.11 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.12 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.13 Study and Site Closure

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

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

Refer to Section 10.12 for country-specific requirements.

10.2 Appendix 2: 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 drugs/vaccines may interact with
- 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 participant' 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 gender, age, medical history and treatment outcomes are 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 which 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 utilizing 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 future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical

records for the main 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 main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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 main 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 utilized 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 e-mailed 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 for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [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/

10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

10.3.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

  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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (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.

10.3.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
    - The following are not acceptable methods of contraception:
        - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
        - Male and female condom cannot be used together.
    - A combination of male condom with either cap, diaphragm or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.
    - 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 penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 18 during the protocol-defined time frame in Section 5.1.

Table 18 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Non-hormonal intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner 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.
● 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 treatment. 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.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of pembrolizumab and up to 180 days after last dose of chemotherapeutic agents, corresponding to time needed to eliminate study treatment after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

10.3.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected and as required locally.

Refer to Section 10.12 for country-specific requirements.

10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 Definition of AE

AE definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • 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 treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use in this study.

Events <u>meeting</u> the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE. • 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 treatment 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 of study treatment 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).

  Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.4.5 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to Section 8.4.5 for protocol specific exceptions

10.4.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient'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) which 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 one 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 department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3 Additional Events Reported in the Same Manner as SAE

Additional events which require reporting in the same manner as SAE
● In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes. ● Is a new cancer (that is not a condition of the study); ● Is associated with an overdose.

10.4.4 Recording AE and SAE

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

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

Assessment of intensity

- 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 Common Terminology Criteria for Adverse Events (CTCAE), version 4]. Any AE which 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 activities of daily living (ADL).
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **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 one time.)
  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
      - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

- **Consistency with Study treatment 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 one 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.

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

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

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

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

10.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 19 will be performed by the local laboratory per the SoA (Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Refer to Section 10.12 for country-specific requirements.

Table 19 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
	Absolute Neutrophil Count			
	Absolute Lymphocyte Count			
Chemistry	Blood Urea Nitrogen (BUN) or urea (one or the other should be collected per institutional standard; both tests are not required)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	A measure of carbon dioxide (CO_2 or Bicarbonate)[a]	Chloride	Phosphorous
	Creatinine[b]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein[a]
	Glucose [Indicate if fasting or nonfasting]	Calcium	Alkaline phosphatase	Lactate Dehydrogenase
Coagulation	PT/INR aPTT/PTT[c]			

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • Glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests[d]	• Thyroid panel[e]: T3/FT3, FT4, TSH • Follicle-stimulating hormone (FSH) (as needed in women of non-childbearing potential only) • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP) • Hepatitis Serology -hepatitis B surface antigen [HBsAg], hepatitis B virus (HBV)-DNA, hepatitis C virus (HCV)-RNA, HCV antibody (if HCV-RNA is not the local standard of care), if required per local regulations. • HIV-RNA (if required by local regulations)

NOTES :

a. If these tests are not done as part of standard of care in your region then these tests do not need to be performed. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte.

b. Creatinine: GFR (measured or calculated) or creatinine clearance can be used in place of creatinine. Creatinine Clearance should be calculated using the Cockcroft-Gault Method: Refer to Section 10.8 for the appropriate calculation.

c. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

d. May use central lab only if local lab is not capable.

e. T3 is preferred. If not available, Free T3 (FT3) may be tested.

All protocol-required safety laboratory assessments will be performed by a local laboratory.

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

10.6 Appendix 6: Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

10.7 Appendix 7: MASCC 2016 Guidelines

DEXAMETHASONE		Dose and Schedule
High Risk	- Acute Emesis	20 mg once (12 mg when used with (fos)aprepitant or netupitant)**
	- Delayed Emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with (fos)aprepitant or netupitant)
Moderate Risk	- Acute Emesis	8 mg once
	- Delayed Emesis	8 mg daily for 2 - 3 days (many panelists give the dose as 4 mg bid)
Low Risk	- Acute Emesis	4 - 8 mg once

* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

** The 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

Rolia F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol (2016) 27 (suppl_5): v119-v133, 2016.

http://www.mascc.org/antiemetic-guidelines

Investigators may use local equivalent or more current guidelines, if available.

10.8 Appendix 8: Calculated Creatinine Clearance

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 1.0}{0.81 \times \text{serum creatinine (μmol/L)}}$$

[a] Age in years.

[b] Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 0.85}{0.81 \times \text{serum creatinine (μmol/L)}}$$

[a] Age in years.

[b] Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
1L	first-line (therapy)
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under curve
BCG	Bacillus Calmette-Guérin vaccine
BICR	blinded independent central review
C1D1	Cycle 1 Day 1
CD28	cluster of differentiation 28
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CT	computed tomography
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTR	Clinical Trials Regulation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DOR	duration of response

Abbreviation	Expanded Term
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eDMC	external Data Monitoring Committee
EDC	electronic data collection
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	EuroQol 5-dimension, 5-level Questionnaire
EU	European Union
FA	final analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IEC	independent ethics committee

Abbreviation	Expanded Term
Ig	immunoglobulin
IgG4	immunoglobulin G4 monoclonal antibody
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	Investigational Medical Product
INR	international normalized ratio
IPASS	Iressa Pan-Asia Study
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	modified RECIST for immune-based therapeutics
iSD	iRECIST stable disease
ITT	intent-to-treat
iUPD	iRECIST unconfirmed progressive disease
IV	intravenous
IVRS/IWRS	interactive voice response system/ integrated web response system
KL-6	Krebs von den Lungen 6; biomarker for ILD
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBPK	physiological based pharmacokinetics
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2

Abbreviation	Expanded Term
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-LC13	Quality of Life Questionnaire and Lung Cancer Module 13
QLQ-LC30	Quality of Life Questionnaire and Lung Cancer Module 30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SCLC	Small cell lung cancer
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SP-D	surfactant protein D
SpO_2	blood oxygen saturation level
SoA	Schedule of Activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
TEA	Treatment Eligibility Assessment
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
TPS	tumor proportion score
T-reg	regulatory T cell
TTD	time to true deterioration
WOCBP	woman of childbearing potential

10.10 Appendix 10: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using iRECIST for participant management (see Table 8 and Figure 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined in Section 7.1.

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

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent into the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

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

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

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

diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit or if RECIST 1.1 PD has not been verified centrally, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.2 and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-progression Resolves

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

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

10.11 Appendix 11: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

10.12 Appendix 12: Country-specific Requirements

10.12.1 Sweden-specific Information

1. Section 4.2.1.2 Safety Endpoints

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

2. Section 10.1 Appendix 1 Regulatory, Ethical and Study Oversight Considerations

   - Code of Conduct for Clinical Trials
     - III. Participant Protection
       - A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) and Health Authorities

         The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to and approved by the applicable Competent Authority and IRB/IEC before the study is initiated in accordance with EU Directive 2001/20/EC, Article 10 (a) and/or local requirements. Any amendments to the protocol will require IRB/IEC and Competent Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants [2001/20/EC, Article 10 (c)].

   - Study and Site Closure

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

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

     In the EU [CT-1 (2010/C 82/01)], the sponsor must send immediate end-of-study notification to the national competent authority and the Ethics Committee of the Member State concerned. The end-of-study notification must be sent within 15 days after the study is halted to clearly describe the reasons and follow-up measures, if any, taken for safety reasons. The 15-day notification applies only for early termination of the study. Otherwise the time window to send end-of-study notification is 90 days in the EU.

10.12.2 Germany-specific Information

1. Section 1.3.1 Schedule of Activities for Initial Treatment Phase
   - HIV testing is required at screening.
   - Hepatitis B and Hepatitis C testing is required at screening.
2. Section 5.2 Exclusion Criteria
   - Exclusion Criterion 17: HIV testing is required for participants who are residents of Germany.
   - Exclusion Criterion 18: Hepatitis B and C testing is required for participants who are residents of Germany.
   - Exclusion Criterion 19: TB testing is required for participants who are residents of Germany.
3. Section 1.3.2 Schedule of Activities for Crossover Treatment Phase

   Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.
4. Section 1.3.3 Schedule of Activities for Second Course Retreatment Phase

   Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.
5. Section 10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

   Monthly urine pregnancy testing after randomization is required during treatment as well as at the end of study treatment.
6. Section 10.5 Appendix 5: Clinical Laboratory Tests

   TB added to Other Tests

10.12.3 Japan-specific Information

Section 1.3 Schedule of Activities – footnotes

1. For the assistance to early diagnosis of pneumonitis/ILD in study participants, the following items such as pulse oximetry monitoring (SpO_2), C-reactive protein (CRP), Krebs von den Lungen 6 (KL-6), and surfactant protein D (SP-D) will be measured in this study. These items should be measured in the following timing:
   - SpO_2: at the timing of vital sign assessment.
   - CRP, KL-6 and SP-D: at Screening*, pre-dose on Day 1 of every cycle, end of treatment and safety follow-up visit (30 days after last dose).

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

2. In the case that pneumonitis/ILD occurs, regardless of causality with study medication, 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.

11. References

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Bergman, B., et al 1994]	Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30A(5):635-42.	[00VTZB]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Cortellini, A., et al 2020]	Cortellini A, Leonetti A, Catino A, Pizzutillo P, Ricciuti B, De Giglio A, et al. Osimertinib beyond disease progression in T790M EGFR-positive NSCLC patients: a multicenter study of clinicians' attitudes. Clin Transl Oncol. 2020;22:844-51.	[05NW9Q]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]

[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[IB Edition 15 2017]	KEYTRUDA (pembrolizumab) Investigator's Brochure, Edition Number 15, 18-Sep-2017.	[04R9W6]
[Maurer, W. and Bretz, F. 2013]	Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.	[03XQVB]
[Mok, T. S. K., et al 2017]	Mok TSK, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): overall survival and biomarker analyses. J Clin Oncol. 2017 Dec 20;35(36):4027-34.	[05NXVP]
[Mok, T. S., et al 2009]	Mok TS, Wu Y-L, Thongprasert S, Yang C.-H., Chu D-T, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:1-11.	[00WBF3]
[Mok, T. S., et al 2017]	Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS. et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640.	[04RCST]
[Morgillo, F., et al 2016]	Morgillo F, Della Corte CM, Fasano M, Ciardiello F. Mechanisms of resistance to EGFR-targeted drugs: lung cancer. ESMO Open. 2016 May 11;1(3):e000060.eCollection 2016.	[04T0HB]

[National Cancer Institute 2016]	National Cancer Institute. SEER Stat Fact Sheets: Lung and bronchus cancer [Internet]. Bethesda, MD: National Cancer Institute; 2016. Available from: http://seer.cancer.gov/statfacts/.	[04FJVR]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Papadimitrakopoulou, V. A., et al 2020]	Papadimitrakopoulou VA, Mok TS, Han JY, Ahn MJ, Delmonte A, Ramalingam SS, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. Ann Oncol. 2020;31(11):1536-44.	[05NW9P]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Paz-Ares, L. G., et al 2013]	Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013 Aug 10;31(23):2895-902.	[04804Z]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]
[Rabin, R. and de Charro, F. 2001]	Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]

[Ramalingam, S. S., et al 2020]	Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020 Jan 2;382(1):41-50.	[05NW9R]
[Ramalingam, S., et al 2017]	Ramalingam S, Reungwetwattana T, Chewaskulyong B, et al. Osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFRm advanced NSCLC: FLAURA. Presented at: 2017 ESMO Congress; Madrid, Spain; September 9-12, 2017.	[04SRRG]
[Reck, M., et al 2016]	Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8. [Epub ahead of print].	[04JNM3]
[Reck, M., et al 2017]	Reck M, Socinski MA, Cappuzzo F, Orlandi F, Stroyakovskii D, Nogami N, et al. Primary PFS and safety analyses of a randomized phase III study of carboplatin + paclitaxel +/- bevacizumab, with or without atezolizumab in 1L non-squamous metastatic nsclc (IMPOWER150)[abstract]. Annals of Oncology. 2017 November;28(11 suppl):xi31. Abstract no. LBA1_PR.	[04T70N]
[Reck, M., et al 2017]	Reck M, Socinski MA, Cappuzzo F, Orlandi F, Stroyakovskii D, Nogami N, et al. Primary PFS and safety analyses of a randomised phase lll study of carboplatin + paclitaxel +/- bevacizumab, with or without atezolizumab in 1L non squamous metastatic NSCLC (lMpower150). Poster session presented at: ESMO immuno-oncology congress; 2017 Sep 8-12; Madrid, Spain.	[04T6DH]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]

[Scagliotti, G. V., et al 2008]	Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C. et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008 Jul 20;26(21):3543-51.	[04Q3DV]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Smith, T. J., et al 2015]	Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Oct 1;33(28):3199-212.	[04KHR8]
[Soria, J. C., et al 2015]	Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):990-8.	[04SRRQ]
[Sulpher, J. A., et al 2013]	Sulpher JA, Owen SP, Hon H, Tobros K, Shepherd FA, Sabri E, et al. Factors influencing a specific pathologic diagnosis of non-small-cell lung carcinoma. Clin Lung Cancer. 2013 May;14(3):238-44.	[040565]

[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[World Health Organization 2012]	Globocan 2012: Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 [Internet]. Lyon (FR): World Health Organization, International Agency for Research on Cancer (IARC). c2014 – [updated 2014 Oct 3]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx	[0402K4]
[Yu, H. A., et al 2013]	Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013 Apr 15;19(8):2240-7.	[04SRR3]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]
[Zhang, Y. L., et al 2016]	Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016 Nov 29;7(48):78985-78993.	[04SRRX]