Official Protocol Title:	A Phase 2 Trial of Pembrolizumab (MK-3475) in Combination with Platinum Doublet Chemotherapy and Radiotherapy for Participants with Unresectable, Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-799).
NCT number:	NCT03631784
Document Date:	17-Nov-2021

TITLE PAGE

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Protocol Title: A Phase 2 Trial of Pembrolizumab (MK-3475) in Combination with Platinum Doublet Chemotherapy and Radiotherapy for Participants with Unresectable, Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-799).

Protocol Number: 799-03

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: 116,833

EudraCT NUMBER: 2018-000714-37

Approval Date: 18-June-2019

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-3475-799-03	18-Jun-2019	Modified the timing of the first interim analysis to be conducted when at least 36 participants in one cohort (rather than in each cohort) have completed a minimum of 15 weeks of follow up due to the large difference in enrollment rates between the 2 cohorts.
MK-3475-799-02	26-Sep-2018	Revised to include oversight by an external DMC per German and French Health Authorities request.
MK-3475-799-01	06-Aug-2018	UK-specific amendment added monitoring for pontential side effects related to cisplatin treatment and medications to be used with caution during cisplatin treatment per UK MHRA request.
MK-3475-799-00	29-May-2018	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 03

Overall Rationale for the Amendment:

Modified the timing of the first interim analysis to be conducted when at least 36 participants in one cohort (rather than in each cohort) have completed a minimum of 15 weeks of follow up due to the large difference in enrollment rates between the 2 cohorts. Clarified radiation treatment prescription and variations of the dose prescription that are allowed.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3.1 Cohort A Schedule: Screening and Treatment Cycle 1 to 3 1.3.2 Cohort B Schedule: Screening and Treatment Cycle 1 to 3 8.2.1.1 Initial Tumor Imaging 8.12.1 Screening	Initial tumor imaging was changed from within 28 days to within 42 days prior to the first dose of trial treatment. Text was added to indicate that MRI is preferred for imaging of the brain, but head CT with contrast is preferred if MRI is contraindicated	Opened window for tumor imaging.
1.3.3 Cohorts A and B: Pembrolizumab Monotherapy (Cycle 4-17) and Post-Treatment Follow Up	Added statement that RNA analysis is collected at Cycle 6 only.	Updated for Clarity.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Text was changed to indicate that the first interim analysis will be conducted when at least 36 participants in one cohort (rather than in each cohort) have completed a minimum of 15 weeks of follow-up.	Clarified requirements for conducting the first interim analysis.
5.1 Inclusion Criteria	Criterion #1 was modified to indicate that participants may be eligible without obtaining the EBUS sample if the primary tumor is considered unresectable and is clinically confirmed IIIA, IIIB, or IIIC NSCLC, and if the presence or absence of metastases in the hilar lymph nodes would not change the radiotherapy plan. For enrollment meeting this criterion, a Sponsor Communication Form should be submitted.	Clarified criteria regarding participants who would be eligible for the study without collection of the EBUS sample
5.2 Exclusion Criteria	A note was added to criterion #4 to indicate that the participant must have been assessed by a radiation oncologist who anticipates the tumor is treatable, as defined in Section 8.1.9.2.4.	Added for clarity to help prevent ineligible participants from being enrolled.
6.3.1.1 Stratification	Stratification statement was updated to indicate that there is no stratification in the study.	Updated for clarity.
6.5.3.2 Chemotherapy	Text was added to indicate that participants in Cohort B should receive appropriate supplementation of intramuscular vitamin B12 1000 mcg.	Added for clarity and consistency.
8.1.9.2 Thoracic Radiation Therapy (TRT)	Text was added to indicate that the V20 should be anticipated to meet the threshold of ≥31%, as specified in the exclusion criteria.	Added for clarity.

Section # and Name	Description of Change	Brief Rationale
8.1.9.2.1 Dose Specifications	Text was edited to indicate that the treatment plan shall be normalized such that 95% of the prescription dose covers at least 99% of the PTV.	Clarified treatment plan dose specifications.
8.1.9.2.2 Variations of Dose Prescription	Protocol constraints and compliance criteria were modified in Table 9.	Clarified variations of the dose prescription that are allowed.
8.1.9.2.7 Organs at Risk	Text was added to indicate that the dose coverage of the PTV will take precedence over a non-critical organ at risk when there is gross disease in close proximity to the esophagus or brachial plexus, preventing meeting protocol constraints.	Clarified radiotherapy dose coverage of the PTV for non-critical organs at risk.
9.1 Statistical Analysis Plan Summary 9.5.1 Efficacy Analysis Populations 9.6.1 Statistical Methods for Efficacy Analyses Table 14 (Efficacy Analysis Methods for Key Efficacy Endpoints)	Efficacy analysis population was changed to All Participants as Treated (APaT) Population and the definition was clarified to be all enrolled participants who received at least 1 dose of study treatment.	As this is a non-randomized, open-label, 2-cohort study, efficacy analysis based on APaT population is more appropriate. The definition was modified for clarity.
9.2 Responsibility for Analyses/In-house Blinding 9.7 Interim Analysis	Statements for DMC responsibility were updated to be consistent with wordings in section 10.1.7 (Committees structure).	Updated for clarity.
9.7 Interim Analyses	Text was added to clarify the first interim analysis timing when the rates of enrollment in two cohorts are different.	Added for clarity.

Section # and Name	Description of Change	Brief Rationale
Table 16 (Decision Rules for Stopping the Trial for Low Percentage of Participants with Grade 3 or Higher Pneumonitis).	Decision rule for stopping the trial is not applicable due to insufficient sample size if only 36-39 participants are available.	Correction of error in the decision rule.
9.7 Interim Analysis	Text was added to indicate the monitoring points in sequential monitoring procedure. Footnotes were also added in Table 16-19 in Section 9.7.	Added for clarity
9.10 Subgroup Analyses	Updated stage subgroup values	Updated for clarity
10.6 Appendix 6: Clinical Laboratory Tests	Urea is acceptable if BUN is not available or acceptable.	Added for flexibility.
Global	Minor typographical errors were corrected throughout.	Corrected for clarity.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase 2 Trial of Pembrolizumab (MK-3475) in Combination with Platinum Doublet Chemotherapy and Radiotherapy for Participants with Unresectable, Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-799).

Short Title:

Phase 2 Trial of Pembrolizumab in Combination with Chemotherapy and Radiotherapy in Stage III NSCLC (KEYNOTE-799).

Objectives/Hypotheses and Endpoints:

- In adult participants with unresectable, locally advanced, Stage III NSCLC treated with pembrolizumab in combination with platinum doublet chemotherapy and standard thoracic radiotherapy (TRT) followed by pembrolizumab monotherapy.

Objective/Hypothesis	Endpoint
Primary	
• Objective: Within each platinum doublet chemotherapy cohort, evaluate the percentage of participants who develop Grade 3 or higher pneumonitis	• Grade 3 or higher pneumonitis
• Hypothesis: Within each platinum doublet chemotherapy cohort, the percentage of participants who develop Grade 3 or higher pneumonitis is <10%	• Confirmed complete response or partial response
• Objective: Within each platinum doublet chemotherapy cohort, estimate the objective response rate as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	

Secondary	
• Objective: Within each platinum doublet chemotherapy cohort, evaluate the progression-free survival (PFS) assessed by BICR according to RECIST v.1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ • Objective: Within each platinum doublet chemotherapy cohort, evaluate overall survival (OS) • Objective: Within each platinum doublet chemotherapy cohort, evaluate the safety and tolerability of each treatment regimen by the percentage of participants who develop AEs	• PFS defined as the time from enrollment to the first documented local recurrence or distant metastasis or death due to any cause, whichever occurs first • OS defined as the time from enrollment to death due to any cause • Adverse events (AEs) • Discontinuations due to AEs

Overall Design:

Study Phase	Phase 2
Clinical Indication	The treatment of participants with NSCLC
Population	Unresectable, locally advanced, Stage III NSCLC
Study Type	Interventional
Type of Design	Multi-site, multi-cohort, parallel-group
Type of Control	No treatment control
Study Blinding	Unblinded, open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 29 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 216 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	There are 2 treatment cohorts. Participants with non-squamous NSCLC are eligible for both cohorts. The choice of platinum doublet chemotherapy will be determined by the investigator prior to treatment allocation. Participants with squamous NSCLC are eligible only for Cohort A. • Cohort A: Participants will receive 1 cycle of carboplatin area under the curve (AUC) 6 with paclitaxel 200 mg/m^2 and pembrolizumab 200 mg on Day 1. Approximately 3 weeks later, participants will receive carboplatin AUC2 with paclitaxel 45 mg/m^2 administered weekly for 6 weeks along with 2 cycles of pembrolizumab 200 mg administered every 3 weeks (Q3W) in conjunction with standard TRT. To conclude the study treatments, participants will receive 14 additional cycles of pembrolizumab 200 mg administered Q3W. • Cohort B: Participants will receive 3 cycles of cisplatin 75 mg/m^2 with pemetrexed 500 mg/m^2 and pembrolizumab 200 mg on Day 1 of each 3-week cycle. Treatment will be given in conjunction with standard TRT in Cycles 2 and 3. To conclude the study treatments, participants will receive 14 additional cycles of pembrolizumab 200 mg administered Q3W.

Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form through the final protocol-specified contact. After a screening phase of approximately 6 weeks, eligible participants will receive assigned treatment as described above for approximately 1 year or until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, or pregnancy of the participant.

	At the end of treatment, each participant will be followed for a minimum of 30 days for AE monitoring. Serious AEs occurring within 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, will be collected, whichever is earlier. Participants will have post-treatment follow-up for disease status, including radiographic imaging as outlined in the protocol, until initiating a non-study anticancer treatment, experiencing disease progression, death, withdrawing consent, becoming lost to follow-up, or end of study. All participants will be followed for OS until death, loss to follow-up or withdrawal of consent.

Study Governance:

Study Governance Committees

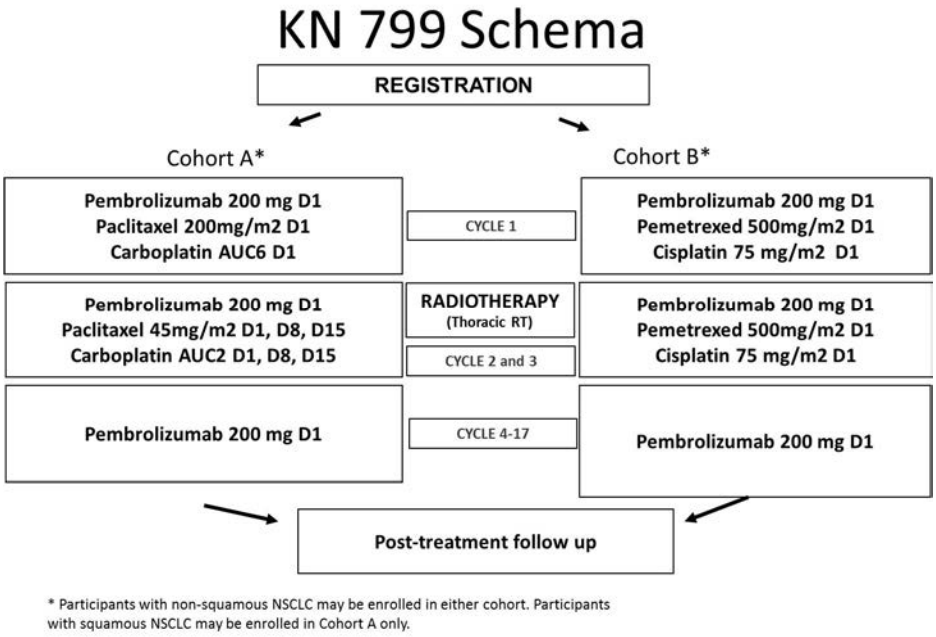
Committee	**Included in this study?**
Steering Committee	No
Executive Oversight Committee	Yes
External Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.



Abbreviations: AUC = area under the curve; D = day; RT = radiotherapy.

Figure 1 Study Diagram

1.3 Schedule of Activities (SoA)

1.3.1 Cohort A Schedule: Screening and Treatment Cycle 1 to 3

Cohort A	Screening Phase	Treatment Cycles (3-Week Cycles)							Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**			**3**			
Day (in Pembrolizumab Cycle)			**1**	**8**	**15**	**1**	**8**	**15**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Administrative Procedures									
Informed Consent	X								Informed consent must be obtained prior to any protocol-related intervention.
Informed Consent for Future Biomedical Research (optional)	X								The future biomedical research consent must be obtained prior to performing any procedure related to the future biomedical research substudy
Inclusion/Exclusion Criteria	X								
Participant Identification Card	X								
Demographics and Medical History	X								Include all active conditions, clinically significant conditions diagnosed within the prior 10 years, and any prior cancer other than NSCLC even if diagnosed greater than 10 years prior to Visit 1.
Prior and Concomitant Medications	<---------->								Prior medications: Record medications taken within 42 days of first dose and medications regularly administered at intervals greater than 42 days prior to first dose. Concomitant medications: Record new medications started during the study through the post-treatment Follow-up and changes to dose, frequency and route occurring during the study period.
NSCLC Disease Details and Prior Treatment	X								
Log in to IWRS	X	X	X	X	X	X	X	X	Log in to IWRS at Cycle 1 to obtain allocation number and at subsequent visits to ensure visits are captured in the IWRS system. A window of – 3 days is allowed.

Cohort A	Screening Phase	Treatment Cycles (3-Week Cycles)							Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**			**3**			
Day (in Pembrolizumab Cycle)			**1**	**8**	**15**	**1**	**8**	**15**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Clinical Procedures / Assessments									
Review AEs	<----------	----------	----------	----------	----------	----------	----------	---------->	All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment must be reported if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention. Report all AEs occurring from the start of treatment through 30 days following cessation of study treatment. Report SAEs occurring from the start of treatment through 90 following cessation of study treatment, or 30 days following cessation of study treatment if a new anticancer therapy is initiated, whichever is earlier
Full Physical Examination	X								Refer to Appendix 7 for country-specific requirements.
Directed Physical Examination		X	X			X			Refer to Appendix 7 for country-specific requirements.
Vital Signs, Weight and Height	X	X	X			X			Vital signs include: temperature, pulse, heart rate, respiratory rate, blood pressure. Height will be measured only at Visit 1.
12-Lead ECG (local)	X								
ECOG Performance Status	X	X	X			X			Screening Visit: ECOG PS is to be performed within 10 days prior to the first dose of study treatment. Treatment Visits: ECOG PS is to be performed prior to the administration of study treatment.
Pulmonary Function Test	X								Pulmonary function tests include pulse oximetry, FEV1 (forced expiratory volume in the first second of expiration), FVC (forced vital capacity), DLCO (diffusing lung capacity for carbon monoxide), and TLC (total lung capacity).

Cohort A	Screening Phase	Treatment Cycles (3-Week Cycles)							Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**			**3**			
Day (in Pembrolizumab Cycle)			**1**	**8**	**15**	**1**	**8**	**15**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory									
Pregnancy Test - Urine or Serum β-HCG	As Clinically Indicated								For women of reproductive potential, a urine pregnancy test must be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine test is not appropriate. Monthly pregnancy testing must be conducted as per local regulations where applicable. Refer to Appendix 7 for country-specific details.
PT/INR and aPTT/PTT	X								Laboratory tests for screening are to be performed within 10 days prior to the first dose of study treatment. After Cycle 1, lab samples can be collected up to 3 days prior to Day 1 of subsequent cycles. Participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function tests are pending.
Hematology	X		X	X	X	X	X	X	
Comprehensive Chemistry Panel	X		X	X	X	X	X	X	
Urinalysis	X								
T3 or FT3, FT4 and TSH	X		X						
Analysis Performed by Central Laboratory									
Pembrolizumab Pharmacokinetics (PK)		X	X						Pre-dose trough PK, and ADA samples will be collected at Cycles 1 and 2 and must be drawn within 24 hours before infusion of pembrolizumab. Post-dose peak PK samples will be collected at Cycle 1 and must be drawn within 30 minutes of the completion of the pembrolizumab infusion.
Anti-pembrolizumab Antibodies (ADA)		X	X						
Blood for Genetic Analysis		X							Whole blood samples must be collected pre-dose. Blood for genetic analysis must be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that 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 signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
Blood for RNA Analyses		X	X						
Blood for Plasma Biomarker Analyses		X							
Blood for Serum Biomarker Analyses		X							
Blood for ctDNA		X							

Cohort A	Screening Phase	Treatment Cycles (3-Week Cycles)							Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**			**3**			
Day (in Pembrolizumab Cycle)			**1**	**8**	**15**	**1**	**8**	**15**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Tumor Biopsies/ Archival Tissue Collection									
Tumor Tissue Collection	X								A tumor tissue sample (ie, core, incisional, or excisional biopsy) must be provided to the central lab within 42 days prior to treatment allocation. FFPE tissue blocks are preferred to slides. In cases where the biopsy is not available or cannot be obtained, a cell block obtained through EUS/EBUS may be submitted after consultation with the Sponsor Clinical Director and documenting approval via a Sponsor Communication Form.
Efficacy Measurements									
Tumor Imaging	X								Baseline tumor imaging must be performed within 42 days of Cycle 1.
FDG-PET or FDG-PET/CT	X								If the participant underwent the required FDG-PET or FDG-PET/CT imaging prior to signing ICF and within 60 days prior to Cycle 1 Day 1, repeat imaging is not required.
MRI Brain With Contrast	X								MRI is preferred; however, head CT imaging with contrast may be acceptable if MRI is medically contraindicated.
Study Treatment Administration									
Carboplatin		X	X	X	X	X	X	X	Study treatment with pembrolizumab and chemotherapy must be administered after all procedures/assessments have been completed Study treatments must be administered in the following order: pembrolizumab (if required on a given day), paclitaxel, carboplatin, TRT (if required on a given day). Confirm/qualify RT prescription. Delays in the protocol specified pembrolizumab treatment schedule due to toxicity or for situations other than treatment-related AEs are described in Section 6.6.1 and 6.6.1.3, respectively. Delays in chemotherapy treatment are described in Section 6.6.2 Delays in TRT are described in Section 6.6.3
Paclitaxel		X	X	X	X	X	X	X	
Thoracic radiotherapy (TRT)			<----------					---------->	
Pembrolizumab		X	X			X			

1. In general, procedures are to be performed on Day 1 and prior to the first dose of the trial treatment for each cycle unless otherwise specified. The window for each visit is ± 3 days unless otherwise noted. If treatment cycles are adjusted all procedures except imaging will be completed according to the cycle number and not weeks on treatment.

1.3.2 Cohort B Schedule: Screening and Treatment Cycle 1 to 3

Cohort B	Screening Phase	Treatment Cycles (3-Week Cycles)			Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**	**3**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	
Administrative Procedures					
Informed Consent	X				Informed consent must be obtained prior to any protocol-related intervention.
Informed Consent for Future Biomedical Research (optional)	X				The future biomedical research consent must be obtained prior to performing any procedure related to the future biomedical research substudy
Inclusion/Exclusion Criteria	X				
Participant Identification Card	X				
Demographics and Medical History	X				Include all active conditions, clinically significant conditions diagnosed within the prior 10 years, and any prior cancer other than NSCLC even if diagnosed greater than 10 years prior to Visit 1.
Prior and Concomitant Medications	<---------->				Prior medications: Record medications taken within 42 days of first dose and medications regularly administered at intervals greater than 42 days prior to first dose. Concomitant medications: Record new medications started during the study through the post-treatment Follow-up and changes to dose, frequency and route occurring during the study period.
NSCLC Disease Details and Prior Treatment	X				
Log in to IWRS	X	X	X	X	Log in to IWRS at Cycle 1 to obtain allocation number and at subsequent visits to ensure visits are captured in the IWRS system. A window of – 3 days is allowed.
Clinical Procedures / Assessments					
Review AEs	<---------->				All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment must be reported if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention. Report all AEs occurring from the start of treatment through 30 days following cessation of study treatment. Report SAEs occurring from the start of treatment through 90 following cessation of study treatment, or 30 days following cessation of study treatment if a new anticancer therapy is initiated, whichever is earlier.

Cohort B	Screening Phase	Treatment Cycles (3-Week Cycles)			Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**	**3**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	
Full Physical Examination	X				Refer to Appendix 7 for country-specific requirements.
Directed Physical Examination		X	X	X	Refer to Appendix 7 for country-specific requirements.
Vital Signs, Weight and Height	X	X	X	X	Vital signs include: temperature, pulse, heart rate, respiratory rate, blood pressure. Height will be measured only at Visit 1.
12-Lead ECG (local)	X				
ECOG Performance Status	X	X	X	X	Screening Visit: ECOG PS is to be performed within 10 days prior to the first dose of study treatment. Treatment Visits: ECOG PS is to be performed prior to the administration of study treatment.
Pulmonary Function Test	X				Pulmonary function tests include pulse oximetry, FEV1 (forced expiratory volume in the first second of expiration), FVC (forced vital capacity), DLCO (diffusing lung capacity for carbon monoxide), and TLC (total lung capacity).
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory					
Pregnancy Test - Urine or Serum β-HCG	As Clinically Indicated				For women of reproductive potential, a urine pregnancy test must be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine test is not appropriate. Monthly pregnancy testing must be conducted as per local regulations where applicable. Refer to Appendix 7 for country-specific details.
PT/INR and aPTT/PTT	X				Laboratory tests for screening are to be performed within 10 days prior to the first dose of study treatment. After Cycle 1, lab samples can be collected up to 3 days prior to Day 1 of subsequent cycles. Participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function tests are pending.
Hematology	X		X	X	
Comprehensive Chemistry Panel	X		X	X	
Urinalysis	X				
T3 or FT3, FT4 and TSH	X		X		

Cohort B	Screening Phase	Treatment Cycles (3-Week Cycles)			Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**	**3**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	
Analysis Performed by Central Laboratory					
Pembrolizumab Pharmacokinetics		X	X		Pre-dose trough PK, and ADA samples will be collected at Cycles 1 and 2 and must be drawn within 24 hours before infusion of pembrolizumab. Post-dose peak PK samples will be collected at Cycle 1 and must be drawn within 30 minutes of the completion of the pembrolizumab infusion.
Anti-pembrolizumab Antibodies		X	X		
Blood for Genetic Analysis		X			Whole blood samples must be collected pre-dose. Blood for genetic analysis must be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that 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 signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR
Blood for RNA Analyses		X	X		
Blood for Plasma Biomarker Analyses		X			
Blood for Serum Biomarker Analyses		X			
Blood for ctDNA		X			
Tumor Biopsy/Archival Tissue Collection					
Tumor Tissue Collection	X				A tumor tissue sample (ie, core, incisional, or excisional biopsy) must be provided to the central lab within 42 days prior to treatment allocation. FFPE tissue blocks are preferred to slides. In cases where the biopsy is not available or cannot be obtained, a cell block obtained through EUS/EBUS may be submitted after consultation with the Sponsor Clinical Director and documenting approval via a Sponsor Communication Form.
Efficacy Measurements					
Tumor Imaging	X				Baseline tumor imaging must be performed within 42 days of Cycle 1.
FDG-PET or FDG-PET/CT	X				If the participant underwent the required FDG-PET or FDG-PET/CT imaging prior to signing ICF and within 60 days prior to Cycle 1 Day 1, repeat imaging is not required.
MRI Brain With Contrast	X				MRI is preferred; however, head CT imaging with contrast may be acceptable if MRI is medically contraindicated.

Cohort B	Screening Phase	Treatment Cycles (3-Week Cycles)			Notes
Pembrolizumab Treatment Cycle	**Screening Visit**	**1**	**2**	**3**	
Scheduling Window (Days):[1]	**-42 to -1**	**+3**	**± 3**	**± 3**	
Study Treatment Administration					
Cisplatin		X	X	X	Study treatment with pembrolizumab and chemotherapy must be administered after all procedures/assessments have been completed. Study treatments must be administered in the following order: pembrolizumab, pemetrexed, cisplatin, TRT (if required on a given day). Confirm/qualify RT prescription. Participants must take a folic acid preparation or multivitamin with folic acid and intramuscular vitamin B_{12}as described in Section 8.1.9.1.3.1. Delays in the protocol specified pembrolizumab treatment schedule due to toxicity or for situations other than treatment-related AEs are described in Section 6.6.1 and 6.6.1.3, respectively. Delays in chemotherapy treatment are described in Section 6.6.2 Delays in TRT are described in Section 6.6.3
Pemetrexed		X	X	X	
Folic acid and Vitamin B_{12}	<----------			---------->	
Thoracic radiotherapy (TRT)			<----	---->	
Pembrolizumab		X	X	X	
1. In general, procedures are to be performed on Day 1 and prior to the first dose of the trial treatment for each cycle unless otherwise specified. The window for each visit is ± 3 days unless otherwise noted. If treatment cycles are adjusted all procedures except imaging will be completed according to the cycle number and not weeks on treatment.					

1.3.3 Cohorts A and B: Pembrolizumab Monotherapy (Cycle 4-17) and Post-Treatment Follow Up

Cohorts A and B	Treatment Cycles (3-Week Cycles)										End of Tx	Post-Treatment			Notes
Treatment Cycle	**4**	**5 & 6**	**7**	**8 & 9**	**10**	**11& 12**	**13**	**14& 15**	**16**	**17**	**DC**	**Safety FU**	**FU[3]**	**Survival FU[4]**	
Scheduling Window (Days):[1]	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Tx DC[2]**	**30 D Post Dose ± 3**	**Per imaging sched[5]**	**Every 12 Week s±14**	
Administrative Procedures															
Concomitant Medications	←	-	-	-	-	-	-	-	-	-	→				Record new medications started during the study through the post-treatment Follow-up and changes to dose, frequency and route occurring during the study period.
Log in to IWRS	X	X	X	X	X	X	X	X	X	X	X				Log in to ensure visits are captured in the IWRS system.
Subsequent Anti-neoplastic Therapy Status												X	X	X	Review all new antineoplastic therapy initiated after the last dose of study treatment.
Survival Status	←	-	-	-	-	-	-	-	-	-	-	-	-	→	After investigator determined PD or start of new anticancer treatment. In addition, 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 [4]	←	-	-	-	-	-	-	-	-	-	→				Report all AEs occurring from the start of treatment through 30 days following cessation of study treatment. Report SAEs occurring from the start of treatment through 90 following cessation of study treatment, or 30 days following cessation of study treatment if a new anticancer therapy is initiated, whichever is earlier.

Cohorts A and B	Treatment Cycles (3-Week Cycles)										End of Tx	Post-Treatment			Notes
Treatment Cycle	**4**	**5 & 6**	**7**	**8 & 9**	**10**	**11& 12**	**13**	**14& 15**	**16**	**17**	**DC**	**Safety FU**	**FU[3]**	**Survival FU[4]**	
Scheduling Window (Days):[1]	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Tx DC[2]**	**30 D Post Dose ± 3**	**Per imag-ing sched[5]**	**Every 12 Week s±14**	
Full Physical Examination											X				
Directed Physical Examination	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			Vital signs include: temperature, pulse, heart rate, respiratory rate, blood pressure.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X			ECOG PS is to be performed prior to the administration of study treatment.
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory															
Pregnancy Test - Urine or Serum β-HCG	As Clinically Indicated														For women of reproductive potential, a urine pregnancy test must be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine test is not appropriate. Monthly pregnancy testing must be conducted as per local regulations where applicable. Refer to Appendix 7 for country-specific details.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X			Lab samples can be collected up to 3 days prior to Day 1 of each cycle. Urinalysis to be repeated every 6 cycles beginning with Cycle 6 and at the 30-Day Follow-up visit. Thyroid function tests to be repeated every other cycle and at the 30-day Follow-up visit. Participants may be dosed while thyroid function tests are pending.
Comprehensive Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis		X				X					X	X			
T3 or FT3, FT4 and TSH	X	X		X	X	X		X	X		X	X			

Cohorts A and B	Treatment Cycles (3-Week Cycles)										End of Tx	Post-Treatment			Notes
Treatment Cycle	**4**	**5 & 6**	**7**	**8 & 9**	**10**	**11& 12**	**13**	**14& 15**	**16**	**17**	**DC**	**Safety FU**	**FU[3]**	**Survival FU[4]**	
Scheduling Window (Days):[1]	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Tx DC[2]**	**30 D Post Dose ± 3**	**Per imag-ing sched[5]**	**Every 12 Week s±14**	
Analysis Performed by Central Laboratory															
Pembrolizumab Pharmacokinetics	X			X		X			X						Pre-dose trough PK , and ADA samples will be collected at Cycles 4, 8, 12 and 16 and must be drawn within 24 hours before infusion of pembrolizumab. Post-dose peak PK samples will be collected at Cycle 8 and must be drawn within 30 minutes of the completion of the pembrolizumab infusion. PK and ADA are not collected at Cycles 9 and 11.
Anti-pembrolizumab Antibodies	X			X		X			X						
Blood for RNA Analyses		X													Whole blood samples must be collected pre-dose. Blood for RNA analyses is collected at Cycle 6 only.
Blood for ctDNA			X		X		X		X				X		Whole blood samples must be collected pre-dose.
Efficacy Measurements															
Tumor Imaging	X		X		X		X		X				X		Imaging is performed every 9 weeks (± 7 days) until Week 54 and then every 12 weeks (± 14 days) until Week 150 and then every 24 weeks (± 28 days). Imaging must be performed based on calendar days from Cycle 1 Day 1 and not based on treatment cycles.

Cohorts A and B	Treatment Cycles (3-Week Cycles)										End of Tx	Post-Treatment			Notes
Treatment Cycle	**4**	**5 & 6**	**7**	**8 & 9**	**10**	**11& 12**	**13**	**14& 15**	**16**	**17**	**DC**	**Safety FU**	**FU[3]**	**Survival FU[4]**	
Scheduling Window (Days):[1]	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Tx DC[2]**	**30 D Post Dose ± 3**	**Per imag-ing sched[5]**	**Every 12 Week s±14**	
Study Treatment Administration															
Pembrolizumab	X	X	X	X	X	X	X	X	X	X					Study treatment with pembrolizumab must be administered after all procedures/assessments have been completed. Delays in the protocol specified pembrolizumab treatment due to toxicity or for situations other than treatment-related AEs are described in Section 6.6.1 and 6.6.1.3, respectively. Treatment delays during Cycle 4 through Cycle 17 ≥12 weeks will result in discontinuation from the Treatment Phase.

Abbreviations: ctDNA = circulating tumor DNA; D = Days; DC = discontinuation; ECOG = Eastern Cooperative Oncology Group; FU = follow up; PD = progression of disease; Tx = treatment.

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of the trial treatment for each cycle unless otherwise specified. The window for each visit is ± 3 days unless otherwise noted. If treatment cycles are adjusted all procedures except imaging will be completed according to the cycle number and not weeks on treatment. Imaging will not be adjusted for delays in treatment cycles and will be performed per calendar schedule and the allowed visit window.
2. The Discontinuation Visit must occur at the time study drug is discontinued for any reason. If the participant has a Discontinuation Visit ≥27 days after the last dose of study treatment, the Safety Follow-up visit is not required.
3. Follow-up visits after treatment discontinuation must coincide with imaging schedule until disease progression or death.
4. Survival follow visits commence once a participant experiences disease progression or starts a new anti-cancer therapy. Visits are conducted by telephone to assess survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.
5. Follow-up visits after treatment discontinuation must coincide with imaging schedule until disease progression, the start of a new anticancer treatment, or death, whichever occurs first.

2. Introduction

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody of the immunoglobulin (Ig) G4/kappa isotype designed to directly block the interaction between programmed cell death protein 1 (PD-1) and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2).

2.1 Study Rationale

Lung cancer is the most common global cancer and is responsible for the majority of cancer deaths [Torre, L. A., et al 2015]. In 2012, the last year for which the World Health Organization statistics are available, an estimated 1.8 million new cases of lung cancer occurred (comprising 13% of total new global cancer cases) and resulted in ~1.5 million deaths. Due to widespread continued cigarette smoking, lung cancer will remain a significant worldwide public health problem for the foreseeable future.

Non-small cell lung cancer (NSCLC) represents 80% of lung cancers and one-third of these patients will present with Stage III disease at the time of initial diagnosis [Benitez-Majano, S., et al 2016]. The standard of care for patients with a good performance status Stage III NSCLC is platinum-based doublet chemotherapy concurrent with radiotherapy (cCTRT). However, the median progression-free survival (PFS) among patients who have received cCTRT is poor (approximately 8 months), and only 17.7% of patients are alive at 5 years [National Cancer Institute 2016].

The PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and is, thus, an attractive target for therapeutic intervention in the treatment of NSCLC. Pembrolizumab has demonstrated durable clinical activity in participants with metastatic NSCLC and is currently approved as monotherapy in many countries for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%). Pembrolizumab in combination with pemetrexed and carboplatin was also approved in the United States (US) on 10-MAY-2017 for the first-line treatment of patients with metastatic non-squamous NSCLC, irrespective of PD-L1 expression.

While advances have been made in improving survival from Stage III NSCLC by optimizing local control, evidence suggests that cCTRT does not reduce the risk of distant relapse. There is still therefore a significant unmet medical need for additional treatment options for use in this patient population to improve treatment outcomes. The scientific rationale regarding the current study and the rationale behind the endpoints are outlined in Section 4.2 of the protocol.

2.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

2.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation 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 [Dong, H., et al 2002] [Sharpe, A. H. and Freeman, G. J. 2002] [Brown, J. A., et al 2003] [Francisco, L. M., et al 2010] [Thompson, R. H., et al 2007] [Hino, R., et al 2010] [Nomi, T., et al 2007] [Gao, Q., et al 2009] [Hamanishi, J., et al 2007] [Fourcade, J., et al 2009] [Cai, G., et al 2004] [Blank, C. and Mackensen, A. 2007], [Iwai, Y., et al 2002] [Tsushima, F., et al 2006] [Korman, A., et al 2007] [Oble, D. A., et al 2009] [Topalian, Suzanne L., et al 2012] [Patnaik, A., et al 2012] [Hodi, F. S., et al 2010] [Chapman, P. B., et al 2011] [Robert, C., et al 2011] [Bellati, F., et al 2009] [Ruffell, B., et al 2010] [Shirabe, K., et al 2010], [Al-Shibli, K., et al 2010] [Clark, C. E., et al 2009] [Diederichsen, A. C. P., et al 2003] [Gao, Q., et al 2007] [Hillen, F., et al 2008] [Laghi, L., et al 2009] [Li, J. F., et al 2008] [Nemolato, S., et al 2008] [Nobili, C., et al 2008] [Oshikiri, T., et al 2003] [Piersma, S. J., et al 2008] [Rao, U. N. M., et al 2010]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, pancreatic, hepatocellular, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [Sasaki, A., et al 2008] [Shen, Z., et al 2010].

The PD-1 receptor-ligand interaction is a major pathway used 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. Programmed cell death protein-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation (CD)28 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) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998].

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 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, protein kinase C-theta, and zeta-chain-associated protein kinase, 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.

2.2.2 Completed Clinical Studies

Several clinical studies have been conducted to evaluate the efficacy of pembrolizumab monotherapy in the treatment of metastatic NSCLC: KEYNOTE-001, KEYNOTE-010, and KEYNOTE-024.

KEYNOTE-001:

An open-label Phase 1 trial (KEYNOTE-001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W), in participants with advanced solid tumors. All 3 dose levels were well tolerated and no dose-limiting toxicities were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the protocol was amended to change the dosing frequency in the expansion cohort to every 3 weeks (Q3W). All cohorts have completed enrollment [Garon, E. B., et al 2015].

In KEYNOTE-001, a total of 495NSCLC participants were treated in several dose expansion cohorts with at least 1 dose of pembrolizumab. The initial data from 495 NSCLC participants were published and reported. The objective response rate (ORR) was 19.4% (18.0% in the 394 previously treated participants and 24.8% in the 101 previously untreated participants). The response rate (RR) was similar regardless of dose, schedule, and histologic analysis. Current or former smokers had a RR of 22.5%, as compared with 10.3% among participants who had never smoked cigarettes.

Participants were required to submit a newly obtained tumor biopsy prior to initiating therapy with pembrolizumab to evaluate the tumors for expression of PD-L1. After evaluation of several methods for pathological assessment, in a training set, membranous PD-L1 expression in at least 50% of tumor cells (TPS ≥ 50%) was selected as the cutoff point defining PD-L1 high. In a validation set of 313 participants, the RR was 45.2% in the 73 participants with a TPS ≥ 50%, including 43.9% in previously treated participants and 50% in previously untreated participants, values that numerically exceeded the RR in the training group.

Pembrolizumab has been generally well tolerated. The most common treatment-related adverse events (AEs) were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). AEs of Grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy.

KEYNOTE-010:

KEYNOTE-010 was a randomized, adaptively designed Phase 2/3 trial of pembrolizumab at 2 dose levels versus docetaxel in participants with NSCLC with PD-L1 positive tumors (TPS ≥1%) who had experienced disease progression after platinum containing systemic therapy. Participants were stratified according to their TPS (extent of PD-L1 expression) defined as follows: a TPS ≥ 50% was considered strongly positive and a TPS = 1% to 49% was considered weakly positive. Approximately 920 participants were planned to be enrolled in this trial to examine the efficacy of pembrolizumab compared to docetaxel in an enriched population [Herbst, R. S., et al 2016].

In KEYNOTE-010, pembrolizumab was superior to docetaxel in the strongly positive TPS ≥ 50% stratum with regard to overall survival (OS), with a hazard ratio (HR) of 0.54 (p = 0.00024) and 0.50 (p = 0.00002) for pembrolizumab 2 mg/kg Q3W versus docetaxel and 10 mg/kg Q3W versus docetaxel, respectively. Pembrolizumab was superior to docetaxel in the overall positive TPS ≥ 1% population with regard to OS, with an HR of 0.71 (p = 0.00076) and 0.61 (p<0.00001) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively. Pembrolizumab was superior to docetaxel in the strongly positive TPS ≥ 50% stratum with regard to progression free survival (PFS) by independent review committee based on RECIST 1.1, 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. Pembrolizumab provided numerically superior benefit in PFS by independent review committee based on RECIST 1.1 compared to docetaxel in the overall positive TPS ≥ 1% population, with an HR of 0.88 and 0.79 for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively; however, the differences were not statistically significant at the 0.001 level required per protocol.

Overall, the results from KEYNOTE-001 and KEYNOTE-010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. The PD-L1 selection employed in KEYNOTE-010 identified patients more likely to benefit from pembrolizumab and resulted in favorable HRs in OS compared to docetaxel.

In previously treated participants with NSCLC with PD-L1 TPS ≥1%, and disease progression following platinum-containing chemotherapy, pembrolizumab provides a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy.

KEYNOTE-024:

KEYNOTE-024 was a multicenter, international, randomized, open-label, controlled trial of pembrolizumab monotherapy versus the choice of multiple standard of care (SOC) platinum-based chemotherapies in participants previously untreated for their Stage IV NSCLC and whose tumors expressed PD-L1 at ≥ 50% [Reck, M., et al 2016].

First-line treatment with pembrolizumab significantly prolonged PFS (HR 0.50; 95% CI [CI]: 0.37, 0.68; p<0.001) and OS (HR 0.60; 95% CI: 0.41, 0.89; p = 0.005) compared with SOC chemotherapy, inclusive of pemetrexed maintenance for participants with non-squamous tumors.

In addition, pembrolizumab was associated with a higher ORR, including a higher complete response (CR), as well as a longer duration of response as compared to SOC.

Pembrolizumab was better tolerated than chemotherapy and AEs were easily managed. The observed safety profile of the pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date. Based on the mechanism of action of pembrolizumab, immune-mediated AEs, including pneumonitis occurred at a greater frequency with pembrolizumab compared to chemotherapy. Most immune-mediated events were of Grade 1 or 2 severity, and none led to death.

These data underscore the substantial benefit of pembrolizumab as initial therapy for participants with previously untreated, advanced NSCLC whose tumors express high levels of PD-L1 (TPS ≥ 50%).

2.2.3 Ongoing Clinical Studies

Ongoing clinical studies to evaluate the efficacy of pembrolizumab in the treatment of metastatic NSCLC include: KEYNOTE-021, KEYNOTE-042, KEYNOTE-091, KEYNOTE-189, KEYNOTE 407 and KEYNOTE-671.

KEYNOTE-021:

This Phase 1/2 trial assessed the safety and efficacy of pembrolizumab in combination with multiple therapeutic agents including chemotherapy (carboplatin and pemetrexed; and carboplatin, paclitaxel, and bevacizumab); epidermal growth factor receptor (EGFR) inhibitors including erlotinib and gefitinib; and the CTLA-4 inhibitor, ipilimumab. Cohort G of the study evaluated the efficacy and safety of pembrolizumab plus carboplatin and pemetrexed (CP) versus CP alone as first-line therapy for advanced non-squamous NSCLC in 123 participants of whom 60 were accrued to the pembrolizumab plus CP arm and 63 to the CP arm. As of 08-AUG-2016, median follow-up was 10.6 months (range, 0.8-19.3); median exposure was 8.0 months for pembrolizumab plus CP and 4.9 months for CP. Pembrolizumab plus CP significantly improved ORR (55% versus 29%; p = 0.0016) and PFS (HR 0.53, 95% CI 0.31 to 0.91, p = 0.010; median 13.0 versus 8.9 months). Overall survival was similar; 6-month survival rates were 92% in each arm [Langer, C. J., et al 2016].

KEYNOTE-042:

This is a multicenter, international, randomized, open-label, controlled trial of pembrolizumab versus SOC platinum-based chemotherapy in participants previously untreated for their advanced or metastatic NSCLC and whose tumors express PD-L1 ≥ 1%. Approximately 1240 participants will be enrolled.

KEYNOTE-091:

This is a worldwide, randomized, placebo-controlled, Phase 3 trial in participants with early stage NSCLC to prospectively investigate whether adjuvant treatment with pembrolizumab after completion of radical surgery (lobectomy / pneumonectomy) with or without standard adjuvant chemotherapy for Stage IB (T ≥ 4 cm) -II-IIIA NSCLC patients improves Disease Free Survival (DFS), as assessed locally by the investigator, compared to placebo. Approximately 1380 participants will be enrolled.

KEYNOTE-189:

This is a worldwide, randomized, active-controlled, parallel group, multi-site, double-blind trial of pembrolizumab combined with platinum-pemetrexed chemotherapy versus saline placebo combined with platinum-pemetrexed chemotherapy in participants with advanced or metastatic non-squamous NSCLC who had not previously received systemic therapy for advanced disease and in whom EGFR or anaplastic lymphoma kinase (ALK)-directed therapy was not indicated. After a median follow-up of 10.5 months, the estimated rate of OS at 12 months was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo combination group (HR for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001). Improvement in OS was seen across all PD-L1 categories

that were evaluated. Median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001). Adverse events of Grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group [Gandhi, L., et al 2018].

KEYNOTE-407:

This is a Phase 3 study of carboplatin and paclitaxel or nano particle albumin-bound paclitaxel (nab-paclitaxel) with or without pembrolizumab in first line metastatic squamous NSCLC. The total planned enrollment is 560 participants.

KEYNOTE-671:

This is a Phase 3, randomized, trial of platinum doublet chemotherapy with or without pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable Stage IIB or IIIA NSCLC. The total planned enrollment is 786 participants.

2.2.4 Information on Other Study-related Therapy

For patients with unresectable Stage IIIA, Stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone and cCTRT is superior to sequential therapy [Blackstock, A. W. 2007]. cCTRT regimens that may be used for any histology (squamous or non-squamous) for initial treatment include cisplatin/etoposide, cisplatin/vinblastine or carboplatin/paclitaxel. For non-squamous NSCLC, other cCTRT regimens include cisplatin/pemetrexed [National Comprehensive Cancer Network 2018]. The guidelines for the treatment of patients with unresectable Stage IIIA, Stage IIIB NSCLC in Europe [Vansteenkiste, J., et al 2013] [Eberhardt, W. E., et al 2015] and Japan [Saijo, N., et al 2010] are in line with those used in the US.

In this study, Cohort A will use carboplatin/paclitaxel backbone with standard TRT and will enroll Stage III NSCLC participants with any histology and Cohort B will use cisplatin/pemetrexed backbone with standard TRT and enroll only Stage III NSCLC participants with non-squamous histology.

For information on carboplatin/paclitaxel and cisplatin/pemetrexed, please refer to their respective product inserts.

The standard TRT for patients with Stage III NSCLC is the most commonly accepted radiation therapy dose (60–63 gray (Gy) in 1·8–2·0 Gy fraction sizes) and was established by the Radiation Therapy Oncology Group (RTOG) 7301 trial. With the idea that increasing radiation dose would improve both local-regional control and OS, RTOG 0617 trial randomly assigned (1:1:1:1) patients to receive either 60 Gy (standard dose), 74 Gy (high dose), 60 Gy plus cetuximab, or 74 Gy plus cetuximab. Higher dose of radiation (74 Gy radiation given in 2 Gy fractions) with concurrent chemotherapy was not better than standard TRT (60 Gy in 2 Gy fractions) plus concurrent chemotherapy for patients with Stage III NSCLC, and might be potentially harmful. Addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in overall survival for these patients [Bradley, J. D., et al 2015].

The current study will use standard TRT (60 Gy in 2 Gy fractions). The details regarding the standard TRT are provided in Section 8.1.9.2 of the protocol.

2.3 Benefit/Risk Assessment

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

As described in Section 4.2, there is a very strong scientific rationale to study pembrolizumab in combination with chemotherapy and radiotherapy in the treatment of unresectable Stage III NSCLC. Considering the high unmet medical need for new and effective systemic treatment options in patients with Stage III NSCLC, the current study will evaluate anti-tumor activity and the safety profiles of a combination of PD-1 blockade with chemotherapy and radiation as a combined modality treatment. Pembrolizumab has been combined with standard chemotherapy in the treatment of patients with Stage IV NSCLC. The combination was generally well tolerated despite a slight increase in AE rates. The AEs, including immune-related AEs (irAEs), were managed effectively with either dose interruptions or use of corticosteroids. Pembrolizumab has also been studied in combination with different radiotherapy methods. Pembrolizumab in combination with chemotherapy and radiotherapy is being explored in the current study. While there is risk associated with this type of approach, the protocol includes all appropriate guidelines to manage anticipated side effects. Overall, the current protocol is evaluating a very promising therapeutic strategy for treatment of patients with Stage III NSCLC and the benefit/risk assessment for patients enrolled in this trial is considered to be favorable.

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 unresectable, locally advanced, Stage III NSCLC treated with pembrolizumab in combination with platinum doublet chemotherapy and standard TRT followed by pembrolizumab monotherapy

Objective/Hypothesis	Endpoint
Primary	
• Objective: Within each platinum doublet chemotherapy cohort, evaluate the percentage of participants who develop Grade 3 or higher pneumonitis • Hypothesis: Within each platinum doublet chemotherapy cohort, the percentage of participants who develop Grade 3 or higher pneumonitis is <10%	• Grade 3 or higher pneumonitis
• Objective: Within each platinum doublet chemotherapy cohort, estimate the ORR as assessed by BICR according to RECIST 1.1	• Confirmed CR or PR
Secondary	
• Objective: Within each platinum doublet chemotherapy cohort, evaluate the PFS assessed by BICR according to RECIST v.1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.	• PFS defined as the time from enrollment to the first documented local recurrence or distant metastasis or death due to any cause, whichever occurs first
• Objective: Within each platinum doublet chemotherapy cohort, evaluate OS	• OS defined as the time from enrollment to death due to any cause
• Objective: Within each platinum doublet chemotherapy cohort, evaluate the safety and tolerability of each treatment regimen by the percentage of participants who develop AEs	• AEs • Discontinuations due to AEs

Objective/Hypothesis	Endpoint
Tertiary/Exploratory	
• Objective: Within each platinum doublet chemotherapy cohort, evaluate time to distant metastases per RECIST 1.1 based on BICR	Time to distant metastases is defined as the time from enrollment to the first documented distant metastases, or death due to any cause, whichever occurs first
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab in combination with platinum doublet chemotherapy and radiotherapy	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry (IHC), and other biomarkers

4. Study Design

4.1 Overall Design

This is a nonrandomized, multi-site, open-label Phase 2 study of pembrolizumab in combination with chemotherapy and standard TRT in participants with Stage III NSCLC (KEYNOTE-799). There are 2 treatment cohorts. Participants with non-squamous NSCLC are eligible for both cohorts. The choice of chemotherapy will be determined by the investigator prior to treatment allocation. Participants with squamous NSCLC are eligible only for Cohort A. Approximately 216 participants will be enrolled: 108 participants per cohort.

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.

This study will use a sequential monitoring procedure based on pre-specified criteria to monitor safety and efficacy. There will likely be multiple interim analyses for each cohort of the study. The first interim analysis will be conducted when at least 36 participants in one cohort have completed a minimum of 15 weeks of follow-up. An external Data Monitoring Committee (DMC) will serve as an additional reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to the Executive Oversight Committee (EOC) of the Sponsor. The DMC responsibilities and review schedules will be outlined in the DMC charter.

Each cohort, as well as the overall study, may be discontinued at interim analysis for safety reasons if the incidence of Grade 3 or higher pneumonitis is unacceptably high or the observed ORR is very low. The study may also be discontinued early if the percentage of Grade 3 or higher pneumonitis is very low and the observed ORR is high. The final sample size of the study will be changed accordingly. Details are described in Section 9.

It is assumed that the 2 cohorts will enroll participants at a reasonably similar pace. If enrollment between the cohorts is vastly different, enrollment will not be paused and each cohort may be evaluated independently. The similarity of the 2 treatment cohorts will be continuously evaluated after at least 36 participants have completed a minimum of 15 weeks of follow-up in each cohort. If at an interim analysis the pneumonitis rates in the 2 cohorts are considered similar, then the 2 cohorts will be combined for study analysis and the trial stops when the stopping rule is met or once 108 participants have been enrolled. If combination rule is not met, the analysis will be based on each cohort. Details are described in Section 9.7.

4.2 Scientific Rationale for Study Design

For patients with unresectable Stage IIIA or Stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone and cCTRT is superior to sequential therapy [Blackstock, A. W. 2007]. Though most clinicians use a combination of a platinum-containing regimen and radiotherapy, no reference regimen for inoperable Stage III NSCLC has been established by randomized trials. The median progression-free survival among patients who have received cCTRT is poor, and only 17.7% of patients are alive at 5 years [National Cancer Institute 2016]. While advances have been made in improving survival from Stage III NSCLC by optimizing local control, evidence suggests that cCTRT does not reduce the risk of distant relapse.

The immune checkpoint inhibitors, including pembrolizumab, have shown significant and durable clinical activity in patients with advanced NSCLC. Tumors that are poorly immunogenic or that have become immunosuppressive can likely be made immunogenic through administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell. Potential priming agents for immunotherapy agents include chemotherapy and radiotherapy. Some cytotoxic therapies, such as anthracyclines or ionizing radiation, promote ‘immunogenic cell death’, which includes the release of ‘danger’ molecules from tumor cells such as calreticulin, high mobility group protein B1 and adenosine triphosphate. These danger molecules polarize dendritic cells towards a pro-inflammatory phenotype and increase priming towards T helper 1 anti-tumor T-cells and away from regulatory T-cells [Vanneman, M. 2012].

The results from recent clinical trials in Stage III unresectable NSCLC are outlined in Table 1. These trials showed no evidence of survival improvement from further consolidation chemotherapy after cCTRT and no evidence of improved survival from increased doses of TRT. Newer approaches including incorporating immune checkpoint inhibitors to standard cCTRT is needed to improve outcomes for patients with Stage III NSCLC.

Table 1 Summary of Recent Trials in NSCLC

Trial Name	Treatment Cohorts	N	ORR (%)	PFS (months)	OS (months)	Pneumonitis Any Gr/Gr 3-5 (%)
PROCLAIM (non-squam NSCLC only) [Senan, S., et al 2016]	Cisplatin/pemetrexed +TRT followed by cisplatin/pemetrexed	301	35.9	11.4	26.8	17/1.8
	Cisplatin/etoposide +TRT followed by cisplatin/etoposide	297	33	9.8	25.0	10.7/2.6
				HR 0.86 (0.71 to 1.04)	HR 0.98 (0.79-1.20)	
RTOG0617 (2x2 factorial) [Bradley, J. D., et al 2015]	CTRT+ cetuximab	237		10.8	25	9/4
	CTRT	228		10.7	24	11/1
				HR 0·99 (0.80–1.22)	HR 1·07 (0.84–1.35)	
	TRT (60Gy	217		11.8	28.7	
	TRT (74Gy	207		9.8	20.3	
				HR 1.19 (0.95–1.47)	HR 1.38 (1.09–1.76)	
KCSG-LU05 [Ahn, J. S., et al 2015]	Cisplatin/docetaxel+RT	211	38.3	8.1	20.6	5.8/1.2
	Cisplatin/docetaxel+RT followed by cisplatin/docetaxel x 3	209	43.1	9.1	21.8	13.3/1.2
				HR 0.91 (0.73-1.12)	HR 0.91 (0.72-1.25)	

Abbreviations : CTRT = chemotherapy with radiotherapy, Gr = grade; HR = hazard ratio; ORR = objective response rate, OS = overall survival; PFS = progression-free survival; RT: radiotherapy; TRT = thoracic radiotherapy.

Recently, a Phase 3 study compared the anti–PD-L1 antibody, durvalumab, as consolidation therapy in patients with Stage III NSCLC who did not have disease progression after 2 or more cycles of platinum-based cCTRT. In the planned interim analysis of this trial, PFS was longer among patients who received durvalumab than among those who received placebo (HR for disease progression or death, 0.52; $p<0.001$). OS was immature at the time of the analysis. The safety profile of durvalumab was consistent with that of other immunotherapies. Although the incidences of some AEs of any cause, including pneumonitis or radiation pneumonitis, were increased with both durvalumab and placebo in this study compared to historical rates from prior studies, the majority of these are Grade 1 or 2 and most of these events were as expected after definitive cCTRT.

The safety and feasibility of consolidation pembrolizumab following cCTRT for unresectable Stage III NSCLC was also evaluated in a single arm Phase 2 study by Hoosier Cancer Research Network, LUN14-179 study [Durm, G. A., et al 2017]. Ninety-three patients were enrolled and received pembrolizumab 200 mg Q3W for 12 months. The preliminary results showed that pembrolizumab following cCTRT was generally well tolerated and the incidence of Grade 3 or higher pneumonitis within the first 3 months was low (6 out of 93 patients or 6.5%). The study is ongoing and the efficacy results have not been presented.

Despite these advances, consolidation therapy with an immune checkpoint inhibitor is only available to patients who have completed cCTRT. A significant number of patients with unresectable Stage III NSCLC will not complete cCTRT or will progress during or after cCTRT, and hence be ineligible for consolidation therapy. Furthermore, the addition of immune checkpoint inhibitors to cCTRT in pre-clinical studies was more effective when given concurrently compared to sequentially.

The purpose of the current Phase 2 study is to evaluate safety and efficacy of pembrolizumab in combination with cCTRT in patients with unresectable Stage III NSCLC. Addition of pembrolizumab to standard chemotherapy has been shown to improve response rates and PFS in KEYNOTE-021G trial [Langer, C. J., et al 2016]. An additional cycle of pembrolizumab and a platinum-doublet prior to cCTRT will ensure that an effective systemic therapy is given while patients are evaluated and planned for TRT. A similar concept is being evaluated with nivolumab in an ongoing NICOLAS trial (NCT02434081). Once the safety and efficacy is established in the current phase 2 study, this regimen will be compared to cCTRT followed by a checkpoint inhibitor in a future Phase 3 trial.

The current study is designed as a single arm study with 2 parallel cohorts. Each cohort will evaluate one of the most commonly used chemotherapy (carboplatin and paclitaxel for Cohort A and cisplatin and pemetrexed for Cohort B) in combination with standard TRT and pembrolizumab. Since pemetrexed-based chemotherapy is usually not recommended for subjects with squamous NSCLC, participants with squamous NSCLC are eligible only for Cohort A. Participants with non-squamous NSCLC are eligible for both cohorts. The choice of chemotherapy will be determined by the investigator prior to treatment allocation. Similar to other studies in adjuvant setting, the overall duration of treatment will be 1 year or total of 17 cycles of pembrolizumab.

The percentage of participants with Grade 3 or higher pneumonitis will be closely monitored by the study team. Please see Section 9 for details regarding the sequential monitoring procedure and the rules for early stopping either due to safety or lack of efficacy. The rationale for assumptions for percentage of participants with Grade 3 or higher pneumonitis is outlined in Section 4.2.1.2.

4.2.1 Rationale for Endpoints

This trial will use ORR by BICR and percent of Grade 3 or higher pneumonitis as the primary endpoints. The trial will be considered positive if the percentage of participants with Grade 3 or higher pneumonitis is< 10%.

4.2.1.1 Efficacy Endpoints

ORR by RECIST 1.1 criteria as assessed by BICR will be one of the primary endpoints for this Phase 2 trial. The preliminary efficacy data from this trial will form the basis to further evaluate this regimen in a future Phase 3 trial.

In metastatic setting, several studies have shown a correlation between response rate and overall survival.

4.2.1.2 Safety Endpoints

The percent of Grade 3 or higher pneumonitis will serve as another primary endpoint. One of the most common side effects from cCTRT is pneumonitis or radiation pneumonitis. In the majority of these cases, it is Grade 1 or 2 and is usually a radiological finding without much clinical sequelae. However, some patients can develop clinically significant Grade 3 or higher pneumonitis.

As outlined in Table 1, in prior studies with cCTRT, the percentage of participants who develop Grade 3 or higher pneumonitis rate is 1% to 3%. In the PACIFIC trial evaluating durvalumab maintenance after cCTRT, the incidence of Grade 3 or higher pneumonitis was 3.4% in the durvalumab arm and 2.6% in the placebo arm [Antonia, S. J., et al 2017]. We proposed that the percentage of participants with Grade 3 or higher in the current study of ≤3% will be desirable for the proposed treatment regimen and the percentage of participants with Grade 3 or higher pneumonitis ≥10% will be considered unacceptable for this treatment regimen to move forward in a Phase 3 trial.

4.2.1.3 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 blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and 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 or tumor

Tumor and 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 immunoassay (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.

4.2.1.4 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 this future biomedical research substudy are presented in Appendix 2.

4.3 Justification for Dose

4.3.1 Rationale for Dose Interval and Study Design

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

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

Among the randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and 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). Three studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KEYNOTE-001 B2, KEYNOTE-001 D, KEYNOTE-002, and KEYNOTE-021), and three studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KEYNOTE -01 B3, KEYNOTE-001 F2 and KEYNOTE-006). 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 KEYNOTE-001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, 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 subject 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.

As discussed in Section 2.2.4, based on the results of RTOG 0617 trial, the current study will use the standard TRT (60 Gy in 2 Gy fractions) and the doses of chemotherapy as outlined in the protocol are aligned with standard clinical practice and the current guidelines.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the Informed Consent Form (ICF). The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, 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

Male/Female participants with unresectable, locally advanced Stage III NSCLC, who have received no prior anticancer therapy for their disease, and 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. Male/female participants, who are at least 18 years of age on the day of signing informed consent with previously untreated, unresectable, pathologically confirmed NSCLC and Stage IIIA, IIIB or IIIC NSCLC by American Joint Committee on Cancer Version 8.

   Note: Sites are encouraged to obtain tissue confirmation of mediastinal nodal involvement if this is safely accessible by endobronchial ultrasound (EBUS)/endoscopic ultrasound (EUS) or mediastinoscopy. However, mediastinal nodal involvement can be declared when the nodes have distinct margins and the size of the shortest axis of at least 1 node must be ≥2.0 cm (positron emission tomography [PET]/magnetic resonance imaging [MRI]/computed tomography [CT] scan). Cases in which the distinct nodes all have short axis of <2.0 cm must have pathologic confirmation of disease presence for participants to be declared eligible.

   Participants are eligible without obtaining the EBUS sample for pathological confirmation of mediastinal nodes < 2.0 cm if a Sponsor Communication Form is submitted and approved by the Sponsor Clinical Director and the following criteria are met:

   1) the primary tumor is considered unresectable and is clinically confirmed IIIA, IIIB, or IIIC NSCLC independent of the hilar lymph nodes and

   2) the presence or absence of metastases in the mediastinal lymph nodes would not change the radiotherapy plan.

   Participants with supraclavicular nodal involvement may be entered into the study. However, participants with cervical nodes are not permitted. The upper border of supraclavicular nodes must not extend above the upper border of the lateral end of the clavicle, extended medially.

2. No evidence of metastatic disease by whole body PET/ CT scan, diagnostic quality CT scan, and brain imaging. The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual.

   NOTE: The presence of pleural/pericardial fluid is presumed indicative of metastatic disease. Participants with effusions that are not visible on routine chest x-ray or are too small to be tapped safely may be entered on this study, provided the remaining inclusion/exclusion criteria are met.

3. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/ radiology.

4. Have provided tumor tissue sample (core, incisional, or excisional biopsy). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. In cases where the core, incisional, or excisional biopsy is not available or cannot be obtained due to anatomical location of tumor or medical condition of the participant, a cell block obtained through EUS/EBUS may be submitted after consultation with the Sponsor Clinical Director and documenting approval via a Sponsor Communication Form.

   Note: If submitting unstained cut slides, newly cut slides must be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).

5. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
6. Have adequate pulmonary function test (PFT) as a forced expiratory volume in 1 second (FEV1) >50% of predicted normal volume and the carbon monoxide lung diffusing capacity (DLCO) >40% of predicted normal value. Participants for whom DLCO measurements are not available will be deemed to have adequate oxygen transfer if their resting capillary/arterial blood gas on room air reveals an oxygen pressure (PO2) >60 mmHg.
7. Have adequate organ function as defined in Table 2.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Serum Creatinine OR Measured or calculated[b] CrCl	≤1.5 × ULN OR ≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin within normal limits for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Endocrine	
TSH	Within normal limits. Note: If TSH is not within normal limits at baseline, the participant may still be eligible if T3 and free T4 are within the normal limits
Coagulation	
INR OR PT 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

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; TSH = thyroid stimulating hormones; ULN = upper limit of normal.
a. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
b. Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Male participants:

8. A male participant must agree to use contraception, as detailed in Appendix 3 for at least 180 days after the last dose of study treatment in Cycles 1 through 3 or for 120 days after the last dose of study treatment in Cycle 4 through the end of treatment and refrain from donating sperm during this period.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Female participants:

9. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and if participant is a woman of childbearing potential (WOCBP), agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 180 days after the last dose of study treatment in Cycles 1 through 3 or for 120 days after the last dose of study treatment in Cycle 4 through the end of treatment.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

10. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial. The participant may also provide consent for Future Biomedical Research. However participant may participate in the main trial without participating in Future Biomedical Research.

5.2 Exclusion Criteria

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

Medical Conditions

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation (see Appendix 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.

   Note: Pregnancy tests within 24 hours prior to treatment allocation to determine eligibility will be required only in those regions where this is required via documented regulatory request, subsequently approved by the Sponsor.

2. Has small cell lung cancer. Mixed tumors will be categorized by the predominant cell type: if small cell elements are present, the participant is ineligible; if non-small cell histology with any squamous element is present (example squamous, adenosquamous), the participant is not eligible for Cohort B (pemetrexed based chemotherapy).

3. Has had documented weight loss >10% in the preceding 3 months.

   Prior/Concomitant Therapy

4. Participants whose radiation treatment plans are likely to encompass a volume of whole lung receiving >20 Gy in total (V20) of more than 31% of lung volume.

   Note: The participant must have been assessed by a radiation oncologist who anticipates the tumor is treatable, as defined in Section 8.1.9.2.4.

5. Has received prior radiotherapy to the thorax, including radiotherapy to the esophagus or for breast cancer.
6. 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).
7. Has received a live vaccine within 30 days prior to the first dose of study drug. 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 (e.g., FluMist®) are live attenuated vaccines and are not allowed.
8. Has had an allogenic tissue/solid organ transplant.

Prior/Concurrent Clinical Study Experience

9. 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

10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg prednisone daily or equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.
11. 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 (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
12. Has severe hypersensitivity (Grade 3 or higher) to pembrolizumab and/or any of its excipients (refer to the IB for a list of excipients).
13. Has a known severe hypersensitivity (Grade 3 or higher) to any of the study chemotherapy agents and/or to any of their excipients (refer to the approved product label(s) for a list of excipients).
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/ interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease that requires steroids.
16. Has an active infection requiring systemic therapy.
17. Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by local health authority. Refer to Appendix 7 for country-specific details.
18. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
    Note: Testing for hepatitis B and/or hepatitis C is not 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 a 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 180 days after the last dose of study treatment in Cycles 1-3 or for 120 days after the last dose of study treatment in Cycle 4 through the end of treatment.
23. Any other specific criterion determined to be required for treatment with standard of care therapies, based on documented regional or country-specific regulatory request, subsequently approved by the Sponsor.

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, vomiting, or esophagitis.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No caffeine, alcohol or tobacco restrictions are required.

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

5.3.3 Activity Restrictions

There are no activity restrictions. Participants may participate in light recreational activities during the study.

5.3.4 Contraception

Pembrolizumab and chemotherapy may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

Participants must 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 (Appendix 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 180 days after the last dose of study medication in Cycles 1 to 3 or for 120 days after the last dose of study medication in Cycle 4 through the end of treatment. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant must not be entered into the study.

5.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with chemotherapy and/or 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 8.4.6.

5.3.6 Use in Nursing Women

It is unknown whether chemotherapy and/or pembrolizumab are 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 enrolled in the study. 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 adverse events (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 from the study 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. Pembrolizumab will be provided centrally by the Sponsor, while carboplatin, paclitaxel, cisplatin, and pemetrexed will be provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

The study treatment(s) to be used in this study are outlined below in Table 3.

Table 3 Study Treatment(s)

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	IMP/NIMP	Sourcing
COHORT A							
Pembrolizumab (MK-3475)	Solution for infusion	25 mg/ml	200 mg	IV infusion	Experimental	IMP	Central
Paclitaxel	Solution for infusion	6 mg /mL	200 mg/m^2 45 mg/m^2	IV infusion	Standard of care	NIMP	Local or Central
Carboplatin	Solution for infusion	10 mg /mL	AUC6 AUC2	IV infusion	Standard of care	NIMP	Local or Central
Thoracic Radiotherapy		2 Gy/fraction	60 Gy	Standard Fractionation	Standard of care	NIMP	Local
COHORT B							
Pembrolizumab (MK-3475)	Solution for infusion	25 mg/ ml	200 mg	IV infusion	Experimental	IMP	Central
Pemetrexed	Solution for infusion	500 mg Lyophilized Powder/ vial	500 mg/m^2	IV infusion	Standard of care	NIMP	Local or Central
Cisplatin	Solution for infusion	1 mg / mL	75 mg/m^2	IV infusion	Standard of care	NIMP	Local or Central
Thoracic Radiotherapy		2 Gy/fraction	60 Gy	Standard Fractionation	Standard of care	NIMP	Local
Definitions: Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.							

All supplies indicated in Table 3 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 (e.g., not applicable in the case where multiple lots or batches may be required due to the length of the study etc.).

Refer to Section 8.1.9 for details regarding administration of the study treatment.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

The dose amount required to prepare the pembrolizumab infusion solution will be based on a fixed dose of 200 mg. Details on dose calculation, preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Dosing and preparation of pembrolizumab will be performed by authorized staff.

Standard chemotherapeutic agents (carboplatin, paclitaxel, cisplatin, or pemetrexed) will be prepared and administered by authorized staff as per the approved product label(s).

Radiotherapy must be administered by authorized staff following guidelines detailed in Radiation Therapy Quality Assurance Manual.

6.2.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study 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

Participants participating in this study will be allocated by nonrandom assignment.

6.3.1.1 Stratification

The study is a nonrandomized, open-label study. There is no stratification in the study. Treatment allocation will be assigned according to the following factors:

1. Predominant tumor histology (squamous versus non-squamous)
2. Physician choice of treatment in non-squamous participants

6.3.2 Blinding

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

6.4 Treatment Compliance

Interruptions from the protocol specified pembrolizumab treatment schedule due to toxicity or for situations other than treatment-related AEs are described in Section 6.6.1 and Section 6.6.1.3, respectively. Treatment delays during Cycle 4 through Cycle 17 ≥9 weeks (ie, 12 weeks between pembrolizumab doses) will result in discontinuation from the Treatment Phase.

6.5 Concomitant Therapy

All medications received within 42 days prior to the first dose of study treatment through post-treatment follow-up must be recorded as described in Section 1.3.

All concomitant medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter (OTC) products, herbal supplements, and intravenous (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.

6.5.1 Acceptable Concomitant Medications

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. Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms.

6.5.2 Prohibited Concomitant Medication

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Participants are prohibited from receiving the following concomitant therapy or vaccination during the course of the trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Surgery or radiotherapy for tumor control not specified in the protocol.
- Investigational agents other than pembrolizumab.
- 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 (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an irAE or for use as a pre-medication for chemotherapeutic agents specified in the protocol or as a pre-medication prior to a CT scan for participants with contrast allergy or for use for chronic obstructive pulmonary disease exacerbation requiring steroid for recovery. Replacement doses of steroids (for example, prednisone 10 mg daily or equivalent) are permitted while on study.

If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from the trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or participant' primary physician. However, the decision to continue the participant on trial therapy requires the mutual agreement of the investigator, the Sponsor, and the participant.

Refer to Appendix 7 for country-specific information regarding concomitant medications to be used with caution.

6.5.3 Rescue Medications and Supportive Care

6.5.3.1 Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Table 6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder,

attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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 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.

6.5.3.2 Chemotherapy

For supportive care measures for the management of AEs that may result from treatment with carboplatin/paclitaxel (Cohort A) or cisplatin/pemetrexed (Cohort B) refer to the approved product labels for these agents.

For Cohort A, all participants should be pre-medicated with oral or intravenous steroid and anti-histamines according to the approved product label and/or standard practice prior to paclitaxel infusion, see Section 8.1.9.1.2.

For Cohort B, all participants should receive the appropriate supplementation of intramuscular vitamin B12 1000 mcg and folic acid according to the approved product label and/or standard practice prior to pemetrexed infusion; see Section 8.1.9.1.3. In addition, all participants should receive the appropriate corticosteroid pre-medications as per the local approved label.

Antiemetic therapy should follow Multinational Association of Supportive Care in Cancer (MASCC) guidelines (http://www.mascc.org/antiemetic - guidelines/; [Roila, F., et al 2016]) and should, for the first 3 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and/or aprepitant as per the MASCC guidelines.

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

6.5.3.3 Radiotherapy

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy (RT). Radiation-induced transverse myelitis rarely occurs at doses lower than 50 Gy to the spinal cord and canal. Radiation-induced cardiac injury may occur at whole heart doses of greater than 30-40 Gy and it will be important to keep a mean heart dose at approximately 20 Gy or less during treatment planning. Radiographic evidence of radiation-induced changes and subsequent fibrosis of the lung may occur within lung volumes receiving ≥20 Gy. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung and other organ injury.

One of the most common side effects of cCTRT is esophagitis. The first symptoms of acute esophagitis usually start in the second or third week of cCTRT, commonly at the dose of 18.0 to 21.0 Gy of standard fractionated RT [Wei, X., et al 2006], and include a sensation of difficult swallowing (dysphagia). This may progress to painful swallowing of food and saliva (odynophagia) and later to constant pain not necessarily related to swallowing. In severe

cases, participants may not be able to swallow at all and may require intravenous hydration, feeding through a gastric tube and, in rare cases, parenteral nutrition.

Esophagitis complaints are common with combined modality therapy [Werner-Wasik, M., et al 2011]. Esophagitis does not constitute a reason to interrupt or delay RT, provided oral intake is sufficient to maintain hydration. Participants should be advised to avoid alcoholic or very cold temperature beverages and acidic or spicy foods and beverages. Acute esophagitis symptoms may persist for 1 to 3 weeks after completion of RT. If Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 esophagitis occurs and treatment is interrupted, every effort should be made to limit the interruption to 3 treatment days or less. Participants requiring hospitalization, placement of a feeding tube in the stomach, or intravenous feedings because of esophagitis may have their treatment interrupted in order to optimize supportive care measures and enteral nutrition. See Section 6.4.

Table 4 lists esophagitis grading and clinical states according to the CTCAE.

Table 4 CTCAE Scale: Acute Esophagitis Related to Radiation

Grade	Clinical State
1	asymptomatic pathologic, radiographic, or endoscopic findings only
2	symptomatic; altered eating/swallowing (for example, altered dietary habits, oral supplements); IV fluids indicated < 24 hours
3	symptomatic and severely altered eating/swallowing (for example, inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated > 24 hours
4	life-threatening consequences (for example, obstruction, perforation)
5	death

Abbreviations: CTCAE = Common Terminology Criteria of Adverse Events; IV = intravenous; TPN = total parenteral nutrition.

Acute esophageal toxicity, which manifests as dysphagia, odynophagia, reflux symptoms, and so forth, should be pharmacologically managed with the recommended treatment options, alone or in various combinations (Table 5), or comparable regimen, and should be initiated at the first signs or symptoms of esophageal toxicity.

Table 5 Suggestions for Management of Radiation Esophagitis

Treatment Options	Management of Esophagitis
1	Ketoconazole 200 mg po QD
2	Fluconazole 100 mg po QD until the completion of radiation
3	Mixture of: 60 mL viscous lidocaine + 30 mL Mylanta (or generic equivalent antacid), + 10 mL sucralfate (1 gm/mL). Approximately 15-30 mL of the mixture po q3-4h PRN
4	Ranitidine 150 mg po BID (or other histamine-2 [H2] receptor blocker or a proton pump inhibitor such as omeprazole) until completion of radiation
5	Grade 4 esophagitis: hold cCTRT until Grade 2 or less.

Abbreviations: BID = twice daily; cCTRT = concurrent chemoradiotherapy; h = hour; po =oral; PRN = when necessary; q = every; QD = every day.

6.6 Dose Modification

Toxicity events may be attributed to pembrolizumab, individual chemotherapy agents, radiotherapy, or to the combination of any of these treatments.

Dose modifications due to toxicity events must be based on the maximum toxicity experienced during a treatment cycle. The CTCAE Version 4.0 must be used to grade the severity of AEs. All dose modifications must be based on the AE requiring the greatest dose modification. Treatment related toxicity must resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, Grade 2 esophagitis, Grade 2 peripheral neuropathy, Grade 2 anemia, endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≥2. Consultation with the Sponsor Clinical Director and documented approval via a Sponsor Communication may be obtained to continue a participant on treatment for an AE Grade ≥2 if in the assessment of the investigator the particular AE does not pose a significant medical risk to the participant to continue the treatment

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 third dose modification to any particular component will have that agent discontinued.

Dose modifications for pembrolizumab, chemotherapy, and radiotherapy are summarized in Section 6.6.1, Section 6.6.2, and Section 6.6.3, respectively.

If toxicity is related to the combination of 3 agents (ie, 2 chemotherapy agents and pembrolizumab), all 3 agents must be interrupted or discontinued according to the recommended dose modifications. Participants may have chemotherapy discontinued and

continue on pembrolizumab alone. Similarly, participants may discontinue pembrolizumab and continue on chemotherapy alone (for first 3 cycles) if appropriate.

Systemic treatment (chemotherapy and/or pembrolizumab) given with radiation should be suspended if continuation of systemic treatment will compromise delivery of full-dose radiation in an uninterrupted manner.

6.6.1 Pembrolizumab

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be delayed as described below or discontinued due to toxicity. Pembrolizumab treatment delays greater than those specified below will result in discontinuation from the Treatment Phase

- Pembrolizumab may be delayed for a maximum of 3 weeks during Cycles 1 to 2 (ie, 6 weeks between pembrolizumab doses) and for a maximum of 3 weeks during Cycles 2 to 3 (ie, 6 weeks between pembrolizumab doses).
- Cycle 4 must be administered within 6 weeks after completion of TRT
- Pembrolizumab may be delayed for up to 9 weeks during Cycles 4 through 17 (ie, 12 weeks between pembrolizumab doses). However, delays greater than 9 weeks will result in discontinuation from the Treatment Phase (see Section 6.4). See Appendix 7 for country-specific pembrolizumab discontinuation guidance.

6.6.1.1 Dose Modification and Toxicity Management for Immune-Related AEs Associated With Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial 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, and/or 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 are provided in Table 6. Guidance for determining severity of pneumonitis is in Table 7.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/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
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent)	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 4 or recurring Grade 3	Permanently discontinue	followed by taper	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.
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/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 1-2mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• 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[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thioamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[1]		
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 1-2mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE	• Ensure adequate evaluation to confirm

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis	administer corticosteroids	etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Table 7 Criteria for Grading of Pneumonitis: Common Terminology Criteria for Adverse Events, Version 4.0

Grade	Clinical State
1	asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	symptomatic; medical intervention indicated; limiting instrumental ADL
3	severe symptoms; limiting self-care ADL; oxygen indicated
4	life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
5	death

Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.
Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria of Adverse Events; Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.; Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Source: [National Cancer Institute 2010]

6.6.1.2 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 8.

Table 8 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 treatment with pembrolizumab**	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).
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 treatment with pembrolizumab.**	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		

6.6.1.3 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 therapy within 3 weeks of the scheduled interruption. The reason for interruption must be documented on the Sponsor Communication Form.

6.6.2 Chemotherapy Dose Modifications

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 1 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. Chemotherapy may be delayed for a maximum of 3 weeks between Cycles 1 to 2 and between Cycles 2 to 3.

Refer to approved product labels for dose modifications regarding carboplatin/paclitaxel (Cohort A) and cisplatin/pemetrexed (Cohort B).

The second cycle of chemotherapy must commence during the first week of radiotherapy. Concurrent phase chemotherapy cycles can only be commenced if there is ongoing radiotherapy. In the event of chemotherapy delays, cycles that are scheduled to resume after the last fraction of radiotherapy will be omitted and not considered a reason for patients to come off of the trial.

6.6.3 Radiotherapy Dose Modification

Radiotherapy may be interrupted or discontinued due to toxicity. Radiotherapy may be interrupted for a maximum of 3 weeks during Cycles 2 to 3.

Every effort must be made to continue the radiotherapy during the concurrent phase in an uninterrupted manner. Should a patient develop severe esophagitis necessitating interruption of chemotherapy, the radiotherapy may continue, provided the investigator believes supportive care will enable the patient to complete this part of the therapy without excess risk.

On days when radiotherapy and/or chemotherapy are delayed for administrative reasons (eg, holidays or weather), this will not be considered a protocol violation, provided the full planned dose of radiotherapy is administered.

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

6.9 Standard Policies

MK-3475 will be provided by the study site as the innovator product pembrolizumab as needed. No generic substitution is permitted.

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 8.12.3.

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 1.3.

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.
- Confirmed radiographic disease progression outlined in Section 8.2.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Recurrent Grade 2 pneumonitis.
- A confirmed positive serum pregnancy test.
- Completion of 17 treatments with pembrolizumab.
- Investigator's decision to discontinue the participant.
- Use of prohibited medications as described in Section 6.5.2.
- The participant interrupts pembrolizumab administration for more than 12 consecutive weeks for an AE/toxicity or for more than 3 weeks for administrative reasons without Sponsor consultation.

See Appendix 7 for country-specific treatment discontinuation requirements.

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.

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research are outlined in Sections 1.3 and 8.1.10.2. 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 assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- 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 maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, 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 qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a 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 qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (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 dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee 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 written 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

Participant demographics and a medical history will be obtained by the investigator or qualified designee.

Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Medical history will also include any prior cancer other than NCSLC even if diagnosed greater than 10 years prior to Visit 1 as well as an assessment of smoking history.

NSCLC history will be recorded separately and not listed as medical history as specified in the SoA.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and will record prior medication taken by the participant within 42 days before the first dose of study medication as well as medications regularly administered at intervals greater than 42 days prior to first dose.

A complete history of the participant's treatment of NSCLC (if any) will be recorded separately and not listed as prior medication as specified in the SoA.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record all medications, if any, taken by the participant during the trial through post-treatment follow-up including all prescription, OTC products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

Concomitant medications prohibited in the study are described in Section 6.5.2.

All medications related to reportable SAEs and ECIs must be recorded as defined in Section 8.4.

8.1.6 Post-Treatment Anticancer Therapy

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of trial treatment.

If a participant initiates a new antineoplastic therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up Visit must occur before the first dose of the new therapy.

Once new antineoplastic therapy has been initiated the participant will move into Survival Follow-up described in Section 8.12.3.3**.**

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to treatment assignment. 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 8.12.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, 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.

8.1.9 Treatment Administration

Administration of pembrolizumab, chemotherapy, and radiotherapy will be witnessed by the investigator or qualified designee.

Dose administrations of pembrolizumab and chemotherapy are described in Section 8.1.9.1. Thoracic radiotherapy treatment is described in Section 8.1.9.2.

Study Treatment should begin within 3 days of the date on which the participant is allocated to a treatment cohort.

8.1.9.1 Timing of Dose Administration

Study treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for Cycle 1, Day 1, where the window is +3 days from randomization.

Study treatment with pembrolizumab and chemotherapy must be administered after all procedures/assessments have been completed as detailed in the SoA. All study treatments will be administered on an outpatient basis.

Pembrolizumab and chemotherapy study treatments will be administered in the following order:

Cohort A: pembrolizumab, paclitaxel, and carboplatin

Cohort B: pembrolizumab, pemetrexed, and cisplatin

During Cycles 2 and 3, it will be preferable to have pembrolizumab and chemotherapy administered prior to TRT delivery. Chemotherapy treatment will end after completion of the TRT regimen.

8.1.9.1.1 Timing of Dose Administration of Pembrolizumab

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites must 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).

Refer to the Pharmacy Manual for detailed instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

8.1.9.1.2 Timing of Dose Administration of Chemotherapy: Cohort A

8.1.9.1.2.1 Paclitaxel

Paclitaxel 200 mg/m^2 will be administered as an IV infusion over 3 hours or per local practice and labels on Day 1 of the 21-day cycle for Cycle 1 and paclitaxel 45 mg/m^2 will be administered as an IV infusion over 1 hour or per local practice and label on Day 1, 8 and 15 of Cycle 2 and Cycle 3 during TRT. Given the variability of infusion pumps from site to site, the time window allowed per local practice or label is permitted. Paclitaxel must be completely administered before initiating carboplatin dose.

All participants should be pre-medicated with steroids and anti-histamines according to the approved product label and/or standard practice. Additional pre-medications should be administered as per standard practice.

Refer to the approved product label for detailed instructions regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.1.9.1.2.2 Carboplatin

Carboplatin AUC6 will be administered as an IV infusion over 15-60 minutes or per local practice or label on Day 1 of the 21-day cycle for Cycle 1 and carboplatin AUC2 will be administered as an IV infusion over 30 minutes or per local standard practice on Day 1, 8 and 15 of Cycle 2 and Cycle 3 during TRT. Given the variability of infusion pumps from site to site, the time window allowed per local practice or label is permitted.

The dose of carboplatin will be calculated using either the Calvert Formula or carboplatin dose calculator approved at the local institution.

Calvert Formula

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

The estimated creatinine clearance (CrCl) used in the Calvert formula should not exceed 125 mL/min

Maximum carboplatin dose (mg) = target AUC 6 (mg•min/mL) x (125 + 25) = 6 x 150 mL/min = 900 mg

Refer to the approved product label for detailed instructions regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.1.9.1.3 Timing of Dose Administration of Chemotherapy: Cohort B

8.1.9.1.3.1 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes or per local practice or label on Day 1 of the 21-day cycle, for Cycle 1, 2 and 3. Given the variability of infusion pumps from site to site, the time window allowed per local practice or label is permitted. Pemetrexed must be completely administered before initiating cisplatin dose.

All participants should be pre-medicated with steroids as per the approved label and local standard practices. In addition, all participants assigned to pemetrexed must take a folic acid preparation or multivitamin with folic acid containing between 350 to 1000 mcg daily. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Participants must also receive 1 intramuscular injection of vitamin B_{12} 1000 mcg 1 week preceding the first dose of pemetrexed (Cycle 1) and on Cycle 3. On Cycle 3, vitamin B_{12} injections may be given the same day as treatment with pemetrexed. Intramuscular vitamin B_{12} cannot be substituted with oral vitamin B_{12}.

Refer to the approved product label for detailed instructions regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.1.9.1.3.2 Cisplatin

Cisplatin 75 mg/m^2 will be administered as an IV infusion over 60 minutes or per local practice or label on Day 1 of the 21-day cycle, for Cycle 1, 2 and 3. Given the variability of infusion pumps from site to site, the time window allowed per local practice or label is permitted. All participants should be pre-medicated with steroids and anti-emetics per the approved label and local standard practices.

Refer to the approved product label for detailed instructions regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.1.9.2 Thoracic Radiation Therapy (TRT)

Prior to inclusion of any participant on this study, the radiation oncologist will evaluate the thoracic CT scan in order to ensure that the treatment volumes are unlikely to significantly exceed the specified normal tissue constraints, particularly that the V20 meets the threshold of ≤ 31%, as specified in the exclusion criteria.

Participants in both cohorts will receive concurrent TRT using a standardized 3-dimensional conformal radiotherapy (3DCRT) technique on a linear accelerator operating at beam energy of ≥6 megavolts (MV). 6MV photons are preferred if possible; 10 MV photons may also be used. Use of photon energies higher than 10 MV is allowed but discouraged. The target total dose of TRT will be 60 Gy in 30 daily fractions of 2 Gy, prescribed to the planning target volume (PTV) as described in Section 8.1.9.2.1. Proton treatment is not allowed.

Beam-Shaping: Multi-leaf collimation will be used to spare normal tissues outside of the target volume.

Intensity Modulated Radiotherapy (IMRT) will be permitted if the appropriate credentialing has been performed. Motion management will be incorporated for an IMRT approach to control respiratory motion to a maximum excursion of 1.0 cm. Acceptable approaches include abdominal compression, breath hold using the active breathing device (ABC) device or other computer-controlled spirometry, gating or other technologies.

Heterogeneity Corrections: All radiation doses will be calculated with heterogeneity corrections that take into account the density differences within the irradiated volume (eg, air, soft tissue, or bone). Dose calculations should be performed on a non-contrast enhanced CT. Alternatively, if calculations are performed on a contrast-enhanced scan, areas of contrast enhancement adjacent to the target volumes or nearby critical structures must be over-ridden with soft tissue density. A list of acceptable dose calculation algorithms that most accurately account for tissue heterogeneities can be found on the QARC website (www.qarc.org).

Center credentialing will be performed according to criteria defined in the RT Quality Assurance (QA) Manual. Participating institutions must comply with the RT QA requirements and procedures described in the RT QA manual. Sites that do not conform to the requirements of the credentialing will not be allowed to participate.

8.1.9.2.1 Dose Specifications

Participants will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction, to a target dose of 60 Gy in 30 fractions. No field reductions will be permitted and the entire PTV must be treated daily. Cycle 2 of chemotherapy and pembrolizumab must be given during the first week of TRT. When both chemotherapy and radiation are administered at the same center/location, it is recommended that radiation should follow within 30 to 60 minutes of the completion of chemotherapy, especially on Day 1 of TRT. When the radiotherapy is delivered at a separate location, logistic considerations may result in radiotherapy being delivered prior to the administration of chemotherapy. On days where TRT and/or chemotherapy are delayed for administrative reasons (eg, holidays or weather), this will not be considered a protocol violation, provided the full planned dose of TRT is administered.

The treatment plan shall be normalized such that 95% of the prescription dose covers at least 99% of the PTV (V57>99%). The minimum PTV dose must not fall below 95% of the prescription dose. All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (that is, air in the lung and bone). The maximum and minimum point doses (within the PTV) will be reported. No more than 0.03 cc of the PTV may receive >120% of the prescription dose (maximum dose constraint).

8.1.9.2.2 Variations of Dose Prescription

No deviation: The treatment plan will be normalized so that ≥ 95% of the PTV is covered by the prescription dose. No more than 0.03 cc of the PTV may receive >120% of the prescription dose (maximum dose constraint).

Variation Acceptable: Deviations of this magnitude are not desirable, but are acceptable. The prescribed dose can cover <95% of the PTV provided it covers at least 90% of the PTV. The minimum dose can fall below 93% of the prescribed dose provided it is at least 90% of the prescription dose, if the areas of underdosing are confined to regions of overlap with critical structures. The maximum dose within the PTV may exceed 120% of the prescribed dose provided it is no more than 125% of the prescription dose, and the areas exceeding 110% of the prescription dose are confined within the GTV and do not overlap with critical structures. Standard naming conventions, protocol constraints, and compliance criteria are tabulated in Table 9.

Table 9 Summary of Protocol Constraints and Compliance Criteria

Structure	Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
PTV	V60Gy	≥95%	≥90%	<90%
	Min dose (D99%)	≥55.8 Gy (93%) ≥57 Gy (95%)	≥54 Gy (90%)	<54 Gy
	Max dose (0.03 cc)	≤72 Gy (120%)	≤75 Gy (125%)	>75 Gy
Spinal cord	Max dose (0.03 cc)	≤50.0 Gy	≤52 Gy	>52 Gy
Lungs (minus GTV)	V20Gy	≤31%	None	>31
	V5Gy	≤60%	≤65%	>65%
	Mean dose	≤20 Gy	≤22 Gy	>22 Gy
Heart	Mean dose	≤20 Gy	≤26 Gy	>26 Gy
Esophagus	Max dose (0.03 cc)	≤63 Gy	≤66 Gy	>66 Gy
	Mean dose	≤34 Gy	≤35 Gy	>35 Gy
	V60Gy	Not circumferential	Circumferential for ≤0.5 cm contiguous length	Circumferential for >0.5 cm contiguous length
Brachial plexus	Max dose (0.03cc)	≤63 Gy	≤66 Gy	>66 Gy

8.1.9.2.3 Localization, Simulation, and Immobilization

Immobilization: Immobilization is necessary to assure reproducibility of the setup. An immobilization device must be used for positioning of each patient. Each participant will be positioned in an institutional specific immobilization device in the treatment position on a flat table.

If a conventional (non-4-dimensional CT) treatment planning CT study is performed, the GTV, clinical target volume (CTV), and PTV will be defined on all slices (see definitions in Section 8.1.9.2.4).

Target volumes (GTV, CTV), PTV, and normal organs will be outlined on all appropriate CT slices. All planning CT scans must be performed in the treatment position using the same immobilization device for set-up as is used at the linear accelerator. Optimal immobilization is critical for this protocol in order to ensure reproducibility of the daily set-up. Conventional CT scans will be performed during quiet, uncoached respiration while the participant undertakes a normal respiration, using 5-mm or finer slices through the entire target volume. The scan volume must include the entire thorax (cricoid to L2) in order to generate dose-volume histograms for the lungs, spinal cord, heart, and esophagus. Radiotherapy must commence within 2 weeks (±) 2 working days of the planning CT scan.

A treatment planning fluorodeoxyglucose (FDG)-PET/CT scan (or FDG-PET alone) with the participant in the treatment position is encouraged for treatment planning. Where a PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

Intravenous contrast during the planning CT is optional, provided that a recent diagnostic chest CT was done with contrast to delineate the major blood vessels and involved mediastinal lymph nodes. If not, intravenous contrast must be given during the planning CT. If contrast is used, the densities can be over-ridden or the contrast scan must be registered to a noncontrast scan for planning purposes.

The use of 4-dimensional CT scans and 4-dimensional radiation treatment planning is permitted. Acceptable methods of accounting for tumor motion include: design of the PTV to cover the excursion of the primary lung cancer and involved nodal CTV during free breathing (motion inclusive), or the more limited excursion during a voluntary or automatic breath-hold (i.e., Elekta ABC device), or a gating approach (eg, Varian RPM system).

8.1.9.2.4 Treatment Planning/Target Volumes

Target Volumes will be defined in accordance with the International Commission on Radiation Units and Measurements Report #62 [Wambersie, A. 1999].

Gross Tumor Volume (GTV) encompasses all identified tumor, identified by radiologic imaging, PET scan, bronchoscopy, or mediastinoscopy. Mediastinal lymph nodes with a short axis ≥1.0 cm or pretreatment PET scan with standardized uptake values >3 will be included in the GTV unless metastases have been shown to be absent using cytologic, histologic, or PET studies. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is allowed.

Clinical Target Volume (CTV) is defined to be the GTV plus a 0.5-cm to 1-cm margin, as appropriate, to account for microscopic tumor extension. For participants with N2 disease, the CTV will include the ipsilateral hilus in the proximity of the tumor if it is felt appropriate to include this region, even if this is radiologically normal. When the hilus is normal, the lower pole of the ipsilateral hilus will be excluded if the primary tumor is located in the upper lobe and vice versa in the case of a tumor in the lower lobe. The CTV may be extended to include the entire ipsilateral hilum that is radiologically normal in cases where the location of the primary tumor makes this an appropriate consideration; for example, tumor in close proximity to the hilum. Inclusion of the hilus is encouraged for centrally located primary lung tumors. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

Planning Target Volume (PTV): The appropriate clinical target volumes (described above) will be enlarged to allow for organ motion and day-to-day set-up variation to define the PTV. Typically the CTV is expanded by 1 cm in all directions (and 1.5 cm superiorly or inferiorly for tumors of the lower lobe or with significant respiratory excursion) if no motion management is used.

Tighter PTV margins may be allowed based on assessments of CTV motion using fluoroscopy and/or 4DCRT. When a 4-dimensional CT scan is performed, a patient-specific internal target volume (ITV) may be directly derived for planning and appropriate margins

added in order to derive a CTV and PTV, respectively. These determinations must be documented but are left to the discretion of the treating radiation oncologist. This PTV will be used to define the treated volume.

The ITV is defined as the CTV plus an internal margin to account for target/organ motion. The final PTV is defined to be the ITV plus a setup margin to account for patient positioning uncertainty and machine tolerance. Table 10 below provides guidance on margins of ITV and PTV.

Table 10 Planning Target Volume

Motion management	Internal margin (cm) (superior-inferior)	Internal margin (cm) Axial	Setup margin (cm, uniform)	Total PTV margin (superior-inferior)	Total PTV margin (axial)
Free breathing	1	0.5	0.5	1.5	1
Breath hold or gating	0.5	0.3	0.5	1	0.8
Abdominal compression	0.8	0.5	0.5	1.3	1
4D CT	Union of CTVs	Union of CTVs	0.5	Union of CTVs+0.5 cm	Union of CTVs +0.5 cm

8.1.9.2.5 Treatment Planning

Three-Dimensional Conformal Radiotherapy (3DCRT)

The PTV is to be treated with any combination of coplanar or noncoplanar 3D conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. The treatment plan used for each participant will be based on an analysis of the volumetric dose, including dose-volume histogram analyses of the PTV and critical normal structures. Each field is to be treated daily.

Intensity Modulated Radiation Therapy (IMRT)

The use of IMRT is permitted, provided that the institution has been credentialed by the central vendor (QARC) for intrathoracic IMRT treatments. As IMRT results in a greater proportion of lung receiving radiation outside the PTV, it is strongly recommended to maintain the total lung V5 level at 60% or less.

8.1.9.2.6 Documentation

Centers participating in this study will perform heterogeneity corrections for all study treatment planning. It is recognized that differences between calculation algorithms in the different treatment planning systems may result in dose variations for individual participants. A list of acceptable dose calculation algorithms that most accurately account for tissue heterogeneities can be found on the QARC website (www.qarc.org).

Portal imaging of each field of 3DCRT or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy in accordance with standard

department protocols but will not be submitted. The films must be compared to localization films and discrepancies corrected.

Weekly verification via orthogonal isocenter images are required to be taken. Images may be taken more often at the discretion of the treating physician. This verification information can be gathered also with a cone-beam CT or other CT devices that are present in the treatment room.

Dose volume histograms will be generated for PTV, both lungs, lungs minus PTV, spinal cord, esophagus, and heart.

8.1.9.2.7 Organs at Risk

Normal tissue constraints shall be prioritized in the following order for treatment planning:

1 = spinal cord, 2 = lungs, 3 = heart, 4 = esophagus, and 5 = brachial plexus

When there is gross disease in close proximity to the esophagus or brachial plexus, it may not be possible to meet this constraint and give full dose to the gross disease. The dose coverage of the PTV will take precedence over a non-critical organ at risk (esophagus or brachial plexus only) structure in close proximity.

Spinal cord: The spinal canal will be contoured and taken to represent the spinal cord and should be contoured from the top of the CT simulation/cricoid to the bottom of the CT simulation/L2. The spinal cord dose limit is the highest priority dose constraint and must be met irrespective of other constraints. No more than 0.03 cc of the spinal cord may receive greater than 50.0 Gy total dose.

Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with spinal cord dose constraints. The volume of both lungs (total lung volume minus GTV) that receive more than 20 Gy (V20) must not exceed 31%. V20s up to 35% will be permitted and viewed as a minor deviation. Lung V5 must be limited to ≤60%. A minor deviation will be considered a V5 of up to 65%.

Heart: The heart will be contoured on all slices. The cranial border will include the infundibulum of the right ventricle and the apex of both atria and exclude the great vessels as much as possible. The caudal border is defined as the lowest part of the left ventricle that is distinguishable from the liver. The following limits are recommended: Mean heart dose ≤ 20 Gy. A mean heart dose of up to 26 Gy will be considered a minor deviation.

Esophagus: The esophagus contour must include the mucosa, submucosa, and all muscular layers out to the fatty adventitia, from the bottom of the cricoid cartilage to the gastroesophageal junction. No more than 0.03 cc of the esophagus may receive >63 Gy. The mean dose to the esophagus must be ≤34 Gy. The esophagus must not be circumferentially irradiated with greater than 60 Gy at any level.

Brachial Plexus: The ipsilateral brachial plexus must be contoured for upper lobe tumors. No more than 0.03 cc of the brachial plexus must receive >63 Gy.

If, after participant enrollment, it is discovered the total tumor dose has to be limited to stay within normal tissue dose constraints and falls below 60 Gy in 30 fractions, the treated participants will be eligible for toxicity evaluation, but additional participants will be

recruited to ensure the appropriate number of participants are treated at the prescribed dose of radiation.

Toxicities documented during radiation therapy will be recorded using the CTCAE version 4.0 scale. Toxicities arising more than 90 days since the completion of radiation therapy and attributed to radiation will be assessed according to CTCAE criteria and counted as late radiation toxicities. As both cohorts use pembrolizumab monotherapy, the toxicities encountered during pembrolizumab monotherapy and during the 30-day follow-up period will not be declared late radiation toxicities unless the events are confined to tissue within the radiation treatment volume.

8.1.9.2.8 Treatment Quality Assurance and Compliance with Protocol-Defined Radiation Prescription (Quality Control)

This study will require a pre-treatment review of the treatment plan for each subject. Details regarding the submission process and the data to be submitted can be found in the RT QA Manual.

QARC will evaluate the treatment plan for each subject within 3 business days of receiving complete data. Feedback from this review will be sent via email to the treating Radiation Oncologist, Principal Investigator, study staff and clinical research associate. Corrective action in response to the QARC pretreatment review must be implemented promptly. A modified treatment plan must be resubmitted for review, but treatment with the modified plan may begin prior to review unless otherwise specified. If requested changes are not made, an immediate response from the radiation oncologist is expected.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Discontinuation visit should be performed (at the time of withdrawal). Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 Survival Follow-up

Participants who withdraw consent for treatment and/or imaging are encouraged to remain on the non-invasive Survival Follow-up portion of the study. The only procedures associated with this phase are telephone contacts to assess survival status and the current state of the participant's NSCLC. The non-invasive nature and societal benefit of Survival Follow-up (every 12 weeks ± 14 days) must be explained to the participant by the site staff, particularly when discontinuing treatment or imaging. Participants may withdraw their consent at any time from any or all portions of the study.

8.1.10.2 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@merck.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.

8.1.11 Participant Blinding/Unblinding

This is an open label study; there is no blinding for this study.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained 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. Tumor imaging is strongly preferred to be acquired by CT. MRI may be used when CT with iodinated contrast is contraindicated or when local practice mandates it.

Brain imaging is required for all participants at screening. MRI is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

The same imaging technique regarding modality, ideally the same scanner, and the use of contrast must be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden.

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, and imaging obtained for other reasons that demonstrate radiologic progression, must 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 disease progression and communicate the results to the study site and Sponsor. Treatment must continue until progressive disease (PD) has been centrally verified if the participant is clinically stable. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement modified RECIST 1.1 for immune-based therapeutics (iRECIST), the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images must continue to be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 42 days prior to the first dose of trial treatment.

MRI is strongly preferred for imaging of the brain; head CT imaging with contrast is preferred if MRI is medically contraindicated. If the participant is unable to have CT contrast, a head CT without contrast is acceptable. Scans performed as part of routine clinical management (ie, CT of the chest, abdomen and pelvis, whole body PET/CT and brain MRI) are acceptable for use as the baseline scan if they are of diagnostic quality, include all required anatomy, and performed within 42 days prior to randomization. These scans will be considered the baseline assessments for the study. PET/CT if acquired within 60 days of randomization does not need to be repeated. Pelvic CT required at baseline only and does not need to be repeated on-study unless clinically indicated.

8.2.1.2 Tumor Imaging During the Study

The first imaging assessment during treatment must be performed at 9 weeks (63 ± 7 days) from Cycle 1 Day 1. Subsequent imaging must be performed every 9 weeks (63 ± 7 days) until Week 54 or more frequently if clinically indicated. Imaging timing must follow calendar days and must not be adjusted for delays in cycle dosing or radiotherapy.

Imaging must continue to be performed until PD is identified by the investigator and verified by BICR, the start of new anticancer treatment, withdrawal of consent for imaging, or death, whichever occurs first; however, if the investigator elects to continue treatment and follow iRECIST after initial radiographic PD, imaging must continue, and images must be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point and determine PD, as well as imaging obtained for other reasons, but captures radiologic progression, must be submitted to the central imaging vendor.

Objective response (PR or CR) must be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed no earlier than 4 weeks after the first indication of a response. Participants will then return to the regular imaging schedule, 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 the confirmatory scans are taken within 4 weeks of the next scheduled tumor scan. Tumor imaging may resume at the subsequent scheduled imaging time point. Note: response does not need to be verified in real time by the central imaging vendor.

Per iRECIST (Section 8.2.1.5), PD must be confirmed by the site 4 to 8 weeks after central verification of the site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed PD may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if the confirmatory scans are taken within 4 weeks of the next scheduled tumor scan. Tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed PD by iRECIST as assessed by the site will discontinue the treatment, unless treatment beyond confirmed progression is approved by the Sponsor, as detailed in Section 8.2.1.5.

8.2.1.3 End of Treatment and Follow-up Imaging

For participants who discontinue study treatment, tumor imaging must 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 PD, this is the final required tumor imaging if the Investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented PD, every effort must be made to continue monitoring disease status by tumor imaging every 9 weeks (±7 days) until Week 54, and then every 12 weeks (± 14 days) until Week 150, and then every 24 weeks (± 28 days) until PD, the start of new anticancer treatment, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. The timing of Follow-up Visits must be scheduled to coincide with the participant's follow-up imaging. The imaging requirements in the study are considered complete once a participant undergoes BICR-verified PD, starts new anti-neoplastic therapy, is lost to follow-up or experiences death. The participant will then enter the Survival Follow-up.

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the 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.

Because the study treatment includes both systemic therapy and focal radiation, RT to a target lesion selected at baseline will not render that lesion non-evaluable, for the purposes of RECIST 1.1 assessment.

In addition to overall assessment by RECIST 1.1, response assessment will include separate evaluation of local progression (ie, growth of existing lesions or appearance of lesions within the same lung lobe as the primary lesion) and metastatic disease (appearance of lesions anywhere else).

Initial tumor imaging showing site-assessed PD must be submitted to the central imaging vendor immediately for verification of PD by BICR. The site will be notified if the BICR verifies PD using RECIST 1.1. The first half of the flowchart in Figure 2 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.5 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 to assess tumor response and progression, and make treatment decisions. When clinically stable, participants must not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. 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. These data will be captured in the clinical database.

A description of the adaptations and iRECIST process is provided here, with additional detail in [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 11 and illustrated as a flowchart in Figure 2.

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic 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 11 and Figure 2). This decision by the investigator must be based on the participant's overall clinical stability.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG performance status.
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

Any participant deemed **clinically unstable** must be discontinued from study treatment upon central verification of site-assessed first radiologic evidence of PD, and is not required to 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 must continue to be sent in to 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), persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (immune [i]SD/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 radiographic iCPD as defined above, but the participant is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging must continue to be performed following the intervals as outlined in Section 8.2.1.2 and be 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 study, 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 is repeated (see Assessment at the Confirmatory Imaging above). 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 scan 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 [Seymour, L., et al 2017].

Table 11 Imaging and Treatment after First Radiologic Evidence of PD

	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 the 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 image should occur according to the regular imaging schedule

Note: If progression 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 rapid review will occur.

BICR=blinded independent central review; iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified RECIST 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.

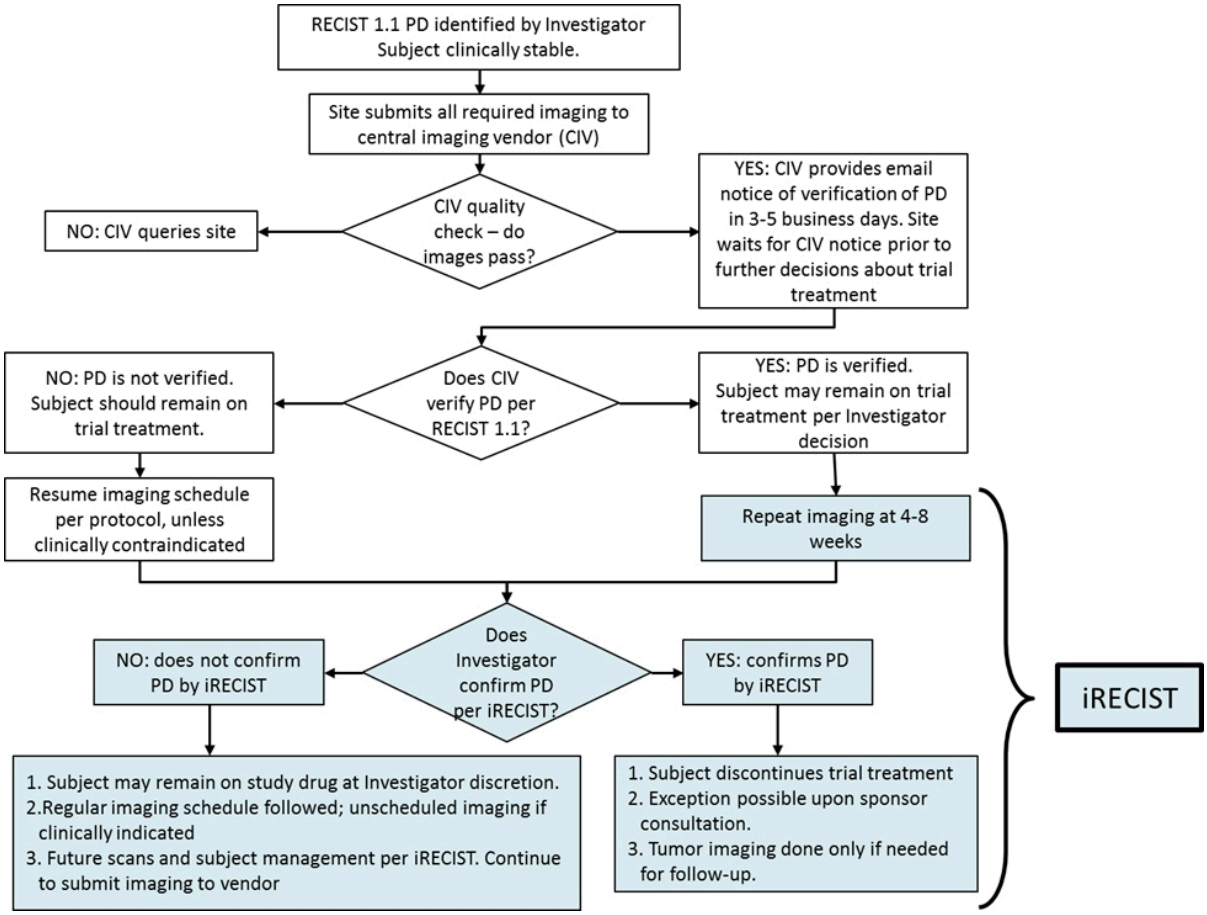


Figure 2 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator

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

8.3.1.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and treatment discontinuation.

Clinically significant abnormal findings at screening must be recorded as medical history. After the first dose of trial treatment, new clinically significant abnormal findings must be recorded as AEs.

Refer to Appendix 7 for country-specific requirements.

8.3.1.2 Directed Physical Examination

The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study treatment administration. Cycles that do not require a full physical exam are defined in the SoA.

New clinically significant abnormal findings after the first dose of treatment must be recorded as AEs.

Refer to Appendix 7 for country-specific requirements.

8.3.2 Vital Signs, Weight, and Height

The investigator or qualified designee will measure vital signs and weight at screening, prior to the administration of each dose of pembrolizumab, end of treatment, and during the 30-day Safety Follow-up visit as specified in the SoA.

Vital signs include temperature, pulse, heart rate, respiratory rate and blood pressure.

Height will be measured at screening only.

8.3.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures once at screening. Additional ECGs at other time points may be performed as clinically necessary.

Clinically significant abnormal findings must be recorded as medical history.

8.3.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status a screening (within 10 days prior to treatment allocation and within the allowed visit windows at subsequent visits), prior to the administration of study treatment, and during the 30 Day Safety Follow-up as specified in the SoA.

The ECOG performance scale is outlined in Appendix 5.

8.3.5 Pulmonary Function Tests

The investigator or qualified designee will assess pulmonary function at screening.

Pulmonary function tests include pulse oximetry, FEV1, forced vital capacity, DLCO, and total lung capacity.

8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 6 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator 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 Appendix 6, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study 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.

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

Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 3 days prior to Day 1 of subsequent cycles. Participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function tests are pending. Refer to the SoA for the timing of laboratory assessments.

Laboratory tests for hematology, chemistry, and urinalysis are specified Appendix 6.

8.3.6.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal (as defined in Appendix 3), must be tested for pregnancy during screening and/or within 72 hours of the first dose of study treatment. Pregnancy tests within 24 hours prior to treatment allocation to determine eligibility will be required only in those regions where this is required via documented regulatory request, subsequently approved by the Sponsor.

Pregnancy testing including monthly pregnancy testing must be conducted as per local regulations where applicable. A serum test can be considered if urine test is not appropriate. Refer to Appendix 7 for country-specific details.

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 or borderline-positive test result.

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 Appendix 4.

Progression of the cancer under study is not considered an AE as described in Section 8.4.5 and Appendix 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, who is a qualified physician, and any designees are responsible for detecting, assessing, 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.

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 consent form is signed 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 180 days following cessation of treatment in Cycles 1 through 3 or for 120 days following cessation of study treatment in Cycles 4 through the end of 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 he/she 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 12.

Table 12 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: - due to intervention - causes exclusion	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, events of clinical interest (ECIs), Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 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 towards 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 monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance

as an SAE within 24 hours of determination that the event is not progression of the cancer under 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), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by ≥5 times the indicated dose (any dose of 1000 mg or greater). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the SoA. Blood samples for PK and ADA collected may be stored. Analysis will be performed only if required. If ongoing PK and/ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.6.1 Blood Collection for Serum Levels of Pembrolizumab

Pre-dose trough PK samples will be collected at Cycles 1 2, 4, 8, 12, and 16. All pre-dose trough samples must be drawn within 24 hours before infusion of pembrolizumab.

Post-dose peak PK samples will be collected at Cycle 1 and 8. All post-dose PK samples must be drawn within 30 minutes of the completion of the pembrolizumab infusion.

Sample collection, storage and shipment instructions will be provided in the Laboratory Manual.

8.6.2 Blood Collection of Anti-Pembrolizumab Antibodies (ADA)

Pre-dose ADA samples will be collected at Cycles 1 2, 4, 8, 12, and 16. All pre-dose samples must be drawn within 24 hours before infusion of pembrolizumab.

Sample collection, storage and shipment instructions will be provided in the Laboratory Manual.

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:

- Archival tumor tissue
- Blood for genetic analysis
- Blood for RNA analyses
- Blood for serum biomarker analyses
- Blood for plasma biomarker analyses
- Blood for circulating tumor DNA (ctDNA)

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 signs the future biomedical research consent. 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 signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- DNA for future research
- Leftover RNA
- Leftover plasma or derivative for ctDNA
- Leftover study tumor tissue
- Leftover plasma from plasma biomarker analyses
- Leftover serum from serum biomarker analyses

8.10 Tumor Tissue Collection

A tumor tissue sample (core, incisional, or excisional biopsy) must be provided to the central laboratory within 42 days prior to treatment allocation.

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archival tissue. In cases where the core, incisional, or excisional biopsy is not available or cannot be obtained due to anatomical location of tumor, a cell block obtained through EUS/EBUS may be submitted after sponsor consultation. If submitting unstained cut slides, newly cut slides must be submitted to the testing laboratory within 14 days from the date slides are cut.

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

8.11 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual. The timing of the samples is listed in the SoA.

8.12 Visit Requirements

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

8.12.1 Screening

Approximately 42 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Screening procedures may be repeated once after consultation with the Sponsor Clinical Director and documentation of the approval via a Sponsor Communication Form. Participants who are rescreened will retain their original screening number.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within approximately 42 days prior to the first dose of study treatment except for the following:

- Evaluation of ECOG is to be performed within 10 days prior to the first dose of study treatment.
- For WOCBP, a urine or serum pregnancy test will be performed within 72 hours (or within 24 hours in those regions where it is required) prior to the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory, will be required.
- Laboratory tests are to be performed within 10 days prior to the first dose of study treatment.
- Tumor imaging must be performed within 42 days prior to the first dose of study treatment.

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.

8.12.2 Treatment Period

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

Unless otherwise specified, assessments/procedures are to be performed prior to the first dose of treatment for each cycle. Unless otherwise specified, the window for each visit is ±3 days.

8.12.3 Post-treatment Period

At the end of treatment, each participant will be followed for a minimum of 30 days for AE monitoring. Serious AEs occurring within 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, will be collected, whichever is earlier.

Participants will have post-treatment follow-up for disease status, including radiographic imaging, until initiating a non-study anti-cancer treatment, experiencing disease progression, death, withdrawing consent, becoming lost to follow-up, or end of study.

All participants will be followed for overall survival until death, loss to follow up or withdrawal of consent.

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

8.12.3.1 30 Day Safety Follow-up Visit

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

If a participant has a discontinuation visit ≥27 days after the last dose of study treatment, the Safety Follow-up Visit is not required.

8.12.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than documented PD will move into the Follow-up Phase. Follow-up visits after treatment discontinuation must coincide with imaging schedule until disease progression, death or end of study. Information regarding post-study anticancer treatment will be collected if a new treatment is initiated.

Every effort must be made to collect imaging until the start of new anticancer therapy, confirmed PD, or death. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

8.12.3.3 Survival Follow-up

Participants who experience confirmed PD or start a new anticancer therapy, will move into the Survival Follow-up Phase and must be contacted by telephone approximately every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

Participants may withdraw their consent at any time from any or all portions of the study. Participants who withdraw consent for treatment and/or imaging are encouraged to remain on the non-invasive Survival Follow-up portion of the study. The only procedures associated with this phase are telephone contacts to assess survival status and the current state of the participant's NSCLC. The non-invasive nature and societal benefit of Survival Follow-up must be explained to the participant by the site staff, particularly when discontinuing treatment and imaging.

8.12.3.3.1 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested at any time 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 DMC 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 electronic data collection tool).

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses after the study has begun, but prior to final database lock, the protocol will

be amended (consistent with ICH guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Reports (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail PK and biomarker analyses.

9.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized. The comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 2, open-label, multi-center, nonrandomized, multi-cohort, parallel group, uncontrolled study of pembrolizumab in combination with platinum doublet chemotherapy and standard thoracic radiotherapy in participants with unresectable locally advanced Stage III NSCLC.
Treatment Assignment	Approximately 216 participants will be enrolled into 2 cohorts (108 participants per cohort). The choice of chemotherapy will be determined by the investigator prior to treatment allocation. Participant with squamous NSCLC are eligible only for Cohort A. Cohort A: Participants will receive 1 cycle of carboplatin AUC6 with paclitaxel 200 mg/m^2 and pembrolizumab 200 mg on Day 1. Approximately 3 weeks later participants will receive carboplatin AUC2 with paclitaxel 45 mg/m^2 administered weekly for 6 weeks with 2 cycles of pembrolizumab 200 mg administered every Q3W in conjunction with standard TRT. To conclude the study treatments, participants will receive an additional 14 cycles of pembrolizumab 200 mg administered Q3W. Cohort B: Participants will receive 3 cycle of cisplatin 75 mg/m^2 with pemetrexed 500 mg/m^2 and pembrolizumab 200 mg on Day 1. Treatment will be given in conjunction with standard TRT in Cycles 2 and 3. To conclude the study treatments, participants will receive an additional 14 cycles of pembrolizumab 200 mg administered Q3W.
Analysis Population	Efficacy: All Participants as Treated (APaT) Safety: All Participants as Treated (APaT)
Primary Endpoints	- Grade 3 or higher pneumonitis - Confirmed complete response or partial response based on RECIST 1.1 as assessed by BICR.
Secondary Endpoints	- PFS based on RECIST 1.1 as assessed by BICR - OS

Statistical Method for Key Efficacy Analyses	The point estimate of ORR and a 90% CI will be provided using the Clopper-Pearson method. Confidence intervals of 80% and 95% will be provided as additional summaries.
Statistical Method for Key Safety Analyses	For the primary endpoint of percentage of participants with Grade 3 or higher pneumonitis, the point estimate and a 90% CI will be provided using the Clopper-Pearson method. Confidence intervals of 80% and 95% will be provided as additional summaries. The overall analysis of safety will follow a tiered approach. Other than percentage of participants with Grade 3 or higher pneumonitis, there are no Tier 1 safety parameters in this trial. All other safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs based on Clopper-Pearson method. Only point estimates will be provided for Tier 3 safety parameters.
Interim Analyses	Multiple interim analyses based on sequential monitoring procedure will be performed to allow the study to stop if the percentage of participants with Grade 3 or higher pneumonitis is unacceptably high, stop for futility if the ORR is low, or stop to enable rapid progression to Phase 3 if the percentage of participants with Grade 3 or higher pneumonitis is very low and the ORR is high. The decision rule and other statistical details are further described in Section 9.7. The 2 cohorts might be combined for the study analysis if the pneumonitis rates in 2 cohorts are similar. Results will be reviewed by an external DMC.
Multiplicity	No multiplicity adjustment is planned.
Sample size	The planned sample size is approximately 216 participants in 2 treatment cohorts (108 participants per cohort). At overall one-sided 5% alpha level and with maximum sample size of 108, the study will provide 83% power to demonstrate Grade 3 or higher pneumonitis is less than 10% if the true rate is 3% in a cohort.

9.2 Responsibility for Analyses/In-house Blinding

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

The trial will be conducted as an open-label study. There is no randomization in the study. The treatment assignment and allocation will be tracked in interactive response technology.

Planned interim analyses are described in Section 9.7.

To supplement the study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The details regarding the external DMC is provided in Section 10.1.7 of this protocol and in DMC charter. The interim analyses performed by the

clinical Biostatistics Department of the Sponsor internally will be reviewed by DMC periodically. The DMC will make recommendations to the Executive Oversight Committee (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 and recommend to the EOC whether the study should continue in accordance with the protocol..

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 are listed below.

9.4.1 Primary Endpoints

Grade 3 or higher pneumonitis: percentage of participants with Grade 3 or higher pneumonitis is percent of participants who have developed Grade 3 to 5 pneumonitis.

Confirmed complete response or partial response: ORR is the proportion of participants who have a confirmed CR or PR per RECIST 1.1 based on BICR.

9.4.2 Secondary Endpoints

Progression-free survival: the time from enrollment to the first documented local recurrence or distant metastasis per RECIST 1.1 based on BICR (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) or death due to any cause, whichever occurs first. See Section 9.6.1 for the definition of censoring.

Overall survival: the time from enrollment to death due to any cause.

Safety and tolerability: AEs and discontinuations due to AEs.

9.4.3 Tertiary/Exploratory Endpoints

1. Time to distant metastases: the time from enrollment to the first documented distant metastases per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first.
2. Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The APaT population will serve as the population for the primary efficacy analysis. All enrolled participants who received at least 1 dose of study treatment will be included in this population.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled participants who received at least 1 dose of study treatment. Participants will be analyzed in the treatment cohort corresponding to the study treatment they actually received. For most participants, this will be the study treatment cohort to which they are enrolled. Participants who take incorrect study treatment cohort for the entire treatment period will be included in the treatment corresponding to the study treatment actually received. Any participant who receives the incorrect study medication for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment cohort and a narrative will be provided for any event that occurs during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory measurement obtained subsequent to at least 1 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.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives based on efficacy parameters including ORR, PFS and OS. Methods related to exploratory objectives will be described in the sSAP.

For the primary endpoint of ORR, the point estimate and a 90% CI will be provided using the Clopper-Pearson method [Clopper, C.J. 1934]. Confidence intervals of 80% and 95% using the Clopper-Pearson method will be provided as additional summaries. Binomial sequential testing will be conducted to assess whether the ORR is less than 50% (in favor of 35%) or greater than 35% (in favor of 50%). An ORR of 35% was set as the lower threshold based on historical data (Table 1) and an alternative ORR rate of 50% was set as the upper threshold for monitoring based on the improvement in ORR expected from the study treatment regimen. Participants in APaT population with missing ORR data will be counted as non-responders.

For the secondary endpoint of PFS, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Since the disease progression is assessed periodically, PD (either local recurrence or distant metastasis) 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 by BICR. Death is always considered as confirmed PD events. 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 the investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECISIT 1.1 as assessed by BICR, 2 sensitivity analyses with a different set of censoring rules from the primary analysis will be performed. For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to the 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 the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis 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 the primary and sensitivity analyses are summarized in Table 13.

Table 13 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
PD or death documented after ≤1 missed disease assessment, and before new anticancer 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 anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; new anticancer 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 treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment.	Censored at last disease assessment	Progressed at date of new anticancer treatment

PD = progressive disease

For the secondary endpoint of OS, the non-parametric KM method will be used to estimate the survival curves. The median estimates from the KM curves will be provided as appropriate. Participants without documented death at the time of analysis will be censored at the last known alive date. In practice, the date of last known contact will be used.

A summary of the efficacy analysis methods for the key efficacy endpoints is provided in Table 14.

Table 14 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variables	Statistical Method	Analysis Population	Missing Data Approach
Primary Efficacy Endpoints			
ORR - RECIST 1.1 by BICR	Exact method based on binomial distribution (Clopper-Pearson method)	APaT	Participants with missing data are considered non-responders.
Secondary Efficacy Endpoints			
PFS – RECIST 1.1 by BICR	Summary statistics using KM method	APaT	Censored according to rules in Table 13. - Primary censoring rule - Sensitivity analysis 1 - Sensitivity analysis 2
OS	Summary statistics using KM method	APaT	Censored at last known alive date

APaT = All Participants as Treated; BICR = blinded independent central review; KM = Kaplan-Meier; ORR=objective response rate;
OS = overall survival; PFS=progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors

9.6.2 Statistical Method for Safety Analyses

Percentage of participants with Grade 3 or higher pneumonitis will be evaluated as primary endpoint. The point estimate and a 90% CI will be provided using the Clopper-Pearson method [Clopper, C.J. 1934]. Confidence intervals of 80% and 95% will be provided as additional summaries. A percentage of participants with Grade 3 or higher pneumonitis of 10% or more is considered unacceptable, while a percentage of 3% or less is most desirable pneumonitis rate. Binomial sequential testing will be conducted to assess whether the pneumonitis rate is less than 10% (in favor of 3%) or greater than 3% (in favor of 10%). The 2 cohorts might be combined for the study analysis if the pneumonitis rates in 2 cohorts are similar at interim analysis.

Safety and tolerability will also be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

The analysis of safety results will follow a tiered approach (Table 15). The tiers differ with respect to the analyses that will be performed. Percentage of participants with Grade 3 or higher pneumonitis is Tier 1 event. Safety parameters including AEs of special interest (AEOSI) will be considered Tier 2 or Tier 3. Tier 2 parameters by cohort and combined treatment group will be assessed via point estimates with 95% CIs based on Clopper-Pearson method; only point estimates by cohort and combined treatment group are provided for

Tier 3. Membership in Tier 2 requires that at least 10% participants in any cohort, all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 10% participants is chosen for Tier 2 event because participants enrolled in this study are in critical conditions and usually experience various adverse events of similar types, events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the meaningful interpretation. Because many 95% CIs may be provided without adjustment for multiplicity, the CI should be regarded as helpful descriptive measure to be used in review, not a formal statistical method for AEs and pre-defined limit of change.

Continuous measures such as changes from baseline in laboratory will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by cohort and combined treatment group if appropriate in table format.

The percentage of participants with any AE, an AEs of special interest, a drug-related AE, an SAE, a Grade 3 to 5 AE, an AE that is both Grade 3 to 5 and drug-related, an AE that is both drug-related and serious, an AE that results in dose modification, death, and who discontinued due to an AE, will be considered Tier 2 endpoints, 95% CIs will be estimated using Clopper-Pearson method.

Table 15 Analysis Strategy for Safety Parameters Excluding Primary Endpoint (Percentage of Participants with Grade 3 or Higher Pneumonitis)

Safety Tier	Safety Endpoints[†]	p-values	95% CI per Cohort and Combined Treatment Group if Needed	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3 to 5 AE		X	X
	Any serious AE		X	X
	Any drug-related AE		X	X
	Any serious and drug-related AE		X	X
	Any Grade 3 to 5 and drug-related AE		X	X
	Dose modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOC or PDLCs[‡] (incidence ≥10% in one of cohort)		X	X
Tier 3	Specific AEs, SOCs or PDLCs[‡] (incidence <10% in both cohorts)			X
	Change from baseline results (labs)			X

[†] Adverse event references apply to both clinical and laboratory AEs.

[‡] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

AE = adverse event; CI = confidence interval; PDLC = Pre-defined limits of change; SOC = system organ class; X = results will be provided.

9.6.3 Summaries of Baseline Characteristics and Demographics

The number and percentage of participants screened, allocated, the primary reasons for screening failure, and primary reasons for discontinuation will be displayed. Demographic variables, baseline characteristics, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables by cohort and combined treatment group if appropriate.

9.7 Interim Analyses

Continuous interim analyses using binomial sequential testing will be performed in the study to allow either treatment cohort to stop if the percentage of participants with Grade 3 or higher pneumonitis is unacceptably high (Table 17), stop for futility if the ORR is low (Table 18), or stop to enable rapid progression to Phase 3 if the percentage of participants with Grade 3 or higher pneumonitis is very low (Table 16) and the ORR is high (Table 19).

The first interim analysis will take place when at least 36 participants have a minimum of 15 weeks of follow up in either cohort. If the rates of enrollment in two cohorts are different, the first interim analysis will occur when the first cohort meets these criteria. The sequential monitoring procedure with binomial sequential testing [Romeu, JL 2013] will be used to evaluate for percentage of participants with Grade 3 or higher pneumonitis and ORR according to rules outlined in Table 16 through Table 19. In the evaluation of pneumonitis, number of participants in APaT population will be considered as the monitoring point in the binomial sequential testing (Table 16 and Table 17). In the evaluation of ORR, number of participants in APaT population, who either discontinue or have at least 2 tumor imaging during the study, will be considered as the monitoring point in the binomial sequential testing (Table 18 and Table 19).

If 1 of cohorts is dropped due to high pneumonitis rate or low ORR rate, the remaining cohort will continue as planned.

The estimated time for the sequential monitoring procedure to start will be approximately 9 months after the first participant is enrolled. However, the incidence of Grade 3 or higher pneumonitis will be closely monitored throughout the study. If Grade 3 or higher pneumonitis is observed in 5 or more participants prior to the first interim analysis within a cohort, the cohort may be stopped early. The estimated time of the final analysis with a maximum of sample size of 108 per cohort will be approximately 16 months after the first participant is enrolled.

Timelines assume the 2 cohorts will enroll participants at a reasonably similar pace. In reality, enrollment of 1 cohort could be much slower than the other cohort. Enrollment will not be paused in either cohort if its enrollment is faster. The similarity of 2 treatment cohorts will be continuously evaluated after at least 36 participants have completed a minimum of 15 weeks of follow-up in each cohort. If at an interim analysis the difference of Grade 3 or higher pneumonitis rates is observed within 1% between 2 cohorts, then the 2 cohorts will be considered similar, and be combined for study analysis. The trial stops when a stopping rule is met or once 108 participants have been enrolled. If combination rule is not met, the analysis will be based on each cohort.

Table 16 Decision Rules for Stopping the Trial for Low Percentage of Participants with Grade 3 or Higher Pneumonitis

Monitoring Points (# Participants)	#Participants with Grade 3 or higher Pneumonitis to Conclude the Rate <10%	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size
36-39	-	--	--
40 – 56	0	0% (0%, 7.2%) for N=40	0% (0%, 5.2%) for N=56
57 – 73	1 or less	1.8% (0.1%, 8.1%) for N=57	1.4% (0.1%, 6.3%) for N=73
74 – 90	2 or less	2.7% (0.5%, 8.3%) for N=74	2.2% (0.4%, 6.8%) for N=90
91 – 107	3 or less	3.3% (0.9%, 8.3%) or N=91	2.8% (0.8%, 7.1%) for N=107
108	4 or less	3.7% (1.3%, 8.3%) for N=108	--

Abbreviations: CI = confidence interval
Decision rule for stopping the trial is not applicable due to insufficient sample size if only 36-39 participants are available.
Monitoring points will be based on number of the participants in APaT population.
Initial interim analysis will be performed for each cohort, respectively. Once the combination rule is met, two cohorts will be pooled for evaluation at the bound specified.
Design assumes overall Type I error of 5% (1-sided) at true rate of 10% and 83% power at true rate of 3%.
[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Table 17 Decision Rules for Stopping the Trial for High Percentage of Participants with Grade 3 or Higher Pneumonitis

Monitoring Points (# Participants)	# Participants with Grade 3 or Higher Pneumonitis to conclude Rate >3%	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size
36 – 46	5 or higher	13.9% (5.6%, 27.0%) for N=36	10.9% (4.4%, 21.5%) for N=46
47 – 63	6 or higher	12.8% (5.7%, 23.7%) for N=47	9.5% (4.2%, 17.9%) for N=63
64 – 80	7 or higher	10.9% (5.3%, 19.6%) for N=64	8.8% (4.2%, 15.8%) for N=80
81 – 97	8 or higher	9.9% (5.0%, 17.1%) N=81	8.2% (4.2%, 14.4%) for N=97
98 – 108	9 or higher	9.2% (4.9%, 15.5%) for N=98	8.3% (4.4%, 14.1%) for N=108

Abbreviations: CI = confidence interval
Monitoring points will be based on number of the participants in APaT population.
Sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, 2 cohorts will be pooled for evaluation at the bound specified.
Design assumes overall Type I error of 5% (1-sided) at true rate of 3% and 83% power at true rate of 10%.
[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Table 18 Decision Rules for Stopping the Trial due to a Low ORR

Monitoring Points (# Participants)	# Participants with Response to Conclude ORR <50%	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size
36 – 37	10 or less	27.8% (15.9%, 42.6%) for N=36	27.0% (15.5%, 41.5%) for N=37
38 – 39	11 or less	28.9% (17.2%, 43.3%) for N=38	28.2% (16.7%, 42.3%) for N=39
40 – 41	12 or less	30.0% (18.3%, 44.0%) for N=40	29.3% (17.8%, 43.1%) for N=41
42- 44	13 or less	31.0% (19.4%, 44.6%) for N=42	29.5% (18.5%, 42.8%) for N=44
45 – 46	14 or less	31.1% (19.9%, 44.3%) for N=45	30.4% (19.4%, 43.4%) for N=46
47 – 48	15 or less	31.9% (20.8%, 44,8%) for N=47	31.3% (20.4%, 44.0%) for N=48
49 – 51	16 or less	32.7% (21.7%, 45.3%) for N=49	31.4% (20.8%, 43.7%) for N=51
52-53	17 or less	32.7% (22.0%, 4.9%) for N=52	32.1% (21.6%, 44.1%) for N=53
54- 56	18 or less	33.3% (22.8%, 45.3%) for N=54	32.1% (21.9%, 43.9%) for N=56
57-58	19 or less	33.3% (23.1%, 45.0%) for N=57	32.8% (22.6%, 44.3%) for N=58
59- 60	20 or less	33.9% (23.7%, 45.3%) for N=59	33.3% (23.3%, 44.7%) for N=60
61-63	21 or less	34.4% (24.4%, 45.7%) for N= 61	33.3% (23.5%, 44.3%) for N= 63
64-65	22 or less	34.4% (24.5%, 45.3%) for N= 64	33.8% (24.1%, 44.7%) for N= 65
66-67	23 or less	34.8% (25.1%, 45.6%) for N= 66	34.3% (24.7%, 45.0%) for N= 67
68-70	24 or less	35.3% (25.7%, 45.9%) for N= 68	34.3% (24.9%, 44.7%) for N= 70
71-72	25 or less	35.2% (25.8%, 45.6%) for N= 71	34.7% (25.4%, 45.0%) for N= 72
73 – 74	26 or less	35.6% (26.3%, 45.8%) for N= 73	35.1% (25.9%, 45.3%) for N= 74
75-77	27 or less	36.0% (26.8%, 46.1%) for N= 75	35.1% (26.0%, 45.0%) for N= 77
78 – 79	28 or less	35.9% (26.9%, 45.8%) for N= 78	35.4% (26.5%, 45.2%) for N= 79
80-82	29 or less	36.3% (27.3%, 46.0%) for N= 80	35.4% (26.6%, 45.0%) for N= 82
83-84	30 or less	36.1% (27.4%, 45.7%) for N= 83	35.7% (27.0%, 45.2%) for N= 84
85 – 86	31 or less	36.5% (27.8%, 45.9%) for N= 85	36.0% (27.4%, 45.4%) for N= 86
87 – 89	32 or less	36.8% (28.2%, 46.1%) for N= 87	36.0% (27.5%, 45.1%) for N= 89
90 – 91	33 or less	36.7% (28.2%, 45.8%) for N= 90	36.3% (27.9%, 45.4%) for N= 91
92-93	34 or less	37.0% (28.6%, 46.0%) for N= 92	36.6% (28.2%, 45.6%) for N= 93
94-96	35 or less	37.2% (28.9%, 46.2%) for N= 94	36.5% (28.3%, 45.3%) for N= 96
97 – 98	36 or less	37.1% (28.9%, 45.9%) for N= 97	36.7% (28.6%, 45.5%) for N= 98
99-100	37 or less	37.4% (29.2%, 46.1%) for N= 99	37.0% (28.9%, 45.7%) for N= 100
101-103	38 or less	37.6% (29.6%, 46.2%) for N= 101	36.9% (29.0%, 45.4%) for N= 103
104 – 105	39 or less	37.5% (29.6%, 46.0%) for N= 104	37.1% (29.3%, 45.6%) for N= 105
106-107	40 or less	37.7% (29.9%, 46.1%) for N= 106	37.4% (29.6%, 45.7%) for N= 107
108	41 or less	38.0% (30.1%, 46.3%) for N= 108	--

Abbreviations: CI = confidence interval
Monitoring points will be based on number of the participants in APaT population who either discontinue or have at least 2 tumor imaging during the study.
Sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, two cohorts will be pooled for evaluation at the bound specified.
Design assumes overall Type I error of 5% (1-sided) at true rate of 50%, and 84% power at true rate of 35%.
[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Table 19 Decision Rules for Stopping the Trial due to a High ORR

Monitoring Points (# Participants)	#Participants with Response to Conclude >35%	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size
36 – 38	21 or higher	58.3% (43.3%, 72.3%) for N=36	55.3% (40.7%, 69.1%) for N= 38
39 -40	22 or higher	56.4% (42.1%, 70.0%) for N=39	55.0% (40.9%, 68.5%) for N= 40
41 – 43	23 or higher	56.1% (42.1%, 69.4%) for N=41	53.5% (39.9%, 66.7%) for N= 43
44 -45	24 or higher	54.5% (41.1%, 67.5%) for N=44	53.3% (40.1%, 66.2%) for N= 45
46 – 47	25 or higher	54.3% (41.3%, 67.0%) for N=46	53.2% (40.3%, 65.8%) for N= 47
48 – 50	26 or higher	54.2% (41.4%, 66.6%) for N=48	52.0% (39.5%, 64.3%) for N= 50
51 – 52	27 or higher	52.9% (40.6%, 65.0%) for N=51	51.9% (39.7%, 64.0%) for N= 52
53 – 54	28 or higher	52.8% (40.7%, 64.7%) for N=53	51.9% (39.9%, 63.7%) for N= 54
55 – 57	29 or higher	52.7% (40.9%, 64.4%) for N=55	50.9% (39.3%, 62.4%) for N= 57
58 -59	30 or higher	51.7% (40.2%, 63.1%) for N=58	50.8% (39.5%, 62.2%) for N= 59
60 -61	31 or higher	51.7% (40.3%, 62.9%) for N=60	50.8% (39.6%, 62.0%) for N= 61
62 -64	32 or higher	51.6% (40.5%, 62.6%) for N=62	50.0% (39.1%, 60.9%) for N= 64
65 – 66	33 or higher	50.8% (39.9%, 61.5%) for N=65	50.0% (39.3%, 60.7%) for N= 66
67 – 68	34 or higher	50.7% (40.1%, 61.4%) for N=67	50.0% (39.4%, 60.6%) for N= 68
69 – 71	35 or higher	50.7% (40.2%, 61.2%) for N=69	49.3% (39.0%, 59.6%) for N= 71
72-73	36 or higher	50.0% (39.8%, 60.2%) for N=72	49.3% (39.2%, 59.5%) for N= 73
74 – 76	37 or higher	50.0% (39.9%, 60.1%) for N=74	48.7% (38.8%, 58.7%) for N= 76
77 – 78	38 or higher	49.4% (39.5%, 59.3%) for N=77	48.7% (38.9%, 58.6%) for N= 78
79 – 80	39 or higher	49.4% (39.6%, 59.1%) for N=79	48.8% (39.1%, 58.5%) for N= 80
81- 83	40 or higher	49.4% (39.8%, 59.0%) for N= 81	48.2% (38.7%, 57.8%) for N= 83
84 – 85	41 or higher	48.8% (39.4%, 58.3%) for N= 84	48.2% (38.9%, 57.7%) for N= 85
86- 87	42 or higher	48.8% (39.5%, 58.2%) for N= 86	48.3% (39.0%, 57.6%) for N= 87
88 -90	43 or higher	48.9% (39.7%, 58.1%) for N= 88	47.8% (38.7%, 56.9%) for N= 90
91 -92	44 or higher	48.4% (39.3%, 57.5%) for N= 91	47.8% (38.9%, 56.9%) for N= 92
93 – 94	45 or higher	48.4% (39.5%, 57.4%) for N= 93	47.9% (39.0%, 56.8%) for N= 94
95 – 97	46 or higher	48.4% (39.6%, 57.3%) for N= 95	47.4% (38.7%, 56.2%) for N= 97
98 – 99	47 or higher	48.0% (39.3%, 56.7%) for N= 98	47.5% (38.9%, 56.2%) for N= 99
100 – 102	48 or higher	48.0% (39.4%, 56.7%) for N= 100	47.1% (38.6%, 55.7%) for N= 102
103 -104	49 or higher	47.6% (39.1%, 56.1%) for N= 103	47.1% (38.7%, 55.6%) for N= 104
105 – 106	50 or higher	47.6% (39.3%, 56.1%) for N= 105	47.2% (38.9%, 55.6%) for N= 106
107 – 108	51 or higher	47.7% (39.4%, 56.0%) for N= 107	47.2% (39.0%, 55.6%) for N= 108

Abbreviations: CI = confidence interval
Monitoring points will be based on number of the participants in APaT population who either discontinue or have at least 2 tumor imaging during the study.
Sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, two cohorts will be pooled for evaluation at the bound specified.
Design assumes overall Type I error of 5% (1-sided) at true rate of 35%, and 84% power at true rate of 50%. Trial is not necessary to stop if the ORR is greater than upper bound.
[a] 90% CIs based on Clopper-Pearson (exact) method are provided

The interim analyses will be performed by the clinical Biostatistics Department of the Sponsor internally and data will be monitored closely by the study team. The DMC will serve as an additional reviewer of the results of the interim analyses and will make recommendations to the EOC to continue, modify, or end the study according to the protocol, considering overall risk benefit to study participants. The DMC responsibilities, review schedules, and additional logistical details will be provided in the DMC Charter.

9.8 Multiplicity

Although there are 2 primary endpoints, there is only 1 hypothesis in the study. There are 2 cohorts in the study, testing of each cohort is controlled by 5% of Type I error (1-sided). Because this is a Phase 2 study, no multiplicity adjustment is planned to control the overall Type I error for the testing of the two cohorts.

Sequential monitoring approach will be used to handle multiplicity issue in interim analyses.

9.9 Sample Size and Power Calculations

Approximately 216 total participants in 2 cohorts (108 participants per cohort) will be enrolled to receive pembrolizumab in combination with platinum-based chemo-radiotherapy. With an approximate maximum of 108 participants enrolled within each cohort, the study provides 83% power to demonstrate that the percentage of participants with Grade 3 or higher pneumonitis is less than 10% if the true rate of Grade 3 or higher pneumonitis is 3% at an overall one-sided 5% alpha-level. During sequential testing, the study also provides 83% power to demonstrate that the percentage of participants with Grade 3 or higher pneumonitis is greater than 3% if the true rate of Grade 3 or higher pneumonitis is 10% at an overall one-sided 5% alpha-level.

The power calculation is based on the binomial SPRT function in the gsDesign package and is carried out using R assuming a null pneumonitis rate of 10%, and alternative pneumonitis rate of 3%, 1-sided type I error of 0.05 and type II error of 0.05 (bionmialSPRT(p0=0.03, p1=0.10, alpha=0.05, beta=0.05, minn=36, maxn=108)). The average sample size needed for the binomial sequential testing procedure within each cohort ranges from 69 to 81 if the true pneumonitis rate is between 3% and 10%. Table 20 summarizes the power and average sample size under various assumptions for pneumonitis.

Table 20 Operating Characteristics of the Sequential Monitoring Approach (Percentage of Participants with Grade 3 or Higher Pneumonitis)

True Rate	Probability of stopping to conclude percentage < 10%	Probability of stopping to conclude percentage >3%	Average Sample Size
3%	0.83	0.02	69
4%	0.65	0.08	77
5%	0.47	0.18	81
6%	0.31	0.31	81
7%	0.20	0.47	77
8%	0.12	0.61	72
9%	0.07	0.74	66
10%	0.04	0.83	60

Using sequential testing, with an approximate maximum of 108 participants enrolled within each cohort, the study also provides 84% power to demonstrate that the ORR exceeds 35% at an overall one-sided 5% alpha-level, if the true ORR is 50%. The study also provides 84% chances to demonstrate ORR is less than 50% if true ORR is 35% at overall one-sided 5% alpha-level.

The power calculation is based on the binomialSPRT function in the gsDesign package and is carried out using R assuming a null ORR of 35%, and alternative ORR of 50%, 1-sided type I error of 0.05 and type II error of 0.05 (binomialSPRT(p0=0.35, p1=0.50, alpha=0.05, beta=0.05, minn=36, maxn=108)). The average sample size for binomial sequential testing procedure within each cohort ranges from 61 to 76 if the true ORR is between 35% and 50%. Table 21 summarized the power and average sample size under various assumptions for ORR.

Table 21 Operating Characteristics of the Sequential Monitoring Approach (ORR)

True ORR	Probability of stopping to conclude ORR < 50%	Probability of stopping to conclude ORR > 35%	Average Sample Size
35%	0.84	0.03	62
40%	0.50	0.18	76
45%	0.17	0.51	75
50%	0.03	0.84	61

The sample size of the study will be between 36 and 108 participants per cohort. If the stopping bounds are not reached, the maximum sample size of 108 will provide a 95% CI for percentage of participants with Grade 3 or higher pneumonitis of 3% to 10% with a half-width ranging from 3.2% to 5.7%, and a 95% CI for ORR of 35% to 50% with half-width ranging from 9.0% to 9.4%.

The similarity of the 2 treatment cohorts will be continuously evaluated after at least 36 participants have completed a minimum of 15 weeks of follow-up in each cohort. If at an interim analysis the difference of Grade 3 or higher pneumonitis rates is observed within 1% between 2 cohorts, then the 2 cohorts will be considered similar, and be combined for study analysis. The trial stops when a stopping rule is met or once 108 participants have been enrolled. If combination rule is not met, the analysis will be based on each cohort. The sample size varies due to different enrollment rate in 2 cohorts and whether the 2 cohorts will be combined.

9.10 Subgroup Analyses

The estimate of the treatment effect for the primary endpoints will be estimated and/or plotted within each category of the following classification variables:

- Age category (< 65 versus ≥65 years)
- Sex (female, male)
- Stage (Stage IIIA versus Stage IIIB versus Stage IIIC)
- ECOG performance status (0 versus 1)
- Predominant tumor histology (squamous versus non-squamous)
- Smoking status (never versus former/current smoker)
- PD-L1 status (TPS <1% versus ≥1%)
- Physician choice of treatment in non-squamous participants

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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 to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and

conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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 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 External Data Monitoring Committee

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

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

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

10.1.8 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 Conference on Harmonization 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 signed ICF, 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.

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

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

a. Participants for Enrollment

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

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

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

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 this substudy. 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

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@merck.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

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

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

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

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

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@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Conference on Harmonization [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

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 two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 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 amenorrhoea method (LAM).
        - Male condom with cap, diaphragm or sponge with spermicide.
        - Male and female condom cannot be used together.
    - 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 22 during the protocol-defined time frame in Section 5.1.

Table 22 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] ● 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 at least 180 days after the last dose of study medication in Cycles 1 through 3 or for 120 days after the last dose of study medication in Cycle 4 through the end of treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test within 72 hours prior to treatment allocation. Note: Pregnancy tests within 24 hours prior to randomization or treatment allocation to determine eligibility will be required only in those regions where this is required via documented regulatory request, subsequently approved by the Sponsor.

Following initiation of treatment additional pregnancy testing will be performed following local regulations and guidelines during the treatment period and at least 180 days after the last dose of study medication in Cycles 1 through 3 or for 120 days after the last dose of study medication in Cycle 4 through the end of treatment. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

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 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 meeting the AE definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are 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 treatment administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Signs, symptoms, or the clinical sequelae of a suspected overdose of either study 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). 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

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 room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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.

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 4.0. 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 his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 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.

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: ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

10.6 Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 23 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator, required by local regulations, or as per approved chemotherapy local practice or label.

Table 23 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit PT/INR and aPTT/PTT	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN) or urea if BUN is not available or acceptable [a]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose, nonfasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal) • Pregnancy test, as needed for women of childbearing potential (WOCBP) within 72 hours prior to first dose of trial treatment. A serum test can be considered if a urine test is not appropriate. Monthly pregnancy testing should be conducted as per local regulation where applicable. Refer to Appendix 7 for country-specific details			
Other Tests	• Thyroid panel: TSH, T3/FT3, and T4/FT4			
[a.] If urea is obtained instead of BUN, a Sponsor Consultation Form should be completed at screening and submitted to the Clinical Director.				

Investigators must document their review of each laboratory safety report.

10.7 Appendix 7: Country-specific Requirements

France

1.3.2 Cohort B Schedule: Screening and Treatment Cycle 1 to 3

Audiogram to be completed at screening.

5.2 Exclusion Criteria

Cohort A only:

a. Participants who experience hemorrhage from tumor
b. Participants who use phenytoïn, or fosphénytoïn .

Cohort B only:

a. Participants with a hearing impairment
b. Participants with pathologies that are a contraindication to hyperhydration prior to chemotherapy administration.
c. Participants who are unable to tolerate use of phenytoïn

6.5.2 Prohibited Concomitant Medications

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

8.3.6.2 Pregnancy Test

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

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

Participants should be discontinued from study treatment if any of the following AEs occur:

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

10.3 Appendix 3, Contraceptive Guidance and Pregnancy Testing

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

Germany

5.2 Exclusion Criteria

Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required as mandated by local regulation.

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

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

8.3.6.2 Pregnancy Test

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

8.12.1 Screening

Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. Exceptions are HIV, hepatitis, and tuberculosis testing which may be done up to 28 days prior to the first dose of study intervention.

For WOCBP, a urine pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory). Monthly pregnancy testing must be conducted.

10.3 Appendix 3, Contraceptive Guidance and Pregnancy Testing

WOCBP must only be included after a negative highly sensitive urine or serum pregnancy test.

Monthly and end of treatment pregnancy testing must be conducted.

10.6 Appendix 6, Clinical Laboratory Tests

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

Poland

8.3.6.2 Pregnancy Test

Pregnancy testing must be conducted monthly during treatment, at the end of treatment, and through 120 days after the last dose of study medication as per local regulations.

10.3 Appendix 3, Contraceptive Guidance and Pregnancy Testing

Pregnancy testing must be conducted monthly during treatment, at the end of treatment, and through 120 days after the last dose of study medication as per local regulations.

United Kingdom

1.3.2 Cohort B Schedule: Screening and Treatment Cycle 1 to 3

Audiogram to be completed at screening.

Full and directed physical examinations are to include neurologic examination performed by the treating physician or designee.

6.5.2 Prohibited Concomitant Medications

Live vaccines are prohibited through 3 months after the end of study treatment.

Caution must be exercised when administering cisplatin together with other nephrotoxic agents (eg, aminoglycosides, diuretics, antihypertensives, other chemotherapy specified in the study, anti-gout therapy) or ototoxic agents (eg, aminoglycosides, loop diuretics) and dose reductions of such concomitant treatments should be considered.

8.3.1.1 Full Physical Exam

Participants in Cohort B who are receiving cisplatin will have a neurologic examination performed by the treating physician or designee at the time of the full physical examination.

8.3.1.2 Directed Physical Exam

Participants in Cohort B who are receiving cisplatin will have a neurologic examination performed by the treating physician or designee at the time of the directed physical examination, while cisplatin treatment is ongoing.

8.3.6.2 Pregnancy Test

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

10.3 Appendix 3, Contraceptive Guidance and Pregnancy Testing

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

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
3DCRT	3-dimensional conformal radiotherapy
ABC	active breathing device
ADA	anti-pembrolizumab antibodies
AE	adverse event
ALT	alanine aminotransferase
APAT	All Participants as Treated
AST	aspartate aminotransferase
AUC	area under curve
BCG	Bacillus Calmette-Guérin
BICR	Blinded independent central review
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
cCTRT	concurrent chemotherapy with radiotherapy
CONSORT	Consolidated Standards of Reporting Trials
CP	carboplatin and pemetrexed
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic t-lymphocyte-associated protein 4
CTV	clinical target volume
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EBUS	endobronchial ultrasound
ECG	electrocardiogram

Abbreviation	Expanded Term
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EUS	endoscopic ultrasound
FDAAA	Food and Drug Administration Amendments Act
FDG	fluorodeoxyglucose
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GTV	Gross tumor volume
Gy	Gray
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
iCPD	immune confirmed progressive disease
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	investigational medicinal product
IMRT	intensity modulated radiotherapy
IND	investigational new drug

Abbreviation	Expanded Term
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapeutics
ITV	internal target volume
IUD	intrauterine device
iUPD	immune unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
KM	Kaplan-Meier
MASCC	Multinational Association of Supportive Care in Cancer
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
MV	megavolts
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically-based pharmacokinetic
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PTV	planning target volume
QA	Quality Assurance
Q2W	every 2 weeks

Abbreviation	Expanded Term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	response rate
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
SLAB	supplemental laboratory test(s)
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
SOC	standard of care
sSAP	supplemental statistical analysis plan
TB	tuberculosis
TPS	tumor proportion score
TRT	thoracic radiotherapy
US	United States
WOCBP	woman/women of childbearing potential

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Supplemental Statistical Analysis Plan (sSAP)

TABLE OF CONTENTS

LISTING OF TABLES

1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization. Separate analysis plans (i.e., separate documents from this sSAP) may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis.

2 SUMMARY OF CHANGES

The sSAP Amendment #3 is based on protocol amendment 3.0 with additional exploratory analyses not specified in protocol SAP as well as clarifications to protocol SAP, to support an additional efficacy interim analysis for a possible regulatory submission as defined in Section 3.7.

Changes from sSAP amendment #2 are listed below:

Section Number	Description of Changes from Protocol
Section 3.5.1	Since all subjects have been enrolled with sufficient follow-up time, primary efficacy analysis population specified in sSAP amendment #2 is not needed. Efficacy data will be analyzed based on APaT population, following protocol amendment #3.
Section 3.6.1.5	Removed the previous primary efficacy analysis population specified in sSAP amendment #2 from efficacy interim analyses and restate the APaT population is to be used for all efficacy analyses.
Section 3.6.1.6	Added details for exploratory analysis of time to distant metastasis.
Section 3.6.2	Clarified pneumonitis analysis is based on data reported by investigators, instead of Clinical Adjudication Committee.
Section 3.10	Regarding subgroup analyses, changed the criteria from "less than 10 subjects in either cohort" to "less than 10 subjects in both cohorts".
Section 3.2, 3.3.1, 3,6,1,2, 3.6.1.6	Minor editorial changes.

3 ANALYTICAL AND METHODOLOGICAL DETAILS FOR GLOBAL STUDY

3.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is provided in Sections 3.2-3.11.

Study Design Overview	A Phase 2, open-label, multi-center, nonrandomized, multi-cohort, parallel group, uncontrolled study of pembrolizumab in combination with platinum doublet chemotherapy and standard thoracic radiotherapy in participants with unresectable locally advanced Stage III NSCLC.
Treatment Assignment	Approximately 216 participants will be enrolled into 2 cohorts (108 participants per cohort). The choice of chemotherapy will be determined by the investigator prior to treatment allocation. Participants with squamous NSCLC are eligible only for Cohort A. Cohort A: Participants will receive 1 cycle of carboplatin AUC6 with paclitaxel 200 mg/m^2 and pembrolizumab 200 mg on Day 1. Approximately 3 weeks later participants will receive carboplatin AUC2 with paclitaxel 45 mg/m^2 administered weekly for 6 weeks with 2 cycles of pembrolizumab 200 mg administered every Q3W in conjunction with standard thoracic radiotherapy. To conclude the study treatments, participants will receive an additional 14 cycles of pembrolizumab 200 mg administered Q3W. Cohort B: Participants will receive 3 cycles of cisplatin 75 mg/m^2 with pemetrexed 500 mg/m^2 and pembrolizumab 200 mg on Day 1. Treatment will be given in conjunction with standard thoracic radiotherapy in Cycle 2 and 3. To conclude the study treatments, participants will receive an additional 14 cycles of pembrolizumab 200 mg administered Q3W.
Analysis Populations	Efficacy: All Participants as Treated (APaT) Safety: All Participants as Treated (APaT)
Primary Endpoints	- Grade 3 or higher pneumonitis - Confirmed complete response or partial response based on RECIST 1.1 as assessed by BICR.
Secondary Endpoints	- PFS based on RECIST 1.1 as assessed by BICR - OS
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR and a 90% CI will be provided using the Clopper-Pearson method. Confidence intervals of 80% and 95% will be provided as additional summaries.
Statistical Methods for Key Safety Analyses	For the primary endpoint of percentage of participants with Grade 3 or higher pneumonitis, the point estimate and a 90% CI will be provided using the Clopper-Pearson method. Confidence intervals of 80% and 95% will be provided as additional summaries. The overall analysis of safety will follow a tiered approach. Other than percentage of participants with Grade 3 or higher pneumonitis, there are no Tier 1 safety parameters in this trial. All other safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs based on Clopper-Pearson method. Only point estimates will be provided for Tier 3 safety parameters.

Interim Analyses	Multiple interim analyses based on sequential monitoring procedure will be performed to allow the study to stop if the percentage of participants with Grade 3 or higher pneumonitis is unacceptably high, stop for futility if the ORR is low, or stop to enable rapid progression to Phase 3 if the percentage of participants with Grade 3 or higher pneumonitis is very low and the ORR is high. The decision rule and other statistical details are further described in Section 3.7. The 2 cohorts might be combined for the study analysis if the pneumonitis rates in 2 cohorts are similar. Results will be reviewed by an external Data Monitoring Committee (DMC). In addition to interim analyses based on sequential monitoring procedure, additional efficacy interim analyses may be conducted to summarize ORR results.
Multiplicity	No multiplicity adjustment is planned to control the overall type I error for the testing of the two cohorts. Sequential monitoring approach will be used to handle multiplicity issue in interim analysis.
Sample Size and Power	The planned sample size is approximately 216 participants in 2 treatment cohorts (108 participants per cohort). At overall one-sided 5% alpha level and with maximum sample size of 108, the study will provide 83% power to demonstrate Grade 3 or higher pneumonitis is less than 10% if the true rate is 3% in a cohort.

3.2 Responsibility for Analyses/In-House Blinding

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

The trial will be conducted as an open-label study. There is no randomization in the study. The treatment assignment and allocation will be tracked in interactive response technology.

Planned interim analyses are described in Section 3.7.

To supplement the study monitoring outlined in the protocol, an external DMC will monitor the interim data from this study. The details regarding the external DMC are provided in section 10.1.7 of the protocol and in DMC charter. The interim analyses performed by the Clinical Biostatistics Department of the Sponsor internally will be reviewed by DMC periodically. The DMC will make recommendations to the Executive Oversight Committee (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, and recommend to the EOC whether the study should continue in accordance with the protocol.

3.3 Hypotheses/Estimation

3.3.1 Primary Objective(s) & Hypothesis(es)

Throughout this document, the term RECISIT 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of target lesions per organ. Refer to section protocol 8.2.1.4 for further details.

In adult participants with unresectable, locally advanced, Stage III NSCLC treated with pembrolizumab in combination with platinum doublet chemotherapy and standard thoracic radiotherapy followed by pembrolizumab monotherapy (with investigator's choice of platinum doublet chemotherapy):

1. **Objective:** Within each platinum doublet chemotherapy cohort, evaluate the percentage of participants who develop Grade 3 or higher pneumonitis.

   Hypothesis: Within each platinum doublet chemotherapy cohort, the percentage of participants who develop Grade 3 or higher pneumonitis is <10%

2. **Objective:** Within each platinum doublet chemotherapy cohort, estimate the ORR as assessed by BICR according to RECIST 1.1.

3.3.2 Secondary Objective(s) & Hypothesis(es)

In adult participants with unresectable, locally advanced, Stage III NSCLC treated with pembrolizumab in combination with platinum doublet chemotherapy and standard thoracic radiotherapy followed by pembrolizumab monotherapy (with investigator's choice of platinum doublet chemotherapy):

1. **Objective:** Within each platinum doublet chemotherapy cohort, evaluate the PFS assessed by BICR according to RECIST 1.1.

2. **Objective:** Within each platinum doublet chemotherapy cohort, evaluate OS

3. **Objective:** Within each platinum doublet chemotherapy cohort, evaluate the safety and tolerability of each treatment regimen by the percentage of participants who develop AEs.

3.3.3 Exploratory Objectives

In adult participants with unresectable, locally advanced, Stage III NSCLC treated with pembrolizumab in combination with platinum doublet chemotherapy and standard thoracic radiotherapy followed by pembrolizumab monotherapy (with investigator's choice of platinum doublet chemotherapy):

1) Objective: Within each platinum doublet chemotherapy cohort, evaluate time to distant metastases per RECISIT 1.1 based on BICR.

2) Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab in combination with platinum doublet chemotherapy and radiotherapy.

3.4 Analysis Endpoints

3.4.1 Primary Endpoints

Grade 3 or higher pneumonitis: percentage of participants who have developed Grade 3 to 5 pneumonitis.

Confirmed complete response or partial response: Objective response rate (ORR) is the proportion of participants who have a confirmed CR or PR per RECIST 1.1 based on BICR.

3.4.2 Secondary Endpoints

Progression-Free Survival: the time from enrollment (i.e. the date of the first study medication) to the first documented local recurrence or distant metastasis per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 3.6.1 for the definition of censoring.

Overall Survival: the time from enrollment (i.e. the date of the first study medication) to death due to any cause.

Safety and tolerability: AEs and discontinuations due to AEs.

3.4.3 Tertiary/Exploratory Endpoints

1. Time to distant metastases: the time from enrollment (i.e. the date of the first study medication) to the first documented distant metastases per RECISIT 1.1 based on BICR or death due to any cause, whichever occurs first.

2. Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variables, proteomics and immunohistochemistry (IHC), and other biomarkers

3.5 Analysis Populations

3.5.1 Efficacy Analysis Populations

The APaT population will serve as the population for efficacy analysis. All enrolled participants who received at least 1 dose of study treatment will be included in this population. Participants will be analyzed in the treatment cohort corresponding to the originally assigned study treatment, which might be different from the study treatment they actually received.

A sensitivity analysis excluding participants who discontinued from study treatment after 1 cycle due to inability to receive thoracic radiation per protocol will be provided.

3.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled participants who received at least 1 dose of study treatment. Participants will be analyzed in the treatment cohort corresponding to the study treatment they

actually received. For most participants, this will be the study treatment cohort to which they are enrolled. Participants who take incorrect study treatment cohort for the entire treatment period will be included in the treatment corresponding to the study treatment actually received. Any participant who receives the incorrect study medication for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment cohort and a narrative will be provided for any event that occurs during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory measurement obtained subsequent to at least 1 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.

3.6 Statistical Methods

3.6.1 Statistical Methods for Efficacy Analyses

The sequential monitoring procedure will use ORR for the evaluation of efficacy. Additional efficacy interim analyses may be conducted for each individual cohort as well as for the combined cohorts.

3.6.1.1 Objective Response Rate (ORR)

For the primary endpoint of ORR, the point estimate and a 90% CI will be provided using the Clopper-Pearson method [1]. Confidence intervals of 80% and 95% using the Clopper-Pearson method will be provided as additional summaries. Binomial sequential testing will be conducted to evaluate ORR, assuming a null ORR of 35% and alternative ORR of 50%, with 1-sided type I error of 5% and 1-sided type II error of 5%. An ORR of 35% was set as the lower threshold based on historical data and an alternative ORR rate of 50% was set as the upper threshold for monitoring based on the improvement in ORR expected from the study treatment regimen. Participants in APaT population with missing ORR data will be counted as non-responders.

3.6.1.2 Progression-Free Survival (PFS)

For the secondary endpoint of PFS, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Since the disease progression is assessed periodically, PD (either local recurrence or distant metastasis) 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 by BICR. Death is always considered as a 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 the investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECISIT 1.1 as assessed by BICR, 2 sensitivity analyses with a different set of censoring rules from the primary analysis will be performed. For the primary analysis, if the events (PD or death) are immediately after more

than 1 missed disease assessment, the data are censored at the last disease assessment prior to the 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 the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis 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 the primary and sensitivity analyses are summarized in Table 1.

Table 1 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
PD or death documented after ≤1 missed disease assessment, and before new anticancer 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 anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; new anticancer 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 treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment.	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD = progressive disease			

3.6.1.3 Overall Survival (OS)

For the secondary endpoint of OS, the non-parametric KM method will be used to estimate the survival curves. The median estimates from the KM curves will be provided as appropriate. Participants without documented death at the time of analysis will be censored at the last known alive date. In practice, the date of last known contact will be used.

3.6.1.4 Duration of Response (DOR)

For participants who demonstrate confirmed CR or PR, duration of response (DOR) is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR will be analyzed to support ORR analysis.

The DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed response or partial response will be included in this analysis.

For 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 a certain number of months prior to the data cutoff date are considered ongoing responders at the time of analysis. Since tumor imaging schedules vary (every 9 weeks (± 7 days) until Week 54, then every 12 weeks(± 14 days) until Week 150, then every 24 weeks(± 28 days) until PD), the definition of ongoing response may change accordingly; therefore, 5 months prior to the data cutoff date will be used as a criterion to identify ongoing participants when there is no participant who has Week 150 assessment, while 9 months prior to the data cutoff date will be used to identify ongoing participants when there is at least one participant who has Week 150 assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Censoring rules for DOR are summarized in Table 2.

Table 2 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.		

3.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 3 summarizes the primary analysis approach for primary and key secondary efficacy endpoints in the additional efficacy interim analyses. Sensitivity analysis methods are described above for each endpoint as applicable.

Table 3 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variables	Statistical Method	Analysis Population	Missing Data Approach
Primary Efficacy Endpoints			
ORR - RECIST 1.1 by BICR	Exact method based on binomial distribution (Clopper-Pearson method)	APaT Population	Participants with missing data are considered non-responders.
Secondary Efficacy Endpoints			
PFS - RECIST 1.1 by BICR	Summary statistics using KM method	APaT Population	Censored according to rules in Table 1. - Primary censoring rule - Sensitivity analysis 1 - Sensitivity analysis 2
OS	Summary statistics using KM method	APaT Population	Censored at last known alive date

APaT = All Participants as Treated; BICR = blinded independent central review; KM = Kaplan-Meier; ORR=objective response rate; OS = overall survival; PFS=progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors

3.6.1.6 Tertiary/Exploratory Analyses

For the exploratory endpoint of Time to distant metastases, the non-parametric KM method will be used to estimate the survival curves. The median estimates from the KM curves will be provided as appropriate. Participants without documented death or distant metastases per RECISIT 1.1 based on BICR or death at the time of analysis will be censored at the last known alive date. In practice, the date of last known contact will be used.

Distant metastasis can occur any time in the time interval between the last assessment where distant metastasis was not documented and assessment when distant metastasis is documented. The true date of distant metastasis will be approximated by the date of the first assessment at which distant metastasis is objectively documented per RECIST 1.1 by BICR. Death is always considered as a distant metastasis event. Participants who do not experience a distant metastasis event will be censored at the last disease assessment. If the event (distant metastasis or death) is immediately after more than 1 missed disease assessment, the endpoint is censored at the last disease assessment prior to the missing visits. For participants receiving new anti-cancer therapy, the endpoint is censored at the last disease assessment prior to the initiation of new anti-cancer therapy. If participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the analysis of time to distant metastasis is summarized in Table 4.

Table 4 Censoring Rules for Analysis of Time to Distant metastasis

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

For details on analyses of biomarker data and genetic data, a separate document may be developed.

3.6.2 Statistical Methods for Safety Analyses

A treatment-emergent adverse event (TEAE) is defined as an adverse event that had an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug, up to 30 days following the last dose of study drug for non-serious AEs or up to 90 days following the last dose of study drug for serious AEs. All AE analyses will be based on TEAEs.

The percentage of participants with Grade 3 or higher pneumonitis will be evaluated as one of the primary endpoints. Adverse events with either AEOSI category “Pneumonitis” or MedDRA preferred term “Radiation Pneumonitis” are included for pneumonitis analyses. The point estimate and a 90% CI will be provided using the Clopper-Pearson method [1]. Confidence intervals of 80% and 95% will be provided as additional summaries. A percentage of participants with Grade 3 or higher pneumonitis of 10% or more is considered unacceptable, while a rate of 3% or less is considered acceptable for Grade 3 or higher pneumonitis. Binomial sequential testing will be conducted to evaluate pneumonitis, assuming a null pneumonitis rate of 10% and alternative pneumonitis rate of 3% with 1-sided type I error of 5% and 1-sided type II error of 5%. The 2 cohorts may be combined for the safety analysis if the pneumonitis rates in 2 cohorts are similar at interim analysis. All pneumonitis analyses will be based on data reported by investigators. The adjudicated Grade 3-5 pneumonitis data by Clinical Adjudication Committee will not be used for analysis. A list of adjudicated pneumonitis events with adjudicated terms, causalities, and toxicity grades will be provided.

Safety and tolerability will also be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Percentage of participants with Grade 3 or higher pneumonitis is Tier 1 event. Safety parameters including AEs of special interest (AEOSI) will be considered Tier 2 or Tier 3. Tier 2 parameters by cohort and combined treatment group will be assessed via point estimates with 95% CIs based on Clopper-Pearson method; only point estimates by cohort and combined treatment group are provided for Tier 3. Membership in Tier 2 requires that at least 10% participants in any cohort, all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 10% participants is chosen for Tier 2 event because participants enrolled in this study are in critical conditions and usually experience various adverse events of similar types, events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the meaningful interpretation. Because many 95% CIs may be provided without adjustment for multiplicity, the CI should be regarded as helpful descriptive measure to be used in review, not a formal statistical method for AEs and pre-defined limit of change.

Continuous measures such as changes from baseline in laboratory parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by cohort and combined treatment group if appropriate in table format.

Table 5 Analysis Strategy for Safety Parameters Excluding Primary Endpoint (Percentage of Participants with Grade 3 or Higher Pneumonitis)

Safety Tier	Safety Endpoints[†]	p-values	95% CI per Cohort and Combined Treatment Group if Needed	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3 to 5 AE		X	X
	Any serious AE		X	X
	Any drug-related AE		X	X
	Any serious and drug-related AE		X	X
	Any Grade 3 to 5 and drug-related AE		X	X
	Dose modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOC or PDLCs[‡] (incidence ≥10% in one of cohort)		X	X
Tier 3	Specific AEs, SOCs or PDLCs[‡] (incidence <10% in both cohorts)			X
	Change from baseline results (labs)			X

[†] Adverse event references apply to both clinical and laboratory AEs.

[‡] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

AE = adverse event; CI = confidence interval; PDLC = Pre-defined limits of change; SOC = system organ class; X = results will be provided.

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of participants screened, allocated, the primary reasons for screening failure, and primary reasons for discontinuation will be displayed. Demographic variables, baseline characteristics, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables by cohort and combined treatment group if appropriate.

Impacts of COVID-19 will be evaluated or summarized if applicable. Discontinuations, protocol deviation, adverse events, and deaths associated with COVID-19 may be either summarized or listed as appropriate.

3.7 Interim Analysis

Continuous assessment using binomial sequential testing will be performed in the study to allow either treatment cohort to stop if the percentage of participants with Grade 3 or higher pneumonitis is unacceptably high (Table 7), stop for futility if the ORR is low (Table 8), or stop to enable rapid progression to Phase 3 if the percentage of participants with Grade 3 or higher pneumonitis is very low (Table 6) and the ORR is high (Table 9). In practice, a cohort will stop accrual if the stopping rule is met prior to full enrollment.

The sequential assessment will start when at least 36 participants have a minimum of 15 weeks of follow up in either cohort. If the rates of enrollment in two cohorts are different, the sequential assessment will start when the first cohort meets these criteria. The sequential monitoring procedure with binomial sequential testing [2] will be used to evaluate for percentage of participants with Grade 3 or higher pneumonitis and ORR according to rules outlined in Table 6 through Table 9. In the evaluation of pneumonitis, number of participants in APaT population will be considered as the monitoring point in the binomial sequential testing (Table 6 and Table 7). In the evaluating of ORR, number of participants in APaT population, who have a minimum of 15 weeks of follow-up, will be considered as the monitoring point in the binominal sequential testing (Table 8 and Table 9). If one of two cohorts is dropped due to high pneumonitis rate or low ORR rate, the remaining cohort will continue as planned.

The estimated time for the sequential monitoring procedure to start will be approximately 9 months after the first participant is enrolled. However, the incidence of Grade 3 or higher pneumonitis will be closely monitored throughout the study. If Grade 3 or higher pneumonitis is observed in 5 or more participants prior to the first interim analysis within a cohort, the cohort may be stopped early. The estimated time of the final analysis with a maximum of sample size of 108 per cohort would be approximately 16 months after the first participant is enrolled.

Timelines assume the 2 cohorts will enroll participants at a reasonably similar pace. In reality, enrollment of 1 cohort could be much slower than the other cohort. Enrollment will not be paused in either cohort if its enrollment is faster. The similarity of 2 treatment cohorts will be continuously evaluated after at least 36 participants have completed a minimum of 15 weeks of follow-up in each cohort. If at an interim analysis the observed difference of Grade 3 or higher pneumonitis rates is within 1% between 2 cohorts, then the 2 cohorts will be considered similar, and be combined for safety analysis. The trial stops when a stopping rule is met or once 108 participants have been enrolled. If combination rule is not met, the analysis will be based on each cohort.

Table 6 Decision Rules for Stopping the Trial for Low Percentage of Participants with of Grade 3 or Higher Pneumonitis

Monitoring Points (# Participants)	#Participants with Grade 3 or higher Pneumonitis to Indicate Low Pneumonitis Rate	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size
36 – 39	-	--	--
40 – 56	0	0% (0%, 8.0%) for N=36	0% (0%, 5.2%) for N=56
57 – 73	1 or less	1.8% (0.1%, 8.1%) for N=57	1.4% (0.1%, 6.3%) for N=73
74 – 90	2 or less	2.7% (0.5%, 8.3%) for N=74	2.2% (0.4%, 6.8%) for N=90
91 – 107	3 or less	3.3% (0.9%, 8.3%) or N=91	2.8% (0.8%, 7.1%) for N=107
108	4 or less	3.7% (1.3%, 8.3%) for N=108	--

Abbreviations: CI = confidence interval

Decision rule for stopping the trial is not applicable due to insufficient sample size if only 36-39 participants are available. Monitoring points will be based on number of the participants in APaT population.

The sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, two cohorts will be pooled for evaluation at the bound specified.

Design assumes overall Type I error of 5% (1-sided) at null hypothesis rate of 10% and 83% power at true rate of 3%.

[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Table 7 Decision Rules for Stopping the Trial for High Percentage of Participants with Grade 3 or Higher Pneumonitis

Monitoring Points (# Participants)	# Participants with Grade 3 or Higher Pneumonitis to indicate High Pneumonitis Rate	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size	Boundary Rates (90% CIs[a]) for the Corresponding Sample Size
36 – 46	5 or higher	13.9% (5.6%, 27.0%) for N=36	10.9% (4.4%, 21.5%) for N=46
47 – 63	6 or higher	12.8% (5.7%, 23.7%) for N=47	9.5% (4.2%, 17.9%) for N=63
64 – 80	7 or higher	10.9% (5.3%, 19.6%) for N=64	8.8% (4.2%, 15.8%) for N=80
81 – 97	8 or higher	9.9% (5.0%, 17.1%) for N=81	8.2% (4.2%, 14.4%) for N=97
98 – 108	9 or higher	9.2% (4.9%, 15.5%) for N=98	8.3% (4.4%, 14.1%) for N=108

Abbreviations: CI = confidence interval

Monitoring points will be based on number of the participants in APaT population.

The sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, 2 cohorts will be pooled for evaluation at the bound specified.

[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Table 8 Decision Rules for Stopping the Trial due to a Low ORR

Monitoring Points (#Participants)	#Participants with Response to Indicate Low ORR	Boundary ORR (90% CIs[a]) for the Corresponding Sample Size	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size
36 – 37	10 or less	27.8% (15.9%, 42.6%) for N=36	27.0% (15.5%, 41.5%) for N=37
38 – 39	11 or less	28.9% (17.2%, 43.3%) for N=38	28.2% (16.7%, 42.3%) for N=39
40 – 41	12 or less	30.0% (18.3%, 44.0%) for N=40	29.3% (17.8%, 43.1%) for N=41
42- 44	13 or less	31.0% (19.4%, 44.6%) for N=42	29.5% (18.5%, 42.8%) for N=44
45 – 46	14 or less	31.1% (19.9%, 44.3%) for N=45	30.4% (19.4%, 43.4%) for N=46
47 – 48	15 or less	31.9% (20.8%, 44,8%) for N=47	31.3% (20.4%, 44.0%) for N=48
49 – 51	16 or less	32.7% (21.7%, 45.3%) for N=49	31.4% (20.8%, 43.7%) for N=51
52-53	17 or less	32.7% (22.0%, 44.9%) for N=52	32.1% (21.6%, 44.1%) for N=53
54- 56	18 or less	33.3% (22.8%, 45.3%) for N=54	32.1% (21.9%, 43.9%) for N=56
57-58	19 or less	33.3% (23.1%, 45.0%) for N=57	32.8% (22.6%, 44.3%) for N=58
59- 60	20 or less	33.9% (23.7%, 45.3%) for N=59	33.3% (23.3%, 44.7%) for N=60
61-63	21 or less	34.4% (24.4%, 45.7%) for N= 61	33.3% (23.5%, 44.3%) for N= 63
64-65	22 or less	34.4% (24.5%, 45.3%) for N= 64	33.8% (24.1%, 44.7%) for N= 65
66-67	23 or less	34.8% (25.1%, 45.6%) for N= 66	34.3% (24.7%, 45.0%) for N= 67
68-70	24 or less	35.3% (25.7%, 45.9%) for N= 68	34.3% (24.9%, 44.7%) for N= 70
71-72	25 or less	35.2% (25.8%, 45.6%) for N= 71	34.7% (25.4%, 45.0%) for N= 72
73 – 74	26 or less	35.6% (26.3%, 45.8%) for N= 73	35.1% (25.9%, 45.3%) for N= 74
75-77	27 or less	36.0% (26.8%, 46.1%) for N= 75	35.1% (26.0%, 45.0%) for N= 77
78 – 79	28 or less	35.9% (26.9%, 45.8%) for N= 78	35.4% (26.5%, 45.2%) for N= 79
80-82	29 or less	36.3% (27.3%, 46.0%) for N= 80	35.4% (26.6%, 45.0%) for N= 82
83-84	30 or less	36.1% (27.4%, 45.7%) for N= 83	35.7% (27.0%, 45.2%) for N= 84

Monitoring Points (#Participants)	#Participants with Response to Indicate Low ORR	Boundary ORR (90% CIs[a]) for the Corresponding Sample Size	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size
85 – 86	31 or less	36.5% (27.8%, 45.9%) for N= 85	36.0% (27.4%, 45.4%) for N= 86
87 – 89	32 or less	36.8% (28.2%, 46.1%) for N= 87	36.0% (27.5%, 45.1%) for N= 89
90 – 91	33 or less	36.7% (28.2%, 45.8%) for N= 90	36.3% (27.9%, 45.4%) for N= 91
92-93	34 or less	37.0% (28.6%, 46.0%) for N= 92	36.6% (28.2%, 45.6%) for N= 93
94-96	35 or less	37.2% (28.9%, 46.2%) for N= 94	36.5% (28.3%, 45.3%) for N= 96
97 – 98	36 or less	37.1% (28.9%, 45.9%) for N= 97	36.7% (28.6%, 45.5%) for N= 98
99-100	37 or less	37.4% (29.2%, 46.1%) for N= 99	37.0% (28.9%, 45.7%) for N= 100
101-103	38 or less	37.6% (29.6%, 46.2%) for N= 101	36.9% (29.0%, 45.4%) for N= 103
104 – 105	39 or less	37.5% (29.6%, 46.0%) for N= 104	37.1% (29.3%, 45.6%) for N= 105
106-107	40 or less	37.7% (29.9%, 46.1%) for N= 106	37.4% (29.6%, 45.7%) for N= 107
108	41 or less	38.0% (30.1%, 46.3%) for N= 108	--

Abbreviations: CI = confidence interval
Monitoring points will be based on number of the participants in APaT population who have a minimum of 15 weeks of follow-up.
The sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, two cohorts will be pooled for evaluation at the bound specified.
[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Table 9 Decision Rules for Stopping the Trial due to a High ORR

Monitoring Points (# Participants)	#Participants with Response to Indicate High ORR	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size
36 – 38	21 or higher	58.3% (43.3%, 72.3%) for N=36	55.3% (40.7%, 69.1%) for N= 38
39 -40	22 or higher	56.4% (42.1%, 70.0%) for N=39	55.0% (40.9%, 68.5%) for N= 40
41 – 43	23 or higher	56.1% (42.1%, 69.4%) for N=41	53.5% (39.9%, 66.7%) for N= 43
44 -45	24 or higher	54.5% (41.1%, 67.5%) for N=44	53.3% (40.1%, 66.2%) for N= 45
46 – 47	25 or higher	54.3% (41.3%, 67.0%) for N=46	53.2% (40.3%, 65.8%) for N= 47
48 – 50	26 or higher	54.2% (41.4%, 66.6%) for N=48	52.0% (39.5%, 64.3%) for N= 50
51 – 52	27 or higher	52.9% (40.6%, 65.0%) for N=51	51.9% (39.7%, 64.0%) for N= 52
53 – 54	28 or higher	52.8% (40.7%, 64.7%) for N=53	51.9% (39.9%, 63.7%) for N= 54
55 – 57	29 or higher	52.7% (40.9%, 64.4%) for N=55	50.9% (39.3%, 62.4%) for N= 57
58 -59	30 or higher	51.7% (40.2%, 63.1%) for N=58	50.8% (39.5%, 62.2%) for N= 59
60 -61	31 or higher	51.7% (40.3%, 62.9%) for N=60	50.8% (39.6%, 62.0%) for N= 61
62 -64	32 or higher	51.6% (40.5%, 62.6%) for N=62	50.0% (39.1%, 60.9%) for N= 64
65 – 66	33 or higher	50.8% (39.9%, 61.5%) for N=65	50.0% (39.3%, 60.7%) for N= 66
67 – 68	34 or higher	50.7% (40.1%, 61.4%) for N=67	50.0% (39.4%, 60.6%) for N= 68
69 – 71	35 or higher	50.7% (40.2%, 61.2%) for N=69	49.3% (39.0%, 59.6%) for N= 71
72-73	36 or higher	50.0% (39.8%, 60.2%) for N=72	49.3% (39.2%, 59.5%) for N= 73
74 – 76	37 or higher	50.0% (39.9%, 60.1%) for N=74	48.7% (38.8%, 58.7%) for N= 76
77 – 78	38 or higher	49.4% (39.5%, 59.3%) for N=77	48.7% (38.9%, 58.6%) for N= 78
79 – 80	39 or higher	49.4% (39.6%, 59.1%) for N=79	48.8% (39.1%, 58.5%) for N= 80
81- 83	40 or higher	49.4% (39.8%, 59.0%) for N= 81	48.2% (38.7%, 57.8%) for N= 83
84 – 85	41 or higher	48.8% (39.4%, 58.3%) for N= 84	48.2% (38.9%, 57.7%) for N= 85

Monitoring Points (# Participants)	#Participants with Response to Indicate High ORR	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size	Boundary ORR (90% CIs [a]) for the Corresponding Sample Size
86- 87	42 or higher	48.8% (39.5%, 58.2%) for N= 86	48.3% (39.0%, 57.6%) for N= 87
88 -90	43 or higher	48.9% (39.7%, 58.1%) for N= 88	47.8% (38.7%, 56.9%) for N= 90
91 -92	44 or higher	48.4% (39.3%, 57.5%) for N= 91	47.8% (38.9%, 56.9%) for N= 92
93 – 94	45 or higher	48.4% (39.5%, 57.4%) for N= 93	47.9% (39.0%, 56.8%) for N= 94
95 – 97	46 or higher	48.4% (39.6%, 57.3%) for N= 95	47.4% (38.7%, 56.2%) for N= 97
98 – 99	47 or higher	48.0% (39.3%, 56.7%) for N= 98	47.5% (38.9%, 56.2%) for N= 99
100 – 102	48 or higher	48.0% (39.4%, 56.7%) for N= 100	47.1% (38.6%, 55.7%) for N= 102
103 -104	49 or higher	47.6% (39.1%, 56.1%) for N= 103	47.1% (38.7%, 55.6%) for N= 104
105 – 106	50 or higher	47.6% (39.3%, 56.1%) for N= 105	47.2% (38.9%, 55.6%) for N= 106
107 – 108	51 or higher	47.7% (39.4%, 56.0%) for N= 107	47.2% (39.0%, 55.6%) for N= 108

Abbreviations: CI = confidence interval
Monitoring points will be based on number of the participants in APaT population who have a minimum of 15 weeks of follow-up.
The sequential monitoring procedure will be performed for each cohort, respectively. Once the combination rule is met, two cohorts will be pooled for evaluation at the bound specified.
Design assumes overall Type I error of 5% (1-sided) at null hypothesis rate of 35%, and 84% power at true rate of 50%. Trial is not necessary to stop if the ORR is greater than upper bound.
[a] 90% CIs based on Clopper-Pearson (exact) method are provided

Additional interim analyses for efficacy may be performed to evaluate ORR by cohort and for the combined cohorts.

The interim analyses will be performed by the clinical Biostatistics Department of the Sponsor internally. Data will be monitored closely by the study team. The DMC will serve as an additional reviewer of the results and will make recommendations to the EOC to continue, modify, or end the study according to the protocol, considering overall risk benefit to study participants.

3.8 Multiplicity

Although there are 2 primary endpoints, there is only 1 hypothesis in the study. There are 2 cohorts in the study, testing of each cohort is controlled by 5% of Type I error (1-sided) Because this is a Phase 2 study, no multiplicity adjustment is planned to control the overall Type I error for the testing of the two cohorts.

Sequential monitoring approach will be used to handle multiplicity issue in interim analyses.

3.9 Sample Size and Power Calculations

Approximately 216 total participants in 2 cohorts (108 participants per cohort) will be enrolled to receive pembrolizumab in combination with platinum-based chemo-radiotherapy. With an approximate maximum of 108 participants enrolled within each cohort, the study provides 83% power to demonstrate that the percentage of participants with Grade 3 or higher pneumonitis is less than 10% if the true rate of Grade 3 or higher pneumonitis is 3% at an overall one-sided 5% alpha-level.

The power calculation is based on the binomial SPRT function in the gsDesign package and is carried out using R assuming a null pneumonitis rate of 10%, and alternative pneumonitis rate of 3%, 1-sided type I error of 0.05 and type II error of 0.05. Since both type I error and type II error are set as 0.05, the binomial SPRT with null pneumonitis rate of 10% and alternative pneumonitis rate of 3% have the same boundary results as the binomial SPRT with null pneumonitis rate of 3% and alternative pneumonitis rate of 10%. Thus, binomialSPRT(p0=0.03, p1=0.10, alpha=0.05, beta=0.05, minn=36, maxn=108) is used for calculation. The average sample size needed for the binomial sequential testing procedure within each cohort ranges from 69 to 81 if the true pneumonitis rate is between 3% and 10%. Table 10 summarizes the power and average sample size under various assumptions for pneumonitis.

Table 10 Operating Characteristics of the Sequential Monitoring Approach (Percentage of Participants with Grade 3 or Higher Pneumonitis)

True Rate	Probability of stopping to Indicate low pneumonitis rate	Probability of stopping to indicate high pneumonitis rate	Average Sample Size
3%	0.83	0.02	69
4%	0.65	0.08	77
5%	0.47	0.18	81
6%	0.31	0.31	81
7%	0.20	0.47	77
8%	0.12	0.61	72
9%	0.07	0.74	66
10%	0.04	0.83	60

Using sequential testing, with an approximate maximum of 108 participants enrolled within each cohort, the study also provides 84% power to demonstrate that the ORR exceeds 35% at an overall one-sided 5% alpha-level, if the true ORR is 50%.

The power calculation is based on the binomialSPRT function in the gsDesign package and is carried out using R assuming a null ORR of 35%, and alternative ORR of 50%, 1-sided type I error of 0.05 and type II error of 0.05 (binomialSPRT(p0=0.35, p1=0.50, alpha=0.05, beta=0.05, minn=36, maxn=108)). The average sample size for binomial sequential testing

procedure within each cohort ranges from 61 to 76 if the true ORR is between 35% and 50%. Table 11 summarized the power and average sample size under various assumptions for ORR.

Table 11 Operating Characteristics of the Sequential Monitoring Approach (ORR)

True ORR	Probability of stopping to indicate low ORR	Probability of stopping to indicate high ORR	Average Sample Size
35%	0.84	0.03	62
40%	0.50	0.18	76
45%	0.17	0.51	75
50%	0.03	0.84	61

The sample size of the study will be between 36 and 108 participants per cohort. If the stopping bounds are not reached, the maximum sample size of 108 will provide a 95% CI for percentage of participants with Grade 3 or higher pneumonitis of 3% to 10% with a half-width ranging from 3.2% to 5.7%, and a 95% CI for ORR of 35% to 50% with half-width ranging from 9.0% to 9.4%.

The similarity of the 2 treatment cohorts will be continuously evaluated after at least 36 participants have completed a minimum of 15 weeks of follow-up in each cohort. If at an interim analysis the observed difference of Grade 3 or higher pneumonitis rate is within 1% between 2 cohorts, then the 2 cohorts will be considered similar, and be combined for safety analysis. The trial stops when a stopping rule is met or once 108 participants have been enrolled. If the combination rule is not met, the analysis will be based on each cohort. The sample size varies due to different enrollment rates in 2 cohorts and whether the 2 cohorts will be combined.

3.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of the treatment effect for the primary endpoint will be estimated and/or plotted within each category of the following classification variables:

- Age category (< 65 versus ≥65 years)
- Sex (female, male)
- Race (white, all others)
- Stage (Stage IIIA versus Stage IIIB versus Stage IIIC)
- ECOG performance status (0 versus 1)
- Predominant tumor histology (squamous versus non-squamous)
- Smoking status (never versus former/current smoker)
- PD-L1 status (TPS <1% versus ≥1%)
- Physician choice of treatment in non-squamous participants

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 in APaT population is less than 10 in both cohorts, 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.

3.11 Extent of Exposure

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

4 REFERENCES

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