Official Protocol Title:	A Phase III, Randomized, Double-blind Trial of Platinum Doublet Chemotherapy +/-Pembrolizumab (MK-3475) as Neoadjuvant/Adjuvant Therapy for Participants with Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer
NCT number:	NCT03425643
Document Date:	29-November-2022

Title Page

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Protocol Title: A Phase III, Randomized, Double-blind Trial of Platinum Doublet Chemotherapy +/- Pembrolizumab (MK-3475) as Neoadjuvant/Adjuvant Therapy for Participants with Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (NSCLC) (KEYNOTE-671)

Protocol Number: 671-11

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

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

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND NUMBER: 116,833

EudraCT NUMBER: 2017-001832-21

Approval Date: 29 November 2022

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 trial 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
Amendment 11	29-NOV-2022	The protocol was amended to add extended annual imaging to the Post-treatment Follow-up Phase and to specify assessments to be conducted during that time period.
Amendment 10	24-MAR-2022	To change the definition of EFS event to utilize investigator assessment as opposed to central review in this double-blind trial.
Amendment 09	23-JUN-2021	The protocol was amended to specify continuation of imaging assessments for participants starting new anticancer therapy who have not yet progressed, incorporate country-specific requirements, and update the dose modification and toxicity management guidelines for immune-related AEs.
Amendment 08 (China-specific)	16-OCT-2020	The protocol was amended to address recommendations from China's regulatory authority regarding the sample size and duration of the Extension Portion of the study in China.
Amendment 07 (China-specific)	26-NOV-2019	The protocol was amended to add China extension and to clarify *EGFR/ALK* testing requirements.
Amendment 06 (Germany-specific)	19-JUL-2019	The protocol was amended to align with the global amendment (671-05).
Amendment 05	18-JUL-2019	The protocol was amended to include Stages IIA and resectable IIIB (N2), to update stratification to Stage II vs Stage III, and to provide additional clarifications throughout the document in order to increase the pool of eligible participants.
Amendment 04 (Germany-specific)	27-AUG-2018	The protocol was amended to align with the global amendment (671-03).

Document	Date of Issue	Overall Rationale
Amendment 03	27-AUG-2018	The protocol was amended to increase the maximum dose of radiotherapy for participants with gross residual disease after surgery or for those participants who do not have surgery, to add a new baseline scan prior to the start of adjuvant pembrolizumab/placebo, to align the SAP with the program standard and to provide additional clarifications throughout the document.
Amendment 02 (Germany specific)	01-MAY-2018	The protocol was amended to align HIV, HBV, HCV, TB, Amylase, Lipase, and pregnancy testing with regulatory requirements at German sites.
Amendment 01	11-APR-2018	The protocol was amended based on the input from the regulatory agency and to align with the pembrolizumab program standard.
Original protocol	07-NOV-2017	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 11

Overall Rationale for the Amendment:

The protocol was amended to add extended annual imaging to the Post-treatment Follow-up Phase and to specify assessments to be conducted during that time period.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
2.4 Schedule of Activities – End of Treatment and Follow-up Visits (Arms A and B)	Added "Year 6 to End of Study" to the Post-treatment Follow-up Phase and specified imaging and safety assessments to be conducted during that time period.	To provide guidance on continued imaging, safety data, and tissue collection for Year 6 to End of Study.
	Added imaging collection to Survival Follow-up Phase and removed statement that imaging was not captured in Survival Follow-up.	To allow for the collection of imaging which may be conducted in Survival Follow-up.
	Changed statement that treatment-related late toxicity may be collected for >90 days instead of 5 years.	Shortened to more accurately reflect duration of treatment-related toxicity in alignment with Section 9.3.
	Added tissue collection.	Added as tissue may be collected at any point during the Post-treatment Phase and should be submitted to central vendor if obtained.

Section # and Name	Description of Change	Brief Rationale
	Corrected formatting of table by bringing up safety assessments to main table rather than previous format of separate table.	Correction.
9.2.1.3 End of Treatment and Follow-up Tumor Imaging 9.10.3.2 Follow-up Visits	Added imaging schedule for Year 6 to End of Study.	To align with revisions to the Schedule of Activities (SoA).
9.1.10.1 Survival Follow-up 9.2.4 Survival Follow-up 9.10.3.3 Survival Follow-up	Added that if imaging is conducted in Survival Follow-up, it is to be collected.	Added to ensure that although per-protocol imaging is not required, any imaging collected during Survival Follow-up is to be submitted.
5.4.1.3 Rationale for Patient-reported Outcomes 9.2.2 Patient-reported Outcomes	Added that ePRO collection continues through Year 5.	Added for clarity.

Section # and Name	Description of Change	Brief Rationale
9.2.1.4 Assessment of Disease	Added that biopsies collected during the Post-treatment Phase are to be submitted.	Added to ensure that if any biopsies are collected in the Post-treatment Phase they will be submitted.
Title Page 12.1 Appendix 1: Study Governance Considerations MSD Code of Conduct for Clinical Trials Throughout document	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
5.3 Beginning and End of Study Definition	Removed example for lost to follow-up and added cross-reference to Sec 8.3. Added definition of study end. Added the European Economic Area (EEA) definition of study start.	To ensure clarity and intent of the section. Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL.

Section # and Name	Description of Change	Brief Rationale
5.4.1.4 Planned Exploratory Biomarker Research	Removed specific reference to pembrolizumab and added broader wording regarding anticancer therapies.	To ensure exploratory biomarker section allows flexibility and current treatment options.
6.1 Inclusion Criteria	Corrected numbering for IC# 6-9.	Correction to ensure numbering in section is accurate.
7.1 Treatments Administered	Added cross-reference to Appendix 7 for country-specific information.	To ensure country-specific information is noted.
7.7.3 Prohibited Concomitant Medications	Added "replication-incompetent" to list of acceptable COVID-19 vaccines.	Added to include Janssen vaccine.
8.3 Lost to Follow-up	Removed the note that a participant is not considered lost to follow-up until the last scheduled visit.	To allow a participant to be considered "lost to follow-up" as appropriate for the study.
9.3 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added text that SAEs associated with medication errors, misuse, or abuse are to be documented.	Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL.

Section # and Name	Description of Change	Brief Rationale
12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added new section with definitions for medication errors, misuse, or abuse are to be documented. Renumbered subsequent sections accordingly.	Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL.
9.3.7 Events of Clinical Interest	Added that ALT/AST elevations are potential DILI events.	Clarity for the investigator/site to define what potential DILI is and to align with this acronym being used in the reporting table.
12.1 Appendix 1: Study Governance Considerations MSD Code of Conduct for Clinical Trials	Throughout appendix, updated to Sponsor's current Code of Conduct wording.	Updated to incorporate current Code of Conduct practices and requirements.

Section # and Name	Description of Change	Brief Rationale
12.7 Appendix 7: Country-specific Requirements China	Added biomarker collection and analysis requirements. Added that enrollment may continue in China after global enrollment is complete. Added that hospitalization is acceptable for treatment if SOC. Added details on urinalysis.	Added at the request of China Health Authority.
12.7 Appendix 7: Country-specific Requirements Japan	Added whether study interventions are considered "test product(s)" in Japan.	Per recent PMDA Regulation changes.
12.7 Appendix 7: Country-specific Requirements United Kingdom	Added that participants assigned male sex at birth are to be advised to seek counselling on sperm storage before starting treatment with pemetrexed, etoposide, and/or platinum-based therapy.	Health Authority standard requirements for United Kingdom.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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LIST OF FIGURES

1. Synopsis

Protocol Title:

Phase III, Randomized, Double-blind Trial of Platinum Doublet Chemotherapy +/- Pembrolizumab (MK-3475) as Neoadjuvant/Adjuvant Therapy for Participants with Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (NSCLC) (KEYNOTE-671)

Short Title:

Chemo +/- Pembrolizumab (MK-3475) as Perioperative Therapy for Stage II, IIIA-Resectable IIIB (N2) NSCLC

Objectives/Hypotheses and Endpoints:

All objectives and hypotheses apply to male/female adult participants (≥18 years of age) with resectable Stages II or IIIA-B (N2) non-small cell lung cancer (NSCLC). Neoadjuvant chemotherapy (NAC) is a platinum doublet chemotherapy of 4 cycles of cisplatin with gemcitabine or pemetrexed.

Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To evaluate event-free survival (EFS) by biopsy assessed by a local pathologist or by investigator-assessed imaging using RECIST 1.1. Hypothesis #1: NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab improves EFS by biopsy assessed by local pathologist or by investigator-assessed imaging using RECIST 1.1 compared to NAC plus placebo followed by surgery and adjuvant placebo.	• EFS is defined as the time from randomization to the first of the following events: disease or local progression, inability to resect tumor, local or distant recurrence, or death (see Section 10.4 for details).
• Objective: To evaluate the overall survival (OS). Hypothesis #2: NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab improves OS compared to NAC plus placebo followed by surgery and adjuvant placebo.	• OS is defined as the time from randomization to death due to any cause.

The study will be considered positive if NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab demonstrates superior EFS or OS at an interim or final analysis compared to NAC plus placebo followed by surgery and adjuvant placebo.	
Secondary	
• Objective: To evaluate the rate of major pathological response (mPR) assessed by blinded central laboratory pathologist following NAC +/- pembrolizumab. Hypothesis #3: NAC plus pembrolizumab improves mPR rate assessed by blinded central laboratory pathologist compared to NAC plus placebo.	• mPR is defined as ≤10% viable tumor cells in the resected primary tumor and all resected lymph nodes.
• Objective: To evaluate the rate of pathological complete response (pCR) in the resected primary tumor and lymph nodes assessed by blinded central laboratory pathologist following NAC +/- pembrolizumab. Hypothesis #4: NAC plus pembrolizumab improves pCR rate assessed by blinded central laboratory pathologist compared to NAC plus placebo.	• pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin stained slides of the resected lung specimen and lymph nodes following completion of neoadjuvant therapy (ie, ypT0/Tis ypN0).
• Objective: To evaluate mean change from baseline in the neoadjuvant phase and in the adjuvant phase in global health status/quality of life (QoL) using the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30.	• The QoL is based on the global health status/QoL scale (items 29 and 30) of the EORTC-QLQ-C30.
• Objective: To evaluate the safety and tolerability of NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab.	• Participant experiencing adverse events (AEs). • Participant discontinuing study drug due to AEs. • Participant experiencing perioperative complications.

Overall Design:

Study Phase	Phase III
Clinical Indication	Neoadjuvant/Adjuvant treatment for participants with Resectable Stage II or IIIA-B (N2) NSCLC
Population	Participants with resectable Stage II or IIIA-B (T3-4N2) NSCLC
Study Type	Interventional
Type of Design	Randomized, multi-site
Type of Control	Placebo-controlled
Study Blinding	Double-blind
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 8.5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 786 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	There are 2 treatment arms: • Treatment Arm A: Neoadjuvant - pembrolizumab (4 cycles) plus chemotherapy (platinum doublet) followed by surgery. Adjuvant - pembrolizumab (13 cycles) o Pembrolizumab: 200 mg fixed dose, intravenously (IV) every 3 weeks (Q3W), in the neoadjuvant and adjuvant treatment periods. o Postoperative radiation therapy (RT) may be administered if microscopic residual disease or gross residual disease remains. • Treatment Arm B: Neoadjuvant - placebo (4 cycles) plus chemotherapy (platinum doublet) followed by surgery. Adjuvant - placebo (13 cycles) o Placebo: intravenously (IV) every 3 weeks (Q3W), in the neoadjuvant and adjuvant treatment periods. o Postoperative radiation therapy (RT) may be administered if microscopic residual disease or gross residual disease remains.

Duration of Participation	Each participant will be in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of 28 days, eligible participants will be stratified and randomized to receive study treatment until one of the conditions for discontinuation of study intervention is met (see Section 8.1). After the end of treatment, each participant will be followed for the occurrence of AEs and participant-reported pregnancy as described under Section 9.3. Participants who discontinue treatment for reasons other than documented disease progression/recurrence will have per protocol post treatment follow-up and imaging for disease status until: disease progression/recurrence is documented by radiograph (utilizing RECIST 1.1) and/or by biopsy when clinically appropriate, consent is withdrawn, or participant is lost to follow-up. All participants will be followed by telephone for overall survival until death, withdraw of consent, or the end of the study.

Study governance considerations are outlined in Appendix 1: Study Governance Considerations. A list of abbreviations used in this document can be found in Appendix 8: List of Abbreviations.

2. Schedule of Activities (SoA)

2.1 Trial Screening Procedures

Trial Period **Visit Number/Title** **Treatment Cycle** **Week** **Scheduled Day (s)**	**Screening**	**Notes:** Participants who discontinue study treatment for reasons other than disease progression will enter Posttreatment Study Follow-up. Participants who discontinue study treatment due to disease progression will enter Safety and Survival Follow-up. Participants may be rescreened once.
Scheduling Window (Days, unless noted)	**-28 to -1**	
Administrative Procedures		
Informed Consent	X	Documented informed consent will be obtained before any protocol-related intervention.
Informed Consent for Future Biomedical Research (FBR; optional)	X	
Participant Identification Card	X	
Inclusion/Exclusion Criteria	X	
Demographics, Disease Details and Complete Medical History (includes substance usage)	X	Substances: tobacco.
Prior/Concomitant Medication Review	X	Prior medications – Record all medications taken within 28 days of first dose as well as medications regularly administered at intervals greater than 28 days prior to first dose. Concomitant medications – Enter new medications started during the study through the posttreatment Safety Follow-up.

Trial Screening Procedures

Trial Period **Visit Number/Title** **Treatment Cycle** **Week** **Scheduled Day (s)**	**Screening**	**Notes:**
Scheduling Window (Days, unless noted)	**-28 to -1**	
Screening Procedures		Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality, include all required anatomy, and performed within 60 days prior to randomization with the exception of the chest/abdomen CT scan, which must be performed within 28 days prior to randomization. These scans will be considered the baseline assessments for the study.
CT Chest and Abdomen	X	If the participant underwent the required CT scans prior to providing documented informed consent and within 28 days prior to randomization, repeat CT scans are not required.
MRI Brain With Contrast	X	If the participant is unable to undergo an MRI, head CT with contrast should be performed. If the participant is unable to have CT contrast, a head CT without contrast is acceptable. If the participant underwent the required brain imaging prior to signing ICF and within 60 days prior to randomization, repeat brain imaging is not required. For each participant, the same modality should be used throughout the study for response evaluation.
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 before randomization, repeat imaging is not required.
Safety Procedures		
Full Physical Examination	X	To be performed by the investigator or qualified designee.
ECOG Performance Status	X	ECOG performance status must be 0 or 1 within 10 days of randomization AND also on the first day of dosing.
Weight, Height and Vital Signs	X	Vital signs to be collected include: temperature, heart rate, respiratory rate, blood pressure.
12-Lead ECG (Local)	X	

Trial Screening Procedures

Trial Period **Visit Number/Title** **Treatment Cycle** **Week** **Scheduled Day (s)** **Scheduling Window (Days, unless noted)**	**Screening** **-28 to -1**	**Notes:**
Urine or Serum β-Human Chorionic Gonadotropin (β-hCG) Pregnancy Test (women of child-bearing potential [WOCBP] only) – as per local standard operating procedure (SOP)	X	Pregnancy testing is required at Screening and 24 hours before administration of every dose of study treatment.
HIV, Hepatitis B And C Screen (Per Site SOP)	X	Testing is not required unless mandated by local health authority.
Hematology	X	Required during Screening (within 10 days before the start of study treatment). After Cycle 1, lab samples can be collected up to 72 hours prior to the next scheduled visit.
Chemistry	X	
Urinalysis	X	Required during Screening (within 10 days before the start of study treatment). After Cycle 1, lab samples can be collected up to 72 hours prior to the next scheduled Cycle.
Coagulation Tests (PT/INR and aPTT/PTT)	X	Required during Screening (within 10 days before the start of study treatment). Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. If clinically indicated, PTT may be performed if the local lab is unable to perform aPTT.
Thyroid Function (TSH, T3/FT3, and T4/FT4)	X	Required during Screening (within 10 days prior to the start of study treatment). After Cycle 1, laboratory samples can be collected up to 72 hours before the next scheduled collection time point.
AE/SAE Review	X	

Trial Period **Visit Number/Title** **Treatment Cycle** **Week** **Scheduled Day (s)**	**Screening**	**Notes:**
Scheduling Window (Days, unless noted)	**-28 to -1**	
Tumor Tissue Sample Collection		
Biopsy (Histology) for diagnosis and biomarkers	X	Tumor tissue (from primary tumor or lymph node) from pretreatment biopsy for Tumor Proportion Score (TPS) and diagnosis testing. Tumor tissue sufficient for histologic determination of PD-L1 TPS must be obtained within 90 days prior to randomization. Common procedures employed to obtain sufficient tissue for histologic examination are: core biopsy of the primary tumor, mediastinoscopic biopsy of lymph nodes with a biopsy forceps, open incisional biopsy of the primary tumor or lymph nodes, and VATs biopsy of the primary tumor or lymph nodes utilizing a biopsy forceps. Other methods that provide sufficient tumor for histology may also be acceptable, seek Sponsor guidance. See the Procedures Manual and Vendor lab manual for additional information. Confirmation from central laboratory that there is an evaluable tissue for TPS is required prior to randomization. Results of PD-L1 testing for stratification will be blinded to study sites.
Tissue Collection for Biomarker Analysis (tested centrally)	X	Tumor tissue from pretreatment biopsy, if available, after TPS testing is performed.
EGFR/ALK testing results	X	Locally performed *EGFR/ALK* results (if available), should be entered into EDC collector.

2.2 Preoperative (Neoadjuvant) Treatment

Trial Period	**Preoperative (Neoadjuvant)**												**Week 13-20**	**Notes:**
Visit Number/Title														
Treatment Cycle	**1**			**2**			**3**			**4**				The maximum interval from the first dose of neoadjuvant therapy to surgery is 20 weeks. If the participant receives fewer than 4 cycles of neoadjuvant therapy, she/he can remain in the study and should undergo surgery within 4-8 weeks following the last dose of protocol therapy and receive adjuvant therapy. Participants who discontinue study treatment for reasons other than disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to disease progression will enter Survival Follow-up. [†]Please see Section 9.1.8 for further details regarding visit windows for Cycles 2 through 4.
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		
Cycle Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		
Scheduling Window (Days, unless noted)	**±3**			**±3[†]**			**±3[†]**			**±3[†]**				
Prior/Concomitant Medication Review	X	X		X	X		X	X		X	X		X	
Treatment Allocation via IVRS	X													Site personnel will access the IVRS prior to dosing on Cycle 1, Day 1 to obtain the participant's allocation/randomization number
Vital Status	←											→		Upon Sponsor request, participants may be contacted for survival information at any time during the study.

Preoperative (Neoadjuvant) Treatment

Trial Period	**Preoperative (Neoadjuvant)**												**Week 13-20**	
Visit Number/Title														
Treatment Cycle	**1**			**2**			**3**			**4**				
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		
Cycle Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		
Scheduling Window (Days, unless noted)	**±3**			**±3†**			**±3†**			**±3†**				
Trial Treatment Administration														Treatment must begin within 3 days of randomization. All study treatments must be initiated on Day 1 of each cycle after all procedures/assessments have been completed. If the participant is unable to receive all the scheduled therapies on Day 1, the non-administered therapies must be initiated within 72 hours of scheduled Cycle Day 1. **Note:** If chemotherapy is interrupted, all 3 therapies (cisplatin, gemcitabine/pemetrexed, and pembrolizumab/placebo) should be withheld for the duration of the interruption. If pembrolizumab/placebo is interrupted, chemotherapy does not have to be withheld. See Section 7.2 for details. Please see Section 9.10.2 for further details regarding visit windows for Cycles 2 through 4.
Pembrolizumab or Placebo	X			X			X			X				
Cisplatin	X			X			X			X				
Pemetrexed	X			X			X			X				Pemetrexed to be used for nonsquamous NSCLC only.
Gemcitabine	X	X		X	X		X	X		X	X			Gemcitabine to be used for squamous NSCLC only.
Surgery													X	Performed as part of planned standard of care (SOC). Participants who do not undergo surgery as originally planned (excluding participants with local disease progression or metastatic disease) should proceed to adjuvant treatment and receive RT followed by planned protocol treatment.

Preoperative (Neoadjuvant) Treatment

Trial Period	**Preoperative (Neoadjuvant)**												**Week 13-20**	
Visit Number/Title														
Treatment Cycle	**1**			**2**			**3**			**4**				
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		
Cycle Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		
Scheduling Window (Days, unless noted)	**±3**			**±3[†]**			**±3[†]**			**±3[†]**				
Tumor Tissue Sample Collection														
Tissue Collection	← As Clinically Indicated →													Biopsies will be obtained for participants with suspected metastatic disease. Samples are to be reviewed by a local pathologist. Samples must also be sent to the central lab for central pathological review. Treatment will be based on the interpretation of the local pathologist.
Efficacy Procedures														
Histopathology (mPR and pCR assessment)													X	Assessment of surgical margins and the resected specimens will be performed by the local pathologist. Samples will be sent to a central lab for evaluation of mPR and pCR.
Preoperative Imaging							X						X	If the participant receives: • **4 cycles:** Imaging 3 weeks after Cycle 2 and 3 weeks after Cycle 4 • **3 cycles:** Imaging 3 weeks after Cycle 2 and 4 weeks after Cycle 3 • **2 cycles:** Imaging 3 weeks after Cycle 2 • **1 cycle:** Imaging 3 weeks after Cycle 1 Note that the imaging window is ± 7 days.

Preoperative (Neoadjuvant) Treatment

Trial Period	Preoperative (Neoadjuvant)												Week 13-20	
Visit Number/Title														
Treatment Cycle	1			2			3			4				
Week	1	2	3	4	5	6	7	8	9	10	11	12		
Cycle Day(s)	1	8	15	1	8	15	1	8	15	1	8	15		
Scheduling Window (Days, unless noted)	±3			±3[†]			±3[†]			±3[†]				
Patient-reported Outcomes (PROs)														
EQ-5D -5L	X										X			PROs should be administered prior to all procedures/assessments. The PROs are to be completed in the following order: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13. If the participant does not complete the PROs for any reason, the reason must be captured. If the participant completes fewer than 4 cycles of neoadjuvant therapy, the PROs should be completed at the last scheduled visit prior to surgery. Collections of all ePROs at 2 different time points must be completed prior to surgery. If the participant does not have surgery (refusal, physician decision, medical illness, etc.), then the second collection of ePROs must be completed within 2 weeks prior to beginning radiotherapy or entering the adjuvant phase.
EORTC QLQ-C30	X										X			
EORTC QLQ-LC13	X										X			

Preoperative (Neoadjuvant) Treatment

Trial Period	**Preoperative (Neoadjuvant)**												**Week 13-20**	
Visit Number/Title														
Treatment Cycle	**1**			**2**			**3**			**4**				
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		
Cycle Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		
Scheduling Window (Days, unless noted)	**±3**			**±3[†]**			**±3[†]**			**±3[†]**				
Safety Procedures														
Directed Physical Examination	X	X		X	X		X	X		X	X			To be performed by the investigator or qualified designee.
ECOG Performance Status	X	X		X	X		X	X		X	X			ECOG performance status must be completed before dosing at each cycle. Prior to Cycle 1, ECOG score must be 0 or 1.
Weight and Vital Signs	X	X		X	X		X	X		X	X			Vital signs to be collected include: temperature, heart rate, respiratory rate, blood pressure.
Urine or Serum β-Human Chorionic Gonadotropin (β-hCG) Pregnancy Test (WOCBP only) – as per local SOP	X			X			X			X				Pregnancy testing is required at Screening and 24 hours prior to administration of every dose of study treatment.

Preoperative (Neoadjuvant) Treatment

Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**			**4**			
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Scheduled Day (s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Scheduling Window (Days, unless noted)	**±3**			**±3†**			**±3†**			**±3†**			
Hematology	X	X		X	X		X	X		X	X		After Cycle 1, lab samples can be collected up to 72 hours prior to the next scheduled cycle. Tests do not need to be repeated at C1D1 if they have been performed within 10 days of study treatment.
Chemistry	X	X		X	X		X	X		X	X		
Urinalysis										X			After Cycle 1, lab samples can be collected up to 72 hours prior to the last scheduled visit prior to surgery.
Coagulation Tests (PT/INR and aPTT/PTT)	← As Clinically Indicated →												Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. If clinically indicated, PTT may be performed if the local lab is unable to perform aPTT. Tests do not need to be repeated at C1D1 if they have been performed within 10 days of study treatment.
Thyroid Function (TSH, T3/FT3, and T4/FT4)					X						X		To be drawn at Week 5, Week 11, and Week 17 (if applicable). After Cycle 1, lab samples can be collected up to 72 hours prior to the next scheduled cycle. Participants may be dosed in subsequent cycles after Cycle 1, Day 1 while thyroid function tests are pending.
AE/SAE Review	← Continuous Reporting →												
CCI													

2.3 Postoperative (Adjuvant Treatment)

Trial Period	Postoperative (adjuvant)								Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-13**	Participants will receive up to 13 cycles of adjuvant therapy. Participants who do not have surgery should have radiotherapy followed by the adjuvant pembrolizumab/placebo treatment phase. Participants who do have surgery and do not receive radiotherapy must begin adjuvant pembrolizumab/placebo treatment within 4-12 weeks following surgery. Participants who have surgery and radiotherapy must begin radiotherapy within 4-8 weeks following surgery. Adjuvant pembrolizumab/placebo must begin within 2-4 weeks following completion of radiotherapy. Participants who do not have surgery should begin radiotherapy within 8 weeks of Day 1 of last chemotherapy cycle. Participants who discontinue study treatment for reasons other than disease progression/recurrence will enter Post-Treatment Study Follow-up. Participants who discontinue study treatment due to disease progression/recurrence will enter Survival Follow-up. Upon completion of adjuvant therapy, participants move into Post-Treatment Study Follow-up. Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to protocol therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays). The reason for interruption should be documented in the participant's record.
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22-37**	
Scheduled Day(s)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures									
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	Concomitant medications – Enter new medications started during the study through the post-treatment Safety Follow up.
Vital Status	⟷								Upon Sponsor request, participants may be contacted for survival information at any time during the study.
Trial Treatment Administration									
Pembrolizumab or Placebo Administration	X	X	X	X	X	X	X	X	To be administered after all procedures/assessments have been completed. Adjuvant therapy should be started within 4-12 weeks following surgery.

Trial Period	Postoperative (adjuvant)								Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-13**	Participants will receive up to 13 cycles of adjuvant therapy. Participants who do not have surgery should have radiotherapy followed by the adjuvant pembrolizumab/placebo treatment phase. Participants who do have surgery and do not receive radiotherapy must begin adjuvant pembrolizumab/placebo treatment within 4-12 weeks following surgery. Participants who have surgery and radiotherapy must begin radiotherapy within 4-8 weeks following surgery. Adjuvant pembrolizumab/placebo must begin within 2-4 weeks following completion of radiotherapy. Participants who do not have surgery should begin radiotherapy within 8 weeks of Day 1 of last chemotherapy cycle. Participants who discontinue study treatment for reasons other than disease progression/recurrence will enter Post-Treatment Study Follow-up. Participants who discontinue study treatment due to disease progression/recurrence will enter Survival Follow-up. Upon completion of adjuvant therapy, participants move into Post-Treatment Study Follow-up. Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to protocol therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays). The reason for interruption should be documented in the participant's record.
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22-37**	
Scheduled Day(s)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Radiotherapy									Participants who have microscopic positive margins or extracapsular nodal extension after surgery should receive radiation therapy to a maximum of 60 Gy. For participants who do not have surgery or who have gross residual disease after surgery, the maximum radiation therapy dose is 70 Gy. Radiotherapy is not allowed for participants with completely resected N2 disease in the absence of extracapsular spread. Radiotherapy must begin within 4-8 weeks after surgery and cannot be administered concomitantly with adjuvant therapy. Adjuvant therapy must be started within 2-4 weeks of completion of radiotherapy. Please see radiotherapy manual for details.

Trial Period	Postoperative (adjuvant)								Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-13**	Participants will receive up to 13 cycles of adjuvant therapy. Participants who do not have surgery should have radiotherapy followed by the adjuvant pembrolizumab/placebo treatment phase. Participants who do have surgery and do not receive radiotherapy must begin adjuvant pembrolizumab/placebo treatment within 4-12 weeks following surgery. Participants who have surgery and radiotherapy must begin radiotherapy within 4-8 weeks following surgery. Adjuvant pembrolizumab/placebo must begin within 2-4 weeks following completion of radiotherapy. Participants who do not have surgery should begin radiotherapy within 8 weeks of Day 1 of last chemotherapy cycle. Participants who discontinue study treatment for reasons other than disease progression/recurrence will enter Post-Treatment Study Follow-up. Participants who discontinue study treatment due to disease progression/recurrence will enter Survival Follow-up. Upon completion of adjuvant therapy, participants move into Post-Treatment Study Follow-up. Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to protocol therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays). The reason for interruption should be documented in the participant's record.
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22-37**	
Scheduled Day(s)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Efficacy Procedures									
Postoperative Imaging	X*	← Every 16 weeks from date of randomization (+/- 14 days)** →							Every 16 calendar weeks (±14 days) from date of randomization. *New baseline CT scans are required PRIOR to the start of adjuvant pembrolizumab/placebo. Please see Section 9.2.1.2 for more details. **May be performed sooner if clinically indicated.

Postoperative (Adjuvant) Treatment

Trial Period	Postoperative (adjuvant)								Notes
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-13**	
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22-37**	
Scheduled Day(s)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Patient-reported Outcomes									
EQ-5D-5L	X	X	X	X			X	X*	ePROs are to be administered prior to all procedures/assessments. PROs are to be completed in the following order: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13. *To be administered at Cycle 10 and Cycle 13.
EORTC QLQ-C30	X	X	X	X			X	X*	
EORTC QLQ-LC13	X	X	X	X			X	X*	
Safety Procedures									
Full Physical Examination	X								
Directed Physical Examination		X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	ECOG performance status must be completed before dosing at each cycle.
Weight and Vital Signs	X	X	X	X	X	X	X	X	Vital signs to be collected include: temperature, heart rate, respiratory rate, and blood pressure.
Urine or Serum β-Human Chorionic Gonadotropin (β-hCG) Pregnancy Test (WCBP only) – as per local SOP	X	X	X	X	X	X	X	X	The protocol requires pregnancy testing within 24 hours prior to every dose of adjuvant treatment.
Hematology	X	X	X	X	X	X	X	X	Laboratory samples can be collected up to 72 hours prior to the next scheduled cycle.
Chemistry	X	X	X	X	X	X	X	X	
Urinalysis	X			X			X	X	Collected within 72 hours prior to Cycles 1, 4, 7, 10 and 13, unless clinically indicated.
Coagulation Tests (PT/INR and aPTT/PTT)	← As Clinically Indicated →								Any participant receiving anticoagulant therapy that requires laboratory testing should have coagulation tests monitored closely throughout the study. PTT may be performed if the local lab is unable to perform aPTT.

Postoperative (Adjuvant) Treatment

Trial Period	Postoperative (adjuvant)								Notes Cycle 13 and Discontinuation Visit can be combined
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-13**	
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22-37**	
Scheduled Day(s)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Thyroid Function (TSH, T3/FT3, and T4/FT4)	X		X		X		X	X	To be drawn every 6 weeks from Cycle 1. Samples can be collected up to 72 hours prior to the next scheduled cycle.
AE/SAE review	← Continuous Reporting →								
CCI									CCI
Tumor Tissue Sample Collection									
Tissue Collection	← As Clinically Indicated →								Biopsies will be obtained for participants with suspected local progression (ie, participants who have not had surgery), metastases, or local recurrence. Samples are to be reviewed by a local pathologist. Samples must also be sent to the central lab for central pathological review. Treatment will be based on the interpretation of the local pathologist.

2.4 End of Treatment and Follow-up Visits (Arms A and B)

Trial Period	End of Treatment	Post-Treatment Follow-up					Survival FU	Notes: Cycle 13 and Discontinuation Visit can be combined. Post-Treatment Follow-up Visit timing should start from the date of last visit, either Discontinuation or Safety Follow-up, whichever is later *See Section 5.3
Treatment Cycle/Day	Discontinuation	Safety FU	Year 2	Year 3	Years 4-5	Year 6 to End of Study*		
Scheduling Window (Days, unless noted)	At time of Treatment Discontinuation	30 days from last dose ±3 days	Q16W ±21 days	Q16W ±21 days	Q6M ±28 days	Q12M ±28 days	Q12 Weeks ± 7 days	
Administrative Procedures								
Prior/Concomitant Medication Review	X	X	← As Clinically Indicated →					
Post-Study Anticancer Therapy Status							X	By telephone contact in Survival FU. Status may be collected more frequently at certain timepoints (refer to Section 9.10.3.3 for details). In addition, upon Sponsor request, participants may be contacted for survival information at any time during the study.
Vital Status	←					→	X	
Efficacy Procedures								
CT Chest and Abdomen	X		X	X	X	X	X*	Imaging timing should follow calendar days (from randomization) and should not be recalculated based on date of previous scans. Imaging is still required for participants who have started a new anticancer treatment. *Participants in Survival Follow-up who have experienced PD should submit SOC imaging to the central vendor. Participants in Survival Follow-up who have not experienced PD should be

Trial Period	End of Treatment	Post-Treatment Follow-up					Survival FU	Notes: Cycle 13 and Discontinuation Visit can be combined. Post-Treatment Follow-up Visit timing should start from the date of last visit, either Discontinuation or Safety Follow-up, whichever is later *See Section 5.3
Treatment Cycle/Day	**Discontinuation**	**Safety FU**	**Year 2**	**Year 3**	**Years 4-5**	**Year 6 to End of Study***		
Scheduling Window (Days, unless noted)	**At time of Treatment Discontinuation**	**30 days from last dose ±3 days**	**Q16W ±21 days**	**Q16W ±21 days**	**Q6M ±28 days**	**Q12M ±28 days**	**Q12 Weeks ± 7 days**	
								given the option of continuing with the protocol-imaging schedule (and if unwilling, SOC images should be submitted).
EQ-5D-5L	X	X	X	X	X			ePROs are to be administered prior to all procedures/assessments. PROs are to be completed in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-LC13.
EORTC QLQ-C30	X	X	X	X	X			
EORTC QLQ-LC13	X	X	X	X	X			
Safety Procedures								
Full Physical Examination	X							
Directed Physical Examination		X	X	X	X			
ECOG Performance Status	X	X	X	X	X			
Weight and Vital Signs	X	X	X	X	X			Vital signs to be collected include: temperature, heart rate, respiratory rate, and blood pressure.
Hematology, Chemistry, Urinalysis	X	X	← As Clinically Indicated →					
Coagulation Tests (PT/INR and aPTT/PTT)	← As Clinically Indicated →							
Thyroid Function (TSH, T3/FT3 and T4)	X	X	← As Clinically Indicated →					
AE/SAE review	← Continuous reporting →							All AEs occurring up until 30 days following end of study treatment and SAEs occurring up until 90 days following end of treatment or 30 days if the participant initiates new

Trial Period	End of Treatment	Post-Treatment Follow-up					Survival FU	Notes: Cycle 13 and Discontinuation Visit can be combined. Post-Treatment Follow-up Visit timing should start from the date of last visit, either Discontinuation or Safety Follow-up, whichever is later *See Section 5.3
Treatment Cycle/Day	Discontinuation	Safety FU	Year 2	Year 3	Years 4-5	Year 6 to End of Study*		
Scheduling Window (Days, unless noted)	At time of Treatment Discontinuation	30 days from last dose ±3 days	Q16W ±21 days	Q16W ±21 days	Q6M ±28 days	Q12M ±28 days	Q12 Weeks ± 7 days	
								anticancer therapy, whichever is earlier should be reported. Treatment-related late toxicity may be collected for >90 days.
Tumor Tissue Sample Collection								
Tissue Collection	←	—	—	—	—	→		Biopsies will be obtained for participants with suspected local progression (ie, participants who have not had surgery), metastases, or local recurrence. Samples are to be reviewed by a local pathologist. Samples must also be sent to the central lab for central pathological review. Treatment will be based on the interpretation of the local pathologist.

3. Introduction

Pembrolizumab (MK-3475) is a potent and highly selective humanized mAb of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2).

3.1 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. Utilizing the eighth edition of the UICC/IASLC lung cancer staging, at the time of diagnosis approximately 63% of patients have clinical Stage IV disease, 9% have Stage I disease, 4% have Stage II, and 27% have Stage III [Chansky, K., et al 2017]. Patients with clinical Stage IIIA disease represent 12% of patients with NSCLC. Similarly, clinical Stage IIIB constitutes 12% of patients with NSCLC. Five-year survival for patients with pathologically determined Stages II, IIIA, and IIIB disease following resection of the tumor approximates 49%, 38%, and 24%, respectively.

Standard treatment for patients with Stage II disease is surgery followed by adjuvant platinum doublet chemotherapy. Numerous trials and meta-analyses have demonstrated a statistically significant 5% improvement in overall survival for patients who received 3-4 cycles of adjuvant chemotherapy [Detterbeck, F. 2008]. Doublets combining platinum with pemetrexed, gemcitabine, vinorelbine or docetaxel have produced similar results [Wakelee, H. A., et al 2016]. Neoadjuvant therapy has also been investigated in patients with Stage II NSCLC. Preoperative chemotherapy is generally better tolerated and permits direct observation of the drug effectiveness. The postoperative morbidity and mortality is not increased. The overall survival benefit is similar to that seen with adjuvant therapy [Hellmann, M. D., et al 2014].

The presence of tumor in the mediastinal (N2) lymph nodes is the stage defining factor for most patients in the Stage IIIA category. However, the time at which the N2 disease is documented (preoperatively vs postoperatively) and the extent of N2 disease determine prognosis and treatment strategies [Kassis, E. S. 2008]. Patients who have a preoperative chest CT and PET that did not suggest metastases to the mediastinal lymph nodes ("falsely negative") and are found to have N2 disease at surgery, have a five-year overall survival of approximately 25% [Detterbeck, F. 2008]. Adjuvant platinum doublet chemotherapy (4 cycles of cisplatin with docetaxel or pemetrexed) improves overall survival by 5% [Detterbeck, F. 2008]. Patients who are found to have N2 disease following biopsy of enlarged mediastinal lymph nodes seen on chest CT and/or biopsy of FDG avid mediastinal lymph nodes have an even worse prognosis. If these patients go directly to surgery, overall five-year survival is 15% [Detterbeck, F. 2008]. Neoadjuvant therapy (chemotherapy ± radiotherapy) has been investigated and recent trials have demonstrated a 25% overall five-

year survival. Neoadjuvant therapy followed by surgery for patients with preoperatively identified N2 disease has become a common therapeutic approach [National Comprehensive Cancer Network 2017]. Patients with Stage IIIB disease are considered potentially operable if the metastases are limited to the N2 lymph nodes. In practice, fewer than 10% of patients with clinical Stage IIIB disease undergo surgery [Chansky, K., et al 2017]. The above discussion regarding treatment of Stage IIIA patients with N2 disease is equally applicable to Stage IIIB patients with N2 disease. Administration of both neoadjuvant and adjuvant chemotherapy has not been adopted, mainly due to the inability of patients to tolerate the toxicity of chemotherapy before and after a thoracic operation.

The current trial builds upon data produced from previous MSD trials and is aligned with the design of other Phase 3 MSD sponsored trials for cancers that incorporate surgery as part of the therapeutic regimen. Comparison of a pembrolizumab-containing arm to current standard of care is necessary in order to demonstrate that pembrolizumab affects the individual study endpoints. A 2-arm trial of neoadjuvant vs. adjuvant pembrolizumab makes the unproven assumption of drug effectiveness. If no difference were to be found between these 2 arms, interpretation of the results would be difficult as both study arms could have been either superior or inferior to standard therapy. Alternatively, a significant difference between the study arms could be explained by the arm with the poorer results performing inferior to the standard of care. A 3-arm trial consisting of neoadjuvant, adjuvant, and standard of care arms would not test the possibility that perioperative (both neoadjuvant and adjuvant) treatment with pembrolizumab is necessary to improve event-free survival and overall survival.

The toxicity profile of pembrolizumab permits prolonged drug administration and allows treatment in the perioperative (both neoadjuvant and adjuvant) setting. KN-522 (breast) and KN-585 (gastric) combine neoadjuvant and prolonged adjuvant pembrolizumab administration. KN-091(lung) incorporates 17 postoperative pembrolizumab cycles. In the metastatic NSCLC setting, the combination of chemotherapy + pembrolizumab produced a greater response rate than chemotherapy alone (KEYNOTE-021) [Langer, C. J., et al 2016]. KN-671 was designed to take advantage of the ability to administer perioperative pembrolizumab and the proven superior response rates produced by the combination pembrolizumab with doublet chemotherapy when compared to chemotherapy alone.

3.2 Background

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

3.2.1 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 programmed cell death protein-1 (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 CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed death-ligand 1 [PD-L2]) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [Nobili, C., et al 2008] [Leffers, N., et al 2009]. Programmed cell death protein-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T-regs and natural killer cells [Nishimura, H., et al 2000] [Pölcher, M., et al 2010]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [Leffers, N., et al 2009] [Suzuki, H., et al 2010] [Chew, V., et al 2010] [Liotta, F., et al 2011]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. Programmed death-ligand 1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. Programmed death-ligand 2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [Suzuki, H., et al 2010]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma [Ropponen, K. M., et al 1997], pancreatic carcinoma [Dudley, M. E., et al 2005], hepatocellular carcinoma [Hunder, N. N., et al 2008], and ovarian carcinoma [Okazaki, T., et al 2001]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in participants with melanoma [Greenwald, R. J., et al 2005].

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma,

and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon-gamma, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Dudley, M. E., et al 2005] [Hamid, Omid, et al 2013] [Peters, S., et al 2012] [Sandler, A. B., et al 2000] [Zatloukal, Petr, et al 2003] [Scagliotti, G. V., et al 2008].

MSD experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

3.2.2 Completed Clinical Studies

Three clinical studies have been conducted to evaluate the efficacy of pembrolizumab monotherapy in the treatment of 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 3 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.

In KEYNOTE-001, a total of 550 NSCLC 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 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 [Garon, E. B., et al 2015].

Pembrolizumab has been generally well tolerated. The most common treatment-related AEs were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events 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 [Garon, E. B., et al 2015].

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 who had experienced disease progression after platinum-containing systemic therapy. Participants were randomized 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.

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 hazard ratios (HR) 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.

In KEYNOTE-010, pembrolizumab was superior to docetaxel in the strongly positive TPS ≥50% stratum with regard to OS, with an 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 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.

KEYNOTE-024:

KEYNOTE-024 was a multicenter, international, randomized, open-label, controlled trial of intravenous (IV) 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%.

First-line treatment with pembrolizumab significantly prolonged PFS (HR 0.50; 95% 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 nonsquamous tumors.

In addition, pembrolizumab was associated with a higher ORR, including a higher CR rate, as well as a longer DOR 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%).

3.2.3 Ongoing Clinical Studies

KEYNOTE-021:

Pembrolizumab has been studied in combination with other agents in NSCLC patients in 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); *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) vs. CP alone as first-line therapy for advanced nonsquamous NSCLC.

KEYNOTE-021 Cohort G contained 123 participants of whom 60 were accrued to the pembrolizumab plus CP arm and 63 to the CP arm. Demographics were generally balanced between treatment arms. 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. In the CP arm, 43 participants discontinued therapy; 32 received subsequent anti-PD-1 therapy as part of crossover (n=20) or off study (n=12). Pembrolizumab plus CP significantly improved ORR (55% vs. 29%; p=0.0016) and PFS (HR 0.53, 95% CI 0.31-0.91, p=0.0102; median 13.0 vs. 8.9 months). Overall survival was similar; 6-month survival rates were 92% in each arm. Without adjusting for exposure, for pembrolizumab plus CP vs. CP, treatment-related AEs led to discontinuation in 10% vs. 13%, were of Grade ≥3 severity in 39% vs. 26%, and led to death in 2% (sepsis, n=1) vs. 3% (sepsis and pancytopenia, n=1 each). The most common any-grade treatment-related AEs were fatigue (64% vs. 40%), nausea (58% vs. 44%), and anemia (32% vs. 53%).

KEYNOTE-042:

This is a multicenter, international, randomized, open-label, controlled trial of IV 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-189:

This is a worldwide, randomized, active-controlled, parallel group, multi-site, double-blind trial of intravenous (IV) pembrolizumab combined with platinum-pemetrexed chemotherapy versus saline placebo combined with platinum-pemetrexed chemotherapy in participants with advanced or metastatic nonsquamous NSCLC who had not previously received systemic

therapy for advanced disease and in whom *EGFR*- or *ALK*-directed therapy was not indicated. The total planned enrollment is 570 participants.

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.

3.2.4 Information on Other Study-Related Therapy

Platinum doublet chemotherapy (4 cycles of cisplatin with gemcitabine or pemetrexed) will be administered along with either pembrolizumab or placebo. For information on cisplatin, gemcitabine, or pemetrexed, please refer to their respective product inserts. The BSA in m^2 for cisplatin, gemcitabine, or pemetrexed should be calculated per local guidance. Please note that the strengths of the locally sourced study treatments may vary based on local country operation.

3.3 Benefit/Risk Assessment

The purpose of this study is to evaluate the safety and efficacy of pembrolizumab in the perioperative setting. As the administration of pembrolizumab with chemotherapy was proven safe and efficacious in KN-021 Cohort G, the Sponsor has chosen to administer pembrolizumab/placebo with each of the preoperative chemotherapy cycles. The current trial has been designed with a total of 17 cycles of pre- and postoperative pembrolizumab/placebo, aligning with the design of other MSD perioperative trials.

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

From the reference safety data in the accompanying Investigator's Brochure (IB)—which includes all participants who received at least one dose of MK-3475 in KN-001 Part B1, B2, B3, D, C, F1, F2, F3; KN-002 (original phase), KN-006, and KN-010—pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications. This is evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%).

Additional details regarding specific benefits and risks for participants in this clinical trial may be found in the accompanying Investigator's Brochure (IB) and Informed Consent documents.

4. Objectives/Hypotheses and Endpoints

All objectives and hypotheses apply to male/female adult participants (≥18 years of age) with resectable Stages II or IIIA-B (N2) non-small cell lung cancer (NSCLC). Neoadjuvant chemotherapy (NAC) is a platinum doublet chemotherapy of 4 cycles of cisplatin with gemcitabine or pemetrexed.

Objective/Hypothesis	Endpoint
Primary	
• Objective: To evaluate event-free survival (EFS) by biopsy assessed by a local pathologist or by investigator-assessed imaging using RECIST 1.1. Hypothesis #1: NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab improves EFS by biopsy assessed by local pathologist or by investigator-assessed imaging using RECIST 1.1 compared to NAC plus placebo followed by surgery and adjuvant placebo.	• EFS is defined as the time from randomization to the first of the following events: disease or local progression, inability to resect tumor, local or distant recurrence, or death (see Section 10.4 for details).
• Objective: To evaluate the overall survival (OS). Hypothesis #2: NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab improves OS compared to NAC plus placebo followed by surgery and adjuvant placebo.	• OS is defined as the time from randomization to death due to any cause.
The study will be considered positive if NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab demonstrates superior EFS or OS at an interim or final analysis compared to NAC plus placebo followed by surgery and adjuvant placebo.	
Secondary	
• Objective: To evaluate the rate of major pathological response (mPR) assessed by blinded central laboratory pathologist following NAC +/- pembrolizumab. • Hypothesis #3: NAC plus pembrolizumab improves mPR rate assessed by blinded central laboratory pathologist compared to NAC plus placebo.	• mPR is defined as ≤10% viable tumor cells in the resected primary tumor and all resected lymph nodes.

Objective/Hypothesis	Endpoint
• Objective: To evaluate the rate of pathological complete response (pCR) in the resected primary tumor and lymph nodes assessed by blinded central laboratory pathologist following NAC +/- pembrolizumab. Hypothesis #4: NAC plus pembrolizumab improves pCR rate assessed by blinded central laboratory pathologist compared to NAC plus placebo.	• pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin stained slides of the resected lung specimen and lymph nodes following completion of neoadjuvant therapy (ie, ypT0/Tis ypN0).
• Objective: To evaluate mean change from baseline in the neoadjuvant phase and in the adjuvant phase in global health status/quality of life (QoL) using the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30.	• The QoL is based on the global health status/QoL scale (Items 29 and 30) of the EORTC QLQ-C30.
• Objective: To evaluate the safety and tolerability of NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab.	• Participant experiencing AEs. • Participant discontinuing study drug due to AEs. • Participant experiencing perioperative complications.
Tertiary/Exploratory	
• Objective: To evaluate changes in health-related QoL assessment from baseline in the neoadjuvant phase and in the adjuvant phase.	• Change from baseline in health-related QoL evaluated using the multi-item and single-item scales of EORTC QLQ-C30 and EORTC QLQ-LC13 scores: o Physical functioning (EORTC QLQC30 items 1-5) o Role functioning (EORTC QLQ C30, items 6-7) o Dyspnea (EORTC QLQC30 item 8) o Cough (EORTC QLQ-LC13 item 31) and o Chest pain (EORTC QLQ-LC13 item 40)

Objective/Hypothesis	Endpoint
• Objective: To characterize health utilities in neoadjuvant and adjuvant phases using EQ-5D-5L.	• Health utilities assessed using EQ-5D-5L.
• 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 plus chemotherapy used as neoadjuvant and in combination with pembrolizumab as adjuvant.	• The relationship between molecular biomarkers and clinical activity that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of the study treatments.

5. Study Design

5.1 Overall Design

This is a randomized, placebo-controlled, double-blind Phase 3 trial of concomitant neoadjuvant platinum doublet chemotherapy plus pembrolizumab (4 cycles) followed by surgery and adjuvant pembrolizumab (13 cycles) vs. concomitant neoadjuvant platinum doublet chemotherapy plus placebo (4 cycles) followed by surgery and adjuvant placebo (13 cycles) for participants with resectable Stage II or IIIA, or IIIB (N2) non-small cell lung cancer (NSCLC). The study will be conducted in conformance with Good Clinical Practices (GCP).

Approximately 786 participants will be randomized in a 1:1 ratio between 2 treatment arms:

(1) Treatment Arm A: Neoadjuvant pembrolizumab plus platinum doublet chemotherapy (4 cycles of cisplatin with gemcitabine or pemetrexed) followed by surgery and adjuvant pembrolizumab (13 cycles).

(2) Treatment Arm B: Neoadjuvant placebo plus platinum doublet chemotherapy (4 cycles of cisplatin with gemcitabine or pemetrexed) followed by surgery and adjuvant placebo (13 cycles).

Stratification factors are as follows:

1) Stage (II, III)

2) TPS (<50%, ≥50%)

3) Histology (Squamous, Nonsquamous)

4) Geographic Region (East Asia, non-East Asia)

Eligibility at Screening will be based on investigator assessment in accordance with the inclusion/exclusion criteria described in Section 6.1 – Inclusion Criteria and 6.2 – Exclusion Criteria.

Preoperative neoadjuvant treatment should begin within 3 days of randomization.

In the preoperative treatment period for Arm A, pembrolizumab IV 200 mg fixed dose Q3W in combination with platinum doublet (cisplatin with gemcitabine or pemetrexed) will be administered for 4 cycles; treatment will begin on Day 1 of each 3-week dosing cycle. For Arm B, a comparative placebo in combination with platinum doublet (cisplatin with gemcitabine or pemetrexed) will be administered during the preoperative treatment period for 4 cycles. During the postoperative treatment period, pembrolizumab IV 200 mg fixed dose Q3W or placebo will be administered for 13 cycles. Participants in either arm will undergo radiation therapy if microscopic residual disease or gross residual disease is present. Radiotherapy is not allowed for participants with completely resected N2 disease in the absence of extracapsular spread. If the participant did not have surgery due to refusal, physician decision, medical illness, or any reason other than local progression or metastatic disease, the participant should receive radiation therapy then continue to the adjuvant phase. Participants whose tumors are found to be unresectable during surgery due to growth into the mediastinum, invasion into major vascular structures, or any other circumstance in which the surgeon is unable to remove the tumor will no longer receive study therapy and will enter Safety and Survival Follow-up. Participants who develop metastatic disease will no longer receive study therapy and will enter Safety and Survival Follow-up.

All participants will have an imaging assessment prior to surgery after Cycle 2 at Week 7 (± 7 days) and after Cycle 4 at Week 13 (± 7 days). All imaging assessments will be evaluated by the investigator and submitted for BICR. Participants will undergo a potentially curative surgical resection performed as part of the local standard of care. Pathological staging will be per AJCC/UICC/IASLC lung cancer staging (8th edition). Assessment of surgical margins will be performed by the local pathologist on all specimen removed during surgery. Samples of tumor tissue collected during the study from participants will be submitted to the designated central laboratories for blinded pathological response assessment and translational research as described in Section 9 –Study Assessments and Procedures.

Adverse events (AE) will be monitored throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Safety follow-up will be performed for participants who receive study treatment and for those with Early Discontinuations. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

There is no crossover treatment phase planned as part of the study design.

The results of the PD-L1 testing will not be communicated to investigators or participants.

The unblinded study treatment arm will not be communicated to investigators or participants until the participant discontinues from the trial due to local progression (participants who have not had surgery), metastases, local recurrence, or study completion.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Data Monitoring Committee and Interim Analyses

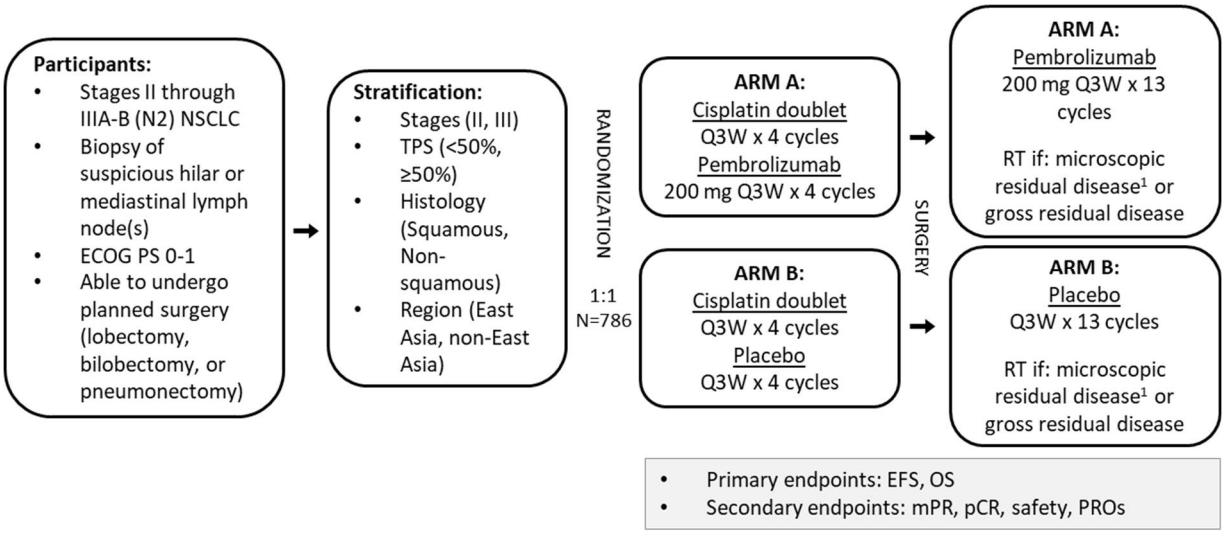
This study will use an external Data Monitoring Committee (DMC) to monitor safety and efficacy. Details of the composition and procedures for the DMC may be found in Appendix 1: Study Governance Considerations and the DMC Charter. The role of the DMC in reviewing interim analysis data is outlined in Section 10.7.

There will be 4 planned interim analyses and 1 final analysis. The first interim analysis will be conducted when approximately 326 EFS events have been observed. The second interim analysis will be conducted when approximately 416 EFS events have been observed. The third and fourth interim analysis will be conducted when approximately 285 and 340 deaths, respectively, have been observed and the final analysis will be conducted when approximately 386 deaths have been observed.

5.1.2 Study Diagram

The study design is depicted in Figure 1.

Figure 1 Study Design



1. Primary tumor - positive margin at bronchus, pulmonary vessels, or structures abutting primary tumor lymph node - extracapsular extension.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; NSCLC = non-small cell lung cancer; PS = performance scale; Q3W = every 3 weeks; mPR = major pathological response; OS = overall survival; pCR = pathological complete response; PRO = participant-reported outcomes; TPS = tumor proportion score

5.2 Number of Participants

Approximately 786 participants will be allocated/randomized as described in Section 10.1.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws from the study or is lost to follow-up (Section 8.3).

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

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

5.3.1 Clinical Criteria for Early Study Termination

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

1. The study may be stopped early for safety at the recommendation of the DMC.
2. The trial may be stopped early for efficacy at the recommendation of the DMC if Arm A demonstrates superiority to Arm B in EFS or OS prior to the final analysis (see Section 10 for details).
3. Quality or quantity of data recording is inaccurate or incomplete as assessed by the Sponsor.
4. Poor adherence to protocol and regulatory requirements.
5. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants.

5.4 Scientific Rationale for Study Design

Neoadjuvant therapy is the standard of care for patients with resectable Stage IIIA (N2) NSCLC identified during initial evaluation in whom surgery is planned [National Comprehensive Cancer Network 2017]. Surgery as initial treatment is standard of care for patient with clinical Stages I-II and some Stage IIIA (not N2) NSCLC. Adjuvant therapy is recommended for those patients whose tumors proved to be pathologic Stage IB (>4cm), II, or IIIA NSCLC [National Comprehensive Cancer Network 2017]). Numerous trials and meta-analyses have demonstrated a statistically significant 5% improvement in overall survival (OS) for patients who received 3-4 cycles of adjuvant chemotherapy [Pignon, J. P., et al 2008]. Doublets combining platinum with pemetrexed, gemcitabine, vinorelbine or docetaxel have produced similar results [Wakelee, H. A., et al 2016].

Though adjuvant therapy has been the standard of care for patients found to have Stages IB (T>4cm), II and IIIA following surgery, administration of neoadjuvant rather than adjuvant therapy has been investigated. Practical and theoretic justification for administration of neoadjuvant therapy to patients with operable NSCLC include: better ability to tolerate therapy and therefore more likely to receive greater amounts of the prescribed treatment, the ability to monitor the effect of therapy on the tumor, shrinkage of the tumor may reduce the extent of surgery, and finally, induction of the abscopal effect to destroy micrometastases.

Neoadjuvant therapy trials have commonly been designed with 2 or 3 cycles of preoperative chemotherapy and no adjuvant therapy. A choice of chemotherapy combinations has generally not been offered and the majority of regimens were platinum based. The modest survival benefits of neoadjuvant therapy in earlier stage disease are similar to those seen when similar treatment is given to the same group of patients in the adjuvant setting [Hellmann, M. D., et al 2014]. Therefore, design of a trial that involves administration of chemotherapy in the neoadjuvant setting may be supported from both a scientific and ethical perspective.

Following the publication of the results of a Phase 3 trial by Scagliotti in 2008, patients with no actionable tumor mutations and Stage IV nonsquamous tumors have commonly been treated with a pemetrexed containing regimen, while those patients with squamous tumors have preferentially been treated with a gemcitabine combination [Scagliotti, G. V., et al 2008]. The use of pemetrexed or gemcitabine based upon histology has been applied to earlier stage disease in both the adjuvant and neoadjuvant settings [Wakelee, H. A., et al 2016]. Gemcitabine and platinum has been safely and efficaciously utilized in a number of neoadjuvant trials [Spaggiari, L., et al 2016] [van Meerbeeck, J. P., et al 2007] [Scagliotti, G. V., et al 2012] [Van Zandwijk, N., et al 2000] as has pemetrexed and platinum [Chaft, J. E., et al 2016] [Scagliotti, G. V., et al 2008]. Cisplatin doublet chemotherapy utilizing pemetrexed and gemcitabine are appropriate to form the backbone chemotherapy for patients with nonsquamous and squamous cell tumors, respectively.

The effect of neoadjuvant therapy on the primary tumor correlates with survival. Retrospective analyses of neoadjuvant therapy studies in NSCLC have consistently demonstrated that those patients who had major pathological responses (mPR) or pathological complete responses (pCR) had the best overall survival (OS) [Hellmann, M. D., et al 2014]. mPR is defined as ≤ 10% viable tumor cells in the primary tumor and all resected lymph nodes. Chemotherapy produces a pCR in approximately 4% of patients and an mPR in approximately 20% [Mouillet, G., et al 2012] [Chaft, J. E., et al 2017] [Junker, K., et al 2001] [Hellmann, M. D., et al 2014]. A recently presented Phase 2 trial of single-agent neoadjuvant nivolumab in patients with resectable Stages I-IIIA NSCLC demonstrated a 43% mPR [Chaft, J. E., et al 2017]. Correlation with radiographic response or survival was not reported.

Keynote-021 Cohort G was a randomized Phase 2 open-label trial of carboplatin and pemetrexed with or without pembrolizumab in patients with advanced, nonsquamous NSCLC. The objective response radiographic rate (ORR) was 55% in patients treated with the 3 drug combination, while ORR was only 29% in the group that received the chemotherapy doublet. The addition of a checkpoint inhibitor to platinum chemotherapy increases the tumor response when compared to chemotherapy alone. OS was not different between the 2 groups, but was not reported separately for those patients who had responded to therapy.

Keynote-024 was an open-label, Phase 3 trial, for patients with previously untreated advanced NSCLC with PD-L1 TPS ≥ 50% comparing pembrolizumab alone to platinum doublet chemotherapy. Pembrolizumab was administered every 3 weeks for 35 cycles. The ORR was 44.8% in the pembrolizumab group and 27.8% in the chemotherapy arm. Median DFS was 10.3 months in the pembrolizumab treated patients and 6.0 months in the chemotherapy group. Correlation of ORR with survival was not reported. In this select group of patients, pembrolizumab outperformed standard doublet chemotherapy.

Additional support for the efficacy of the combination of pembrolizumab and chemotherapy is provided by the recently presented I-SPY 2 trial breast cancer trial. This was a Phase 2 randomized, controlled, multicenter trial for women with newly diagnosed, locally advanced breast cancer (Stage II/III). Patients were treated with weekly standard chemotherapy (paclitaxel) for 12 weeks, with or without pembrolizumab, followed by doxorubicin and cyclophosphamide every 3 weeks for 4 cycles. Forty-six of the 69 patients randomized to receive pembrolizumab underwent surgery.

In the 21 patients with triple-negative breast cancer, an absolute increase in the estimated pCR of 40% was observed in the pembrolizumab arm (based on the estimated pathological complete response rate of 60% with pembrolizumab plus standard therapy compared to 20% with standard therapy alone) [Nanda, R., et al 2017].

The majority of patients with resected Stage II and IIIA NSCLC are destined to suffer tumor recurrence despite the administration of standard adjuvant or neoadjuvant therapy. Survival following neoadjuvant therapy appears to correlate with the extent of the pathological response. The checkpoint inhibitor nivolumab alone produced a 43% mPR and in combination with doublet chemotherapy (in more advanced tumors), a 55% radiographic response. Long-term administration of pembrolizumab in patients with Stage IV disease has proven both feasible and efficacious. These observations support the investigation of pembrolizumab in combination with standard chemotherapy in the neoadjuvant setting and the continued administration of pembrolizumab as adjuvant therapy [Chaft, J. E., et al 2017].

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

This trial will use overall survival (OS) and event-free survival (EFS) as primary endpoints. Major pathological response (mPR) rate and pathological complete response (pCR) rate will be evaluated as secondary endpoints.

OS is a standard assessment of clinical benefit in participants with NSCLC.

EFS is a common surrogate endpoint for OS that is used to evaluate the efficacy of neoadjuvant and adjuvant cancer therapy and is sometimes used as primary endpoint. See Section 10.4 for the primary and secondary endpoint definitions.

Although no neoadjuvant therapy for NSCLC has been approved on the basis of mPR or pCR, there is support among physicians for using these endpoints [Hellmann, M. D. 2014], defined as follows:

mPR for this trial is defined as ≤10% viable tumor cells in primary resected tumor and all resected lymph nodes [Hellmann, M. D. 2014].

pCR for this trial is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the resected lung specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0).

5.4.1.2 Rationale for Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence,

causality, and outcome of adverse events (AEs)/serious adverse events (SAEs); and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.

5.4.1.3 Rationale for Patient-reported Outcomes (PROs) Endpoints

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated via the following tools: EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L PROs are to be completed by participants at various time points, beginning with baseline assessment, pre- and post-surgery, and continuing every 4 months for Year 2, then biannually in Year 3 followed by annual follow-up through Year 5.

5.4.1.3.1 EORTC QLQ-C30

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

For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Mean change from baseline in global health status/QoL scale of the EORTC QLQ-C30 will be evaluated as a secondary objective.

5.4.1.3.2 EORTC QLQ-LC13

The EORTC QLQ-LC13 is a disease-specific questionnaire developed and validated to address measurements specific to lung cancer. It is a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) covering 13 typical symptoms of lung cancer patients. The EORTC QLQ C30 and EORTC QLQ LC13 are used together to assess the quality of life of cancer patients in clinical trials: (1) the EORTC QLQ-C30 is a core quality of life questionnaire that covers general aspects of health-related quality of life, and (2) the EORTC QLQ-LC13 asks additional disease- or treatment-specific questions. Together, the lung cancer questionnaire module comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and side-effects from conventional chemo- and radiotherapy (ie, hair loss, neuropathy, sore mouth and dysphagia).

5.4.1.3.3 EQ-5D-5L

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

5.4.1.4 Planned Exploratory Biomarker Research

CCI

[redacted]

5.4.1.5 CCI

CCI

[redacted]

5.4.1.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) 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 are presented in Appendix 2: Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for the Use of Comparator/Placebo

Normal saline infusion Q3W will be used as placebo for pembrolizumab. The use of saline placebo in combination with chemotherapy will ensure the objectivity of the investigator. The use of a placebo will test the hypotheses that (1) pembrolizumab and chemotherapy is superior to the combination of placebo and chemotherapy in participants with NSCLC, as measured by the rate of mPR and rate of pCR based on histologic examination of the resected specimen; and that (2) perioperative (neoadjuvant and adjuvant) pembrolizumab and neoadjuvant chemotherapy is superior to the combination of perioperative placebo and neoadjuvant chemotherapy in participants with NSCLC, as measured by EFS and OS.

5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

The dose of pembrolizumab planned to be studied in this trial is 200 mg fixed dose Q3W.

5.5.2 Rationale for Dose Interval and Trial Design

Pembrolizumab is currently approved in the United States at a fixed dose of 200 mg Q3W. In the European Union (EU), pembrolizumab is currently approved for melanoma and previously treated NSCLC at 2 mg/kg Q3W and at 200 mg Q3W for all other indications. The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized mAbs, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other participant covariates on exposure, using available data from 1139 participant (from KEYNOTE-001 and KEYNOTE-002) has been performed. The majority of these participants (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual patient exposures within the exposure range established in melanoma as associated

with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other tumor indications, similar flat exposure-response relationships for efficacy and safety as observed in participants with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in participants with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types.

A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

The optimal duration of pembrolizumab has not been tested. At this time, the recommended duration for treatment for patients with metastatic disease is 24 months. The Sponsor believes that the 17 cycles are important for participants with resected NSCLC and for participants whose tumors will be resected. Therefore, the Sponsor has elected to administer 4 cycles of pembrolizumab concomitantly with the neoadjuvant chemotherapy and the remaining 13 cycles as adjuvant therapy.

5.6 Documentation of Local Progression and Metastases

5.6.1 Local Progression

During the neoadjuvant phase, progression will be documented radiologically. A biopsy is not required. During the adjuvant and EOT Follow-up Phase, local progression will be confirmed via biopsy if not medically contraindicated. In the event that biopsy is not diagnostic or does not reveal malignancy, the investigator should reassess the corresponding radiographic progression.

5.6.2 Metastatic Disease

During all phases of the trial, metastatic disease should be confirmed via biopsy unless medically contraindicated. Note that fine needle aspiration is acceptable for the assessment of metastatic disease. In the event that biopsy is not diagnostic or does not reveal malignancy, the investigator should reassess the corresponding radiographic progression/recurrence.

6. Study Population

6.1 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 informed consent with previously untreated and pathologically confirmed resectable Stage II, IIIA, or IIIB (N2) NSCLC. (AJCC Version 8). Lymph node disease requires

pathologic confirmation, while T3 (rib destruction) disease requires only radiographic documentation. A PET scan may be utilized as a surrogate for pathologic staging of N1 lymph nodes for participants with T2b and T4 tumors (the presence or absence of tumor in the N1 lymph nodes will not change the actual stage by which the participant is stratified). Similarly, biopsy confirmation of N2 disease is not required for pathologically confirmed T3N1 tumors and T4N0-1 tumors, as knowledge of the N2 status will not change the stage.

2. Be able to undergo protocol therapy, including necessary surgery.

Male participants:

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

   - Chemotherapy: 95 days

- Refrains from donating sperm

  PLUS either:

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

  OR

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

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

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

4. Removed.

Female participants:

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

   - Not a WOCBP

     OR

- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 3 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:
    - Chemotherapy: 180 days
    - MK-3475: 120 days

    The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 9.5.4.2.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

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

Disease-state Specific Criteria

7. Have available formalin-fixed paraffin-embedded (FFPE) tumor tissue sample blocks for submission. If blocks are not available, have unstained slides for submission for central PD-L1 testing. See Vendor Lab Manual for further details.
8. Have an ECOG performance status of 0 to 1 within 10 days of randomization.

9. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated[b] creatinine clearance **OR** GFR	≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN **OR** GFR criterion, eg, 60 mL/min/1.73 m^2
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	
Thyroid stimulating hormones (TSH)	Within normal limits. Note: If TSH is not within normal limits at baseline, the participant may still be eligible if T3 (or free T3) and free T4 are within the normal limits
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal. [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 **OR** GFR criterion. Note that creatinine levels must be ≤1.5 × ULN. 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.	

6.2 Exclusion Criteria

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

1. Removed in Amendment 10 for duplication of requirement with IC #5.
2. Has one of the following tumor locations/types:
   - NSCLC involving the superior sulcus
   - Large cell neuro-endocrine cancer (LCNEC)
   - Sarcomatoid tumor

3. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease that requires steroids.
4. Has an active infection requiring systemic therapy.
5. Has had an allogenic tissue/solid organ transplant.
6. Has a known severe hypersensitivity (≥ Grade 3) to pembrolizumab, its active substance and/or any of its excipients. (Refer to the respective Investigator's Brochure for a list of excipients.)
7. Has a known severe hypersensitivity (≥ Grade 3) to any of the study chemotherapy agents and/or to any of their excipients.
8. 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.
9. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
10. 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: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.
11. Has a known history of active tuberculosis (TB; *Bacillus* tuberculosis).
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial.

Prior/Concomitant Therapy

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
15. Has received prior systemic anticancer therapy including investigational agents for the current malignancy prior to randomization/allocation.

    Note: Must have recovered from all AEs due to previous therapies for other medical conditions to ≤ Grade 1 or baseline. Residual ≤ Grade 2 neuropathy is acceptable.

    Note: Must have recovered adequately from any previous surgical procedure prior to starting trial treatment

16. Has received prior radiotherapy within 2 weeks of start of trial treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
17. Has received a live or live attenuated vaccine within 30 days prior to the first dose of trial 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 (eg, FluMist®) are live attenuated vaccines and are not allowed.

    Refer to Section 7.7.3 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

19. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.
20. Has a known additional malignancy that is progressing or requires active treatment within the past (5 years).

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, noninvasive bladder carcinoma, or any carcinoma in situ (eg, in situ cervical cancer or breast carcinoma) that have undergone potentially curative therapy are not excluded.

Other Exclusions

21. Removed in Amendment 10 for duplication of requirement with IC #5.

6.3 Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No caffeine, alcohol or tobacco restrictions are required.

6.3.3 Activity

No activity restrictions are required.

6.4 Screen Failures

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

6.5 Participant Replacement Strategy

A participant who discontinues from trial treatment or withdraws from the trial will not be replaced.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatment(s) to be used in this trial are outlined below in Table 2. Country-specific differences are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm A	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle for 4 cycles followed by surgery and 13 cycles	Test Product	IMP	Central
Arm A	Experimental	Cisplatin	Drug	Solution for Infusion	1 mg/mL	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment	NIMP	Local or Central
Arm A	Experimental	Gemcitabine (squamous tumors)	Drug	Solution for Infusion	1000 mg/vial	1000 mg/m^2	IV Infusion	Day 1 and Day 8 of each 21-day cycle for 4 cycles	Background Treatment	NIMP	Local or Central
Arm A	Experimental	Pemetrexed (nonsquamous tumors)	Drug	Solution for Infusion	500 mg/vial	500 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment	NIMP	Local or Central
Arm B	Placebo Comparator	Normal saline	Drug	Solution for Infusion	N/A	N/A	IV Infusion	Day 1 of each 21-day cycle for 4 cycles followed by surgery and 13 cycles	Placebo	IMP	Local
Arm B	Placebo Comparator	Cisplatin	Drug	Solution for Infusion	1 mg/mL	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment	NIMP	Local or Central
Arm B	Placebo Comparator	Gemcitabine (squamous tumors)	Drug	Solution for Infusion	1000 mg/vial	1000 mg/m^2	IV Infusion	Day 1 and Day 8 of each 21-day cycle for 4 cycles	Background Treatment	NIMP	Local or Central
Arm B	Placebo Comparator	Pemetrexed (nonsquamous tumors)	Drug	Solution for Infusion	500 mg/vial	500 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment	NIMP	Local or Central

EEA =European Economic Area; IMP=investigational medicinal product; N/A=not applicable; NIMP=noninvestigational medicinal product; Q3W=every 3 weeks.
The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

7.2 Dose Modification (Escalation/Titration/Other)

If appropriate, the investigator may attribute each toxicity event to cisplatin, pemetrexed, gemcitabine, or pembrolizumab (either to the agent alone or to the combination of these agents) and use a stepwise dose reduction. Dose modifications must be based on the maximum toxicity experienced during a cycle. Treatment-related toxicity must resolve to Grade ≤1 or baseline before resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, and endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2. Dose modifications and toxicity management guidelines for immune-related AEs associated with pembrolizumab are outlined in Section 7.2.1 and Table 3 below.

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. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to that chemotherapy agent. 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 in the approved product labels. Please refer to approved local product labels for dose modifications regarding the chemotherapy regimen for cisplatin/pemetrexed and cisplatin/gemcitabine.

The following dose levels and dose modification are recommended if a dose modification is needed (Table 6, Table 7, and Table 8). If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications.

Participants may have chemotherapy discontinued and continue on pembrolizumab/saline placebo alone. Similarly, participants may discontinue pembrolizumab/saline placebo and continue on chemotherapy alone during the first 4 cycles if appropriate.

Please note that if one or more of the chemotherapy agents are interrupted, all 3 therapies (cisplatin, gemcitabine/pemetrexed, and pembrolizumab/placebo) should be withheld for the

duration of the interruption. If only pembrolizumab/placebo is interrupted, chemotherapy may continue during the pembrolizumab/placebo interruption. However, if the complication leading to the pembrolizumab interruption would be made worse by continued chemotherapy (i.e. hepatitis), the chemotherapy should either be interrupted or reduced.

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

7.2.2 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 4.

Table 4 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 (e.g., 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 (e.g., 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).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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.		

7.2.3 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. The reason for interruption should be documented in the participant's study record.

7.2.4 Chemotherapy Dose Modifications

Please refer to approved local product labels for dose modifications regarding the chemotherapy regimen for cisplatin/pemetrexed and cisplatin/gemcitabine. The following dose levels and dose modification are recommended if a dose modification is needed.

Table 5 Dose Modifications

	Dose level 0	Dose level -1	Dose level -2	Dose level -3
Cisplatin	75 mg/m^2	56 mg/m^2	38 mg/m^2	Discontinue
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue
Gemcitabine	1000 mg/m^2	750 mg/m^2	500 mg/m^2	Discontinue
The BSA in m^2 should be calculated per local guidance.				

Table 6 Recommended Dose Modifications for Cisplatin/Pemetrexed for Hematological Toxicity

			Pemetrexed	Cisplatin
Platelets (10^6/L)		**ANC (10^6/L)**	**Dose level (DL) from Table 5**	
≥50,000	AND	≥ 500	DL 0	DL 0
≥50,000	AND	< 500	DL -1	DL -1
<50,000 without bleeding	AND	ANY	DL -1	DL -1
<50,000 with Grade ≥ 2 bleeding	AND	ANY	DL -2	DL -2
ANY	AND	< 1,000 + fever ≥ 38.5°C (101°F)	DL -1	DL -1

Table 7 Recommended Dose Modifications for Cisplatin/Gemcitabine for Hematological Toxicity

			Gemcitabine	Cisplatin
Platelets (10^6/L)		**ANC (10^6/L)**	DL level from Please refer to approved local product labels for dose modifications regarding the chemotherapy regimen for cisplatin/pemetrexed and cisplatin/gemcitabine. The following dose levels and dose modification are recommended if a dose modification is needed. Table 5	DL level from Please refer to approved local product labels for dose modifications regarding the chemotherapy regimen for cisplatin/pemetrexed and cisplatin/gemcitabine. The following dose levels and dose modification are recommended if a dose modification is needed. Table 5
≥100,000	AND	≥1000	DL0	DL 0
50,000-99,999	OR	500-999	DL-1	DL-1
<50,000	OR	<500	Hold	Hold

Table 8 Recommended Dose Modifications for Chemotherapy for Non-Hematological Toxicity

		Pemetrexed	Cisplatin	Gemcitabine
Event	**CTC Grade**	Dose level (DL) from Please refer to approved local product labels for dose modifications regarding the chemotherapy regimen for cisplatin/pemetrexed and cisplatin/gemcitabine. The following dose levels and dose modification are recommended if a dose modification is needed. Table 5		
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL -1	Hold
Mucositis	Grade 3 or 4	DL -2	DL 0	Hold
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	Hold
Transaminase elevation	Grade 3	DL -1	DL -1	Discontinue
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1	Hold

**NOTE: Permanently discontinue gemcitabine for any of the following non-hematologic adverse reactions:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab + chemotherapy or placebo + chemotherapy, respectively.

7.3.1 Stratification

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

1. Stage (II, III)
2. TPS (<50%, ≥50%)
3. Histology (Squamous, Non-squamous)
4. Region (East-Asia, non-East-Asia)

7.4 Blinding

A double-blinding technique with in-house blinding will be used. Pembrolizumab and placebo will appear identical so that the blind is maintained. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.
See Section 9.1.11 for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Dosing and preparation of pembrolizumab will be performed by an unblinded pharmacist. Concomitant chemotherapeutic/immunotherapeutic agents will be prepared and administered as per the approved product label(s).

7.5.2 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 trial 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 trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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.

7.6 Treatment Compliance

An interval from first dose of neoadjuvant therapy to surgery of >20 weeks without an approved Sponsor Consultation Form will result in discontinuation from the study. Interruption >12 weeks between 2 consecutive cycles in the adjuvant treatment phase will result in discontinuation from study treatment.

7.6.1 Administration and Compliance of IV Study Treatments (Pembrolizumab/Placebo and Chemotherapy)

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

In the adjuvant phase, participants will receive 13 cycles of adjuvant treatment.

Instructions for preparing and administering pembrolizumab are provided in the Pharmacy Manual. Chemotherapy should be prepared and administered per the approved product labels.

7.7 Concomitant Therapy

Record all medications taken within 28 days of first dose as well as medications regularly administered at intervals greater than 28 days prior to first dose and up to 30 days after the last dose of study treatment. All concomitant medications administered during SAEs and ECIs are to be recorded as defined in Section 9.3.

7.7.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.

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.

7.7.1.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- To mediate potential immune-related AEs as guided in Table 3.
- As pre/post-medication to prevent AEs associated with chemotherapy or IV contrast.
- Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g., for COPD exacerbation).
    - Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

7.7.1.2 Pemetrexed Premedication

All participants receiving pemetrexed should be premedicated with steroids as per 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 one intramuscular injection of vitamin B12 1000 mcg during the week preceding the first dose of pemetrexed and during Cycle 3.

7.7.1.3 Antiemetic Use

For participants receiving chemotherapy, antiemetic therapy should follow Multinational Association of Supportive Care in Cancer (MASCC) or appropriate local guidelines (Appendix 8: MASCC 2016 Guidelines; Appendix 9, Table 19) and should, for all cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and aprepitant (or equivalent NK-1 receptor antagonist) as per the guideline followed.

7.7.2 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. All concomitant medication will be recorded on the case report form (eCRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF. Denosumab or zoledronic acid administered for treatment of osteoporosis is permissible.

7.7.3 Prohibited Concomitant Medications

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

Listed below are prohibited concomitant therapies or vaccinations during screening and the course of the study:

1. Antineoplastic systemic chemotherapy or biological therapy.
2. Immunotherapy not specified in this protocol.
3. Chemotherapy not specified in this protocol.
4. Radiation therapy not specified in this protocol.
5. Investigational agents other than pembrolizumab.

6. Live or live attenuated vaccines within 30 days prior to the first dose of trial treatment and while receiving study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) 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.

   Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as it is an mRNA vaccine, replication-incompetent adenoviral vaccine, or inactivated vaccine. These vaccines will be treated just as any other concomitant therapy.

   Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

7. Systemic corticosteroids except for AE management as described in Section 7.7.1.1.
8. For participants receiving radiotherapy, prophylactic growth factor support such as erythropoietin or granulocyte-colony stimulating factor is not permitted while receiving radiotherapy.

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

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

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

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.11, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.10 Standard Policies

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

For trials using Controlled Substances, all Federal, State, Province, Country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the trial is being conducted.

At the close of the trial after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the Sponsor's product to provide the following advice:

"You have participated in a trial conducted by the Sponsor. This is to advise you that you were among those who received a look-alike infusion created to resemble the drug Keytruda (pembrolizumab) as much as possible. You did not receive the active drug Keytruda (pembrolizumab) as manufactured by MSD."

8. Discontinuation/Withdrawal Criteria

8.1 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 2 - Schedule of Activities and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped 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 trial 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 9.1.10 – Withdrawal/Discontinuation. Participants who wish to discontinue from treatment and/or imaging may retain consent specifically for the noninvasive Survival Follow-up portion of the study. All participants are encouraged to be followed for vital status until death or the closure of the study, if they consent to do so.

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
- Local progression that precludes surgery during the neoadjuvant phase (does not require biopsy)
- Biopsy-proven metastases during the neoadjuvant phase, unresectable disease (as determined during surgery) and biopsy-proven recurrent disease during the adjuvant phase as outlined in in Section 5.6

- Local progression or biopsy-proven metastatic disease for those participants who have not undergone surgery, have received radiation, and have entered the adjuvant phase
- Unacceptable adverse experiences
- 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
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 7.2
- Participant who does not have surgery **and** does not have radiotherapy
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to discontinue the participant
- Administrative reasons

For participants who are discontinued from study treatment but continue to be monitored in the trial, see Section 2 – Schedule of Activities (SoA), and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the Study for those procedures to be completed at each specified visit.

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

8.2 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 Section 9.1.10 – Withdrawal/Discontinuation. 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 8.3 – Lost to Follow Up.

8.3 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, phone 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.

9. 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 trial 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 procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, 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.

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

9.1.1.1 General Informed Consent

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

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

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

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

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

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

9.1.2 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.

9.1.3 Participant Identification Card

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

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

9.1.4 Medical History

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

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days prior to first dose as well as medications regularly administered at intervals greater than 28 days prior to first dose.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial through the Safety Follow-up visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 9.3.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization or treatment allocation. 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 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

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

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

9.1.8 Treatment Administration

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

Study Treatment should begin within 3 days of randomization for Cycle 1, Day 1. After Cycle 1 in the neoadjuvant phase, cycle visits can occur from 21 days up to 12 weeks after the prior cycle, so that the neoadjuvant cycle visit is at least a minimum of 21 days from the prior cycle to avoid the dose overlap. The total duration of the neoadjuvant phase should not exceed 20 weeks. During the adjuvant treatment phase, the treatment cycle visit window is ± 3 days. The specific time of pembrolizumab infusion (e.g., time of the week for first administration; time of the day for each administration) should be taken into consideration for study visit procedures. All trial treatments will be administered on an outpatient basis. All study treatments must be initiated on Day 1 of each cycle after all procedures/assessments have been completed. If the participant is unable to receive all the scheduled therapies on Day 1, the non-administered therapies must be given within 72 hours of scheduled Cycle Day 1.

9.1.8.1 Timing of Dose Administration

Depending on the treatment arm and chemotherapy, study treatments will generally be administered in the following order: pembrolizumab or matching placebo, gemcitabine or pemetrexed, and cisplatin. Details of administering the individual components are discussed below.

Cycle 1 must begin given within 3 days of randomization. All study treatments must be initiated on Day 1 of each cycle. Study treatment is to be administered on Day 1 of each cycle after all procedures/assessments have been completed. If the participant is unable to receive all the scheduled therapies on Day 1, the non-administered therapies must be initiated within 72 hours of scheduled Cycle Day 1.

9.1.8.2 Timing of Dose Administration of Pembrolizumab or Matching Placebo

Study treatment with pembrolizumab/placebo should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the SoA (Section 2). All study treatments should be administered on an outpatient basis. Study treatment of pembrolizumab/placebo in the neoadjuvant phase has a +3 day visit window from randomization to C1D1. Study treatment of pembrolizumab/placebo may be administered up to 3 days before or after the scheduled Day 1 of each cycle in the adjuvant phase due to administrative reasons.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration of infusion solution. Pembrolizumab will be prepared by the unblinded pharmacist and will be dispensed by the blinded pharmacist and administered by blinded and qualified trial site personnel.

The placebo will be a normal saline solution prepared by the unblinded pharmacist. The placebo will be dispensed by the blinded pharmacist and administered by blinded and qualified trial site personnel in the same manner as the investigational product (pembrolizumab).

9.1.8.3 Timing of Dose Administration of Chemotherapy

9.1.8.3.1 Cisplatin

Cisplatin 75 mg/m^2 will be administered as an IV infusion over 60 minutes (-5 min/+10 minutes) OR as outlined in local standard practices on Day 1 of every 3-week neoadjuvant cycle following pemetrexed or gemcitabine. All participants should be premedicated with steroids and anti-emetics as per the approved label and local standard practices.

9.1.8.3.2 Gemcitabine

Gemcitabine 1000 mg/m^2 will be administered as an IV infusion over 30 minutes (-5 min/+10 minutes) on Day 1 and Day 8 of every 3-week neoadjuvant cycle. All participants should be pre-medicated as per the approved label and local standard practices.

9.1.8.3.3 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes (-2 min/+5 minutes) on Day 1 of every 3-week neoadjuvant cycle. Although participant receives pemetrexed on Day 1 of every 3-week cycle, they are to report to study site for completion of safety labs on Day 8, as stated in Section 2.2 of Schedule of Activities. All participants should be premedicated 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 one intramuscular injection of vitamin B12 1000 mcg during the week preceding the first dose of pemetrexed and during Cycle 3.

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

9.1.8.3.4 Radiotherapy

Participants who have microscopic positive margins or extracapsular nodal extension should receive radiation therapy to a maximum of 60 Gy. For participants who do not have surgery or who have gross residual disease after surgery, the maximum radiation therapy dose is 70 Gy. Radiotherapy is not allowed for participants with completely resected N2 disease in the absence of extracapsular spread. Radiotherapy must begin within 4-8 weeks after surgery, and cannot be administered concomitantly with adjuvant therapy. Radiotherapy local testing requirements should be followed. In addition, radiotherapy records must be submitted to the central radiologist according to the guidelines in the Radiotherapy Manual. Adjuvant therapy must begin within 2-4 weeks of completing radiation therapy.

9.1.9 Surgical Procedure Guidelines

9.1.9.1 Preoperative Evaluation

Physiologic Evaluation

A Cardiology consultation is recommended if the participant is taking any cardiac medications, has a suspected cardiac disease, is unable to climb 2 flights of stairs, or has a Thoracic Cardiac Risk Index (ThRCRI) >1.5 [Brunelli, A., et al 2013].

As reference, the following criteria outline the scoring for Thoracic Cardiac Risk Index Points:

- Pneumonectomy: 1.5 points
- Previous ischemic heart disease: 1.5 points
- Previous stroke or transient ischemic attack: 1.5 points
- Creatinine >2 mg/dL: 1 point.

Pulmonary Evaluation

If the predicted post-operative (PPO) forced vital capacity (FEV_1) and percent predicted postoperative diffusing capacity for carbon monoxide (PPO DLCO) >60%, no further preoperative pulmonary tests are recommended.

If either PPO FEV1 <30% or PPO DLCO <30%, a formal cardiopulmonary exercise test (CPET) with measurement of maximal oxygen consumption (VO_2 max) is recommended. A VO_2 max <10 mL/kg/min or <35% predicted indicates a high risk for perioperative death and cardiopulmonary complications with major anatomic lung resection through thoracotomy. Evaluation by a Pulmonologist and Cardiologist should occur prior to surgery. Non-operative treatment of the lung cancer should be considered.

9.1.9.2 Intraoperative Guidance

Routine general anesthesia according to institutional guidelines should be performed. Perioperative antibiotics and steroids are administered per institutional guidelines. Surgeons are encouraged to avoid the use of steroids where possible. Prohibited medications are detailed in Section 7.7 – Concomitant Therapy. Any permitted perioperative

steroids should be administered after all study-related tissue and blood samples have been collected.

Primary Tumor

Surgery must be a lobectomy, bilobectomy, pneumonectomy, sleeve lobectomy, sleeve pneumonectomy, or chest wall resection with any of the previously listed resections. Please note that wedge resection or segmentectomy is NOT permitted. The surgeon should describe in the operative report the extent of macroscopic disease with particular comparison to extent at initial presentation.

Lymph Node

Preferred mediastinal lymph node (N2) dissection consists of complete removal of all accessible ipsilateral mediastinal lymph node levels. N1 lymph nodes are generally removed as part of the resected lobe or lung. N1 lymph nodes removed separately from the specimen should be accurately labeled and submitted to the pathologist as separate specimens. The operative report should contain a detailed description of the lymph node dissection including the nodal levels and, if possible, the number of lymph nodes removed.

Acceptable lymph node dissection involves removal of at least 2 N2 levels (one of which is Level 7).

Additional lymph node requirements include:

- Lymph node level specimens should be labeled with the appropriate number/description prior to leaving the operating room
- If a lymph node level is explored and no lymph nodes are present, the exploration and negative findings should be documented in the operative note
- All lymph nodes which contained documented metastatic disease prior to neoadjuvant therapy should be removed during surgery
- Lymph nodes levels will be defined according to the criteria of the joint AJCC/UICC classification shown in the IASLC Staging Manual (2nd Edition)

9.1.9.3 Perioperative Complications

Morbidity associated with pulmonary surgery includes both intraoperative and postoperative complications, which may contribute to increased length of inpatient hospital stay and delay time to initiation of adjuvant therapy. Management is at the discretion of the treating physician as per local SOC.

9.1.9.4 Evaluation and Reporting of Postoperative Complications

Potential postoperative complications include but are not limited to:

- Bronchopleural fistula
- Bacterial pneumonia
- Acute respiratory failure
- Postoperative hemorrhage
- Atelectasis
- Aspiration pneumonia
- Acute pulmonary edema
- Wound infection
- Pneumothorax
- Bronchospasm
- Pulmonary embolism
- Acute Respiratory Distress Syndrome
- Bronchitis
- Pleural effusion
- Purulent pleuritis
- Deep Vein Thrombosis

All postoperative complications will be reported and graded, if applicable, in the same way as other AEs (see Appendix 4) and will be identified by the investigator and/or surgeon as post-surgical complications.

9.1.9.5 Postoperative Care

Postoperative care should proceed per institutional guidelines

9.1.9.6 Pathology Specimen

The primary resection specimen submitted to a local pathologist should include the entire surgically resected lesion and all resected lymph nodes. On pathological examination, margins are defined as negative (R0) if:

- No invasive cancer at bronchial margin or soft tissue surrounding bronchus
- No invasive cancer at pulmonary artery or pulmonary vein margins or surrounding soft tissue
- No invasive cancer at medial, lateral, superior and inferior margins of chest wall resection
- No minimal margin distance
- Bronchial dysplasia is considered a negative margin

Margins are defined as positive if:

- Microscopic invasive cancer at bronchial, pulmonary vein or pulmonary arterial margins or surrounding soft tissue (R1)
- Carcinoma in situ at bronchial margin (R1)
- Gross residual disease (R2)

Specimens should be processed per institutional guidelines but should include separation of lymph node specimens into distinct levels prior to pathology submission.

Communication from surgeon to local pathologist should follow local practice and institutional guidelines. Sample transport, storage, and shipment instructions for pathology specimens obtained during surgery will be provided in the Laboratory (or equivalent) Manual.

Representative specimens (slides or blocks) of tumor tissue collected during surgery from all participants will be submitted to the designated central laboratories (see Laboratory Manual or equivalent) for blinded pathological response assessment of the pCR and mPR endpoints.

9.1.10 Withdrawal/Discontinuation

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 trial, all applicable activities scheduled for the discontinuation visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.10.1 Survival Follow-up

Participants who withdraw consent for treatment and/or imaging are encouraged to remain on the noninvasive Survival Follow-up portion of the study. The only procedures associated with this phase are telephone contacts to assess vital status and the current state of the participant's NSCLC. The noninvasive nature and societal benefit of Survival Follow-up (every 12 weeks ± 7 days) should be explained to the participant by the site staff, particularly when discontinuing treatment or imaging. Although per-protocol scheduled imaging ends when participants enter Survival Follow-up, all imaging that is conducted thereafter should be submitted. Participants may withdraw their consent at any time from any or all portions of the study.

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

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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.

9.1.11 Participant Blinding/Unblinding

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

When the investigator or delegate needs to identify the drug used by a participant and the dosage administered in case of emergency eg, the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or delegate must enter the intensity/toxicity grade of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

For studies that require unblinding as part of the study design (e.g., disease recurrence, progression, or completion of study treatment) to support treatment decisions, the Site must first contact the Sponsor for approval of non-emergent unblinding at the time of local laboratory confirmation of disease recurrence, disease progression, or completion of study treatment. Once authorization is granted by the Sponsor for non-emergent unblinding, the site will contact IVRS/IVXS to receive the participant's unblinded treatment arm. The emergency unblinding center should not be used for non-emergent unblinding.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for participant safety.

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

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

9.1.12 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important

information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment-as required for inclusion labs and safety assessments
- Imaging equipment-as required for efficacy assessments
- Drug administration equipment-as required for storage, preparation and administration (infusion) of protocol treatment

See protocol-specified guidance in the Administrative Binder, Procedures Manual, and Pharmacy Manual.

9.1.13 Tumor Tissue Collection for Biomarker Analysis

PD-L1 expression will be tested by a central laboratory as part of screening. A biopsy that produces tissue suitable for histologic determination of PD-L1 TPS is required and may be obtained from either the primary tumor or lymph node containing metastatic disease (not previously irradiated). Methods that produce suitable specimens include, but are not limited to: percutaneous core needles and cup forceps/incisional biopsies via mediastinoscopy, thoracoscopy, thoracotomy, and mediastinotomy. The specimen must be provided to the central laboratory during screening and must have been obtained within 90 days prior to randomization. FFPE tissue blocks are preferred to slides. Detailed instructions for tissue collection, processing, and shipment are provided in the Vendor Lab Manual.

The tissue analysis will include PD-L1 TPS used for stratification.

9.2 Efficacy Assessments

9.2.1 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 computed tomography (CT). Magnetic resonance imaging (MRI) should be used only when CT is contraindicated or for imaging of the brain. 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 and the use of contrast should be used in a participant throughout the trial to optimize the visualization of existing and new tumor burden.

All images from the sites will be sent to a central imaging vendor.

Note: The exact same image acquisition and processing parameters should be used throughout the study per the Site Imaging Manual.

9.2.1.1 Initial Tumor Imaging

Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality, include all required anatomy, and performed within 60

days prior to randomization with the exception of the chest CT scan, which must be performed within 28 days prior to randomization. These scans will be considered the baseline assessments for the study.

9.2.1.2 Tumor Imaging During Trial

For participants receiving all 4 cycles of neoadjuvant therapy, the first on-trial imaging assessment will be performed 3 weeks after completion of 2 cycles of preoperative therapy, at approximately 7 weeks (42 days ±7 days) after the first dose of trial treatment (or earlier if clinically indicated). The second imaging assessment will take place 3 weeks after 4 cycles of preoperative therapy, at approximately 13 weeks (84 days ±7 days) after the first dose of trial treatment, before surgery (or earlier if clinically indicated).

If the participant receives fewer than 4 cycles, the following schedule should be followed:

- If the participant receives 3 cycles: Imaging performed 3 weeks after Cycle 2 and 4 weeks after Cycle 3
- If the participant receives 2 cycles: Imaging performed 3 weeks after Cycle 2
- If the participant receives 1 cycle: Imaging performed 3 weeks after Cycle 1

Note: If the participant receives only 1 or 2 cycles, then s/he will have just one set of CT scans in the neoadjuvant phase.

Following resection of their lung cancer, participants must have new baseline imaging within 4 weeks prior to the start of adjuvant pembrolizumab/placebo treatment. Participants who receive post-operative radiotherapy must have new baseline imaging after completion of the radiotherapy, but within 4 weeks prior to the start of adjuvant pembrolizumab/placebo treatment.

Imaging in the adjuvant phase will be performed every 16 weeks (±14 days), or more frequently if clinically indicated, starting from the date of randomization. If the first scheduled image in the adjuvant phase falls within ±4 weeks of the new baseline scan, the first scheduled image in the adjuvant phase is not required.

All participants who discontinue study treatment for reasons other than progressive disease or recurrence enter the post treatment Follow-up Phase. Imaging will be based upon the date of randomization.

Participants who do not undergo surgery and do not undergo radiotherapy are not required to have new baseline imaging. Participants will be followed in the Follow-up Phase to perform imaging every 16 weeks (± 21 days) from date of randomization. Imaging will be performed for assessment of local progression and/or metastatic disease.

Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until local disease progression or metastatic disease, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor. All imaging acquired within the protocol-specified window of time around a scheduled imaging visit can be classified as pertaining to that visit.

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer from the date the response was first documented, unless the participant is scheduled for surgery. The tumor imaging performed to confirm a response may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

All participants who discontinue study treatment for any reason, including completion of 13 cycles of adjuvant treatment, should have tumor imaging performed at the time of treatment discontinuation (±4 week window). If imaging was obtained within 4 weeks before the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

For participants who discontinue study treatment for reasons other than progressive disease or recurrence, every effort should be made to continue monitoring their disease status by tumor imaging using the post treatment Follow-up Phase imaging schedule of every 16 weeks (± 21 days) through the end of year 3, then every 6 months (± 28 days) for years 4 and 5, and then every 12 months (± 28 days) thereafter. Imaging will be based upon the date of randomization to monitor disease status until local disease progression or metastatic disease, withdrawal of consent from imaging, or death, whichever occurs first.

NOTE: For participants who have started a new anticancer therapy for reasons other than disease progression, imaging assessments will continue as indicated in Section 2.4. Where allowed, participants who have not progressed but have declined study-specific imaging should be encouraged to submit imaging performed as standard of care (even retrospectively).

For participants who discontinue protocol-specified imaging for progressive disease or recurrence based on investigator assessment, where allowed, all efforts should be made to send in subsequent standard of care imaging (even retrospectively) to the central imaging vendor for potential review.

9.2.1.4 Assessment of Disease

During the neoadjuvant phase and for those participants who have not had or will not have surgery, RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of trial therapy). In the postoperative adjuvant phase, chest and abdominal CT scans will be performed at regular intervals for assessment of disease recurrence. Other radiologic tests may be performed as clinically indicated. Biopsy confirmation of metastatic disease that occurs during the neoadjuvant phase or recurrent disease that occurs during the adjuvant phase or Post-treatment Follow-up Phase is required unless medically contraindicated.

9.2.2 Patient-reported Outcomes

The EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 questionnaires will be administered by trained study site personnel and completed electronically by the participants in the following order: EQ-5D-5L first, then EORTC eQLQ-C30, and lastly the EORTC eQLQ-LC13. The questionnaires should be administered prior to dosing at Cycle 1 and Cycle

4 Week 11 during the neoadjuvant treatment phase and then at Cycles 1, 2, 3, 4, 7, 10, and 13 during the adjuvant treatment. They also need to be completed at the EOT, 30 day Safety Follow-up, and the post-treatment follow-up visits through Year 5.

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

9.2.3 Medical Resource Utilization and Health Economics

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

9.2.4 Survival Follow-up

Once a participant experiences a progression/recurrence, the participant moves into the Survival Follow-up Phase and will be contacted by telephone approximately every 12 weeks ± 7 days to assess vital status until death, withdrawal of consent, or the end of the study, whichever occurs first. Post-study treatments and the participant's response to them will also be collected. Participants in Survival Follow -up who have experienced PD should submit SOC imaging to the central vendor. Participants in Survival Follow-up who have not experienced PD should be given the option of continuing with the protocol-imaging schedule (and if unwilling, SOC images should be submitted).

If a participant withdraws consent for treatment and/or imaging, the participant is still encouraged to remain in the Survival Follow-up Phase and sites should ensure the participant understands the noninvasive nature of this phase.

MSD will request vital status data more frequently than every 12 weeks at specific time points during the study. For example, vital status may be requested prior to an external DMC safety review, efficacy interim analyses, and final analysis. All participants who are in the Follow-up and Survival Follow-up Phases and not known to have died prior to the request for these additional vital status time points will be contacted at that time.

9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (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: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

Adverse events will not be collected for participants during the pre-screening 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.

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

All AEs, SAEs and other reportable safety events that occur after the participant provides documented informed consent but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the trial, 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 study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.
- All-cause hospitalizations and all-cause emergency room (ER) visits (except as related to scheduled surgery and the use of a hospital specialty unit [HSU] according to the institution guidelines) 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 using HOSP form for hospitalization and HSU form for ER visits.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the Sponsor or designee within the timeframes as indicated in Table 9.

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

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

Type of Event		Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period		Timeframe to Report Event and Follow-up Information to Sponsor:
Pregnancy/ Lactation Exposure		Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	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 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

9.3.2 Method of Detecting AE, SAE 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 non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3 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, ECI, 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 8.3). 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: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

9.3.4 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 Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 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 9.3.1.

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 trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Global Safety as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, 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 trial 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.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. Potential DILI events defined as 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).
3. Surgical complications which will be considered as SAEs include broncho-pleural fistulas, re-operation, supraventricular arrhythmia, pneumonia, and respiratory failure [Scagliotti, G. V., et al 2012]. This list is not exhaustive and other serious surgical complications, such as deep vein thrombosis and pulmonary embolism, should be reported within 24 hours of learning of event. SAEs will be assessed as defined by CTCAE, Version 4.0.

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

All ECIs that occur from the time of treatment randomization through 30 days following cessation of study treatment must be reported by the investigator to MSD within 24 hours of the learning of the event.

9.4 Treatment of Overdose

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

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

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

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

9.5 Safety

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

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Examination

The investigator or qualified designee will perform a directed physical examination as clinically indicated prior to the administration of the trial treatment. Cycles that do not require a full physical examination are defined in Section 2. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study treatment, and during the Follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at Screening only.

9.5.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 6: Clinical Laboratory Tests 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 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 non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified Appendix 6. Refer to the SoA for the timing of laboratory assessments.

9.5.4.2 Pregnancy Test

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 6.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 6.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
    - Chemotherapy: 180 days
    - MK-3475: 120 days
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

9.5.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening (within 10 days prior to randomization), prior to the administration of each dose of study treatment, and during the Follow-up period as specified in the SoA. The ECOG performance scale is outlined in Appendix 5.

9.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Biomarkers

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

- Blood for Genetic Analyses
- Blood for RNA Analyses
- Blood for Serum Biomarker Analysis
- Blood for Plasma Biomarker Analysis
- Blood for ctDNA
- Tissue for Biomarker Analysis

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

9.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

9.9 Future Biomedical Research Sample Collection

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

- Leftover DNA
- Leftover RNA
- Leftover main trial tumor tissue
- Leftover plasma from plasma biomarker analyses
- Leftover serum from serum biomarker analyses
- Leftover plasma or derivative for ctDNA

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Approximately 28 days prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 6.1 and 6.2.

Documented 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 28 days prior to the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study treatment. An exception is hepatitis testing (only required if indicated by local health authority), which may be done up to 28 days prior to the first dose of study treatment.
- Evaluation of ECOG is to be performed within 10 days prior to randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study treatment in both the neoadjuvant and adjuvant treatment phases. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study treatment. Newly obtained tumor tissue may be obtained within 90 days prior to randomization.
- Baseline imaging must be done within 60 days, except for repeat CT of chest and abdomen, which must be done within 28 days.

Participants may be rescreened once after initially failing to meet the inclusion/exclusion criteria or failing to complete the required testing within the 28 day Screening Period, and will retain their original screening number.

Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria are met.

9.10.2 Treatment Period

Visit requirements are outlined in Section 2—Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9—Study Assessments and Procedures. Unless otherwise specified, assessments/procedures are to be performed prior to the first dose of treatment for each cycle. Neoadjuvant visits can occur from 21 days up to 12 weeks after the prior cycle, so that the neoadjuvant visit is at least a minimum of 21 days

from the prior cycle (to avoid the dose overlap). The total duration of the neoadjuvant period should not exceed 20 weeks. During the adjuvant phase the visit window is ±3 days.

Treatment in the neoadjuvant phase will occur every 21 days (1 cycle) for 4 cycles. Treatment in the adjuvant phase will occur every 21 days (1 cycle) up to a maximum of 13 cycles.

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

9.10.3.1 Safety Follow-up Visit

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

9.10.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than biopsy-proven or radiologically documented progressive disease (PD) will move into the Follow-up Phase and should be assessed with imaging every 16 weeks through year 3, every 6 months through years 4-5, and then every 12 months (± 28 days) thereafter. The Sponsor may request vital status to be assessed at additional time points during the course of the study (not to exceed approximately every 12 weeks). Every effort should be made to collect imaging (including in those participants who start anticancer therapy) until biopsy-proven progression or recurrence or death. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

9.10.3.3 Survival Follow-up

Participants who experience local progression that precludes surgery during the neoadjuvant phase, metastases during the neoadjuvant phase, unresectable disease (as determined during surgery) and recurrent disease during the adjuvant phase or EOT Follow-up Phase as outlined in Section 5.6 will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for vital 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 noninvasive Survival Follow-up portion of the study. The only procedures associated with this phase are telephone contacts to assess vital status and the current state of the participant's NSCLC. Although per-protocol scheduled imaging ends when participants enter Survival Follow-up, all imaging that is conducted thereafter should be submitted. The noninvasive nature and societal benefit of Survival Follow-up should be explained to the participant by the site staff, particularly when discontinuing treatment and imaging.

9.10.3.4 Vital Status

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

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail biomarker analyses. The PRO analysis plan will be included in the sSAP.

10.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in Sections 10.2 -Responsibility for Analyses/In-house Blinding through 10.12 – Extent of Exposure.

Study Design Overview	A Phase III, randomized, double-blind trial of pembrolizumab plus chemotherapy versus placebo plus chemotherapy as neoadjuvant/adjuvant therapy for participants with resectable Stage II through IIIA-B (N2) NSCLC
Treatment Assignment	Approximately 786 participants will be randomized in a 1:1 ratio between 2 treatment arms: (Arm A) Neoadjuvant pembrolizumab plus platinum doublet chemotherapy (4 cycles) followed by surgery and adjuvant pembrolizumab (13 cycles) (referred to as pembrolizumab plus chemotherapy arm) (Arm B) Neoadjuvant placebo plus platinum doublet chemotherapy (4 cycles) followed by surgery and adjuvant placebo (13 cycles) (referred to as placebo plus chemotherapy arm) Stratification factors are as follows: 1) Stage (II, III) 2) TPS (<50%, ≥50%) 3) Histology (Squamous, Nonsquamous) 4) Geographic Region (East Asia, non-East Asia)
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT) PRO: Full Analysis Set (FAS)

Primary Endpoint(s)	• Event-free survival (EFS) • Overall survival (OS)
Secondary Endpoints	• Major pathological response (mPR) rate • Pathological complete response (pCR) rate • PRO outcome • Safety and tolerability
Statistical Methods for Key Efficacy Analyses	The hypotheses will be evaluated by comparing pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to EFS and OS using a stratified log-rank test, and with respect to mPR and pCR rates using the stratified Miettinen and Nurminen method. For EFS and OS, hazard ratios will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The difference in mPR rate and pCR rate will be estimated using the stratified Miettinen and Nurminen method with strata weighting by sample size.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the unstratified Miettinen and Nurminen method.

Interim Analyses	Four interim analyses and one final analysis are planned for this study. Results will be reviewed by an external DMC. Details are provided in Section 10.7-Interim Analyses.
	• Interim analysis (IA1): when approximately 326 EFS events have been observed and ~ 5 months after the last participant is randomized (~48months after the first participant is randomized)
	  ○ Purpose: mPR rate analysis, pCR rate analysis, interim EFS analysis (~78% of target EFS events) and interim OS analysis (~41% of target OS events)
	• Interim analysis (IA2): when approximately 416 EFS events have been observed (~60 months after the first participant is randomized)
	  ○ Purpose: final EFS analysis and interim OS analysis (~58% of target OS events)
	• Interim analysis (IA3): when approximately 285 deaths have been observed (~72 months after the first participant is randomized)
	  ○ Purpose: interim OS analysis (~74% of target OS events)
	• Interim analysis (IA4): when approximately 340 deaths have been observed (~84 months after the first participant is randomized)
	  ○ Purpose: interim OS analysis (~88% of target OS events)
	• Final analysis (FA): when approximately 386 deaths have been observed (~96 months after the first participant is randomized)
	  ○ Purpose: final OS analysis
	Note that for IA3 and IA4, if the OS events accrue slower than expected, the Sponsor may conduct the analysis with additional 3 months of follow-up, or when the specified number of events is observed, whichever occurs first. If the final targeted OS events cannot be reached by the end of year 5 after last

	participant randomized, the final OS analysis will be conducted at the end of year 5 after last participant randomized at the latest.
Multiplicity	The overall Type I error rate over the multiple endpoints will be strongly controlled at 2.5% (one-sided). A 0.01% (one-sided) Type I error rate will be initially allocated to test mPR rate, 0.01% (one-sided) allocated to test pCR rate, 1.0% (one-sided) allocated to test EFS and 1.48% (one-sided) allocated to test OS. The graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] will be applied to re-allocate alpha among the hypotheses for mPR rate, pCR rate, EFS and OS. Group sequential methods will be used to allocate alpha among the interim and final analyses for the EFS and OS endpoints.
Sample Size and Power	The planned sample size is approximately 786 participants. The trial is event-driven and completes after substantial efficacy evidence of EFS and/or OS are observed. With 416 EFS events, the study has 90% power for detecting a hazard ratio (HR) of 0.7 at a 1.0% (one-sided) significance level. With 386 deaths, the study has 90% power for detecting a HR of 0.7 at a 1.48% (one-sided) significance level. Based on the time that approximately 326 EFS events have been observed, the study has 99.1% power for detecting a 20 percent point difference in mPR rate and 99.3% power for detecting a 16 percent point difference in pCR rate at a 0.01% (one-sided) significance level.

10.2 Responsibility for Analyses/In-House Blinding

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

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol. Randomization will be implemented in IVRS/IWRS.

Planned interim analyses are described in Section 10.7 – Interim Analyses. Blinding to treatment assignment will be maintained at all investigational sites. Treatment-level results of the planned interim analyses will be provided by the external unblinded statistician to the DMC. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the interim analyses, if required, in order to act on the recommendations of the DMC (e.g., interaction with regulatory agencies). The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external unblinded statistician.

The DMC will serve as the primary reviewer of the results of the interim analyses and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level in order to act on these recommendations. The DMC responsibilities, review schedules, and additional logistical details will be provided in the DMC Charter.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4 – Objectives/Hypotheses and Endpoints.

10.4 Analysis Endpoints

Primary and secondary efficacy, safety and PRO endpoints that will be evaluated for within- and/or between-treatment differences are listed below. Exploratory endpoints will be described in the sSAP.

10.4.1 Efficacy Endpoints

Primary

Event-free Survival

EFS is defined as the time from randomization to the first of the following events:

- Radiographic disease progression per RECIST 1.1 (for participants who have not had or will not have surgery, or participants who have gross residual disease after an incomplete resection [R2 resection])
- Local progression (primary tumor or regional lymph nodes) precluding planned surgery
- Inability to resect the tumor
- Local or distant recurrence (for participants who are disease free after surgery or participants with microscopic positive margins [R1 resection])
- Death due to any cause

Imaging and biopsy are investigator-assessed. For radiographic progression/recurrence, the EFS event will be declared when:

- Only imaging is performed, and progression/recurrence confirmed
- Only pathology is done, and progression/recurrence confirmed
- Both pathology and imaging are done, and progression/recurrence confirmed (by at least one). In this case, whatever examination comes first, the first date is considered as the EFS event date.

In the event that biopsy is not diagnostic or does not reveal malignancy, the investigator should reassess the corresponding radiographic progression/recurrence.

See Section 10.6.1 for the definition of censoring.

Overall Survival

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

Secondary

Major Pathological Response (mPR) Rate

The mPR rate is defined as the proportion of participants having ≤10% viable tumor cells in the resected primary tumor and all resected lymph nodes.

Pathological Complete Response (pCR) Rate

The pCR rate is defined as the proportion of participants having an absence of residual invasive cancer on hematoxylin and eosin stained slides of the resected lung specimen and lymph nodes following completion of neoadjuvant therapy (ie, ypT0/Tis ypN0).

10.4.2 Safety Endpoints

Safety measurements are described in Section 5.4.1.2 - Rationale for Safety Endpoints and Section 9.5- Safety.

10.4.3 Patient-reported Outcome (PRO) Endpoints

Change from baseline (C1 in neoadjuvant phase) to follow up assessments in the neoadjuvant phase and in the adjuvant phase in global health status/QoL score using the EORTC QLQ-C30 (items 29-30) questionnaire will be assessed.

Exploratory PRO endpoints as described in Section 5.4.1.3 will also be evaluated. Details will be provided in the sSAP.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analyses. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 10.6 – Statistical Methods.

10.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. For the analysis of perioperative complications, the All Participants receiving Surgery (APrS) population will be used, which consists of all randomized participants who receive at least one dose of neoadjuvant study treatment and also undergo on-study surgery. For both the APaT and APrS populations, participants will be included in the treatment group corresponding to the study treatment they actually received. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study medication for one cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a

narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained 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.

Details on the approach to handling missing data for safety analyses are provided in Section 10.6 – Statistical Methods.

10.5.3 PRO Analysis Population

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

10.6 Statistical Methods

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

10.6.1 Statistical Methods for Efficacy Analyses

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8 – Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

The stratification factors used for randomization will be applied to all stratified efficacy analyses, including stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method. In the event that some strata are of small size, they may be pooled for analyses in a meaningful way. Details regarding the pooling of strata will be specified in the sSAP prior to database lock for the first interim efficacy analysis.

10.6.1.1 Event-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 7.3.1 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

For the primary EFS analysis, the true date of event will be approximated by the date of the first assessment at which event is objectively documented. Participants who do not experience an event at the time of analysis will be censored at the last disease assessment.

The primary approach for EFS will be based on investigator assessment. A sensitivity analysis by using the central review of imaging and biopsy will also be conducted. Other sensitivity analyses may be conducted using different censoring rules and will be documented in the sSAP.

In case the proportional hazards assumption is not valid, the Restricted Mean Survival Time (RMST) method may be conducted for EFS to account for the possible non-proportional hazards effect as a sensitivity analysis.

10.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 7.3.1– Stratification) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact.

In case the proportional hazards assumption is not valid, the Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect as a sensitivity analysis.

10.6.1.3 Major Pathological Response Rate

The stratified Miettinen and Nurminen's method will be used for comparison of the mPR rates between the 2 treatment groups. The difference in mPR rates and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The stratification factors used for randomization (see Section 7.3.1-Stratification) will be applied to the analysis.

Participants who are discontinued from the study treatment but receive other neoadjuvant treatment not specified by the study prior to surgery will be classified as not having an mPR (nonresponders) in the efficacy analyses, regardless of the results obtained from the surgery. Participants who are discontinued from study treatment due to reasons that preclude surgery are considered nonresponders.

10.6.1.4 Pathological Complete Response Rate

The stratified Miettinen and Nurminen's method will be used for comparison of the pCR rates between the 2 treatment groups. The difference in pCR rates and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The stratification factors used for randomization (see Section 7.3.1-Stratification) will be applied to the analysis.

Participants who are discontinued from the study treatment but receive other neoadjuvant treatment not specified by the study prior to surgery will be classified as not having an pCR (nonresponders) in the efficacy analyses, regardless of the results obtained from the surgery. Participants who are discontinued from study treatment due to reasons that preclude surgery are considered nonresponders.

10.6.1.5 Summary of Primary Analysis Approach for Key Efficacy Endpoints

Table 10 summarizes the primary analysis approach for key efficacy endpoints.

Table 10 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method[†]	Analysis Population	Missing Data Approach
Primary			
EFS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Censored at the last disease assessment
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Censored at last known alive date
Secondary			
mPR rate	Stratified Miettinen and Nurminen method with sample size weights	ITT	Participants with relevant data missing are considered nonresponders
pCR rate	Stratified Miettinen and Nurminen method with sample size weights	ITT	Participants with relevant data missing are considered nonresponders
[†]Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 7.3.1– Stratification) will be applied to the analysis.			

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, and interim analyses is described in Section 10.7 – Interim Analyses and in Section10.8 – Multiplicity.

10.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms), surgical complications, and events that meet predefined limits of change in laboratory, vital signs, and ECG parameters are either pre-specified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEs of special interest (AEOSIs) that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p -values and 95% CIs provided for between-group comparisons. AEOSIs that are immune-mediated or potentially immune-mediated are well-documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Based on toxicity data across the pembrolizumab program, the combination of pembrolizumab with chemotherapy is not anticipated to produce toxicity beyond what is expected for these therapies alone. Thus, there are no events of interest that warrant elevation to Tier 1 in this study.

Tier 2 Events

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

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

Tier 3 Events

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

Continuous Safety Measures

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific AE (≥10% of participants in one of the treatment groups)	X	X
	Any Serious AE (≥5% of participants in one of the treatment groups)	X	X
	Any Grade 3-5 AE (≥5% of participants in one of the treatment groups)	X	X
Tier 3	Any AE, surgical complications[1]		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X
[1] Analyses for perioperative complications are based on the APrS population as defined in Section 10.5.2.			

10.6.3 Statistical Methods for PRO Analyses: EORTC QLQ-C30 Global Health Status/QoL Score

To assess the treatment effect on the EORTC QLQ-C30 global health status/QoL score, a constrained longitudinal data analysis (cLDA) model will be applied, with this PRO score as the response variable, and treatment by time interaction as well as stratification factors as covariates. The least square mean change from baseline will be summarized. Treatment effect on this PRO score change from baseline will be primarily evaluated in the neoadjuvant phase (at last scheduled visit prior to surgery) and adjuvant phase (at approximately 6 months following the first dose of adjuvant therapy).

Details of PRO analyses including the exploratory endpoints will be described in the sSAP.

10.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age, gender) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

10.7 Interim Analyses

10.7.1 Interim Safety Analyses

The DMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the DMC charter.

10.7.2 Interim Efficacy Analyses

Four interim efficacy analyses are planned in addition to the final analysis for this study. The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 12. The timing of interim analyses may be adjusted if less than 4 months of time or more than 12 months of time is predicted to accrue the events required performing the analyses. Also, the timing of interim analyses may be altered if events accrue at a substantially different rate than anticipated. For IA3 and IA4, if the OS events accrue slower than expected, the Sponsor may conduct the analysis with additional 3 months of follow-up, or when the specified number of events is observed, whichever occurs first. If the final targeted OS events cannot be reached by the end of year 5 after last participant randomized, the final OS analysis will be conducted at the end of year 5 after last participant randomized at the latest.

Table 12 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	mPR rate pCR rate EFS OS*	~ 326 EFS events have been observed and ~ 5 months after last participant is randomized.	~48 months	• Demonstrate mPR rate superiority • Demonstrate pCR rate superiority • Interim evaluation of EFS superiority • Interim evaluation of OS superiority
IA2	EFS OS*	~ 416 EFS events have been observed.	~60 months	• Demonstrate EFS superiority • Interim evaluation of OS superiority
IA3	OS	~ 285 deaths have been observed.	~72 months	• Interim evaluation of OS superiority
IA4	OS	~ 340 deaths have been observed.	~84 months	• Interim evaluation of OS superiority
FA	OS	~ 386 deaths have been observed.	~96 months	• Demonstrate OS superiority

* The estimated observed OS events at IA1 and IA2 are approximately 159 and 225, respectively. Note that IA1 and IA2 are EFS event-driven, so there is no OS events count requirement to proceed with these 2 analyses. Note that for IA3 and IA4, if the OS events accrue slower than expected, the Sponsor may conduct the analysis with additional 3 months of follow-up, or when the specified number of events is observed, whichever occurs first. If the final targeted OS events cannot be reached by the end of year 5 after last participant randomized, the final OS analysis will be conducted at the end of year 5 after last participant randomized at the latest.

Results of the interim analyses will be reviewed by the DMC. If the EFS or OS null hypothesis is rejected prior to the final analysis, the DMC may recommend stopping the trial early for efficacy. Details on how the above planned analyses are incorporated into establishing Type I error control and efficacy boundaries are discussed further in Section 10.8 – Multiplicity.

10.8 Multiplicity

The overall Type I error rate is strongly controlled at a 0.025 (one-sided) α level. The trial uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as interim efficacy analyses; this method specifically extends previous graphical multiplicity methods to cases where individual hypotheses are tested in a group sequential fashion using an error spending approach. Figure 2 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. This is further explained below.

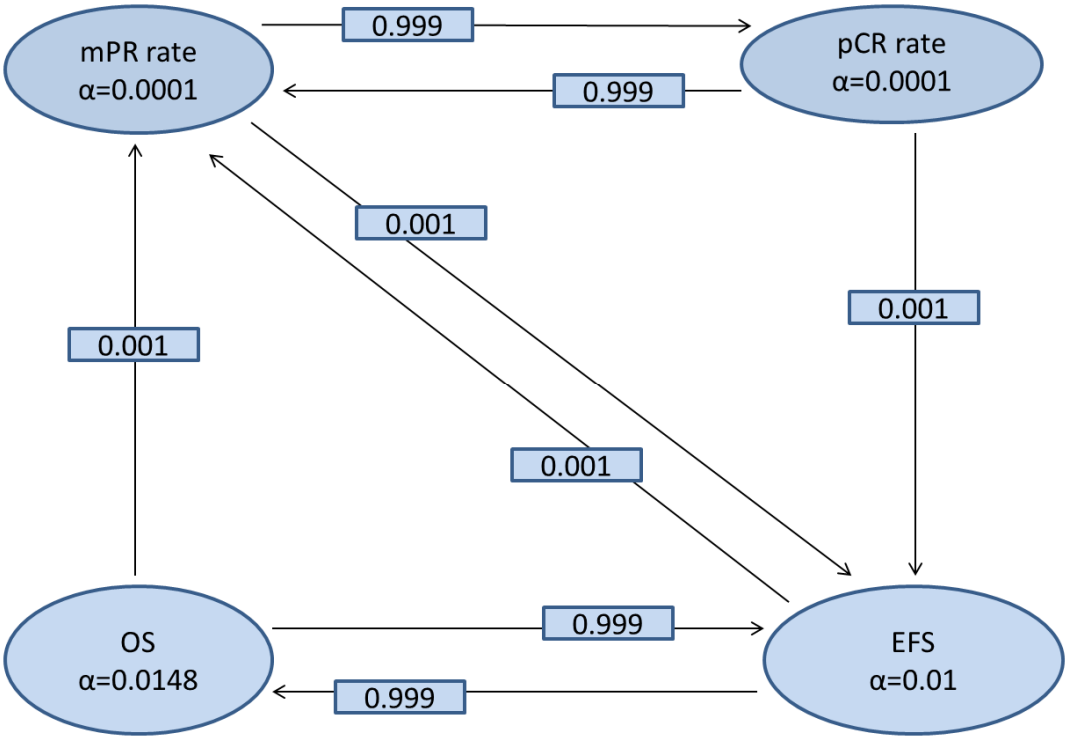


Figure 2 Multiplicity Graph for Type I Error Control

10.8.1 Major Pathological Response Rate

The trial initially allocates α=0.0001, one-sided, to test mPR rate. If the null hypothesis for pCR rate is rejected, Figure 2 shows that its α=0.0001 is essentially fully reallocated to mPR rate hypothesis testing. Only data from IA1 will be used to test the mPR rate. However, if the test does not reach statistical significance at IA1, the p-value from IA1 can be compared to an updated α-level if the null hypotheses for both EFS and OS are rejected at a later time. Power at the possible α-levels as well as the approximate treatment difference required to reach the bound (⊿mPR rate) are shown in Table 13, assuming underlying 22% and 42% mPR rates in the control and experimental groups, respectively.

Table 13 Possible α-levels and Approximate mPR Rate Difference Required to Demonstrate Efficacy for mPR rate

A	~⊿mPR rate	Power
0.0001	12.38%	0.991
0.0002	11.78%	0.994
0.0249	6.53%	1.000
0.025	6.37%	1.000

10.8.2 Pathological Complete Response Rate

The trial initially allocates α=0.0001, one-sided, to test pCR rate. If the null hypothesis for mPR rate is rejected, Figure 2 shows that its α=0.0001 is essentially fully reallocated to pCR rate hypothesis testing. Only data from IA1 will be used to test the pCR rate. However, if the test does not reach statistical significance at IA1, the p-value from IA1 can be compared to an updated α-level if the null hypotheses for EFS, OS and mPR rate are all rejected at a later time. Power at the possible α-levels as well as the approximate treatment difference required to reach the bound (⊿pCR rate) are shown in Table 14, assuming underlying 8% and 24% pCR rates in the control and experimental groups, respectively.

Table 14 Possible α-levels and Approximate pCR Rate Difference Required to Demonstrate Efficacy for pCR rate

A	~⊿pCR rate	Power
0.0001	9.73%	0.993
0.0002	9.26%	0.996
0.025	5.13%	1.000

10.8.3 Event-free Survival

The trial initially allocates α=0.01, one-sided to test EFS. If the null hypothesis for OS is rejected, Figure 2 shows that its α=0.0148 is essentially fully reallocated to EFS hypothesis testing. If the null hypotheses for mPR rate and pCR rate are both rejected, their accumulative α=0.0002 is fully reallocated to EFS hypothesis testing. The EFS null hypothesis may be tested at α=0.01 (if OS null hypothesis is not rejected, and not both of mPR and pCR null hypotheses are rejected), α=0.0102 (if both of mPR and pCR null hypotheses are rejected while OS null hypothesis is not), α=0.0248 (if OS null hypothesis is rejected while not both of mPR and pCR null hypotheses are rejected), or α=0.025 (if null hypotheses for mPR, pCR and OS are all rejected). Table 15 shows the boundary properties for α=0.01 and α=0.025 for the planned analysis testing of EFS, which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for EFS at each α-level. If the actual number of EFS

events at the interim analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly.

Table 15 Efficacy Boundaries and Properties for Planned Analyses of EFS

Analysis	**Value**	**α = 0.01**	**α=0.025**
IA1: 78%* N: 786 Events: 326 Month+: 48	Z statistics	2.6842	2.2772
	p (1-sided)§	0.0036	0.0114
	HR at boundI	0.7428	0.7770
	P (Cross) if HR = 1†	0.0036	0.0114
	P (Cross) if HR = 0.7#	0.7045	0.8264
IA2: N: 786 Events: 416 Month+: 60	Z statistics	2.3697	2.0207
	p (1-sided) §	0.0089	0.0217
	HR at boundI	0.7925	0.8201
	P (Cross) if HR = 1†	0.0100	0.0250
	P (Cross) if HR = 0.7#	0.9010	0.9495

*Percentage of total number of required events needed at each interim analysis.
§The nominal α for testing.
IThe approximate HR required to reach an efficacy bound.
†The probability of crossing a bound under the null hypothesis.
+The analysis timeline is projected based on blinded clinical data monitoring.
#The probability of crossing a bound under the alternative hypothesis.

Note that if the OS null hypothesis is rejected at an interim or final analysis, the previously computed EFS test statistics for the EFS interim or final analyses may be re-evaluated versus the updated bounds considering the α reallocation from the OS hypothesis.

10.8.4 Overall Survival

The OS hypothesis may be tested at α=0.0148 (if EFS null hypothesis is not rejected, and not both of mPR and pCR null hypotheses are rejected), α=0.0248 (if EFS null hypothesis is rejected while not both of mPR and pCR null hypotheses are rejected), or α=0.025 (if null hypotheses for mPR, pCR and EFS are all rejected). Table 16, analogous to the EFS table above, shows the boundary properties for OS hypothesis testing, which were derived using a Lan-DeMets O'Brien-Fleming spending function. If the actual number of OS events at the interim analyses differs from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly. Note that if the OS event accumulation is much slower than expected and the final targeted OS events cannot be reached by the end of year 5 after last participant randomized, the final OS analysis will be conducted at the end of year 5 after last participant randomized at the latest. In this situation, all of the remaining available alpha by then will be used in the final OS analysis.

Table 16 Efficacy Boundaries and Properties for Planned Analyses of OS

Analysis	Value	α=0.0148	α=0.025
IA1: 41%* Events: 159 Month+: 48	Z statistics	3.6216	3.3023
	p(1-sided) §	0.0001	0.0005
	HR at bound‖	0.5630	0.5922
	P(Cross) if HR = 1†	0.0001	0.0005
	P(Cross) if HR = 0.7#	0.0849	0.1458
IA2: 58%* Events: 225 Month+: 60	Z statistics	2.9968	2.7292
	p(1-sided) §	0.0014	0.0032
	HR at bound‖	0.6706	0.6949
	P(Cross) if HR = 1†	0.0014	0.0033
	P(Cross) if HR = 0.7#	0.3759	0.4809
IA3: 74%* Events: 285 Month+: 72	Z statistics	2.6433	2.4075
	p(1-sided) §	0.0041	0.0080
	HR at bound‖	0.7310	0.7518
	P(Cross) if HR = 1†	0.0046	0.0091
	P(Cross) if HR = 0.7#	0.6496	0.7334
IA4: 88%* Events: 340 Month+: 84	Z statistics	2.4109	2.1965
	p(1-sided) §	0.0080	0.0140
	HR at bound‖	0.7699	0.7880
	P(Cross) if HR = 1†	0.0094	0.0169
	P(Cross) if HR = 0.7#	0.8183	0.8703
FA: Events: 386 Month+: 96	Z statistics	2.2666	2.0666
	p(1-sided) §	0.0117	0.0194
	HR at bound‖	0.7939	0.8103
	P(Cross) if HR = 1†	0.0148	0.0250
	P(Cross) if HR = 0.7#	0.9004	0.9318

*Percentage of total number of required events needed at each interim analysis.
§The nominal α for testing.
‖The approximate HR required to reach an efficacy bound.
†The probability of crossing a bound under the null hypothesis.
+The analysis timeline is projected based on blinded clinical data monitoring.
#The probability of crossing a bound under the alternative hypothesis.

10.8.5 Safety Analyses

The DMC has responsibility for assessment of overall risk:benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. DMC review of efficacy data to assess the overall risk:benefit to trial participants will not require a multiplicity adjustment typically associated with a planned efficacy interim analysis. However, to account for any multiplicity concerns raised by the DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for EFS and OS adopting a conservative multiplicity adjustment will be pre-specified in the sSAP. This analysis will be performed if requested by the DMC.

10.9 Sample Size and Power Calculations

10.9.1 Sample Size and Power for Efficacy Analyses

The study is event-driven, and approximately 786 participants will be randomized in a 1:1 ratio into the pembrolizumab plus chemotherapy arm and the placebo plus chemotherapy arm.

For EFS, based on a target number of ~416 events at IA2 (ie, FA for EFS), the study has power of 90.1% to detect a hazard ratio of 0.7 at α=0.01. Power is increased to 94.9% at α=0.025. For OS, based on a target number of ~ 386 deaths at FA, the study has power of 90% (α=0.0148) or 93.2% (α=0.025) to detect a hazard ratio of 0.7. The sample size and power calculation for EFS and OS are based on the following assumptions:

- EFS follows an exponential distribution with a median of 21 months for the control group and 30 months for the experimental group.
- OS follows an exponential distribution with a median of 34 months for the control group and 48.6 months for the experimental group.
- The hazard ratio for EFS and OS between the experimental and control groups is 0.7.
- The enrollment period is 36 months with a ramp up period of 6 months.
- The monthly drop-out rate is 1% for both EFS and OS.

Based on the 786 participants, there is 99.1% power to detect a difference in mPR rates at the allocated α=0.0001 assuming an underlying 22% mPR rate in the control group and 42% in the experimental group. There is 99.3% power to detect a difference in pCR rates at the allocated α=0.0001 assuming an underlying 8% pCR rate in the control group and 24% in the experimental group.

The sample size and power calculations were performed in EAST and R (Package "gsDesign").

10.9.2 Sample Size and Power for Safety Analyses

For safety comparisons, risk differences between any 2 treatment groups are summarized in Table 17 for a variety of hypothetical observed incidence rates. The table demonstrates the width of the corresponding 95% confidence intervals for different incidence rates in the

treatment groups. These calculations assume there are 393 participants for each treatment group.

Table 17 Two-sided 95% Confidence Intervals of Differences in Incidence of AE Rates Between the Two Treatment Groups for 393 Participants in Each Treatment Arm

Incidence of Adverse Event		**Risk Difference**	
Treatment Group A (%)	Treatment Group B (%)	Percentage Points	95% CI[†]
5	15	-10	(-14.2, -5.8)
15	25	-10	(-15.8,-4.6)
25	35	-10	(-16.3,-3.5)
45	55	-10	(-17.1, -3.2)
55	65	-10	(-16.7, -3.1)
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. [†] Based on an asymptotic method [Farrington, C. P. and Manning, G. 1990].			

10.10 Subgroup Analyses

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

- Tumor stage (II, III)
- TPS (<50%, ≥50%)
- Histology (squamous, nonsquamous)
- Geographic region (East Asia, non-East Asia)
- Age category (<65, ≥65 years)
- Sex (female, male)
- Race (white, non-white)
- Smoking status (never, former, current)
- Known *EGFR* activating mutation status (Yes, No)
- *ALK* translocation status (Yes, No)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

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12. Appendices

12.1 Appendix 1: Study Governance Considerations

MSD Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are

reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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.

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.

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 institutional review board, ethics review committee (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 trial 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.

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 trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form 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 trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

Committees Structure

Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee comprises:

- Sponsor personnel
- Investigators participating in the trial
- Consulting therapeutic-area experts and clinical trialists

The Trial Steering Committee will provide guidance on the operational aspects of the trial.

Specific details regarding responsibilities and governance of the Trial Steering Committee will be described in a separate charter.

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) or Trial Steering Committee regarding the study.

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not

be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial 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 KN671 team; meeting facilitation; the trial 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.

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.

Compliance with Trial 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 trial is solely responsible for determining whether the trial 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 trial, 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 trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (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 Good Clinical Practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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 MSD 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 trial reimbursed to the investigator by the Sponsor.

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

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

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.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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.

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this trial as outlined in Section 9.9 – Future Biomedical Research Sample Collection will be used in various experiments to understand:

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

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

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

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

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial 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 trial site under secure storage for regulatory reasons.

A template of each trial 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 electronic Case Report Forms (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 trial purposes.

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

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial 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 trial 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 trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3,4]

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

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

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may

withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3,4]

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

Specimens from the trial 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 trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

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

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

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

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

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

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

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

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

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. 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. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Appendix 3: Contraceptive Guidance

Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

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

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

Definition of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

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 <u>Meeting</u> the AE Definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, 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.

Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study).

  Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 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 9.3.5 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.

A 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a 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, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe 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 Adverse Event case report forms/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 for Adverse Events (CTCAE), version 4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  ● Grade 1: Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
  ● Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  ● Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or 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 adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event 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 adverse event:
    - **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 trials 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 trial is a single-dose drug trial); 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 trial?
      - 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **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 case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 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 adverse event 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 adverse event 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 AE, SAE, 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 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection 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 electronic data collection 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).

12.5 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 (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* 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.	

12.6 Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 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 the approved chemotherapy package insert guidelines.

Table 18 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH % Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
	PT/INR and aPTT/PTT			
Chemistry	Blood Urea Nitrogen (BUN)[1]	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 or Carbon Dioxide[2]	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 • Microscopic examination (if blood or protein is abnormal) • Pregnancy test, as needed for women of childbearing potential (WOCBP) during screening and and/or within 24 hours of first dose (neoadjuvant and adjuvant treatment phases)			
Other Tests	• Serology: HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody, if mandated by local health authority • Thyroid panel: TSH, T3/FT3, and T4/FT4			
1. Urea sample will be analyzed if the site cannot perform BUN. 2. If this test is not done as part of local standard of care, this test does not need to be performed.				

Investigators must document their review of each laboratory safety report.

12.7 Appendix 7: Country-specific Requirements

12.7.1 Germany-specific Requirements

Section 2.1 Trial Screening Procedures:

- HIV, hepatitis B and C screen, and TB testing is required during Screening.
- Pancreatic function (amylase and lipase) test is required (within 10 days prior to the start of study treatment).

Section 2.3 Postoperative (Adjuvant Treatment): Pancreatic function (amylase and lipase) test is required.

Section 2.4 End of Treatment and Follow-up Visits (Arm A and B):

- Pancreatic function (amylase and lipase) test is required as clinically indicated.

Section 6.1 Inclusion Criteria

- Inclusion Criterion # 9: Amylase and lipase ≤1.5 ULN is required for inclusion.

Section 6.2 Exclusion Criteria

- Exclusion Criterion #9: HIV testing is required.
- Exclusion Criterion #10: Hepatitis B and hepatitis C testing is required.
- Exclusion Criterion #11: TB testing is required.

Section 12.6 Appendix 6: Clinical Laboratory Tests

- TB testing is required.
- Amylase and lipase tests are required.

12.7.2 China-specific Requirements

Biomarker sample collection, testing, and analysis as described in the following sections will be dependent on approval by the Human Genetic Resources Administration of China for participants enrolled in China:

Section 2 Schedule of Activities

Section 5.4.1.4 Planned Exploratory Biomarker Research

Section 6 Study Population

Section 9.8 Biomarkers

Future Biomedical Research will not be conducted in China.

Section 5.1 Overall Design

After enrollment of the global study is complete, the study may remain open to enrollment in China until the target number of participants in China has been enrolled to meet local requirements.

Section 7.1 Treatments Administered

All study interventions will be administered on an outpatient basis; however, hospitalization is acceptable if it is standard procedure for the local site.

Appendix 6 Clinical Laboratory Tests

Routine urinalysis by dipstick: A urine leukocyte is acceptable when the leukocyte esterase by dipstick cannot be performed.

Section 2.1 Trial Screening Procedures:

- *EGFR/ALK* testing results: In China, results will be collected from participants with nonsquamous histology and entered into the EDC collector.

Section 7.1 Treatment Administered

- Cisplatin unit dose strength is 20mg/vial.
- Cisplatin and pemetrexed dose formulation are lyophilized powder.

Section 10.5.1 Efficacy Analysis Populations:

- Participants in China randomized in the extension portion of the study will not be included in the above primary efficacy analysis population. The ITT participants in China, including all participants in China randomized in the global study and the extension portion of the study will be analyzed.

Section 10.5.2 Safety Analysis Populations:

- The participants in China randomized and treated in the extension portion of the study will not be included in the primary safety analysis population. The APaT participants in China, including all randomized participants in China (in the global study and extension portion of the study) who received at least 1 dose of study treatment, as well as the APrS participants in China, including all randomized participants in China (in the global study and extension portion of the study) who receive at least 1 dose of neoadjuvant study treatment and also undergo on-study surgery, will be analyzed per local regulatory requirements.

12.7.3 Japan-specific Requirements

Section 2 Schedule of Activities (footnotes)

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

  SpO2 at the timing of vital sign assessment.

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

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

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

Section 7.1 Treatments Administered

Table 2 Study Interventions

Pemetrexed used in this study is categorized as “test product(s)” in Japan.

Intravenous solution, not provided by the Sponsor, as placebo for pembrolizumab in this protocol is not categorized as “product(s) used in the clinical trial” in Japan.

12.7.4 Ireland

Section 2.1 Trial Screening Procedures:

- HIV, hepatitis B and C screen, and TB testing is required during Screening.

Section 7.7 Concomitant Therapy

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

  Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 7.7.3 for information on COVID-19 vaccines.

12.7.5 United Kingdom

Section 6.1 Inclusion Criteria - Demographics

Participants assigned male sex at birth are to be advised to seek counselling on sperm storage before starting treatment with pemetrexed, etoposide, and/or platinum-based therapy as per respective SmPCs.

Section 7.7 Concomitant Therapy

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

  Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 7.7.3 for information on COVID-19 vaccines.

12.8 Appendix 8: List of Abbreviations

Abbreviation/Term	Definition
1L	first-line
3X	3 times
AE	adverse event
AEOSI	adverse event of special interest
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ALT	alanine aminotransferase
ALK	anaplastic lymphoma kinase
APaT	all participants as treated
APrS	all participants receiving surgery
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BCG	*Bacillus* Calmette-Guérin
BICR	Blind, independent committee review
BSA	Body Surface Area
CBC	complete blood count
CPET	cardiopulmonary exercise test
CI	confidence interval
C_{max}	serum maximum concentration
CR	complete response
CrCl	calculated creatinine clearance
CRF	case report form
CRP	C-reactive protein
C-Path	Critical Path Institute
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ePRO	electronic patient-reported outcome
ECIs	events of clinical interest
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
EFS	Event-free survival
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee

Abbreviation/Term	Definition
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Cancer
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30
EORTC-QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer 13
EOT	end of treatment
ERC	Ethics Review Committee
FA	final analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FSR	first site ready
FEV_1	forced vital capacity
GCP	Good Clinical Practice
GFR	glomerular filtration rate
Gy	Gray
HCV	hepatitis c virus
HIV	human immunodeficiency virus
HOSP	Hospitalization form
HPRA	Health Products Regulatory Authority
HR	hazard ratio
HRQoL	health-related quality of life
HSU	hospital specialty unit
IA1	interim analysis 1
IA2	interim analysis 2
IA3	interim analysis 3
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IC	investigator's choice
IEC	Independent Ethics Committees
IRB	Institutional Review Board
ITT	intent-to-treat
IV	Intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
KL-6	Krebs von den Lungen 6
KN	Keynote

Abbreviation/Term	Definition
MASCC	Multinational Association of Supportive Care in Cancer
mPR	Major pathological response
MRI	magnetic resonance imaging
MSD K.K.	Merck Sharp & Dohme Kabushiki Kaisya
MSI	microsatellite instability
N2	mediastinal lymph node
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSCLC-SAQ	The Non-small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
pCR	Pathological complete response
PD	Progressive disease
PD-1	programmed cell death protein-1
PFS	progression-free survival
PK	pharmacokinetic
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PPO	predicted post-operative
PPO DLCO	percent predicted postoperative diffusing capacity for carbon monoxide
PRO	patient-reported outcome
PR	partial response
PS	performance scale
PT	prothrombin time
QLQ-LC13	Quality of Life Questionnaire and Lung Cancer Module 13
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
RNA	Ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
RMST	restricted mean survival time
RR	response rate
RT	radiation therapy
SAE	serious adverse events
SAP	Statistical Analysis Plan
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOA	schedule of activities
SOC	standard of care

Abbreviation/Term	Definition
SOP	Standard operating procedure
SP-D	surfactant protein-D
SpO2	peripheral capillary oxygen saturation
sSAP	supplemental Statistical Analysis Plan
TB	Tuberculosis
TPS	tumor proportion score
TSH	Thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VO2 max	maximal oxygen consumption
WOCBP	Woman of childbearing potential

12.9 Appendix 9: MASCC 2016 Guidelines

Table 19 Recommended Doses of Corticosteroids* (Dexamethasone)

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

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

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

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

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