Official Protocol Title:	A Phase 3, Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of Stereotactic Body Radiotherapy (SBRT) with or without Pembrolizumab (MK-3475) in Participants with Unresected Stage I or II Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-867)
NCT number:	NCT03924869
Document Date:	11-OCT-2024

TITLE PAGE

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Protocol Title:

A Phase 3, Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of Stereotactic Body Radiotherapy (SBRT) with or without Pembrolizumab (MK-3475) in Participants with Unresected Stage I or II Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-867)

Protocol Number: 867-08

Compound Number: MK-3475

Sponsor Name: Merck Sharp & Dohme LLC

(hereafter called the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

NCT	NCT04380636
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JRCT	JRCT2080224826
WHO	Not applicable
UTN	U1111-1275-8515
IND	116,833

Approval Date: 11 October 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 8	11-OCT-2024	This change was made to address new data and recommendations of the eDMC after an interim review of the data; specifically, to stop the study as pembrolizumab in combination with SBRT did not demonstrate an improvement in event-free survival or overall survival, the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial.
Amendment 7	24-APR-2024	Update definitions of disease recurrence and biopsy information to capture event-free survival events more accurately.
Amendment 6	29-NOV-2023	The primary purpose of this amendment is to update the statistical analysis plan based on new data from literature.
Amendment 5	07-JUN-2022	Update to include female contraception requirements following radiotherapy.
Amendment 4	14-DEC-2021	Update inclusion criteria to include male contraception requirements.
Amendment 3	24-AUG-2021	Update inclusion criteria and stratification factors from Stage I-IIA to Stage I-II. Also, update SBRT regimens to better reflect current global standard of care in the study population. To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
Amendment 2	26-FEB-2021	Update inclusion criteria and stratification factors to include patients who are medically operable but refuse surgery to the study population.
Amendment 1	16-SEP-2019	Expansion of the available SBRT regimens for peripheral tumors.
Original Protocol	14-FEB-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

This change was made to address new data and recommendations of the eDMC after an interim review of the data; specifically, to stop the study as pembrolizumab in combination with SBRT did not demonstrate an improvement in event-free survival or overall survival, the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Hypotheses, Objectives, and Endpoints: Added NOTE to confirm that based on the data from an interim safety and efficacy analysis, the study will be stopped. Safety endpoints analyses will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after the IA1 cutoff date. Participants who are still on study treatment will no longer need to provide some samples and assessments. Follow-up and Survival Follow-up visits will no longer be conducted.	This change was made to address new data and recommendations of the eDMC after an interim review of data.

Section # and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 1.1, Synopsis	Study Governance Committees: Executive Oversight Committee and eDMC are no longer applicable.	Refer to Section 1.1 rationale above..
Section 1.3, Schedule of Activities (SoA)	Added text that participants who are still on study treatment will no longer need to provide some samples and assessments. Follow-up and Survival Follow-up visits will no longer be conducted.	Refer to Section 1.1 rationale.

Section # and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 2.3, Benefit/Risk Assessment	Added NOTE to confirm that based on the data from an interim safety and efficacy analysis, the study will be stopped. Safety endpoints analyses will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after IA1 cutoff date.	Refer to Section 1.1 rationale.
Section 3, HYPOTHESES, OBJECTIVES, AND ENDPOINTS	Added NOTE to confirm that based on the data from an interim safety and efficacy analysis, the study will be stopped. Safety endpoints analyses will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after IA1 cutoff date. Participants who are still on study treatment will no longer collect some samples and assessments. Follow-up and Survival Follow-up visits will no longer be conducted.	Refer to Section 1.1 rationale.
Section 4.1, Overall Design	Added NOTE to confirm that based on the data from an interim safety and efficacy analysis, the study will be stopped. Safety endpoints analyses will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after IA1 cutoff date. Participants who are still on study treatment will no longer collect some samples and assessments. Follow-up and Survival Follow-up visits will no longer be conducted.	Refer to Section 1.1 rationale.
	Added text that early study termination as part of participants who discontinue.	To align with text in section 8.11.4.1 and 8.11.4.2.
Section 6.1, Study Intervention(s) Administered	Added text that participants who are still on study treatment will no longer collect some samples and assessments. Follow-up and Survival Follow-up visits will no longer be conducted.	Refer to Section 1.1 rationale.
Section 6.3.3, Blinding	Added text that the study was unblinded.	Refer to Section 1.1 rationale.

Section # and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 7.1, Discontinuation of Study Intervention	Added NOTE to confirm that based on the data from an interim safety and efficacy analysis, the study will be stopped. Safety endpoints analyses will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after IA1 cutoff date. Participants who are still on study treatment will no longer collect some samples and assessments. Follow-up and Survival Follow-up visits will no longer be conducted.	Refer to Section 1.1 rationale.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added text that Central tumor response assessments will be discontinued, and local tumor imaging should continue per SOC schedule.	Refer to Section 1.1 rationale.
Section 8.2.1.3, Assessment of Disease Recurrence	Added text that Disease recurrence assessments will be discontinued.	Refer to Section 1.1 rationale.
Section 8.8, Biomarkers	Text added that Biomarker sample collections will be discontinued.	Refer to Section 1.1 rationale.
Section 9, Statistical Analysis Plan	Amended the SAP and added NOTE to confirm that based on the data from an interim safety and efficacy analysis, the study will be stopped. Safety endpoints analyses will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after IA1 cutoff date.	Refer to Section 1.1 rationale.

Section # and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 9.1, Statistical Analysis Plan Summary	Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints collected from participants after IA1 cutoff date.	Refer to Section 1.1 rationale.
	Interim Analyses: Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.	Refer to Section 1.1 rationale.
	Sample Size and Power: Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.	Refer to Section 1.1 rationale.
Section 9.6, Statistical Methods	Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints collected from participants after IA1 cutoff date.	Refer to Section 1.1 rationale.
Section 9.7, Interim Analyses	Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.	Refer to Section 1.1 rationale.
Section 9.8, Multiplicity	Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.	Refer to Section 1.1 rationale.
Section 9.9, Sample Size and Power Calculations	Added text that all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.	Refer to Section 1.1 rationale.
Section 10.1.1, Code of Conduct for Interventional Clinical Trials	Expanded MSD.	To reflect entity name.
	Added EU CTR number.	Refer to Section 4.4 rationale for EU CTR.

Section # and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 10.1.3, Data Protection	Specified that the Sponsor will conduct this study in compliance with all applicable data and information of EU-approved rules.	Refer to Section 4.4 rationale for EU CTR.
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Added EU CTR number and corresponding website.	Refer to Section 4.4 rationale for EU CTR.
Section 10.1.7, Compliance with Law, Audit, and Debarment	Added serious breach reporting requirements.	Refer to Section 4.4 rationale for EU CTR.
Section 10.1.8, Data Quality Assurance	Added EU CTR requirement stipulating 25-year retention period after end of study.	Refer to Section 4.4 rationale for EU CTR.
	Updated text records and documents, including participants documented informed consent.	To provide clarity for text records and documents.
Throughout	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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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of Stereotactic Body Radiotherapy (SBRT) with or without Pembrolizumab (MK-3475) in Participants with Unresected Stage I or II Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-867)

Short Title: Phase 3 study of SBRT ± pembrolizumab for participants with unresected Stage I or II NSCLC

Acronym: MK-3475-867-08

Hypotheses, Objectives, and Endpoints:

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

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE¬867 (data cutoff 11-JUN-2024), the eDMC recommended stopping the study since pembrolizumab in combination with SBRT did not demonstrate an improvement in EFS (Event-Free Survival) or OS (Overall Survival), the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. All prespecified interim analyses after IA1 (Interim Analysis 1) and final analysis of the study described in the SAP (Statistical Analysis Plan) will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO (electronic patient-reported outcome) endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024.

In alignment with the study update memo sent to Investigators on 29-AUG-2024, all study participants must stop ongoing treatment with pembrolizumab/placebo. These participants must complete EOT (End of Trial) visit followed by Safety Follow-up visit per protocol. All remaining study participants who have completed the safety reporting windows for AEs and SAEs per protocol must be discontinued from the study. All study participants will undergo unblinding at the end of the study. Investigators may apply for unblinding participants per protocol in the interim.

As of Amendment 08, information regarding ePRO assessments (EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL EQ-5D-5L), biomarker samples (blood for genetic analysis, blood for ctDNA analysis, optional tumor sample), biopsies, and tumor imaging for BICR (blinded independent central review) will no longer be collected. Tumor imaging, biopsies, and disease management should be performed per local SOC and Investigator's discretion. Efficacy data collection, including Follow-up and Survival Follow-up visits for efficacy will no longer be conducted. Safety reporting for AEs and SAEs must adhere to time windows per protocol. Updated analyses are described in Section 9.

All objectives will compare administration of SBRT + pembrolizumab versus SBRT + placebo, unless otherwise indicated.

In male and female participants who are at least 18 years of age with unresected Stage I or II (limited Stage IIB N0, M0) NSCLC who have received no prior anticancer therapy for the present lung cancer:

Primary Objective	**Primary Endpoint**
Objective: To compare the Event-free Survival (EFS). **Hypothesis:** SBRT + pembrolizumab prolongs EFS compared to SBRT + placebo.	EFS: The time from randomization to an event defined as local, regional, or distant recurrence of the treated NSCLC or death from any cause.
Secondary Objectives	**Secondary Endpoints**
Objective: To compare Overall Survival (OS). **Hypothesis:** SBRT + pembrolizumab prolongs OS compared to SBRT + placebo.	OS: The time from randomization to death from any cause.
Objective: To evaluate the time to death or distant metastases.	Time to death or distant metastases: The time from randomization to the first documented distant metastases or death from any cause, whichever occurs first.
Objective: To evaluate the safety and tolerability of SBRT + pembrolizumab.	• Adverse events • Study intervention discontinuations due to AEs
Objective: To evaluate the change from baseline scores in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning scale.	Change from baseline scores, calculated for the following scales/items at a prespecified time point: global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 1), chest pain (EORTC QLQ-LC13 Item 10), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1-5).

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of Non-Small Cell Lung Cancer
Population	Participants with unresected Stage I or II (limited Stage IIB) NSCLC
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo-controlled
Study Blinding	Double-blind
Blinding Roles	Investigator Participants or Subjects Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 84 months 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 436 participants will be randomized in this study.

Intervention Groups and Duration:

Intervention Group Name	Drug / Treatment	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Arm 1	Pembrolizumab (MK-3475)	25 mg/mL	200 mg	IV Infusion	Q3W x17 cycles (~1 year) x 17 cycles (~1 year)	Test Product
Arm 1	SBRT	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48-50 Gy in 4 fractions (acceptable); 50-55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48-50 Gy in 4 fractions; 50-55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60-70 Gy in 8 fractions	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48 50 Gy in 4 fractions (acceptable); 50 55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48 50 Gy in 4 fractions; 50 55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60 70 Gy in 8 fractions	External Beam Radiation	~Q3D over 2 weeks	Background Treatment
Arm 2	Placebo	N/A	N/A	IV Infusion	Q3W × 17 cycles (~1 year)	Placebo

Intervention Group Name	Drug / Treatment	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Arm 2	SBRT	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48-50 Gy in 4 fractions (acceptable); 50-55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48-50 Gy in 4 fractions; 50-55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60-70 Gy in 8 fractions	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48 50 Gy in 4 fractions (acceptable); 50 55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48 50 Gy in 4 fractions; 50 55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60 70 Gy in 8 fractions	External Beam Radiation	~Q3D over 2 weeks	Background Treatment

C=cycle; D=day; IV=intravenous; N/A=not applicable; Q3D=every 3 days; Q3W=every 3 weeks; SBRT=stereotactic body radiotherapy

Total Number of Intervention Groups/Arms	2 arms
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent form (ICF) through the final protocol-specified contact. After a Screening phase of up to 42 days, each participant will be randomized to receive study intervention until disease recurrence is documented, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, death from any cause, investigator decision, participant decision, or withdrawal of consent, or until the participant has received 17 administrations of pembrolizumab or placebo (approximately 1 year). After the end-of-treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4. Participants who discontinue treatment for reasons other than documented disease recurrence, or recurrence has not been verified by Blinded Independent Central Review (BICR), will have posttreatment follow-up imaging for disease status until disease recurrence is documented radiographically and verified by BICR, withdrawing consent, pregnancy, death, or loss to follow-up, whichever occurs first. Images will also continue to be obtained after initiating the new anticancer therapy if recurrence has not been documented or verified by BICR. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study. Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

As of Amendment 08, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable as outlined 10.1.4.1 and 10.1.4.2.

Study Accepts Healthy Participants:

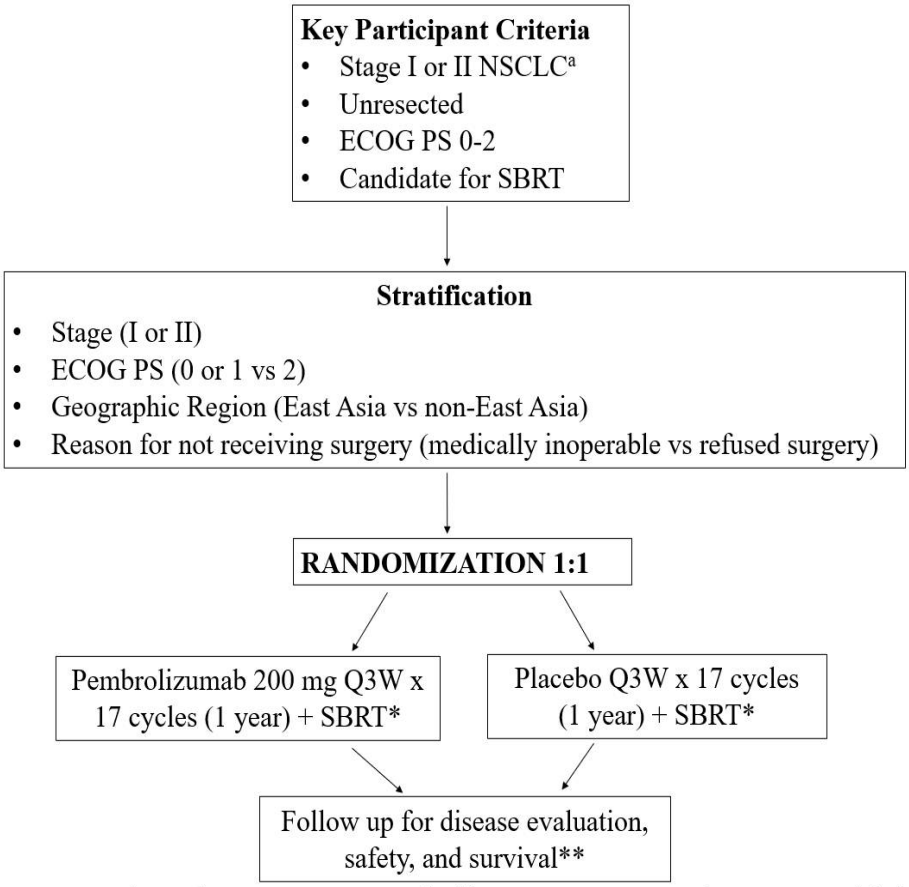
No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



Abbreviations: ECOG=Eastern Cooperative Oncology Group; NSCLC=non-small cell lung cancer; Q3W=every 3 weeks; SBRT=stereotactic body radiotherapy
[a] Includes limited Stage IIB (N0, M0) patients only
* Peripheral tumors: 45-60 Gy in 3 fractions (preferred); 48-50 Gy in 4 fractions (acceptable); 50-55 Gy in 5 fractions (acceptable)
Abutting the chest wall: 48-50 Gy in 4 fractions; 50-55 Gy in 5 fractions
Central tumors: 50-55 Gy in 5 fractions; 60-70 Gy in 8 fractions
**Telephone contact every 12 weeks

1.3 Schedule of Activities (SoA)

Table 1 Study Schedule of Activities: Pembrolizumab & SBRT Treatment

As of Amendment 08, information regarding ePRO assessments (EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL EQ-5D-5L), biomarker samples (blood for genetic analysis, blood for ctDNA analysis, optional tumor sample), biopsies, and tumor imaging for BICR will no longer be collected. Tumor imaging, biopsies, and disease management should be performed per local SOC and Investigator's discretion. Efficacy data collection, including Follow-up and Survival Follow-up visits for efficacy will no longer be conducted. Safety reporting for AEs and SAEs must adhere to time windows per protocol. Updated analyses are described in Section 9.

Study Period	Screening Phase	Treatment/Intervention (3-week cycles)				EOT	Posttreatment			Notes
Visit Number/Title	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 onward	DC	Safety FU	FU Visits	Survival FU	
Scheduling window (days)	-42 to -1	+3	±3	±3	±3	At time of DC + 7 days	30 days from last dose + 14 days	Q16W[a] (±7 days)	Q12W (±7 days)	
Administrative Procedures										
Informed Consent	X									
Informed Consent for Future Biomedical Research	X									FBR consent is optional.
Inclusion/Exclusion Criteria	X									
Participant Identification Card	X									
Medical/Surgical History	X									
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X		Prior and concomitant medications should be tracked from Day -42 forward.
Intervention (Randomization)	X									
Subsequent Antineoplastic Therapy Status						X	X	X	X	

Study Period	Screening Phase	Treatment/Intervention (3-week cycles)				EOT	Posttreatment			Notes
Visit Number/Title	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 onward	DC	Safety FU	FU Visits	Survival FU	
Scheduling window (days)	-42 to -1	+3	±3	±3	±3	At time of DC + 7 days	30 days from last dose + 14 days	Q16W[a] (±7 days)	Q12W (±7 days)	
Survival Status		←==========							X	After investigator-determined recurrence or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Drug Administration										
Pembrolizumab or Placebo		X	X	X	X					Maximum of 17 total cycles.
SBRT		X								Administered over a maximum 2-week interval, concurrent with Cycle 1. Preferably starting on C1D1 with a +7-day window allowed (up to C1D8 inclusive) following pembrolizumab/placebo administration.
Safety Procedures										
Complete physical examination including height and weight	X					X				To be performed within 7 days before start of study intervention.
Directed Physical Examination		X	X	X	X		X	X		Conducted at all treatment visits.
Vital Signs (pulse rate, blood pressure)	X	X	X	X	X	X	X	X		Conducted at all treatment visits.
12-lead ECG	X									

Study Period	Screening Phase	Treatment/Intervention (3-week cycles)				EOT	Posttreatment			Notes
Visit Number/Title	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 onward	DC	Safety FU	FU Visits	Survival FU	
Scheduling window (days)	-42 to -1	+3	±3	±3	±3	At time of DC + 7 days	30 days from last dose + 14 days	Q16W[a] (±7 days)	Q12W (±7 days)	
Urine or Serum Pregnancy Test (WOCBP only)	X		X	X	X	X	X	X		Screening test must be performed within 24 hours for urine or within 72 hours for serum prior to first dose of study intervention.
HIV, hepatitis B and C screen	X									Not required unless mandated by the local health authority.
Hematology and clinical chemistry laboratory assessment	X		X	X	X	X	X			Screening test must be performed within 7 days prior to first dose of study intervention. For all subsequent visits, laboratory assessments may be performed within 7 days prior to the visit.
PT/INR aPTT	X									Coagulation factors should be monitored closely throughout the study if participant is on anticoagulation therapy.

Study Period	Screening Phase	Treatment/Intervention (3-week cycles)				EOT	Posttreatment			Notes
Visit Number/Title	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 onward	DC	Safety FU	FU Visits	Survival FU	
Scheduling window (days)	-42 to -1	+3	±3	±3	±3	At time of DC + 7 days	30 days from last dose + 14 days	Q16W[a] (±7 days)	Q12W (±7 days)	
TSH, T3/FT3, T4/FT4	X		X		X	X	X			T3/FT3 and T4/FT4 only required if TSH is abnormal. Thyroid function tests are to be repeated at alternate cycles after Cycle 4. Beginning with Cycle 2, participants may receive pembrolizumab or placebo while thyroid function tests are pending. Screening test must be performed within 7 days prior to first dose of study intervention. Subsequent tests may be performed within 7 days prior to the visit.
Urinalysis	X				See Note	X	X			Screening test must be performed within 7 days prior to first dose of study intervention. Repeat test every 6 cycles during treatment phase within 7 days prior to the visit.
AE/SAE review		X	←==========				==========→	X	X	
ECOG performance status	X		X	X	X		X	X		To be assessed within 7 days prior to first dose of study intervention and prior to dosing during all subsequent scheduled visits.

Study Period	Screening Phase	Treatment/Intervention (3-week cycles)				EOT	Posttreatment			Notes
Visit Number/Title	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 onward	DC	Safety FU	FU Visits	Survival FU	
Scheduling window (days)	-42 to -1	+3	±3	±3	±3	At time of DC + 7 days	30 days from last dose + 14 days	Q16W[a] (±7 days)	Q12W (±7 days)	
Efficacy Measurements										
Tumor Imaging (CT/MRI)	X				See Note	X		X		Scans performed within the Screening period but before signing informed consent may be used if consistent with protocol requirements per Site Imaging Manual. Scans to be performed at Week 12, then Q16W from Week 12 until Week 156, and Q6M thereafter. Scans will continue to be performed after initiating new anticancer therapy if recurrence has not been documented or verified by BICR. Confirmation scans of recurrence should be performed 4 to 6 weeks after initial recurrence when biopsy is not medically appropriate.
Tumor Imaging (FDG-PET)	X									
Tumor Biopsy					See Note					Where medically appropriate, disease recurrence should be verified by biopsy at the first documented instance of recurrence by imaging or physical examination.

Study Period	Screening Phase	Treatment/Intervention (3-week cycles)				EOT	Posttreatment			Notes
Visit Number/Title	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 onward	DC	Safety FU	FU Visits	Survival FU	
Scheduling window (days)	-42 to -1	+3	±3	±3	±3	At time of DC + 7 days	30 days from last dose + 14 days	Q16W[a] (±7 days)	Q12W (±7 days)	
Biomarkers										
Blood for Genetic Analyses		X								Collect predose (see Section 8.8.1 for additional information).
Blood for ctDNA Analysis		X	X	X	See Note	X		X		Collect predose, C1, C2, C3, C6, then every 3 cycles through C15 and at EOT/DC. For the second year forward, align with imaging visits. During FU Visits, if a clinic visit is not feasible, blood for ctDNA collection will not be collected.
Optional Tumor Tissue Sample for Biomarker Analyses	X									Collection of a biopsy is not required for trial, and submission is contingent on signing Optional Tumor Tissue Collection Consent.
Patient-reported Outcomes (PROs)										
EORTC QLQ-C30		X			See Note	X	X	X		Administered prior to dosing at C1, C5, C9, C13, and C17. Also administered at treatment discontinuation, safety follow-up, and concurrently with follow-up tumor imaging (Q16W for the first 3 years, Q6M thereafter).
EORTC QLQ-LC13		X			See Note	X	X	X		
EuroQol (EQ)-5D-5L		X			See Note	X	X	X		

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CT=computed tomography; ctDNA=circulating tumor DNA; D=day; DC=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Core 30; EORTC QLQ-LC13=European Organization for Research and Treatment of Cancer Quality of Life Cancer Quality of Life Questionnaire Lung Cancer 13; EOT=end-of-treatment; EuroQoL EQ-5D-5L=European Quality of Life Five-dimension Five-level Scale Questionnaire; FBR=future biomedical research; FDG-PET=fluorodeoxyglucose-positron emission tomography; FU=follow-up; HIV=human immunodeficiency virus; MRI=magnetic resonance imaging; PT/INR=prothrombin time/international normalized ratio; Q6M=every 6 months; Q16W=every 16 weeks; SAE=serious adverse event; SBRT=stereotactic body radiotherapy; SOP=standard operating procedure; T3/FT3=(free) triiodothyronine; T4/FT4=(free) thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

Note: Country-specific differences are noted in Appendix 7.

a. Follow-up visits should be aligned to CT scans as described in the tumor imaging section of Table 1– Schedule of Activities.

2 INTRODUCTION

Lung cancer is the most common malignancy in the world, with an estimated global incidence in 2018 of 2.1 million new cases of lung cancer (comprising 12% of total new global cancer cases) and an associated 1.8 million deaths [Bray, F., et al 2018]. Due to widespread continued cigarette smoking, lung cancer will remain a significant worldwide public health problem for the foreseeable future.

NSCLC represents 80% to 85% of all lung cancers [National Cancer Institute 2016]. At the time of diagnosis, approximately 57% of patients with NSCLC had metastatic (Stage IV) disease, and 22% have tumors with regional (including nodal) spread (some Stage IIB and III) [National Cancer Institute 2018]. Patients with local disease and no nodal involvement (Stage I, IIA, and some IIB) constitute 16% of cases at initial diagnosis, with the remaining 5% not having staging completed [National Cancer Institute 2018].

Standard treatment for patients with Stage I or II NSCLC (any T, N0, M0 staging) is surgical resection, typically lobectomy [National Comprehensive Cancer Network 2018] [Postmus, P. E., et al 2017] [Pisters, K. M. W. and Le Chevalier, T. 2005]. However, in a subset of patients (approximately 4% of all lung cancers diagnosed), surgery is not an option due to underlying comorbidities. These patients may be deemed medically inoperable due to severe single organ impairment, or to moderate or severe multiple organ impairment [Guckenberger, M., et al 2017] [Videtic, G. M. M., et al 2017] [Rodrigues, G., et al 2015] [De Ruysscher, D., et al 2017] [Charlson, M. E., et al 1987] [Brunelli, A., et al 2013] [Fleisher, L. A., et al 2014]. There is no accepted definition of the physiologic abnormalities that render a patient unable to undergo thoracic surgery. Typically, the decision to pursue non-operative therapy is made by the medical oncologist/radiation oncologist in consultation with a thoracic surgeon. Institutions with a multidisciplinary tumor board often discuss the management of these complicated patients and make recommendations to the treating physician.

For medically inoperable patients, or patients refusing surgery, with Stage I or II NSCLC, SBRT is the recommended course of treatment [Tandberg, D. J., et al 2018]. SBRT consists of ablative doses of radiotherapy applied over a short period of time. The local control rate with SBRT is similar to that achieved with surgery. Although the 5-year survival is between 50% and 70% [Garrett, M., et al 2017], SBRT has been reported to have a poorer long-term survival rate than lobectomy [Bryant, A. K., et al 2018]. Thus, additional therapy, or a combination that would be tolerated by this medically compromised patient cohort, is needed to improve treatment results. While surgical resection is the preferred treatment for early-stage NSCLC, SBRT is currently considered the standard of care for patients with early-stage NSCLC who have elected not to have an operation after appropriate multidisciplinary consultation [Postmus, P. E., et al 2017] [Guckenberger, M., et al 2017] [Videtic, G. M. M., et al 2017] [National Comprehensive Cancer Network 2020]. Multiple prospective and retrospective studies have shown that SBRT, when delivered to operable early-stage NSCLC patients, achieved 3-year OS rates of 77% to 95%, 5-year OS rates of 45% to 70%, and 5-year local control rates of 86% to 97%, which are comparable to long-term surgical data [Daniels, C. P., et al 2019].

2.1 Study Rationale

SBRT and immunotherapy, such as pembrolizumab, are synergistic due to the immunogenic cell death caused by the former and the mechanism of action, efficacy, and favorable toxicity profile of the latter. Animal experiments have documented that tumor necrosis caused by high dose hypo-fractionated radiotherapy, such as that used in SBRT, results in increased antigen production, increased antitumor T-cells, and a decrease in T-reg cells [Lugade, A. A., et al 2005] [Schaue, D., et al 2012]. Radiotherapy has also been shown to favorably affect the immune response by facilitating: 1) the translocation of calreticulin to the tumor cell surface, which increases the uptake of tumor cells by dendritic cells (DC) [Gameiro, S. R., et al 2014], 2) the extracellular release of HMGB1, which interacts with the DC surface TLR4 and aids in antigen presentation to T-cells [Apetoh, L., et al 2007], 3) release of ATP, which stimulates DCs to secrete interleukins necessary for priming T-cells [Aymeric, L., et al 2010].

Published studies have demonstrated the benefit and safety of chemoradiotherapy followed by the sequential administration of a checkpoint inhibitor for patients with NSCLC. The PACIFIC trial compared maintenance durvalumab to placebo in patients with unresectable Stage III NSCLC who had no evidence of disease progression following definitive chemoradiotherapy [Antonia, S. J., et al 2017] [Antonia, S. J., et al 2018]. Significant improvement in progression-free survival (PFS) and OS was obtained with an acceptable small increase in AEs. In a secondary analysis of KEYNOTE-001, PFS and OS were significantly longer in patients with NSCLC treated with pembrolizumab who had previously received extracranial radiotherapy than in those patients who had not received extracranial radiotherapy [Shaverdian, N., et al 2017].

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

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

objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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

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

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

There are no other trials currently being conducted by MSD in this patient population.

2.2.4 Information on Other Study-related Therapy: SBRT

SBRT has become the treatment of choice for patients with unresected NSCLC who refuse surgery or are medically inoperable [National Comprehensive Cancer Network 2018] [Guckenberger, M., et al 2017] [Postmus, P. E., et al 2017]. Hypo-fractionation schedules place less of a burden on the patient and provide a local control rate similar to that obtained with conventional radiotherapy [Chang, J. Y., et al 2014] [Sun, B., et al 2017]. Prescribed dose and fractionation ranges are determined by whether the lung tumor location is central, peripheral, or abutting the chest wall [Guckenberger, M., et al 2017]. A biologically effective dose (BED) ≥100 Gy is accepted as required for efficacy [Guckenberger, M., et al 2017] [Postmus, P. E., et al 2017] [Senthi, S., et al 2013]. This BED can be achieved with the dosing described in this protocol.

Though dose and scheduling vary within the above categories, KEYNOTE-867 is designed with validated schedules that fall within published guidelines [National Comprehensive Cancer Network 2018] [Guckenberger, M., et al 2017]. In this study, peripheral tumors will be treated with 3 fractions totaling 45 to 60 Gy (preferred regimen), or 4 fractions totaling 48 to 50 Gy (acceptable regimen), or 5 fractions totaling 50 to 55 Gy (acceptable regimen) while central tumors, defined as within 2 cm of the proximal bronchial tree and/or abutting the mediastinal pleural, will receive 5 fractions totaling 50 to 55 Gy or 8 fractions totaling 60 to 70 Gy, and tumors abutting the chest wall will receive 4 fractions totaling 48 to 50 Gy or 5 fractions totaling 50 to 55 Gy. Ultra-central tumors, defined as tumors whose PTV directly contacts or overlaps the proximal bronchial tree, trachea, mainstem bronchus, esophagus, pulmonary vein, or pulmonary artery, are excluded. Details of the required equipment, treatment planning, and credentialing of the site are contained within the Radiotherapy QA manual.

Recently, results of a Phase 2 randomized (1:1) open-label study evaluating SBRT with or without nivolumab in patients with stage IA-IIB (N0) NSCLC per AJCC 8th staging system who are medically inoperable or refuse surgery were published [Chang, J. Y., et al 2023]. The primary endpoint was 4-year EFS (local, regional, or distant recurrence; second primary lung cancer; or death). A total of 156 patients were randomly assigned, and 141 patients received assigned therapy (75 SBRT and 66 SBRT + nivolumab). At median 33-month follow-up, in the ITT analysis, the 4-year EFS in the SBRT group was 53% (42%–67%) and in the SBRT + nivolumab group was 77% (66%–91%) with HR 0.42; 95% CI 0.22–0.80; p=0.0080).

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. However, pembrolizumab and SBRT are independently effective in the treatment of NSCLC. Available evidence demonstrates that the 2 modalities can be administered in proximity without increased toxicity [Theelen, W. S. M. E., et al 2019] [Campbell, A. M., et al 2018].

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

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE¬867 (data cutoff 11-JUN-2024), the eDMC recommended stopping the study since pembrolizumab in combination with SBRT did not demonstrate an improvement in EFS or OS, the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. All prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE¬867 (data cutoff 11-JUN-2024), the eDMC recommended stopping the study since pembrolizumab in combination with SBRT did not demonstrate an improvement in EFS (Event-Free Survival) or OS (Overall Survival), the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. All prespecified interim analyses after IA1 (Interim Analysis 1) and final analysis of the study described in the SAP (Statistical Analysis Plan) will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO (electronic patient-reported outcome) endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024.

In alignment with the study update memo sent to Investigators on 29-AUG-2024, all study participants must stop ongoing treatment with pembrolizumab/placebo. These participants must complete EOT (End of Trial) visit followed by Safety Follow-up visit per protocol. All remaining study participants who have completed the safety reporting windows for AEs and SAEs per protocol must be discontinued from the study. All study participants will undergo unblinding at the end of the study. Investigators may apply for unblinding participants per protocol in the interim.

As of Amendment 08, information regarding ePRO assessments (EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL EQ-5D-5L), biomarker samples (blood for genetic analysis, blood for ctDNA analysis, optional tumor sample), biopsies, and tumor imaging for BICR (blinded independent central review) will no longer be collected. Tumor imaging, biopsies, and disease management should be performed per local SOC and Investigator's discretion. Efficacy data collection, including Follow-up and Survival Follow-up visits for efficacy will no longer be conducted. Safety reporting for AEs and SAEs must adhere to time windows per protocol. Updated analyses are described in Section 9.

All objectives will compare administration of SBRT + pembrolizumab versus SBRT + placebo, unless otherwise indicated.

In male and female participants who are at least 18 years of age with unresected Stage I or II (limited Stage IIB N0, M0) NSCLC who have received no prior anticancer therapy for the present lung cancer:

Primary Objective	**Primary Endpoint**
Objective: To compare the Event-free Survival (EFS). **Hypothesis:** SBRT + pembrolizumab prolongs EFS compared to SBRT + placebo.	EFS: The time from randomization to an event defined as local, regional, or distant recurrence of the treated NSCLC or death from any cause.
The study is considered to have met its primary objective if pembrolizumab plus SBRT is superior to placebo plus SBRT in EFS at an interim analysis or final analysis.	
Secondary Objectives	**Secondary Endpoints**
Objective: To compare Overall Survival (OS). **Hypothesis:** SBRT + pembrolizumab prolongs OS compared to SBRT + placebo.	OS: The time from randomization to death from any cause.
Objective: To evaluate the time to death or distant metastases.	Time to death or distant metastases: The time from randomization to the first documented distant metastases or death from any cause, whichever occurs first.
Objective: To evaluate the safety and tolerability of SBRT + pembrolizumab.	• Adverse events • Study intervention discontinuations due to AEs
Objective: To evaluate the change from baseline scores in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning scale.	Change from baseline scores, calculated for the following scales/items at a prespecified time point: global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 1), chest pain (EORTC QLQ-LC13 Item 10), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1-5).

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
Objective: To evaluate the time to subsequent treatment (TTST).	TTST: The time from randomization to first day of next line of therapy or death from any cause.
Objective: To evaluate the disease-specific survival (DSS).	DSS: The time from randomization to death due to disease under study.
Objective: To evaluate the time to recurrence/progression on subsequent line of therapy (TRSLT).	TRSLT: The time from randomization to first day of the recurrence/progression on the next line of therapy or death from any cause.
Objective: To characterize health utility using the 5 level version of the European Quality of Life (EuroQoL) 5 dimension Questionnaire (EQ-5D-5L) to generate utility scores for use in economic models.	Health utilities assessed using the 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 SBRT + pembrolizumab.	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

4 STUDY DESIGN

4.1 Overall Design

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE¬867 (data cutoff 11-JUN-2024), the eDMC recommended stopping the study since pembrolizumab in combination with SBRT did not demonstrate an improvement in EFS or OS, the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. All prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024.

In alignment with the study update memo sent to Investigators on 29-AUG-2024, all study participants must stop ongoing treatment with pembrolizumab/placebo. These participants must complete EOT visit followed by Safety Follow-up visit per protocol. All remaining study participants who have completed the safety reporting windows for AEs and SAEs per protocol must be discontinued from the study. All study participants will undergo unblinding at the end of the study. Investigators may apply for unblinding participants per protocol in the interim.

As of Amendment 08, information regarding ePRO assessments (EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL EQ-5D-5L), biomarker samples (blood for genetic analysis, blood for ctDNA analysis, optional tumor sample), biopsies, and tumor imaging for BICR will no longer be collected. Tumor imaging, biopsies, and disease management should be performed per local SOC and Investigator's discretion. Efficacy data collection, including Follow-up and Survival Follow-up visits for efficacy will no longer be conducted. Safety reporting for AEs and SAEs must adhere to time windows per protocol. Updated analyses are described in Section 9.

This is a multisite, placebo-controlled, randomized, double-blind study designed to compare the efficacy and safety of SBRT + pembrolizumab versus SBRT + placebo in participants with unresected Stage I or II (N0, M0) NSCLC (AJCC 8th edition, Appendix 9). Eligible patients must have histologically or cytologically confirmed Stage I or II (N0, M0) NSCLC that has not been previously treated.

The study will be conducted in conformance with Good Clinical Practices (GCP). Approximately 436 participants will be randomized. After a Screening phase of up to 42 days, each eligible participant will be randomized in a 1:1 ratio to receive SBRT + pembrolizumab 200 mg Q3W × 17 cycles or SBRT + placebo Q3W × 17 cycles. SBRT will be given as outlined in Table 3. The first SBRT administration will preferably start on Cycle 1 Day 1 (+7 days allowed up to Cycle 1 Day 8, inclusive) following pembrolizumab/placebo administration. All randomized patients will receive either pembrolizumab or placebo regardless of if they complete SBRT. Randomization will be stratified by stage of disease (Stage I vs Stage II), Eastern Cooperative Oncology Group

(ECOG) performance scale (0 or 1 vs 2), geographic region of enrollment site (East Asia vs non-East Asia), and reason for not receiving surgery (medically inoperable vs refused surgery). Histology was not chosen as a stratification factor because the differentiation between squamous and nonsquamous histology is frequently inaccurate when utilizing cytology specimens, which is likely to represent the majority of diagnostic specimens in this medically compromised population [Nizzoli, R., et al 2011]. In addition, many cytology samples cannot be assigned to either histologic category and are merely reported as NSCLC, not otherwise specified [Ebrahimi, M., et al 2016].

The primary endpoint of the study is EFS. Participants will be evaluated with radiographic imaging to assess response to treatment. The first on-trial imaging assessment will be performed at 12 weeks (±7 days) from the date of randomization (at least 10 weeks post completion of SBRT). This scan is considered the reference point for monitoring local recurrence (see Section 8.2.1.3.1). Subsequent tumor imaging will be performed every 16 weeks (Q16W ±7 days) until 156 weeks post randomization; and every 6 months (Q6M ±14 days) thereafter. All imaging obtained on study will be submitted for BICR. The central radiologists will assess the images for determination of EFS. Adverse event (AE) monitoring will be ongoing throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The primary endpoint EFS will be assessed CCI CCI and the secondary endpoint OS will be assessed at CCI final analysis.

Treatment with pembrolizumab or placebo control will continue until 17 cycles have been administered (approximately one year), or until disease recurrence, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, death from any cause, investigator decision, or participant decision or withdrawal of consent, whichever occurs first.

Participants who discontinue for reasons other than disease recurrence, or where radiographic disease recurrence has not been verified by BICR, will have posttreatment follow-up imaging until disease recurrence is documented radiographically and verified by BICR, withdrawing consent, pregnancy, death, loss to follow-up or early study termination, whichever occurs first. Images will continue to be obtained even after initiating the new anticancer therapy if recurrence has not been documented or verified by BICR.

After the end-of-treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4.

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

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3, Table 1 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

SBRT and immunotherapy, such as pembrolizumab, are synergistic due to the immunogenic cell death caused by the former and the mechanism of action, efficacy, and favorable toxicity profile of the latter. Published studies have demonstrated the benefit and safety of chemoradiotherapy followed by the sequential administration of a checkpoint inhibitor for patients with NSCLC. The PACIFIC trial compared maintenance durvalumab to placebo in patients with unresectable Stage III NSCLC who had no evidence of disease progression following definitive chemoradiotherapy [Antonia, S. J., et al 2017] [Antonia, S. J., et al 2018]. Significant improvement in PFS and overall survival (OS) was obtained with an acceptable small increase in adverse events. In a secondary analysis of KEYNOTE-001, PFS and overall survival (OS) were significantly longer in patients with NSCLC treated with pembrolizumab who had previously received extracranial radiotherapy than in those patients who had not received extracranial radiotherapy [Shaverdian, N., et al 2017].

Treatment with pembrolizumab/placebo will be administered over a maximum of 17 cycles, consistent with other adjuvant trials within the pembrolizumab program. Additionally, as the participants in this trial will have significant comorbidities and would typically have minimal surveillance following SBRT (ie, “watchful waiting” consisting of 2 to 4 CT scans/year) as part of their standard of care, one year of pembrolizumab/placebo was seen as lowering the burden to participants as well as encouraging compliance with the visit schedule compared to the longer line-treatment plan of 2 years.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use EFS as assessed by BICR as the primary endpoint. EFS is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. Images will be submitted to an imaging vendor and read by an independent central reviewer blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic recurrence will be based on the central assessment of recurrence, rather than a local site investigator/radiology assessment. Expedited verification of radiologic recurrence as determined by central review will be communicated to the site. Where a biopsy has been performed locally at site to confirm/rule out recurrence of disease, the results of the biopsy will overrule the radiologic findings when they conflict. Recurrence will be assessed by (1) BICR, using qualitative assessment of recurrence at the primary lesion site and evaluation of possible new lesions following RECIST 1.1 principles, (2) pathology by local assessment, or (3) physical examination confirmed by local pathology assessment and/or BICR radiographic recurrence. The earliest of the 3 possible means of documenting recurrence will be used as the date of recurrence. For example, if recurrence is identified by physical examination and subsequently confirmed by biopsy or BICR, the date of the abnormal physical finding will be utilized to calculate the date of recurrence. Similarly, if a suspected radiographic abnormality is biopsy negative, but later enlarges and re-biopsy demonstrates metastatic cancer, the date of the first CT scan will be utilized as the date of recurrence.

EFS is a primary endpoint. The study is considered to have met its primary objective if pembrolizumab plus SBRT is superior to placebo plus SBRT in EFS at an interim analysis or final analysis. All alpha is allocated to EFS with step down to OS, for more detail see Section 9.

4.2.1.2 Safety Endpoints

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

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. As part of the analyses for this study, health-related quality of life (HRQoL) and disease-related symptoms will be investigated among all participants via the following assessment tools: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ LC13, and EuroQoL EQ-5D-5L 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.

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EORTC QLQ-LC13

The EORTC Quality of Life Questionnaire and Lung Cancer Module 13 (QLQ-LC13), a supplemental lung cancer-specific module used in combination with QLQ-C30, is comprised of multi-item and single item measures of lung cancer associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia) [Bergman, B., et al 1994]. It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, and 4=very much) and has been translated and validated into more than 60 languages.

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

4.2.1.3.3 EuroQoL EQ-5D

The EuroQoL-5D (EQ-5D) 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 include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

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

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

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a ‘hyper-mutated’

state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

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

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

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

4.2.1.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

The current standard of care (SOC) in this patient population is SBRT followed by regular imaging surveillance for recurrence of disease. This SOC can be mimicked using a placebo control when adding pembrolizumab to the standard SBRT therapy. A placebo control is necessary to minimize confounding factors, such as the more frequent office visits and physical exams required for administration of pembrolizumab, as well as control for knowledge of treatment effects on patient-reported outcome data.

4.3 Justification for Dose

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

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

- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings

(treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KEYNOTE-001 Cohort B2, KEYNOTE-001 Cohort D, KEYNOTE-002, KEYNOTE-010, and KEYNOTE-021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KEYNOTE-001 Cohort B3, KEYNOTE-001 Cohort F2 and KEYNOTE-006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

Drug administration will continue every 3 weeks for one year (17 cycles), similar to the interval chosen for patients enrolled in other Merck lung cancer trials that involve resection of the lung tumor (KN-091 and KN-671) as well as Merck trials for other early-stage cancers where the intent of treatment is curative. Though the lung cancer is not physically removed, the destructive effect of radiotherapy is thought to be comparable to surgery and therefore the 2-year treatment interval, which has become the SOC for patients with residual/metastatic disease, is not thought to be necessary.

The current trial will use the standard SBRT dosing as outlined in the protocol and aligned with standard clinical practices and the current guideline documents.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor

receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Male/female participants who are at least 18 years of age with unresected Stage I or II (limited Stage IIB, N0, M0) NSCLC and who have received no prior anticancer therapy for the present lung cancer will be randomized in this study.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

1. Has previously untreated NSCLC diagnosed by histology or cytology and confirmed as Stage I or II (T1 to limited T3, N0, M0) NSCLC (AJCC 8th edition) by chest CT and PET scan. Prospective participants with mediastinal lymph nodes measured on chest CT as >1 cm in the short axis or PET avid lymph nodes may be eligible if the lymph node(s) in question is biopsied and is histologically benign. Note: participants with pericardium invasion, >2 nodules or 2 nodules that cannot be treated in one field (>2 cm apart and/or total planned target volume [PTV] >163 cc) and diaphragm elevation suggestive of phrenic nerve invasion are excluded.
2. Cannot undergo thoracic surgery due to existing medical illness(es) or anatomically unresectable tumor as determined by the site's multidisciplinary tumor board. Medically operable participants who decide to treat with SBRT as definitive therapy rather than surgery are also eligible, if patient's unwillingness to undergo surgical resection is clearly documented. If there is no tumor board, then this decision will be made by the investigator in consultation with a thoracic surgeon and a radiation oncologist if the investigator is not a radiation oncologist.
3. Has an ECOG performance status of 0, 1, or 2.
4. Is able to receive SBRT and does not have an ultra-centrally located tumor as defined in the radiation manual.
5. Has adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days prior to the start of study intervention.

Table 2 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 creatinine clearance OR GFR	≥30 mL/min ≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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.

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.

Demographics

6. Is male or female, ≥18 years of age, at the time of signing the informed consent.

Male Participants

7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of radiotherapy:

- Refrain from donating sperm.

  PLUS either:

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

OR

- Must agree to use 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:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP (see Section 10.5) who is not currently pregnant. Note: Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

Female Participants

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

- Is not a WOCBP.

  OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after last dose of pembrolizumab/placebo and 180 days after the last radiotherapy dose. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

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

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

  - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4.2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

9. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the study without participating in future biomedical research.
10. Has a radiation therapy plan approved by the central radiation therapy quality assurance vendor.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Is a WOCBP who has a positive highly sensitive pregnancy test within 24 hours for urine or 72 hours for serum prior to randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: If 24 hours for urine or 72 hours for serum have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

Prior/Concomitant Therapy

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
3. Has received prior radiotherapy to the thorax, including radiotherapy to the esophagus, mediastinum, or breast. Participants receiving radiotherapy to the contralateral breast at least 5 years prior to randomization may still be eligible.
4. Has received a live vaccine within 30 days prior to the first dose of study intervention. 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 6.5 for information on COVID-19 vaccine.

Prior/Concurrent Clinical Study Experience

5. Has received an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention administration.

Diagnostic Assessments

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.
7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. A prior NSCLC that occurred and was treated curatively at least 2 years prior to the date of the current diagnosis would be considered a separate primary lung cancer, and therefore an additional malignancy.

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

8. Has a known hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
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 an active autoimmune disease that has required systemic treatment in past 2 years except replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).
12. Has an active infection requiring systemic therapy.
13. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
14. Has a known history of active tuberculosis (TB; *Bacillus* tuberculosis). No TB testing is required unless mandated by local health authority.
15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
16. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

17. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after last dose of pembrolizumab/placebo and 180 days after the last radiotherapy dose.
18. Has had an allogeneic tissue/solid organ transplant.
19. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

Note: Country-specific differences are noted in Appendix 7.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants should maintain a normal lifestyle; however, may be encouraged to restrict tobacco use on the study.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

In alignment with the study update memo sent to Investigators on 29-AUG-2024, all study participants must stop ongoing treatment with pembrolizumab/placebo. These participants must complete EOT visit followed by Safety Follow-up visit per protocol. All remaining study participants who have completed the safety reporting windows for AEs and SAEs per protocol must be discontinued from the study. All study participants will undergo unblinding at the end of the study. Investigators may apply for unblinding participants per protocol in the interim.

The study interventions to be used in this study are outlined in Table 3.

Country-specific differences are noted in Appendix 7.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab (MK-3475)	Drug	Injection, Solution	25 mg/mL	200 mg	IV Infusion	Q3W x17 cycles (~1 year)	Test Product	IMP	Central
Arm 1	Experimental	SBRT	Radiation	Not Applicable	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48-50 Gy in 4 fractions (acceptable); 50-55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48-50 Gy in 4 fractions; 50-55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60-70 Gy in 8 fractions	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48 50 Gy in 4 fractions (acceptable); 50 55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48 50 Gy in 4 fractions; 50 55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60 70 Gy in 8 fractions	External Beam Radiation	~Q3D over 2 weeks	Background Treatment	NIMP/AxMP	Local
Arm 2	Placebo Comparator	Placebo	Drug	Injection, Solution	N/A	N/A	IV Infusion	Q3W × 17 cycles (~1 year)	Placebo	IMP	Local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formula-tion	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/AxMP	Sour-cing
Arm 2	Active Comparator	SBRT	Radiation	Not Applicable	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48-50 Gy in 4 fractions (acceptable); 50-55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48-50 Gy in 4 fractions; 50-55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60-70 Gy in 8 fractions	Peripheral Tumors: 45-60 Gy in 3 fractions (preferred); 48 50 Gy in 4 fractions (acceptable); 50 55 Gy in 5 fractions (acceptable) Abutting the chest wall: 48 50 Gy in 4 fractions; 50 55 Gy in 5 fractions Central Tumors: 50-55 Gy in 5 fractions; 60 70 Gy in 8 fractions	External Beam Radiation	~Q3D over 2 weeks	Background Treatment	NIMP/AxMP	Local

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous, N/A=not applicable; NIMP/AxMP=noninvestigational/auxiliary medicinal product.Q3W=every 3 weeks; SBRT=stereotactic body radiotherapy

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

All study interventions will be administered on an outpatient basis.

All products indicated in Table 3 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab and placebo are provided in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab with SBRT or placebo with SBRT, respectively.

6.3.2 Stratification

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

- Disease stage: Stage I versus Stage II
- ECOG performance status: 0 or 1 versus 2
- Geographic region of enrollment site: East Asia versus non-East Asia
- Reason for not receiving surgery: medically inoperable versus refused surgery

6.3.3 Blinding

In alignment with the study update memo sent to Investigators on 29-AUG-2024, all study participants must stop ongoing treatment with pembrolizumab/placebo. These participants must complete EOT visit followed by Safety Follow-up visit per protocol. All remaining study participants who have completed the safety reporting windows for AEs and SAEs per protocol must be discontinued from the study. All study participants will undergo unblinding at the end of the study. Investigators may apply for unblinding participants per protocol in the interim.

The subsection below is retained for reference.

A double-blinding technique will be used. Pembrolizumab and placebo (normal saline) will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant’s medical record.

Interruptions from the protocol-specified treatment >12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

Participants are prohibited from receiving the following concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol
- Live or liveattenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study.
  Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
  Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or chronic obstructive pulmonary disease (COPD) exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

  - Treatment of radiation pneumonitis. Refer to Table 4 to follow the same management guidelines for irAE pneumonitis

- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD

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

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 42 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.7.

6.5.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6, Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

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

6.6 Dose Modification (Escalation/Titration/Other)

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks. An interruption of study intervention for more than 12 weeks will require Sponsor approval before treatment can be resumed (see Section 6.4). See Appendix 7 for country-specific dose modification requirements.

If radiotherapy is not completed for any reason, the participant may continue with pembrolizumab/placebo for up to 17 total treatment cycles (1 year). If SBRT is interrupted due to toxicity, all fractions of radiotherapy must be completed prior to Cycle 2 Day 1 of pembrolizumab/placebo (day second dose is administered) or SBRT must be discontinued early. Should the participant develop radiation pneumonitis, refer to Table 4 to follow the same management guidelines for irAE pneumonitis, specifically with action taken for study intervention, and treat as per local SOC.

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

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

Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations are provided in Table 4.

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

General instructions:

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

irAEs	**Toxicity Grade (CTCAE v4.0)**	**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		

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
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	

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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]		
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		

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.
[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.
[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
CTCAE = Common Terminology Criteria for Adverse Event; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug; po = orally. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Study site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate participants, to assign study intervention to participants, and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

6.9.1 Study Site Retention Samples

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to the participants, and the amount remaining at the conclusion of the study. For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

Clinical supplies must be stored in a secure, limited access location under the storage conditions specified on the label.

Receipt and dispensing of study medication must be recorded by an authorized person at the study site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE¬867 (data cutoff 11-JUN-2024), the eDMC recommended stopping the study since pembrolizumab in combination with SBRT did not demonstrate an improvement in EFS or OS, the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. All prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024. The subsections below are retained for reference.

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 12 weeks without Sponsor Approval.
- The participant does not start SBRT for any reason.
- The participant's treatment assignment has been intentionally unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center. Note: if a participant's treatment is unintentionally unblinded, the participant is not required to discontinue treatment.

- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- Pathological recurrence of disease or radiographic recurrence of disease outlined in Section 8.2.1.3. If the radiographic recurrence is biopsied and the pathology is negative, the patient may continue treatment until pathological or radiographic confirmation of recurrence by repeat imaging or biopsy.
- The participant has a confirmed positive serum pregnancy test.
- Completion of 17 doses (approximately 1 year) of pembrolizumab/placebo.
- Prohibited concomitant therapy or vaccinations as defined in Section 6.5 are administered during the study.
- Recurrent Grade 2, Grade 3, or Grade 4 pneumonitis of any cause and Grade 3 colitis.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed. Participants who discontinue treatment for reasons other than pathologically confirmed recurrence of disease (ie, by biopsy), should continue to be monitored by tumor imaging until BICR-verified disease recurrence as described in Section 8.2.1.4, withdrawing consent, pregnancy, death, or loss to follow-up, whichever occurs first. Participants assigned to placebo will not have an opportunity to crossover to pembrolizumab at the time of recurrence within the scope of this clinical trial; however, pembrolizumab may be administered as a subsequent therapy off-study based on the current pembrolizumab product labeling if indicated for that participant's disease state at the time of recurrence or at any point in the course of the disease.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study is described in operations/laboratory manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

The medical history must include documentation of the reason(s) the participant is undergoing definitive SBRT instead of surgery, as determined by the site's multidisciplinary tumor board. If there is no tumor board, then this decision will be made by the investigator in consultation with a thoracic surgeon and a radiation oncologist if the investigator is not a radiation oncologist. This documentation will be kept with the participant's study records.

If the participant is considered medically inoperable due to one or more comorbidities, these comorbidity(ies) should be included in the participant's study records. Reasons a participant may be considered medically inoperable include, but are not limited to, a history of poor pulmonary function, heart disease, diabetes, vascular disease, or a combination of several unrelated comorbidities that, taken together, contribute to the decision that the participant is not suitable for surgery.

If the participant's tumor is in an anatomically unresectable location, this should be documented in the medical history as the reason the participant is considered inoperable. If the participant has refused surgery, this must also be documented clearly at site as part of the participant's medical history.

To ensure the ethical inclusion of prospective participants with medically operable NSCLC without any undue coercion, these participants will be clearly informed of the advantages of surgery and be sufficiently aware that surgical resection is the preferred treatment for early-stage NSCLC. This discussion occurs prior to providing the participant with any information regarding the KEYNOTE-867 study and in advance of any offer to be screened for enrollment in the study. Thus, the participant's election to forego surgery will be a well-informed decision, made in advance of and with no specific knowledge of the KEYNOTE-867 study, so that inclusion in the study would not impact the opportunity for decision to undergo surgery.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 42 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

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

8.1.8 Study Intervention Administration

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

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab or Matching Placebo

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

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

The first dose of pembrolizumab or placebo should be administered prior to start of SBRT.

8.1.8.1.2 Stereotactic Body Radiotherapy

Radiotherapy will be administered in 3 fractions totaling 45-60 Gy (preferred regimen), 4 fractions totaling 48-50 Gy, or 5 fractions totaling 50-55 Gy (acceptable regimens) for peripheral tumors, 4 fractions totaling 48-50 Gy or 5 fractions totaling 50-55 Gy for tumors abutting the chest wall, and 5 fractions totaling 50-55 Gy or 8 fractions totaling 60-70 Gy for central tumors, defined as within 2 cm of the proximal bronchial tree and/or abutting the mediastinal pleural. Ultra-centrally located tumors, defined as tumors whose PTV directly contacts or overlaps the proximal bronchial tree, trachea, mainstem bronchus, esophagus, pulmonary vein, or pulmonary artery are not appropriate for SBRT and are excluded from enrollment in this study.

SBRT will be administered preferably starting on C1D1, following administration of pembrolizumab/placebo. There is an allowed window of +7 days to begin SBRT treatment (SBRT treatment must begin between C1D1 and C1D8, inclusive). SBRT will be administered over no more than 2 weeks.

Center credentialing for radiotherapy will be performed according to criteria defined in the Radiotherapy QA manual. Participating institutions must comply with the radiation therapy quality assurance (RT QA) requirements and procedures described in the Radiotherapy QA manual. Sites that do not conform to the requirements of the credentialing will not be allowed to participate.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.2.

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

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or

already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

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

For studies that require nonemergency unblinding as part of the study design (eg, disease progression) to support treatment decisions, instructions in the Procedures Manual should be followed. The emergency unblinding center should not be used for this purpose.

Once an emergency unblinding or a nonemergency unblinding that is part of the study design has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 08: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. Tumor imaging, biopsies, and disease management should be performed per local SOC and Investigator's discretion. The subsections below are retained for reference.

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. Screening imaging must also be submitted to the radiation therapy quality assurance vendor as part of the radiation treatment plan approval process; details of this process are found in the RT QA manual. The same imaging technique regarding modality and use of contrast should be used consistently throughout the study. The imaging schedule should follow calendar days and should not be adjusted for cycle delays.

Screening imaging:

- CT with IV and oral contrast (preferred) of the chest and abdomen for all participants, or non-contrast CT of the chest and magnetic resonance imaging (MRI) of the abdomen with IV gadolinium for participants in whom iodinated contrast is contraindicated. Additional anatomy (eg, pelvis/brain) should be captured as clinically indicated. A whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan should also be performed.

Post allocation imaging:

- CT of the chest and abdomen, consistent with the method used at screening. Additional anatomy (pelvis/brain/extremity/etc.) should be captured as clinically indicated.

Local site investigator/radiology assessment of PET imaging to confirm staging (T1 or 2, N0, M0) will be used to determine participant eligibility. All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, all other imaging (including all modalities and anatomies) obtained at an unscheduled time point to determine disease recurrence, as well as supplemental imaging obtained for other reasons that captures radiologic recurrence, must be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Scans

Initial tumor imaging (whole-body FDG-PET and CT of chest and abdomen) at screening must be performed within 42 days prior to the date of randomization. The site investigator/local radiology reviewer must review screening images to confirm the participant has no nodal or metastatic involvement. The screening images must be submitted to the central imaging vendor for retrospective review. This scan is considered the reference point for regional or distant recurrence on study.

Tumor imaging via PET/CT performed as part of routine clinical management (prior to documented informed consent signature) is acceptable for use as screening tumor imaging if the CT portion is of diagnostic quality, is performed within 42 days prior to the date of randomization and can be assessed by the central imaging vendor retrospectively.

8.2.1.2 Tumor Scans During the Study

The first scheduled post randomization imaging assessment (chest and abdomen CT) should be performed at 12 weeks (±7 days) from the date of randomization (at least 10 weeks post completion of SBRT). This scan is considered the reference point for monitoring local recurrence (see Section 8.2.1.3), however, unscheduled imaging due to new clinical symptoms can occur at any time, including prior to the Week 12 assessment, to identify either new metastatic/regional disease or recurrence of local treated disease. Subsequent tumor imaging should be performed every 16 weeks (Q16W ± 7 days) until 156 weeks post-randomization; and every 6 months (Q6M ± 14 days) thereafter [Schneider, B. J., et al 2019]. Images will continue to be obtained (Q6M ± 14 days) even after initiating the new anticancer therapy if recurrence has not been document or verified by BICR.

Timing of tumor imaging should follow calendar days and should not be adjusted for delays in cycle starts. (Note: the date imaging is performed is the date of assessment, not the date the images are reviewed.) Imaging should continue to be performed until disease recurrence as assessed by local investigator/radiologist, withdrawal of consent, pregnancy, loss to follow-up, or death, whichever occurs first. Supplemental imaging must be submitted to the central imaging vendor if it shows evidence of recurrence.

8.2.1.3 Assessment of Disease Recurrence

As of Amendment 08: Disease recurrence assessments will be discontinued. The subsections below are retained for reference.

Following randomization, the site investigator/radiologist will assess all study imaging for local, regional, or distant disease recurrence as defined in this protocol. The CT imaging captured at 12 weeks post randomization will be considered the reference scan for qualitative assessment of local recurrence. Recurrence must be verified by biopsy where medically appropriate, and by sequential imaging (at least 4 weeks after initial recurrence) where biopsy is not medically appropriate.

8.2.1.3.1 Local Disease Recurrence

Local disease recurrence is radiographically defined as the regrowth of the primary lesion as compared to the reference imaging acquired at 12 weeks post randomization or the appearance of new disease (per the principles of RECIST 1.1) elsewhere within the same lobe. For the assessment conducted at 12 weeks, the site radiological review must consider the potential for local tissue effects due to SBRT, which may make disease assessment challenging. If there are changes that are questionable, scanning should continue at least 4 weeks later or at the next scheduled scan, and if later imaging shows that the local growth continues, the time of recurrence will be assigned to the scan where the changes were first observed. Local recurrence must be confirmed with a biopsy unless a biopsy is not medically

appropriate per investigator decision. Due to the effects of SBRT, PET-positivity is not sufficient to determine local recurrence in the absence of other factors (eg, unequivocal regrowth, positive biopsy).

8.2.1.3.2 Regional or Distant Disease Recurrence

Regional disease recurrence is radiographically defined as the appearance of new lesions in a different lobe of the lung ipsilateral to where the primary tumor originated, or malignant thoracic lymph nodes (thoracic nodes as defined in AJCC v8 staging guideline, Figure 3 and Figure 4) as compared to the screening PET/CT. Distant disease recurrence is radiographically defined as the appearance of new lesions in lobes of the lung contralateral to where the primary tumor originated, malignant pleural/pericardial nodules or effusions, organs other than the lungs, or the appearance of malignant non-thoracic lymph nodes as compared to the screening PET/CT. Palpable lesions should be confirmed by biopsy and captured by imaging for central review. New lesions should be identified following the principles of RECIST 1.1 and should be unequivocal. If new lesions are equivocal, the participant should continue on study (either on treatment or in follow-up if treatment was completed/discontinued) to the next scheduled imaging assessment. This follow-up evaluation will be used to clarify if the equivocal lesion represents recurrent disease; if it does, the recurrence should be dated to the first appearance of the lesion or malignant node. This imaging assessment can be performed early if clinically indicated. Recurrence must be confirmed with a biopsy unless a biopsy is not medically appropriate per investigator decision. PET avidity is typically considered sufficient to identify a new lesion or support of malignancy for an equivocal lesion, according to RECIST 1.1; however, in this study, caution should be used when PET avidity is assessed, particularly in the anatomical areas within the radiotherapy window for SBRT. SBRT is known to cause changes in tissue that can cause PET avidity that can continue beyond the treatment dates for SBRT. When medically appropriate, new lesions noted on PET or PET/CT must be confirmed with a biopsy.

Regional and distant disease recurrence can be determined at the 12-week reference scan or any point thereafter.

If a biopsy is obtained to confirm disease, a solitary new lung cancer with histology identical to the primary lung cancer, as determined by investigator, will be considered as disease recurrence. A solitary lung cancer with a different histology from the primary tumor, as determined by investigator, will be considered as a separate new lung cancer and must be documented as a SAE per Section 10.3.3.

8.2.1.4 Central Verification of Disease Recurrence

Initial tumor imaging showing site assessed disease recurrence should be submitted immediately for central imaging vendor verification of recurrence. The site and Sponsor will be notified whether the central imaging vendor verifies disease recurrence. If the central imaging vendor does not verify site-identified recurrence, the participant should remain on study (in treatment or in follow-up if treatment was completed/discontinued) until the next scheduled imaging assessment, which would again be submitted for verification of

recurrence. This repeat imaging may be performed earlier than the next scheduled imaging assessment if clinically indicated. If the recurrent disease was confirmed by biopsy, repeat imaging and repeat verification of recurrence is not required.

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

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

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

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

- Disease progression as defined by RECIST 1.1 verified by BICR
- Pregnancy
- Death
- Withdrawal of consent
- The end of the study

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then EORTC QLQ-LC13, then EuroQoL EQ-5D-5L.

The questionnaires should be administered prior to dosing at Cycle 1, Cycle 5, Cycle 9, Cycle 13, and Cycle 17 during treatment, at the treatment Discontinuation Visit and at the Safety Follow-up Visit. Posttreatment, the questionnaires will be administered every 16 weeks for the first 3 years, followed by every 6 months from the fourth year onwards, and should be performed concurrently with the follow-up tumor imaging.

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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in the SoA in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiration rate. All vital signs should be collected prior to administration of pembrolizumab/placebo.

Country-specific differences are noted in Appendix 7.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA (Section 1.3).
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 7 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.4.2 Pregnancy Test

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1. WOCBP require negative highly sensitive pregnancy test (urine or serum) within 24 hours for urine or within 72 hours for serum before first dose of study intervention. The definition of WOCBP is provided in Appendix 5. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy tests (such as monthly testing) must be performed prior to each study dose, and additional testing 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. See Appendix 7 for further country-specific details.

- Pregnancy testing (serum as required by local regulations) should be conducted every treatment cycle (Q3W) during study intervention.
- Pregnancy testing (serum or urine as required by local regulations) should be conducted for the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1.
- 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 subject's participation in the study.

8.3.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

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

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

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

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality. Disease recurrence of the cancer under study is not considered an AE, as described in Section 8.4.6.

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

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

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 6.

Note: Country-specific differences are noted in Appendix 7.

Table 6 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
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
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (requiring regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - requiring regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (does not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

ECI=event of clinical interest.

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is reportable to the Sponsor.

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

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

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

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth

must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

Any event that is disease recurrence of the cancer under study will not be reported as an AE or SAE as described in Section 8.4.6.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not considered recurrence of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not recurrence of the cancer under study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. 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.*
   *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 studysite guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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.

Overdose for SBRT is defined as either >20% of the planned total dose, >50% of a planned single fraction, or any fraction(s) to an incorrect treatment site. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA: **As of Amendment 08: Biomarker samples (blood for genetic analysis, blood for ctDNA analysis, optional tumor sample), biopsies, and tumor imaging for BICR will no longer be collected. The subsection below is retained for reference.**

- Blood for genetic analysis
- Blood for ctDNA analysis
- An optional tumor tissue sample for biomarker analyses may be collected, including core biopsy, bronchoscopic biopsy, or pellet from cytologic examination.

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

8.8.1 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.

8.9 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 for future research
- Leftover main study tumor tissue (including any extracted material from tissue)

- Leftover plasma or derivative for ctDNA

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

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

8.11.1 Screening

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

Screening procedures are to be completed within 42 days before the first dose of study intervention. except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
- For WOCBP, a highly sensitive pregnancy test (urine or serum) within 24 hours for urine or within 72 hours for serum prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Optional tumor tissue sample collection is not required to be obtained within 42 days prior to the first dose of study intervention.

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

8.11.2 Treatment Period Visit

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

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

When a participant discontinues study intervention in the Intervention Phase, procedures for discontinuation will be performed.

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional safety follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7 Discontinuation of Study Intervention and Participant Withdrawal.

8.11.4 Posttreatment Visit

8.11.4.1 Safety Follow-up Visit

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

8.11.4.2 Follow-up Visits

Participants who discontinue study intervention for a reason other than disease recurrence will move into the Follow-up Phase and should be assessed every 16 weeks to monitor disease status for the first 3 years, and then every 6 months thereafter. Every effort should be made to collect information regarding disease status until disease recurrence, death, or the end of the study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Images will continue to be obtained after the start of the new anticancer therapy if recurrence has not been documented or verified by BICR.

8.11.4.3 Survival Follow-up

Participants who experience confirmed disease recurrence will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.11.5 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

As of Amendment 08: The Statistical Analysis Plan is amended as follows:

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE¬867 (data cutoff 11-JUN-2024), the eDMC recommended stopping the study since pembrolizumab in combination with SBRT did not demonstrate an improvement in event-free survival or overall survival, the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. All prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024.

This section outlines the statistical analysis strategy and procedures for the study. Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 08 were documented in previous protocol amendments, (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data and biomarker data) will be documented in separate analysis/operational plans.

9.1 Statistical Analysis Plan Summary

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

As of Amendment 08, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024. The SAP summary has been updated accordingly.

Study Design Overview	This is a Phase 3, randomized, placebo-controlled clinical study to evaluate the safety and efficacy of SBRT with or without pembrolizumab in participants with unresected Stage I/II NSCLC.
Treatment Assignment	Approximately 436 eligible participants will be randomized in a 1:1 ratio to one of the following 2 treatment arms: • Arm 1: SBRT + pembrolizumab • Arm 2: SBRT + placebo Randomization stratification factors are: • Disease stage: Stage I, Stage II • ECOG performance status: 0 or 1, 2 • Geographic region of enrollment site: East Asia, non-East Asia • Reason for not receiving surgery: medically inoperable vs refused surgery
Analysis Populations	Efficacy: Intent to Treat (ITT) Safety: All Participants as Treated (APaT) PRO: Full Analysis Set (FAS)
Primary Endpoints	1. Event-free survival (EFS)
Secondary Endpoints	1. Overall survival (OS) 2. Time to death or distant metastases 3. Safety and tolerability 4. PRO outcome
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis will be evaluated by comparing SBRT + pembrolizumab arm to SBRT + placebo arm with respect to EFS using a stratified log-rank test. The hazard ratio (HR) will be estimated using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	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% CIs provided for between-group comparison; 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 Miettinen and Nurminen method.
Interim Analyses	**As of Amendment 08, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.** CCI [redacted]

Multiplicity	CCI [redacted] Details are provided in Section 9.9.
Sample Size and Power	**As of Amendment 08, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed.** The planned sample size is approximately 436 participants. CCI [redacted]

9.2 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, the central radiologist(s) will perform the imaging review without knowledge of treatment group assignment.

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

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

9.3 Hypothesis/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

9.4.1.1 Primary Endpoints

Event-free Survival (EFS)

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

- Local, regional, or distant recurrence of disease as assessed by:
  - Radiographic recurrence by BICR

- Positive pathology by local assessment
- Physical examination by local assessment confirmed by positive pathology and/or radiographic recurrence by BICR

- Death due to any cause

9.4.1.2 Secondary Endpoint

Overall Survival (OS)

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

Time to Death or Distant Metastases

Time to death or distant metastases is defined as the time from randomization to the first documented distant metastases or death from any cause, whichever occurs first.

9.4.1.3 Exploratory Endpoints

Time to Subsequent Treatment (TTST)

TTST is defined as the time from randomization to first day of next line therapy or death from any cause**.**

Disease-specific Survival (DSS)

DSS is defined as the time from randomization to death due to disease under study.

Time to Recurrence/Progression on Subsequent Line of Therapy (TRSLT)

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

- Recurrence/progression of disease by local assessment on the subsequent line of treatment
- Death due to any cause

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2.

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

9.4.3 PRO Endpoints

Scores calculated for the following PRO scales/items will be evaluated as described in Section 4.2.1.3 as secondary endpoint:

- Global health status/QoL scale (EORTC QLQ-C30 Items 29, 30)
- Cough (EORTC QLQ-LC13 Item 1)
- Chest pain (EORTC QLQ-LC13 Item 10)
- Dyspnea (EORTC QLQ-C30 Item 8)
- Physical functioning scale (QLQ-C30 Items 1-5)
- EQ-5D-5L will be evaluated as an exploratory endpoint

Treatment effect on PRO score change from baseline will primarily be evaluated at CCI. If the overall PRO completion or compliance rates at CCI are less than 60% or 80%, respectively, then the latest analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance.

9.4.4 Other Exploratory Endpoints

Relationships between molecular (genomic, metabolic, and/or proteomic) biomarkers and clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments may be evaluation.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

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

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

At least 1 laboratory or vital sign obtained after at least 1 dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling safety analyses are provided in Section 9.6.2.

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO FAS population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention.

9.6 Statistical Methods

NOTE: As of Amendment 08, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further pre-planned analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date of 11-JUN-2024. The subsections below are retained for reference.

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity. If there are a small number of events in one or more strata, for the purpose of analysis, strata will be combined to ensure sufficient number of events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

9.6.1 Statistical Methods for Efficacy Analyses

9.6.1.1 Event-free Survival (EFS)

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 (ie, HR) between the treatment arms. The HR 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 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease recurrence is assessed periodically, recurrence can occur any time in the time interval between the last assessment where an event was not documented and the assessment when an event is documented. For the primary EFS analysis, the true date of recurrence will be approximated by the date of the first assessment at which an event is objectively documented, regardless of discontinuation of study medicine or missed study visits. Death is always considered as a confirmed EFS event. Participants who do not experience an EFS event will be censored at the last disease assessment (Table 7). Sensitivity analyses may be conducted using different censoring rules and will be documented in the sSAP as needed.

Table 7 Censoring Rules for Primary Analysis of EFS

Situation	Primary Analysis
Recurrence, or death documented; ≤1 missed disease assessment; and event is before new anti-cancer treatment initiation, if any	EFS event at date of documented recurrence, or death
Recurrence or death documented; either immediately after having ≥2 consecutive missed disease assessments or event is after new anti-cancer treatment initiation, if any	EFS event at date of documented recurrence, or death
No recurrence and no death; and new anti-cancer treatment is not initiated	Censored at last disease assessment
No recurrence and no death; new anti-cancer treatment is initiated	Censored at last disease assessment

If the proportional hazards assumption is not valid, supportive analyses using RMST method [Uno, H., et al 2014] may be conducted for EFS to account for the possible non-proportional hazards effect.

9.6.1.2 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 (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Participants without documented death at the time of analysis will be censored at the last known alive date. The Restricted Mean Survival Time (RMST) method [Uno, H., et al 2014] may be conducted for OS to account for the possible non-proportional hazards effect.

9.6.1.3 Time to Death or Distant Metastases (TDDM)

The non-parametric Kaplan-Meier method will be used to estimate the TDDM curve in each treatment group. The treatment difference in TDDM 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 (ie, HR) between the treatment arms. The HR 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 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since distant metastasis is assessed periodically, it can occur any time in the time interval between the last assessment where an event was not documented and the assessment when an event is documented. The true date of distant metastasis will be approximated by the date of the first assessment at which an event is objectively documented, regardless of discontinuation of study medicine or missed study visits. Death is always considered as a confirmed TDDM event. Participants who do not experience a TDDM event will be censored at the last disease assessment.

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

Table 8 summarizes the primary analysis approach for key efficacy endpoints.

Table 8 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Analyses			
EFS	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 7
Key Secondary Analyses			
OS	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

Abbreviations: EFS=event-free survival; ITT=intent to treat; OS=overall survival

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

Analysis strategy for the exploratory efficacy endpoints will be described in the sSAP.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach as shown in Table 9. The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory, and vital signs are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEs of interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as SBRT+pembrolizumab does not seem to produce toxicity beyond what is expected for these therapies alone based on the early result of the use of pembrolizumab and SBRT in the metastatic setting [Theelen, W., et al 2018] [Campbell, A. M., et al 2018].

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events via the Miettinen & Nurminen method [Miettinen, O. and Nurminen, M. 1985] and will be presented using forest plots.

Membership in Tier 2 requires that at least 1% of participants in any treatment group exhibit the event (with the exception of any AE, which requires at least 10%). The threshold of at least 1% of participants was chosen because the population randomized in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 1% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. Grade 3 to 5 AEs (≥1% of participants in one of the treatment groups) and SAEs (≥1% of participants in one of the treatment groups) are considered as Tier 2 endpoints. Any AE (≥10% of participants in one of the treatment groups) is also considered as a Tier 2 endpoint (the cutoff 10% is chosen due to the higher incidence of any AE). 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 rather than formal methods for assessing the statistical significance of the between-group differences. All other AEs and predefined limits of change will belong to Tier 3 endpoints.

Tier 3 Events

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

Continuous Safety Measures

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

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in one of the treatment groups)	X	X
	Any SAE (≥1% of participants in one of the treatment groups)	X	X
	Any Grade 3 to 5 AE (≥1% of participants in one of the treatment groups)	X	X
Tier 3	Other specific AEs, SOCs or PDLCs		X
	Change from baseline results (laboratory test results, vital signs)		X

Abbreviations: AE=adverse event; CI=confidence interval; PDLC=predefined limit of change; SAE=serious adverse event; SOC=system organ class; X=results will be provided.

9.6.3 Analysis Methods for PRO Endpoints

A constrained longitudinal data analysis (cLDA) model will be applied for each endpoint, with the PRO score as the response variable, and treatment, time, treatment by time interaction, and clinical study stratification factors as covariates. Least square mean change from baseline will be summarized for each outcome. The difference in the least square mean change from baseline will be reported at the primary analysis time point.

Descriptive analyses will assess the empirical mean change (with 95% CIs) from baseline across all time points for the Global health status/QoL (QLQ-C30 items 29, 30), cough (QLQ-LC13 item 1), chest pain (QLQ-LC13 item 10), and dyspnea (QLQ-LC13 item 8) scores.

The number and proportion of patients who “improved”, “remained stable”, or “deteriorated” from baseline will be summarized.

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

9.6.4 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

NOTE: As of Amendment 08, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. The subsections below are retained for reference.

Blinding to treatment assignment will be maintained at all investigational sites. The results of IAs will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An eDMC will serve as the primary reviewer of the results of the IAs of the study and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee (EOC) of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to results at the treatment-level in order to act on these recommendations. Limited additional Sponsor personnel may also be unblinded to the treatment-level results of the interim analysis(es), if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing. The extent to which individuals are unblinded with respect to results of IAs will be documented by the unblinded statistician. Additional logistical details will be provided in the DMC charter.

Treatment-level results from the interim analysis will be provided to the DMC by the unblinded statistician. Prior to final study unblinding, the 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 IAs.

9.7.1 Efficacy Interim Analyses

CCI

Table 10 CCI [redacted]

CCI [redacted]

9.8 Multiplicity

NOTE: As of Amendment 08, all the prespecified interim analyses after IA1and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to strongly control multiplicity CCI [redacted] Figure 2 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. CCI [redacted] The study will be considered a success if CCI [redacted]

Figure 2 CCI

9.8.1 Multiplicity Control for Efficacy Interim Analyses

9.8.1.1 Event-free Survival (EFS)

Table 11 CCI

CCI

[redacted]

9.8.1.2 Overall Survival

CCI

[redacted]

Table 12 CCI

CCI

[redacted]

CCI

9.9 Sample Size and Power Calculations

NOTE: As of Amendment 08, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The sample size is estimated based on the secondary endpoint OS.

A total of approximately 436 participants will be randomized in a 1:1 ratio to the SBRT + pembrolizumab arm and the SBRT + placebo arm.

CCI

CCI

[redacted]

9.10 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 and key secondary endpoint will be estimated and plotted by treatment group within each category of the following classification variables:

- Stage of disease (I, II)
- ECOG performance status (0 or 1, 2)
- Geographic region of enrollment site (East Asia, non-East Asia; EU, non-EU)
- Histology (squamous, nonsquamous)
- Smoking status (never, ever)
- Age category (≥65, <65 years)
- Sex (female, male)
- Race (white, non-white)
- Tumor location (peripheral, abutting the chest wall, central) defined as body site location of SBRT administration
- Reason for not receiving surgery (medically inoperable, refused surgery)

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

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), 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), Regulation (EU) 536/2014, the 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 (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim

study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

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

10.1.4.2 Executive Oversight Committee

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	BUN[a]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin if total bilirubin is >ULN)
	Albumin	Bicarbonate or CO_2[b]	Chloride	Phosphorous
	Creatinine[c]	Sodium	ALT/SGPT	Total protein
	Glucose (fasting, or nonfasting)	Calcium	Alkaline phosphatase	
Coagulation[d]	• PT/INR • aPTT			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• T3[e], FT4, and TSH • Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine β-hCG pregnancy test (as needed for WOCBP) • Serology (HIV antibody, HBsAg, and HCV antibody) as per local requirements			

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=human chorionic gonadotropin; BUN=blood urea nitrogen; FT4=free thyroxine; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; PT=prothrombin time; RBC=red blood cells; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; TSH=thyroid-stimulating hormone (thyrotropin); ULN=upper limit of normal; WOCBP=women of child bearing potential.

a. BUN is preferred; if not available, urea may be tested.
b. If these tests are not performed as part of standard of care in your region then these tests do not need to be performed. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte.
c. Creatinine: GFR (measured or calculated) or creatinine clearance can be used in place of creatinine. Creatinine clearance should be calculated using the Cockcroft-Gault Method:
d. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study. aPTT is preferred. If not available, PTT is acceptable.
e. T3 is preferred. If not available, free T3 (FT3) may be tested.

The investigator (or medically qualified designee) must document their review of each laboratory safety report. Safety laboratory test results (with the exception of thyroid tests) must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study medication. Unresolved abnormal laboratory test results that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end-of-treatment if laboratory test results are within normal range.

Country-specific differences are noted in Appendix 7.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

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

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not a condition of the study).
  - Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

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

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention 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 their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

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

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

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

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

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

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

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

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Argentina-specific Requirements:

- Exclusion Criterion 10: Hepatitis B and Hepatitis C testing is mandatory.
- Exclusion Criterion 13: HIV testing is mandatory.

10.7.2 EU Countries-specific Requirements:

According to the CTFG guideline, monthly pregnancy testing should be performed in WOCBP during the same period as contraception is mandatory.

10.7.3 Germany-specific Requirements:

- Exclusion Criterion 10: Hepatitis B and Hepatitis C testing is mandatory.
- Exclusion Criterion 13: HIV testing is mandatory.
- Exclusion Criterion 14: TB testing is mandatory.
- Section 8.4.1: All AEs meeting serious criteria are to be collected for 120 days after the last dose of study intervention.

10.7.4 Japan-specific Requirements:

- For the assistance to early diagnosis of pneumonitis/ILD in study participants, the following items such as pulse oximetry monitoring (SpO_2), CRP, KL-6, and SP-D will be measured in this study. These items should be measured in the following timing.
  - SpO_2: at the timing of vital sign assessment.
  - CRP, KL-6, and SP-D: at screening*, predose of Day 1 of every cycle, end-of-treatment, and Safety Follow-up Visit (30 days after last dose).

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

- 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 5.2 Exclusion Criteria

- Exclusion Criterion 14: Known history of active tuberculosis specifies active, ongoing tuberculosis. Tuberculosis documented in medical history that is no longer active or ongoing is not exclusionary.

Section 6.1 Study Intervention(s) Administered

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.

10.7.5 South Korea-specific Requirements:

- Participants must be 19 years old or older.

10.7.6 Romania-specific Requirements:

- Exclusion Criterion 10: Hepatitis B and Hepatitis C testing is mandatory.
- Exclusion Criterion 13: HIV testing is mandatory.

10.7.7 United Kingdom-specific Requirements

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

10.7.8 Italy-specific Requirements

Section 1.3 Schedule of Activities

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

Section 5.2 Exclusion Criteria

- Has a known history of HIV infection.
- History of hepatitis B (defined as HBsAg reactive) or known active hepatitis C (defined as detectable HCV RNA [qualitative]) infection.

10.8 Appendix 8: Eastern Cooperative Oncology Group

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

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

10.9 Appendix 9: NSCLC Staging Definitions

The staging allowed in this trial includes NSCLC Stage I and Stage II, per AJCC version 8 NSCLC staging guideline [Detterbeck, F. C., et al 2017].

Figure 3 Excerpt From AJCC v8 NSCLC Staging Guideline on Appropriate Staging of N0 Disease.

T/M	Label	N0
T1	T1a *≤1*	IA1
	T1b *>1-2*	IA2
	T1c *>2-3*	IA3
T2	T2a *Cent, Visc Pl*	IB
	T2a *>3-4*	IB
	T2b *>4-5*	IIA
T3	T3 *>5-7*	IIB
	T3 *Inv*	IIB
	T3 *Satell*	IIB

Figure 4 Excerpt From AJCC v8 NSCLC Staging Guideline on Primary Tumor Sizing Criteria.

T (Primary Tumor)		Label
T0	No primary tumor	
Tis	Carcinoma in situ (Squamous or Adenocarcinoma)	Tis
T1	Tumor ≤3 cm,	
T1a(mi)	Minimally Invasive Adenocarcinoma	T1a*(mi)*
T1a	Superficial spreading tumor in central airways[a]	T1a *SS*
T1a	Tumor ≤1 cm	T1a *≤1*
T1b	Tumor >1 but ≤2 cm	T1b *>1-2*
T1c	Tumor >2 but ≤3 cm	T1c *>2-3*
T2	Tumor >3 but ≤5 cm or tumor involving:	
	visceral pleura[b],	T2 *Visc Pl*
	main bronchus (not carina), atelectasis to hilum[b]	T2 *Centr*
T2a	Tumor >3 but ≤4 cm	T2a *>3-4*
T2b	Tumor >4 but ≤5 cm	T2b *>4-5*
T3	Tumor >5 but ≤7 cm	T3 *>5--7*
	or invading chest wall, pericardium, phrenic nerve	T3 *Inv*
	or separate tumor nodule(s) in the same lobe	T3 *Satell*

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate Aminotransferase
BCG	*bacillus* Calmette–Guérin
BDS	blood drug screen
BED	biologically effective dose
BICR	blinded independent central review
CAC	Clinical Adjudication Committee
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRF	Case Report Form
CRP	C-reactive protein
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSS	disease-specific survival
ECG	electrocardiogram
ECI	event of clinical interest

Abbreviation	Expanded Term
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
EEA	European Economic Area
EFS	event-free survival
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C13	EORTC Quality of Life Questionnaire C13
EORTC QLQ-C30	EORTC Quality of Life Questionnaire C30
EORTC QLQ-LC13	EORTC Quality of Life Questionnaire and Lung Cancer Module 13
EOT	End of Trial
ePRO	electronic patient-reported outcome(s)
EU	European Union
EuroQoL EQ-5D-5L	EuroQoL-5 Dimension Questionnaire
FAS	Full Analysis Set
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Expanded Term
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iCRO	imaging Contract Research Organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
IO	Immune-oncology
irAE	immune-related adverse events
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	Interactive Voice Response System
KL-6	Krebs von den Lungen-6
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OS	overall survival

Abbreviation	Expanded Term
PBPK	physiologically-based PK
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PRO	patient-reported outcomes
PS	performance scale
PTV	planned target volume
Q3D	every 3 days
Q3W	every 3 weeks
QA	quality assurance
QoL	quality of life
QP2	department of quantitative pharmacology and pharmacometrics
RNA	ribonucleic acid
RMST	restricted mean survival time
SAE	serious adverse event
SBRT	stereotactic body radiotherapy
siDMC	Standing Internal Data Monitoring Committee
SoA	schedule of activities
SOC	standard of care
SP-D	surfactant protein D
SpO_2	oxygen saturation
sSAP	Supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TLR4	toll-like receptor 4
TMDD	target-mediated drug disposition
TRSLT	time to recurrence/progression on subsequent line of therapy

Abbreviation	Expanded Term
TB	*Bacillus* tuberculosis
TTST	time to subsequent treatment
UDS	urine drug screen
US	United States
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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