Official Protocol Title:	A Randomized, Phase 3, Open-label Study to Investigate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab versus Intravenous Pembrolizumab, Administered with Platinum Doublet Chemotherapy, in the First-Line Treatment of Participants with Metastatic Squamous or Nonsquamous Non-Small-Cell Lung Cancer
NCT number:	NCT04956692
Document Date:	12-JULY-2023

Title Page

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Protocol Title: A Randomized, Phase 3, Open-label Study to Investigate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab versus Intravenous Pembrolizumab, Administered with Platinum Doublet Chemotherapy, in the First-Line Treatment of Participants with Metastatic Squamous or Nonsquamous Non-Small-Cell Lung Cancer

Protocol Number: A86-07

Compound Number: MK-3475

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	147059
EudraCT	2020-002729-27

Approval Date: 12 July 2023

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 07	12-JUL-2023	To remove Tertiary/Exploratory objective that includes pharmacoeconomic substudy (Time and Motion study) and the corresponding endpoint as it is no longer needed and to add an option of IV pembrolizumab in the Second Course of the study available to participants randomized to the SC treatment arm.
CCI [redacted]		
Amendment 05	21-JUL-2022	CCI [redacted]
Amendment 04	31-MAR-2022	To correct a typographical error in the inclusion criterion for adequate renal function.
Amendment 03	03-MAR-2022	Update the CCI [redacted] C_{trough} primary endpoint from an observed endpoint to a model-based endpoint and to further clarify the PP population definitions and requirements.
Amendment 02 (Country-specific for Japan)	15-JUL-2021	Updates made to Section 10.7.5 (Japan-specific appendix) inclusion criteria to clarify breastfeeding eligibility and clarify ICF requirement for participants under 20 years of age.
Amendment 01	26-MAY-2021	Changes made in response to FDA feedback to update Section 6.6.2.2 Table 4, *Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab*, to add guidance for injection reactions related to SC pembrolizumab. Given that this study is looking at both SC and IV pembrolizumab, safety information about administration reactions in this table is required for both the IV infusion and SC injection.

Document	Date of Issue	Overall Rationale
Original Protocol	26-MAR-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 07

Overall Rationale for the Amendments:

To remove Tertiary/Exploratory objective that includes pharmacoeconomic substudy (Time and Motion study) and the corresponding endpoint as it is no longer needed and to add an option of IV pembrolizumab in the Second Course of the study available to participants randomized to the SC treatment arm.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
3 Hypotheses, Objectives, and Endpoints 4.2.1.5 Pharmacoeconomic Endpoints	Tertiary/Exploratory objective that includes pharmacoeconomic substudy (Time and Motion study) and the corresponding endpoint and Section 4.2.1.5 have been removed.	It is no longer needed.
1.3.4 Second Course Retreatment Phase 4.1 Overall Design 6.6.3 Second Course	Text added to allow IV pembrolizumab option for SC treatment arm patients during the Second Course.	To provide an option of IV pembrolizumab in the Second Course to participants randomized to the SC treatment arm.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Phase 3, Open-label Study to Investigate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab versus Intravenous Pembrolizumab, Administered with Platinum Doublet Chemotherapy, in the First-Line Treatment of Participants with Metastatic Squamous or Nonsquamous Non-Small-Cell Lung Cancer

Short Title: Phase 3 study of pembrolizumab SC versus pembrolizumab IV, administered with platinum doublet chemotherapy, in 1L metastatic squamous or nonsquamous NSCLC

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In males and females with treatment-naïve metastatic squamous or nonsquamous non-small-cell lung cancer who will be receiving chemotherapy:

Primary Objectives	Primary Endpoints
• Objective: To compare AUC between pembrolizumab SC vs pembrolizumab IV. • Hypothesis: Pembrolizumab SC is non-inferior to pembrolizumab IV for CCI [redacted].	• CCI [redacted]
• Objective: To compare C_{trough} between pembrolizumab SC vs pembrolizumab IV. • Hypothesis: Pembrolizumab SC is non-inferior to pembrolizumab IV for CCI [redacted]	• CCI [redacted]
Secondary Objectives	Secondary Endpoints
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to ORR per RECIST 1.1 as assessed by blinded independent central review (BICR).	• OR: CR or PR

Secondary Objectives	Secondary Endpoints
• Objective: To evaluate exposure of pembrolizumab SC compared to pembrolizumab IV.	• CCI •
• Objective: To evaluate the safety and tolerability of pembrolizumab SC compared to pembrolizumab IV.	• AE • Study intervention discontinuation due to AEs
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to PFS per RECIST 1.1 as assessed by BICR.	• PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to OS.	• OS: the time from randomization to death due to any cause
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to DOR per RECIST 1.1 as assessed by BICR.	• DOR: the time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first
• Objective: To evaluate the development of ADAs following administration of pembrolizumab SC compared to pembrolizumab IV.	• Anti-pembrolizumab antibody levels

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	First-line treatment of metastatic squamous or nonsquamous NSCLC with pembrolizumab SC administered with platinum doublet chemotherapy
Population	Adult patients with treatment-naïve metastatic squamous or nonsquamous NSCLC
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 512 participants will be randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	Pembrolizumab SC	CCI	CCI	SC	CCI	Test Product
Arm B	Pembrolizumab IV	CCI				
Arms A and B (Squamous Histology)	Paclitaxel	200 mg/m^2		IV		Background Treatment
Arms A and B (Squamous Histology)	Nab-paclitaxel	100 mg/m^2		IV		Background Treatment
Arms A and B (Squamous and Non-squamous Histology)	Carboplatin	Squamous: AUC 6 mg/mL/min Non-squamous: AUC 5 mg/mL/min		IV		Background Treatment
Arms A and B (Non-squamous Histology)	Cisplatin	75 mg/m^2		IV		Background Treatment
Arms A and B (Non-squamous Histology)	Pemetrexed	500 mg/m^2		IV	Until progression, intolerable AE, participant or physician decision	Background Treatment

Abbreviations: AUC = area under curve; IV=intravenous; CCI SC=subcutaneous.

Total Number of Intervention Groups/ Arms: 2

Duration of Participation	Each participant will participate in the study for approximately 4 years from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who complete study intervention after receiving CC [redacted] After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Abbreviations: AE = adverse event; ALK = Anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IV = intravenous; NSCLC = non-small cell lung cancer; PD-L1 TPS = programmed cell death ligand 1 tumor proportion score; CCI

1.3 Schedule of Activities

1.3.1 Screening and Intervention Phase

Study Period	**Screening Phase**	**Intervention Phase** CCI	**Notes**
CCI [redacted]			
Schedule Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**	
Administrative Procedures			
Informed Consent	X		If the investigator plans to treat beyond the initial radiologic disease progression per RECIST 1.1, additional consent will be required prior to post-progression intervention (see Section *General Informed Consent*).
Informed Consent for FBR	X		This is optional for the participant. Participants can still participate in the study if they decline to provide the FBR ICF.
Inclusion/ Exclusion Criteria	X		
Participant Identification Card	X	X	The Participant Identification Card should be updated with the randomization number at the time of randomization.
Demographics and Medical History	X		
Prior/ Concomitant Medication	<----------	---------->	Prior medications: Record medications taken within 28 days prior to first dose and medications regularly administered at intervals greater than 28 days prior to first dose. Concomitant medications: Record new medications started during the study through the postintervention follow-up, as well as any changes to dose, frequency, and route that occur.

Study Period	**Screening Phase**	**Intervention Phase** CCI	**Notes**
CCI [redacted]			
Schedule Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**	
NSCLC Disease Details and Prior Treatment	X		
Randomization		X	Randomization can occur up to 3 days prior to C1D1 (study drug administration).
Vital Status		<--------	See Section *Vital Status* for full details. Upon Sponsor request, participants may be contacted for vital status at any time during the study.
Clinical Procedures/Assessments			
AE/SAE Review		<--------	AEs: Report all AEs occurring from the start of study intervention through 30 days after the last dose of study intervention. SAEs: Report all SAEs from the start of study intervention through 90 days after the last dose of study intervention, or 30 days following the last dose of study intervention if the participant initiates new anticancer therapy, whichever occurs first.
Complete Physical Examination, Height	X		

Study Period	Screening Phase	Intervention Phase CCI	Notes
CCI			
Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**	
CCI			
Weight	<----------	---------->	Taken prior to intervention administration.
Vital Signs	<----------	---------->	To be measured at screening and prior to dosing study intervention.
12-lead ECG	X		Additional ECGs performed as clinically indicated.
ECOG Performance Status	<----------	---------->	ECOG performance status will be evaluated within 7 days prior to randomization, as well as before administration of study intervention in each cycle.

Study Period	Screening Phase	Intervention Phase CCI	Notes
CCI [redacted]			
Schedule Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**	
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory			
Pregnancy Testing	X	X	A WOCBP must have a negative highly sensitive pregnancy test (as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention. Serum test is required if urine test is positive or not evaluable. Pregnancy testing (urine or serum as required by local regulations or as clinically indicated) should be conducted at every cycle during intervention.
PT or INR and aPTT/PTT	X		PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during intervention and safety Follow-up Phase.
HBV, HCV, and HIV Testing	X		Testing at Screening only required if mandated by local health authority or institutional guidelines. Refer to Appendix 7, for country-specific requirements.
Urinalysis	X		Screening samples to be collected within 10 days prior to the first dose of study intervention.
Hematology and Chemistry	X	X X X* X* X X* X* X X* X* X X* X* X X	Screening samples to be collected within 10 days prior to the first dose of study intervention. On treatment samples to be collected and reviewed prior to administration of study intervention, which can be conducted within 72 hours prior to the first dose of study intervention in each cycle. *Predose ANC and platelet count are required on Days 8 and 15 of Cycles 1-4 only for participants receiving nab-paclitaxel.

CCI

[redacted]

Study Period	Screening Phase	Intervention Phase CCI						Notes
CCI [redacted]								
Schedule Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**						
Tumor Tissue Collection								
Archival or Newly Obtained Tissue Collection for PD-L1 IHC and Other Biomarkers	X							A new incisional or core biopsy will be required if archival tissue is not available. PD-L1 IHC will be mandatory to stratify participants prior to randomization. The biopsy will also be utilized for EGFR, ALK, and ROS1 testing prior to randomization if this testing was not already completed locally.
Efficacy Measurements								
CCI [redacted]								

Study Period	Screening Phase	Intervention Phase	Notes
CCI			
Schedule Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**	
CCI			

Study Period	Screening Phase	Intervention Phase CCI	Notes
CCI			
Schedule Window		**± 1 day for Cycles 1-7; ±3 days for Cycle 8 onward**	
Patient-reported Outcomes (PRO)			
CCI			

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

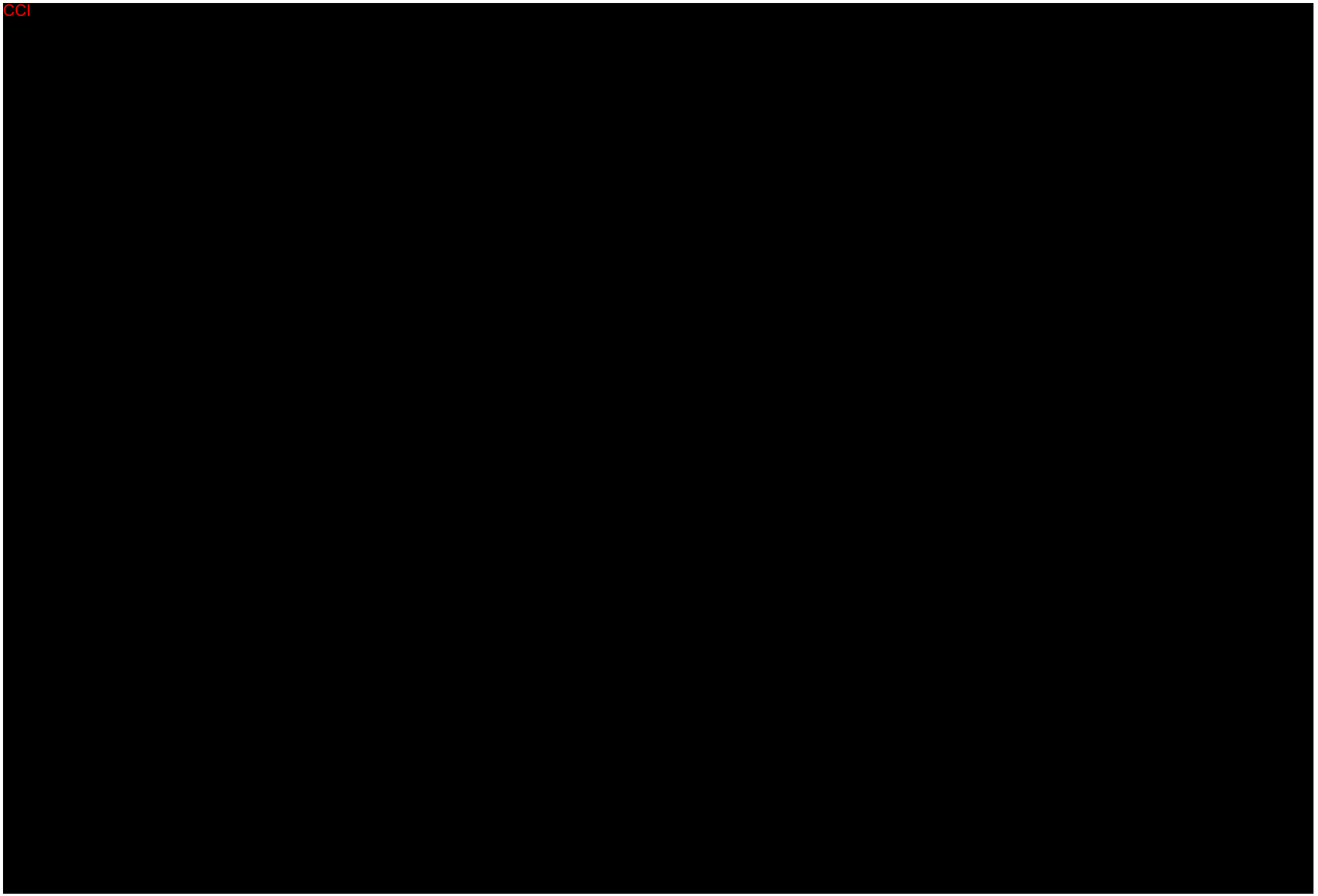
Study Period	**End of Intervention**	**Post-Intervention Visits**			**Notes**
Visit Title	**Discontin-uation**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Schedule Window	**At Tx DC**	**30 Days After Last Dose (If DC visit occurs ≥30 days from last dose of Tx, a Safety FU visit is not required)**	**Follow-up imaging to maintain same schedule as while on treatment**	**Q12W 30 Days Post Discon (±14 days)**	
Patient-reported Outcomes (PRO)					
EORTC QLQ-C30	X	X			PROs are completed at the intervention discontinuation visit and 30-day safety follow-up visit. Perform ePROs in the following order listed: EORTC QLQ-C30 followed by EQ-5D-5L.
EQ-5D-5L	X	X			

AE=adverse event; ADA=Antidrug Antibodies; BICR=Blinded independent central review; CrCl=creatinine clearance; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; DC/Discon=discontinuation; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30; ePRO=electronic patient-reported outcome; EQ-5D-5L=EuroQol 5-dimension, 5-level Questionnaire; FT4= free thyroxine; FU=follow-up; IV=intravenous; MRI=magnetic resonance imaging; NSCLC=non-small cell lung cancer; PD=progressive disease; PD-L1=programmed cell death ligand 1; PK=pharmacokinetics; PRO=patient-reported outcome; QXW=every X weeks; SAE=serious adverse event; SC=subcutaneous; T3/FT3= free or total triiodothyronine; TSH= thyroid-stimulating hormone; Tx=treatment.

Note: See Appendix 7 for country-specific requirements.

CCI

[redacted]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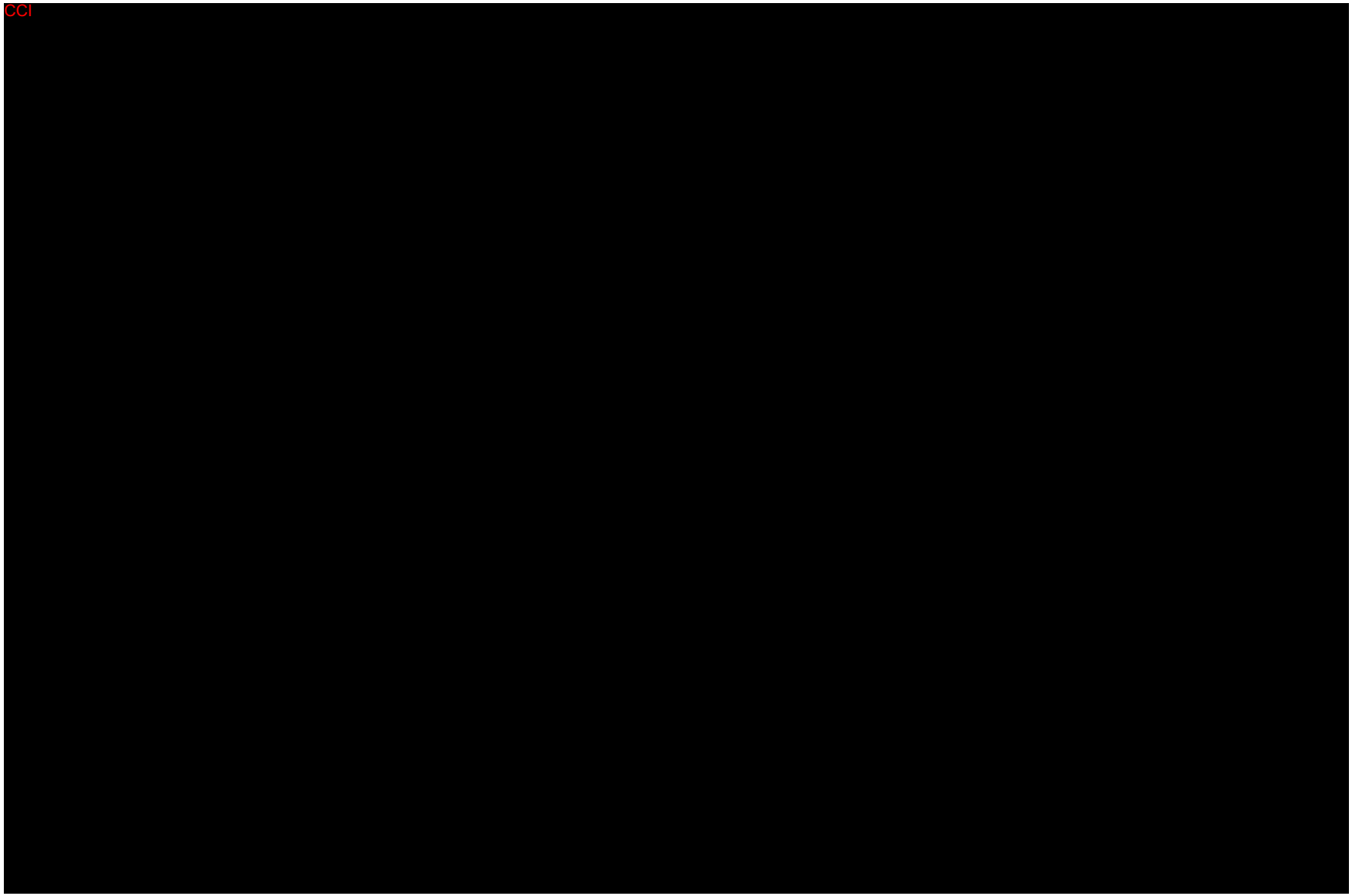

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2 INTRODUCTION

This clinical study will evaluate pembrolizumab SC as first-line therapy in the treatment of metastatic squamous and nonsquamous NSCLC by assessing the PK, safety, and efficacy of pembrolizumab when administered as an SC injection [redacted] in combination with standard-of-care chemotherapy.

2.1 Study Rationale

Pembrolizumab is currently indicated for a number of tumor types including both squamous and nonsquamous NSCLC as monotherapy and in combination with chemotherapy. Adult patients are currently to be treated with pembrolizumab at an IV dose of 200 mg every 3 weeks (Q3W). However, there is high demand for SC formulations, with over 80% of patients preferring SC to IV administration [Rummel, M., et al 2017] [Pivot, X., et al 2013]. A SC formulation of pembrolizumab has been developed for use as an alternative to the IV formulation of pembrolizumab. [redacted]
Benefits of SC administration include time savings for patients and providers, convenience, reduced administration costs, ease of administration, and reduced health care resource burden. Additionally, a SC dosing option will reduce patient chair time, thus making it feasible for infusion centers to treat more patients.

2.2 Background

2.2.1 Key Benefits of Subcutaneous Versus Intravenous Formulation

Confirmed benefits of SC administration include improved patient convenience and reduced use of hospital resources and health care professionals. In a 2013 Lancet manuscript describing an open-label randomized study of the preference for SC or IV administration of trastuzumab in patients with HER2-positive early breast cancer, 216 of 236 participants preferred SC administration to IV administration [Pivot, X., et al 2013]. The 2 main reasons participants gave for preferring SC administration were time savings (195 of 216 participants) and less pain and discomfort (88 of 216 participants). Most of participants reported their overall preference for SC administration as “very strong” (67.4%; 95% CI: 61.0% to 73.3% SC versus 3.4%; 95% CI: 1.5% to 6.6% IV). Health care professionals were also more satisfied with SC administration (73.8%; 76 of 103 SC versus 1.9%; 2 of 103 IV); the remaining 25 (24.3%) health care professionals expressed no preference for route of administration. Similar results were reported in a 2017 manuscript describing the preference for SC or IV administration of rituximab among patients with CD20+ diffuse large B-cell lymphoma or follicular lymphoma [Rummel, M., et al 2017].

2.2.2 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD 1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

2.2.3 Non-Small-Cell Lung Cancer

Lung cancer is the most common malignancy in the world, with an estimated incidence in 2018 of 2.1 million and an associated 1.8 million deaths [Bray, F., et al 2018]. Among males, the estimated incidence rates of new diagnoses are highest in Central and Eastern Europe (49.3 per 100,000/year) and Eastern Asia (47.2), while the incidence rates among females are highest in Northern America (30.7), Northern Europe (26.9), Western Europe (25.7), and Micronesia/Polynesia (24.3) [Bray, F., et al 2018]. Mortality from lung cancer is the leading cause of cancer death in men and the second leading cause in women [Bray, F., et al 2018]. In the US in 2020, there were an estimated 229,000 new cases and 136,000 deaths from lung cancer [National Cancer Institute 2020].

Non-small-cell lung cancer represents approximately 80% to 85% of all lung cancers [American Cancer Society 2019] and consists of 2 major types: nonsquamous carcinoma (~65% to 70% of cases) and squamous carcinoma (~30% to 35% of cases) [Mok, T. S. K., et al 2019] [Reck, M., et al 2020] [Hellmann, M. D., et al 2018]. At the time of diagnosis, 79% of patients with lung cancer have locally advanced or metastatic disease that is not amenable to surgical resection [National Cancer Institute 2019]. Of those patients diagnosed with early-stage NSCLC and treated with surgery, a significant percentage subsequently develop distant recurrence [Pisters, K. M. W. and Le Chevalier, T. 2005]. These factors contribute to the dismal 5 year relative survival rates of 23% in patients diagnosed with NSCLC, and a mere 6% in those with advanced/metastatic disease [American Cancer Society 2019].

Importantly, in nonsquamous NSCLC, molecular profiling and availability of targeted therapy have helped change the treatment approach for a subset of patients. The EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib have showed marked superiority over chemotherapy in patients with activating EGFR mutations; and osimertinib in front line has shown improved outcomes over earlier generations of EGFR tyrosine kinase inhibitors. Similarly, multiple ALK inhibitors, including crizotinib, ceritinib, alectinib, and brigantinib have shown significant activity in ALK-rearranged NSCLC and have received regulatory approval for use. Interestingly, the ALK inhibitors are also active in a rare subgroup of ROS-1-rearranged NSCLC patients; and crizotinib and entrectinib have received regulatory approval in ROS-1-rearranged lung cancers. Data have shown poorer outcomes in patients with tumors harboring a targetable mutation that are not treated with a tyrosine kinase inhibitor [Kris, M. G., et al 2014]. In contrast, no targeted therapy has been approved for maintenance therapy in squamous cell NSCLC. While squamous cell lung cancers harbor putative oncogenic drivers, these have little clinical relevance and cannot be targeted.

Immunotherapy, in particular pembrolizumab as monotherapy or in combination with chemotherapy, has changed the treatment paradigm for those patients with NSCLC. In the Phase 3 study, KEYNOTE-024, pembrolizumab showed statistically significant increases in OS and PFS compared with platinum-based chemotherapy for treatment-naïve participants

with metastatic NSCLC whose tumors expressed high levels of PD-L1 (TPS ≥50%) with no EGFR or ALK genomic tumor aberrations, leading to regulatory approval for this indication in the US and other countries around the world. Approximately 23% to 28% of patients with newly diagnosed, advanced NSCLC highly express PD-L1 to a TPS ≥50% [Reck, M., et al 2016]. With the findings from KEYNOTE-042, the TPS cutoff has been lowered, as pembrolizumab monotherapy significantly improved OS for participants with NSCLC who had TPS ≥1% (16.7 months vs 12.1 months; HR: 0.81), compared with chemotherapy alone, while continuing to show an OS benefit in those with TPS ≥50% (20.0 months versus 12.2 months; HR: 0.69). Thus, both KEYNOTE-024 and KEYNOTE-042 showed that pembrolizumab monotherapy is effective in participants with PD-L1 positive metastatic NSCLC.

To further expand on the efficacy of pembrolizumab, KEYNOTE-407, KEYNOTE-021 Cohort G, and KEYNOTE-189 were designed to combine the agent with chemotherapy in participants with metastatic NSCLC, as chemotherapy has been shown to augment the antitumor immune response.

- KEYNOTE-407 is a Phase 3 study that randomized 559 participants with newly diagnosed metastatic squamous NSCLC to pembrolizumab with carboplatin and a taxane (paclitaxel or nab-paclitaxel) versus carboplatin and a taxane (paclitaxel or nab-paclitaxel) [Paz-Ares, L., et al 2018]. The study showed a clinically meaningful and statistically significant improvement in OS for participants in the pembrolizumab combination arm (median OS of 15.9 months versus 11.3 months; HR: 0.64 [95% CI: 0.49-0.85, p=0.008]), compared with chemotherapy alone. Similarly, there was significant PFS benefit for participants in the pembrolizumab combination arm (median PFS of 6.4 months versus 4.8 months; HR: 0.56 [95% CI: 0.45-0.70, p<0.0001]), compared with chemotherapy alone. ORR also was significantly improved in the pembrolizumab combination arm (58.4%) compared with chemotherapy alone (35%), p = 0.0004. Importantly all subgroups benefited from pembrolizumab in combination with carboplatin and taxane-based chemotherapy, including participants whose tumors did not express PD-L1; therefore, extending the benefit of pembrolizumab to those with PD-L1 negative tumors.
- KEYNOTE-021 (Cohort G) is a Phase 2 study that randomized 123 participants to pembrolizumab with pemetrexed and carboplatin versus pemetrexed with carboplatin in participants with metastatic nonsquamous NSCLC in whom there were no EGFR or ALK genomic tumor aberrations who had not previously received systemic therapy for their advanced disease. The study met its primary endpoint of improvement in ORR, as well as the key secondary endpoint of PFS [Borghaei, H., et al 2017], leading to FDA accelerated approval of pembrolizumab in combination with pemetrexed/carboplatin. In an updated analysis, the following were noted: improvement in ORR was 24.8% (95% CI: 7.2 to 40.9) with 56.7% for the pembrolizumab with chemotherapy arm and 31.7% for the control; PFS HR 0.54 (95% CI: 0.33 to 0.88) with median PFS 19.0 versus 8.9 months, for the pembrolizumab with chemotherapy arm compared with the control, respectively; and OS HR 0.59 (95% CI: 0.34 to 1.05) with median OS not reached in the pembrolizumab combination arm and 20.9 months in the control [Borghaei, H., et al 2017].

- KEYNOTE-189 is a global, multicenter, placebo-controlled trial that randomized 616 participants with untreated Stage IV nonsquamous NSCLC in a 2:1 fashion to receive pemetrexed and investigator's choice of either carboplatin or cisplatin in combination with pembrolizumab or saline placebo for 4 cycles, followed by pembrolizumab or saline for a total of 35 cycles, plus pemetrexed maintenance therapy. Participants in the saline placebo arm had the option to cross over to pembrolizumab monotherapy if progressive disease had been verified by BICR and other safety criteria were met. The study showed a clinically meaningful and statistically significant improvement in OS with an HR of 0.56 (95% CI: 0.45 to 0.70) and a median OS of 22.0 months in the pembrolizumab combination arm compared with 10.7 months in the chemotherapy alone arm [Gadgeel, S., et al 2020]. Similarly, there was significant PFS benefit with an HR of 0.48 (95% CI: 0.40 to 0.58) with a median PFS of 9.0 months and 4.9 months in the pembrolizumab combination arm vs. chemotherapy alone arm, respectively. ORR also was significantly improved in the pembrolizumab combination arm (48.0%) compared with chemotherapy alone (19.4%). Importantly, all subgroups benefited from pembrolizumab in combination with pemetrexed and carboplatin or cisplatin, including participants whose tumors did not express PD-L1; therefore, extending the benefit of pembrolizumab to those with PD-L1 negative tumors.

2.2.4 Subcutaneous Formulation

KEYNOTE-555 was designed to estimate the relative bioavailability of an SC versus an IV dose of pembrolizumab, and to characterize the PK profile of pembrolizumab administered SC. Participants in the study were limited to those with a diagnosis of advanced melanoma, and the crossover design was chosen to eliminate effects of interindividual variability inherent in a parallel-group design. The relative bioavailability of 2 different SC formulations of pembrolizumab CCI was estimated in this study using the SC dose CCI of pembrolizumab compared with the IV dose of pembrolizumab (200 mg). CCI Participants then received an IV infusion of 200 mg pembrolizumab CCI

CCI

Additionally, CCI

2.2.5 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 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]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in metastatic squamous NSCLC and nonsquamous NSCLC.

2.2.6 Preclinical and Clinical Studies

For a summary of preclinical and clinical study data for pembrolizumab, refer to the IB.

2.2.7 Ongoing Clinical Studies

For a summary of ongoing clinical study data for pembrolizumab, refer to the IB.

2.2.8 Information on Other Study-related Therapy

As described above, pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel has become the standard of care in patients with metastatic squamous NSCLC due to the positive results of the randomized Phase 3 study, KEYNOTE-407. Similarly, with the results of KEYNOTE-189, the standard of care 1L therapy for patients with treatment naïve metastatic nonsquamous NSCLC is pembrolizumab in combination with pemetrexed and cisplatin or carboplatin.

Based on safety and efficacy data from these combination studies with pembrolizumab, the current study will use pembrolizumab in combination with carboplatin plus paclitaxel or nab-paclitaxel OR pembrolizumab in combination with platinum (cisplatin/carboplatin) plus pemetrexed at approved doses.

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.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In males and females with treatment-naïve metastatic squamous or nonsquamous non-small-cell lung cancer who will be receiving chemotherapy:

Objectives	Endpoints
Primary	
• Objective: To compare AUC between pembrolizumab SC vs pembrolizumab IV. • Hypothesis: Pembrolizumab SC is non-inferior to pembrolizumab IV for CCI [redacted].	• CCI [redacted]
• Objective: To compare C_{trough} between pembrolizumab SC vs pembrolizumab IV. • Hypothesis: Pembrolizumab SC is non-inferior to pembrolizumab IV for CCI [redacted]	•
Secondary	
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to ORR per RECIST 1.1 as assessed by blinded independent central review (BICR).	• OR: CR or PR
• Objective: To evaluate exposure of pembrolizumab SC compared to pembrolizumab IV.	• CCI [redacted] •
• Objective: To evaluate the safety and tolerability of pembrolizumab SC compared to pembrolizumab IV.	• AE • Study intervention discontinuation due to AEs

Objectives	Endpoints
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to PFS per RECIST 1.1 as assessed by BICR.	• PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to OS.	• OS: the time from randomization to death due to any cause
• Objective: To evaluate pembrolizumab SC and pembrolizumab IV with respect to DOR per RECIST 1.1 as assessed by BICR.	• DOR: the time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first
• Objective: To evaluate the development of ADAs following administration of pembrolizumab SC compared to pembrolizumab IV.	• Anti-pembrolizumab antibody levels
Tertiary/Exploratory	
• Objective: To evaluate the change from baseline in HRQoL following treatment with pembrolizumab SC or pembrolizumab IV.	• Score change from baseline at predefined time point evaluated by EORTC QLQ-C30 in the following items: - Global health status/QoL (C30/Items 29 and 30) - Physical functioning (C30/Items 1 through 5) - role functioning (C30/Items 6 and 7)
• Objective: To evaluate health status using the EQ-5D-5L.	• Change from baseline per predefined time point of EQ-5D-5L VAS score

Objectives	Endpoints
• CCI [redacted]	[redacted]
• [redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multisite, open-label study of pembrolizumab SC administered with platinum doublet chemotherapy (Arm A) versus pembrolizumab IV administered with platinum doublet chemotherapy (Arm B) in 512 participants with metastatic squamous or nonsquamous NSCLC. Participants must have newly diagnosed, untreated Stage IV NSCLC, an ECOG PS of 0 to 1, and no current pneumonitis or interstitial lung disease at enrollment.

After providing the informed consent, candidate participants will be screened against all of the eligibility criteria. Eligible participants will be randomly assigned to study intervention arm in a CCI [redacted] (Arm A to Arm B).

- Arm A – Participants will receive up to CCI [redacted] of CCI [redacted] pembrolizumab SC CCI [redacted] administered with platinum doublet chemotherapy
- Arm B – Participants will receive up to 35 cycles of 200 mg pembrolizumab IV Q3W administered with platinum doublet chemotherapy
- Platinum Doublet Chemotherapy:
  - Participants with squamous NSCLC will receive 4 cycles of carboplatin in combination with a taxane, investigator's choice (paclitaxel/nab-paclitaxel).
  - Participants with nonsquamous NSCLC will receive 4 cycles of pemetrexed with a platinum, investigator's choice (cisplatin/carboplatin), followed by pemetrexed maintenance until progression, an intolerable AE, or discontinuation by participant or physician decision.

Randomization will be performed to avoid bias in the assignment of participants to study intervention, to increase the likelihood that known and unknown participant attributes are balanced across intervention arms, and to ensure the validity of statistical comparisons between intervention arms. CCI [redacted]

One interim analysis and one final analysis are planned for this study. Details regarding the interim analysis are provided in Section 9.7. An external DMC will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to the study to an EOC of the Sponsor (Section 10.1.4). The eDMC responsibilities and review schedules will be outlined in the eDMC charter.

A decision to stop the trial early due to futility will be based on the eDMC recommendations with review by the Sponsor EOC after IA 1. If a decision is made to stop the trial, all participants that have already been randomized and are receiving pembrolizumab treatment, SC or IV, will be given the option to continue on IV pembrolizumab. Enrollment will continue during the period of the futility analysis.

The primary objectives of the study are to compare CCI [redacted] pembrolizumab SC versus pembrolizumab IV, administered with platinum doublet chemotherapy. Non-inferiority will be evaluated with the non-inferiority margin of 0.8.

Efficacy will be evaluated by ORR, DOR, and PFS per RECIST 1.1 as determined by BICR, and OS. On-study imaging assessments will be performed as described in Section 1.3. RECIST 1.1 (Section 4.2.1.3.1) will be used by the site for therapy decisions for both arms until verification of the initial site-assessed PD by BICR. Participants may not crossover to the other intervention arm.

Adverse event monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0 (Section 8.4). Adverse events will be reported by the investigator or delegate from the start of study intervention through 30 days after cessation of study intervention. Serious AEs will be reported by the investigator or delegate from the start of intervention through either 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

Health related quality of life and patient health utilities will be estimated using EORTC-QLQ-C30 and EQ-5D-5L questionnaires.

In addition, blood/tissue for identification of molecular biomarkers (genomic, metabolic, and/or proteomic) that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab will be collected at regular intervals (see Section 4.2.1.7).

Tumor imaging showing site-assessed PD will be submitted for verification by BICR. Treatment beyond centrally verified PD per RECIST 1.1 may be permitted at the discretion of the investigator after consulting the Sponsor and receiving documented informed consent addendum from the participant.

Participants who discontinue treatment for reasons other than centrally verified progressive disease will have Efficacy Follow-up for disease status (including imaging) until progressive disease, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up. After documented progressive disease, each participant will be contacted by telephone approximately every 12 weeks (84 ±14 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow-up, death, or end of the study, whichever occurs first.

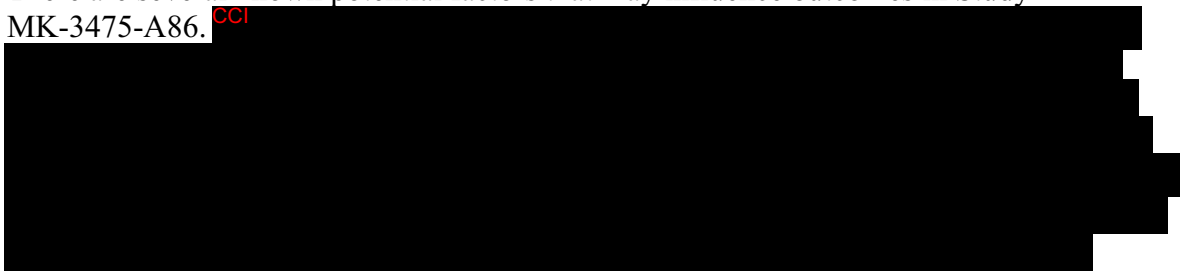
CCI

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

4.2 Scientific Rationale for Study Design

In multiple countries, pembrolizumab in combination with standard chemotherapy is indicated for the 1L treatment of patients with metastatic squamous or nonsquamous NSCLC. Further improvements can be made for patients to receive intervention by SC injection as an alternative to IV infusion. The results of this study will determine the similarity in exposure of pembrolizumab administered SC compared with pembrolizumab administered IV, as well as determine the safety of pembrolizumab SC in participants with advanced NSCLC.

There are several known potential factors that may influence outcomes in Study MK-3475-A86. CCI



CCI [redacted] Scagliotti, G. V., et al 2008] [Paz-Ares, L., et al 2018] [Gandhi, L., et al 2018]. Tumor expression of PD-L1 has been identified as a biomarker associated with clinical benefit for participants with NSCLC treated with pembrolizumab. CCI [redacted]

4.2.1 Rationale for Endpoints

4.2.1.1 Pharmacokinetic Endpoints

CCI [redacted]

Dual primary endpoints:

- CCI [redacted]
-

Secondary endpoints:

CCI [redacted]

4.2.1.2 Safety Endpoints

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

4.2.1.3 Efficacy Endpoints

Secondary endpoints will include ORR, DOR, and PFS per RECIST 1.1 as assessed by BICR and OS. These endpoints are commonly accepted endpoints by both regulatory authorities and the oncology community.

4.2.1.3.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (see Section 8.2.1.5). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.4 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, HRQoL and disease-related symptoms will be investigated among all participants via the following assessment tools: EORTC QLQ-C30 and 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.

4.2.1.4.1 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 tertiary objectives.

4.2.1.4.2 EQ-5D-5L

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

4.2.1.5 Antidrug Antibodies

Formation of pembrolizumab ADA can potentially confound drug exposures at therapeutic doses and prime for subsequent toxicities. The presence of ADAs will be determined for participants at time points outlined in the SoA in Section 1.3 to understand drug exposure and immunogenicity. Incidence of ADAs and neutralizing ADAs will be evaluated over time.

CCI

[redacted]

CCI

[redacted]

Proteomics and IHC using blood or tumor

CCI

[redacted]

4.2.2 Rationale for the Use of Comparator

All participants will be receiving pembrolizumab, administered with platinum doublet chemotherapy based on histology.

The use of the active comparator pembrolizumab IV ensures that participants receive the current approved formulation in the control arm. In this study, the PK of pembrolizumab SC will be compared versus pembrolizumab IV.

In order to reduce patient and site burden, the different routes of administration, SC versus IV, will not be masked and therefore the study will be unblinded open-label.

4.3 Justification for Dose

4.3.1 Justification of Pembrolizumab IV 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 an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

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

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

CCI [redacted] Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg

Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.3.2 Justification of Pembrolizumab SC Dose

The planned dose of pembrolizumab SC for this study is CCI [redacted]. Based on data from KEYNOTE-555 Cohort A, the bioavailability of pembrolizumab SC is estimated at CCI [redacted]

To ensure robust SC dose selection, both mean level and stochastic simulations (considering variability) were performed using PK parameter estimates from the combined SC and IV PK model, which was informed by the reference pembrolizumab IV PK dataset (including 2993 participants with melanoma or NSCLC, pooled from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024) and SC PK dataset from KEYNOTE-555 Cohort A. Pembrolizumab PK was simulated for SC doses ranging from CCI [redacted] using estimates of typical values of PK parameters, covariate effects, between-participant variability and residual error. CCI [redacted]

CCI

4.3.3 Justification of Chemotherapy Dose

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

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 (ie, the participant is unable to be contacted by the investigator).

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

4.4.1 Clinical Criteria for Early Study Termination

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

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

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

Type of Participant and Disease Characteristics

1. Has pathologically (histologically or cytologically) confirmed diagnosis of squamous or nonsquamous NSCLC.

2. Has Stage IV (T any, N any, M1a, M1b, or M1c - American Joint Committee on Cancer 8th Edition) squamous or nonsquamous NSCLC.

3. Has confirmation that EGFR, ALK, or ROS1-directed therapy is not indicated (documentation of absence of tumor-activating EGFR mutations AND absence of ALK and ROS1 gene rearrangements, OR presence of a KRAS mutation) in nonsquamous NSCLC as well as mixed nonsquamous/squamous NSCLC. Participants with purely squamous NSCLC do not require testing.

4. Has not received prior systemic treatment for their metastatic NSCLC. Participants who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease.

Demographics

5. Participants are at least 18 years of age at the time of providing informed consent.

6. Has an ECOG PS of 0 or 1 (as assessed within 7 days prior to randomization, see Appendix 10).

Male Participants

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.

7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 95 days from the last dose of chemotherapy:

- 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 [Appendix 5]) 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 who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Female Participants

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

See Section 10.7.5 for Japan-specific requirements.

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), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 180 days after the last dose of chemotherapy or 120 days after the last dose of pembrolizumab, whichever occurs last, and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this same time period after the last dose of study intervention. 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 (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 is positive or not evaluable, a serum test will be required.

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

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.

- 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.

Refer to Appendix 7 for country-specific requirements.

Informed Consent

9. The participant (or legally acceptable representative) provides 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 main study without participating in future biomedical research.

Additional Categories

10. Has measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.

11. Submit an archival tumor tissue sample or newly obtained core or incisional biopsy of a tumor lesion not previously irradiated for PD-L1 status determination prior to randomization. FFPE tissue blocks are preferred to slides. Biopsies obtained prior to receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible. Details pertaining to tumor tissue submission can be found in the [redacted]

12. Has adequate organ function as detailed in Table 1. Specimens must be collected within 10 days prior to the start of study intervention.

Table 1 Adequate Organ Function Laboratory Values

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

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

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

[b] Creatinine clearance (CrCl) should be calculated per the Cockcroft-Gault formula.

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.

2. Has known central nervous system (ie, brain and/or spinal cord) metastases and/or carcinomatous meningitis. Participants with treated brain metastases (eg, whole brain

radiation treatment [WBRT], stereotactic radiosurgery, or equivalent) may participate only if they satisfy all of the following:

- Have no evidence of new or enlarging brain metastases confirmed by post-treatment repeat brain imaging (using the same modality) performed at least 4 weeks after pre-treatment brain imaging, and

- Are neurologically stable without the need for steroids for at least 14 days before first dose of trial treatment as per local site assessment.

3. Has severe hypersensitivity (≥Grade 3) to study intervention and/or any of its excipients (refer to the IB and/or approved product label(s) for a list of excipients).

4. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

5. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. Lymphangitic spread of the NSCLC is not exclusionary.

6. Has an active infection, requiring systemic therapy.

7. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

8. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

   Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

9. Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

10. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.

11. Has symptomatic ascites or pleural effusion. A participant who is clinically stable after treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

12. Before the first dose of study intervention:

    - Has received prior systemic cytotoxic chemotherapy for metastatic NSCLC.
    - Has received antineoplastic biological therapy (eg, erlotinib, crizotinib, cetuximab) for metastatic NSCLC.
    - Has had major surgery (<3 weeks prior to first dose).
    - 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).

13. Received radiation therapy to the lung that is >30 Gray within 6 months of the first dose of study intervention.

14. Is expected to require any other form of antineoplastic therapy while on study.

Pemetrexed-Specific Concomitant Therapy

15. Is unable to interrupt aspirin or other NSAIDs, other than an aspirin dose ≤1.3 g/day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

16. Is unable or unwilling to take folic acid or vitamin B12 supplementation.

Prior/Concomitant Therapy

17. Has received prior radiotherapy within 2 weeks of start of study intervention or have had a history of radiation pneumonitis.

    Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

18. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Killed vaccines are allowed.

    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

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

Note: Participants who have entered the Follow-up Phase of an investigational study may participate if the last dose of the previous investigational agent was at least 4 weeks prior to the first dose of study intervention.

Diagnostic Assessments

20. 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 intervention.

Other Exclusions

21. Has had an allogenic tissue/solid organ transplant.

Refer to Appendix 7 for country-specific requirements.

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

There are no restrictions on caffeine, alcohol, or tobacco.

5.3.3 Activity Restrictions

There are no restrictions on activity.

5.4 Screen Failures

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

Participants who fail screening may be rescreened one time for eligibility.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws consent 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.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

When concurrently administered, pembrolizumab should be given prior to chemotherapy; chemotherapy should be given as per local SOC.

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

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.

Refer to Appendix 7 for country-specific requirements.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	CCI	Use	IMP or NIMP/ AxMP	Sourcing
Arm A	Experimental	Pembrolizumab SC	Drug	CCI	CCI		SC		Test Product	IMP	Central
Arm B	Active comparator	Pembrolizumab IV	Drug	Solution for Infusion			IV		Test Product	IMP	Central
Arms A and B (squamous)	Other	Paclitaxel	Drug	Solution for infusion	6 mg/mL	200 mg/m^2	IV		Background Treatment	NIMP/ AxMP	Local or central
Arms A and B (squamous)	Other	Nab-paclitaxel	Drug	Lyophilized Powder for IV infusion	5 mg/mL	100 mg/m^2	IV		Background Treatment	NIMP/ AxMP	Local or central
Arms A and B (squamous and non-squamous)	Other	Carboplatin	Drug	Solution for infusion	10 mg/mL[b]	Squamous: AUC 6 mg/mL/min Nonsquamous: AUC 5 mg/mL/min	IV		Background Treatment	NIMP/ AxMP	Local or central
Arms A and B (non-squamous)	Other	Cisplatin	Drug	Solution for infusion	1 mg/mL	75 mg/m^2	IV		Background Treatment	NIMP/ AxMP	Local or central
Arms A and B (non-squamous)	Other	Pemetrexed[c]	Drug	Lyophilized Powder for IV infusion	500 mg[b]	500 mg/m^2	IV		Background Treatment	NIMP/ AxMP	Local or central

Arm Name	Arm Type	Interven-tion Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
CCI [redacted]											

6.1.1 Medical Devices

CCI [redacted]

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab SC and pembrolizumab IV are provided separately in the CCI [redacted]

Carboplatin, cisplatin, pemetrexed, paclitaxel, and nab-paclitaxel should be prepared per local and institutional guidelines according to the approved product labels.

The rationale for selection of doses to be used in this study is provided in Section 4.3.

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

Treatment randomization will occur centrally using an IRT system. There are 2 study intervention arms (Arm A and Arm B). After Screening, eligible participants will be randomly assigned in a CCI into the 2 arms and receive corresponding study intervention as described in Section 4.1.

CCI

[redacted]

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

Refer to Section 6.6.2 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

6.5 Concomitant Therapy

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

The following medications or vaccinations are prohibited during the study (exceptions noted; also see Appendix 7 for country-specific information):

1. Antineoplastic systemic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
2. Investigational agents other than pembrolizumab
3. Surgery or radiotherapy for tumor control not specified in the protocol
    - Note: Participants are allowed to receive palliative radiotherapy for painful bone lesions. Targeted external beam irradiation should not be used in the primary lung field where assessment for tumor is indicated. Radiation therapy to the brain may be allowed after Sponsor consultation.

4. Live or live attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study. See Appendix 7 for country-specific requirements. Note: Killed vaccines are allowed.
    - Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, 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.

5. Anticancer hormonal therapy (eg, androgen deprivation, androgen receptor blockade, antiestrogens).
    - Note: Hormonal replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.

6. 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 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
- For use as premedication for chemotherapeutic agents specified in Section 6.5.1

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

7. Phenytoin during therapy with cisplatin/carboplatin.

In addition to the medications listed here, site staff should refer to the approval product labels for prohibited medications, as well as drug-drug interactions for each chemotherapy agent used in this study.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, all study intervention must be discontinued.

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

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.7.

6.5.1 Rescue Medications and Supportive Care

6.5.1.1 Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

6.5.1.2 Chemotherapy

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

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

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

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

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

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

6.6 Pembrolizumab Courses, Immune-Related Events and Dose Modification

Dose modification and toxicity management will be the same for both formulations of pembrolizumab (SC and IV), therefore, SC and IV formulations are not specified in this section.

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

6.6.1 Intervention Phase or First Course

CCI [redacted]

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

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be temporarily suspended as described below or discontinued due to toxicity. Pembrolizumab treatment suspensions greater than those specified below will result in discontinuation.

6.6.2.1 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.

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

Refer to Appendix 7 for country-specific requirements.

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

General instructions:

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

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

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

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

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

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

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

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

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

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

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

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

6.6.2.2 Dose Modification and Toxicity Management of Infusion/Injection Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion/injection reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion/injection and generally resolve completely within 24 hours of completion of infusion/injection. Dose modification and toxicity management guidelines on pembrolizumab associated infusion/injection reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion/Injection Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; IV infusion interruption/holding the second SC injection 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 IV infusion interruption/holding the second SC injection but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop IV infusion/hold the second SC injection (if not already given). 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). Similarly, if symptoms resolve within 1 hour of holding the second SC injection, the second injection may be given. 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/injection of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of IV infusion/second SC injection hold); 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 IV infusion/hold the second SC injection (if not already given). 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
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

6.6.2.3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention.

CCI [redacted]

CCI [redacted]

CCI

[redacted]

6.6.4 Dose Modifications for Chemotherapy

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

Dose modifications due to AEs will depend on the investigator's assessment of causality. If appropriate, the investigator may attribute each toxicity event to paclitaxel/nab-paclitaxel, pemetrexed, and cisplatin/carboplatin, or pembrolizumab alone, or to the combination, and use a stepwise dose modification (Table 5 through Table 7).

Dose modifications and toxicity management guidelines for immune-related AEs associated with pembrolizumab are outlined in Section 6.6.2 and Table 3.

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

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

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be delayed/interrupted for a maximum of 12 weeks for an adverse event [Section 6.4].

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

- ANC <1500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <8 g/dL
- Total bilirubin level >1.5 × ULN
- AST and ALT levels ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present
- CrCl will be based on the Cockcroft-Gault formula or another acceptable standard formula. Alternatively, CrCl can be determined from a 24-hour urine collection.
  - For participants receiving cisplatin, the scheduled dose of cisplatin may only be administered if the calculated CrCl is ≥50 mL/min.

If CrCl falls to <50 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider intravenous (IV) hydration. When CrCl improves to ≥50 mL/min, decrease cisplatin to dose level (DL) -1 (Table 5). Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the second occurrence of CrCl <50 mL/min, decrease cisplatin to DL -2 upon improvement of CrCl to ≥50 mL/min. Alternatively, if in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the third occurrence of CrCl <50 mL/min, cisplatin should be discontinued. If in the investigator's judgment it is in the best interest of the participant, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, at the discretion of the investigator and in consultation with the Sponsor.

- For participants receiving carboplatin, the scheduled dose of carboplatin may only be administered if the calculated CrCl is ≥40 mL/min.

If CrCl falls to <40 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥40 mL/min, decrease carboplatin to DL-1 (Table 5).

At the second occurrence of CrCl <40 mL/min, decrease carboplatin to DL -2 (Table 5) upon improvement of CrCl to ≥40 mL/min.

- At the third occurrence of CrCl <40 mL/min, carboplatin should be discontinued.

During concurrent chemotherapy treatment:

- If paclitaxel/nab-paclitaxel or pemetrexed dosing is delayed or interrupted on Day 1, the platinum agent and pembrolizumab should also be delayed/interrupted. If platinum-based chemotherapy doublet is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.

- If platinum dosing is delayed or interrupted on Day 1, pembrolizumab and pemetrexed/paclitaxel/nab-paclitaxel should also be delayed/interrupted. If platinum-based chemotherapy doublet is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.

- If pembrolizumab dosing is delayed or interrupted, platinum-based chemotherapy can continue as scheduled. Pembrolizumab administration should be attempted at the next cycle of therapy.

- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 days) despite supportive treatment. If only one of the agents is thought to be causing the specified toxicity leading to a 21 day delay of administration of the next cycle, that chemotherapeutic agent can be withheld and treatment can continue with pembrolizumab and the remaining chemotherapy drug. Pembrolizumab dosing can continue with 1 agent or as monotherapy.

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

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

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

The CTCAE 5.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 5 through Table 7. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent.

Table 5 Dose-level Modifications for Chemotherapeutic Agents

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

AUC=area under the curve.

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 6 and Table 7. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. These data are based on Day 1 cell counts.

Table 6 Recommended Chemotherapy Dose Modifications for Hematological Toxicity

Drug-related Toxicity[a]	**Cisplatin**	**Carboplatin**	**Paclitaxel**	**Nab-paclitaxel**	**Pemetrexed**
	Dose Level (DL) from Table 5				
Neutrophils (ANC) <500/mm^3 without fever	DL -1	DL -1	DL-1	DL-1	DL-1
Febrile neutropenia (fever ≥38.5°C and ANC <1,000/mm^3)	DL -1	DL -1	DL-1	DL-1	DL-1
Platelets <50,000/mm^3 without significant bleeding or requiring blood transfusion	DL -1	DL -1	DL-1	DL-1	DL-1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring blood transfusion	DL -2	DL -2	DL-2	DL-2	DL-2
Grade 4 hemoglobin	DL -1	DL -1	DL-1	DL-1	DL-1

ANC=absolute neutrophil count; DL=dose level.

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

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

Table 7 Recommended Chemotherapy Dose Modifications for Nonhematological Toxicity

Drug-Related Toxicity[a]	**CTCAE Grade**	**Cisplatin**	**Carboplatin**	**Paclitaxel**	**Nab-paclitaxel**	**Pemetrexed**
		Dose Level (DL) from Table 5				
Nausea/vomiting	Grade ≥3[b]	DL -1	DL -1	DL-1	DL-1	No modification
Mucositis	Grade ≥3[b]	DL -1	DL -1	DL-1	DL-1	DL-2
Diarrhea	Grade ≥3[b]	DL -1	DL -1	DL-1	DL-1	DL-1
Peripheral neuropathy	Grade 2	DL -1[c]	No modification	DL-1	DL-1	No modification
	Grade 3	Discontinue[d]	DL -1	Discontinue	Discontinue	DL-1
	Grade 4	Discontinue	DL -1	Discontinue	Discontinue	DL-1
Total bilirubin	Grade 2	No modification	No modification	DL-2	DL-2	No modification
	Grade 3	No modification	No modification	Discontinue	Discontinue	No modification
	Grade 4	No modification	No modification	Discontinue	Discontinue	No modification
AST or ALT Elevation	Grade 3	DL -1	DL -1	Discontinue	Discontinue	DL-1
	Grade 4	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Other nonhematologic toxicity (except fatigue and transient arthralgia and myalgia)	Grade ≥3	DL -1	DL -1	DL-1	DL-1	DL-1

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

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

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

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

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

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

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. [redacted] or pembrolizumab IV [25 mg/mL]) is included in the label text; random code/disclosure envelopes or lists are not provided.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.11.4 unless the participant has withdrawn from the study (Section 7.2).

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.

- Interruption of chemotherapy (carboplatin and/or taxane [paclitaxel/nab-paclitaxel] for squamous NSCLC; pemetrexed and/or carboplatin/cisplatin for nonsquamous NSCLC) for more than 6 weeks. Participants may continue on study upon consultation with Sponsor.

Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1 require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant

will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.

- The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

- The participant has a confirmed positive serum pregnancy test.

- Radiographic disease progression outlined in Section 8.2.1.2; however, after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression.

- 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.

Note: The number of treatments is calculated starting with the first dose. CCI [redacted]

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 future biomedical research, 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.

7.4 Potential Early Discontinuation of Study Due to Futility

Decision to stop the trial early due to futility will be based on the eDMC recommendations with review by the Sponsor EOC. If a decision is made to stop the trial, all participants that have already been randomized and are receiving pembrolizumab treatment, SC or IV, will be given the option to continue on IV pembrolizumab. Enrollment will continue during the period of the futility analysis.

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 procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), 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 outlined in the CCI [redacted]

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

- If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

The participant identification 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.

8.1.4.1 Non-small Cell Lung Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's NSCLC.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record new medication, if any, taken by the participant during the study through the postintervention follow-up visits. In addition, new medications started during the Second Course Retreatment Phase through the Second Course Safety Follow-up visit should be recorded.

8.1.5.3 Subsequent Antineoplastic Therapy

Details of subsequent therapies for cancer and/or details of radiation therapy and surgery for the treatment of the cancer, after discontinuation of study intervention, will be collected. Reasons for starting subsequent antineoplastic therapies, including access to other PD 1/PD L1 inhibitors or investigational drugs will be collected.

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

Any participant who is rescreened will retain the original screening number assigned at the initial Screening visit.

8.1.8 Study Intervention Administration

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

Study intervention should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

CCI

[redacted]

Chemotherapy regimen is determined by histology. Participants with squamous NSCLC will receive 4 cycles of carboplatin in combination with a taxane, investigator's choice of paclitaxel or nab-paclitaxel, as the chemotherapy. Participants with nonsquamous NSCLC will receive 4 cycles of pemetrexed with a platinum, investigator's choice of cisplatin or carboplatin, followed by pemetrexed maintenance until progression, an intolerable AE, or discontinuation by participant or physician decision.

CCI

[redacted]

8.1.8.1.1 Pembrolizumab IV and SC

Pembrolizumab IV will be administered as a 30-minute IV infusion Q3W, and it will be administered prior to chemotherapy. 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 minutes/+10 minutes). The pharmacy manual contains specific instructions for pembrolizumab storage, reconstitution, preparation of the infusion fluid, and administration.

CCI

[redacted]

8.1.8.1.2 Chemotherapy

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

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

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

Calvert Formula (Squamous dose):

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert Formula should not exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 6 × (125 + 25)
  = 6 × 150
  = 900 mg

Calvert Formula (Nonsquamous dose):

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert Formula should not exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 5 × (125 + 25)
  = 5 × 150
  = 750 mg

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

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

Alternatively, CrCl can be determined from a 24-hour urine collection.

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

Additional premedications should be administered as per standard practice.

8.1.8.1.2.2 Paclitaxel or Nab-paclitaxel (Squamous)

Paclitaxel or nab-paclitaxel will be administered immediately after pembrolizumab and should be completely administered prior to initiating the carboplatin dose.

- Paclitaxel (200 mg/m^2 Q3W) will be administered as an IV infusion over 3 hours for 4 cycles as per local practice and labels. All participants should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

- Nab-paclitaxel (100 mg/m^2) will be administered at as an IV infusion over 30 minutes for 4 cycles as per local practice and labels. Participants will be dosed on Day 1, 8, and 15 of each 3-week cycle.

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

8.1.8.1.2.3 Pemetrexed (Nonsquamous)

Pemetrexed (500 mg/m^2 Q3W) will be administered as an IV infusion over 10 minutes. All participants should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis as listed below (or as per local label):

- Folic acid 350 to 1000 µg PO: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

- Dexamethasone prophylaxis 4 mg PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1-4 but not to exceed doses in MASCC guidelines (Section 8.1.8.1.3).

8.1.8.1.2.4 Cisplatin (Nonsquamous)

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

Participants are allowed to switch from cisplatin to carboplatin if the participant becomes ineligible for further cisplatin therapy according to local guidelines and the investigator considers switching to carboplatin to be in the best interest of the participant. This switch from cisplatin to carboplatin requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

8.1.8.1.3 Antiemetic Therapy

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

8.1.9 Discontinuation and Withdrawal

Section 7.2 provides a complete description of withdrawal of consent from the study.

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

Not applicable.

8.1.12 Calibration of Equipment

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

8.1.13 Tumor Tissue for Biomarker Status

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

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

or

- An archival tumor tissue sample if a new biopsy is unavailable

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

Details pertaining to tumor tissue submission can be found in the CCI [redacted]

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status in participants with NSCLC for treatment with pembrolizumab.

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

In addition to survival, efficacy will be assessed based on scans to evaluate changes in tumor burden over time, until the participant is discontinued from the study or enters the survival follow-up. The process for scan collection and transmission to the iCRO can be found in the Site Imaging Manual. CT scans are preferred over other tumor imaging methods. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same type of scan should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment. Note: for the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Magnetic resonance scans are preferred for brain imaging; however, CT scans are acceptable, if MRI is medically contraindicated.

All scheduled scans for all study participants from the sites will be submitted to the central imaging vendor. In addition, scans (including via other modalities, such as PET-CT, X-ray) that are obtained at an unscheduled time point to determine disease progression, and scans obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of randomization. Any imaging obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

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

Brain imaging is required for all participants at screening. Participants with treated brain metastases (eg, whole brain radiation treatment [WBRT], stereotactic radiosurgery, or equivalent) may participate only if they satisfy all of the following: Have no evidence of new or enlarging brain metastases confirmed by post-treatment repeat brain imaging (using the same modality) performed at least 4 weeks after pre-treatment brain imaging, and are neurologically stable without the need for steroids for at least 14 days before first dose of trial treatment as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.2.1.2 Tumor Imaging During the Study

CCI

Imaging should continue to be performed until disease progression is identified by the investigator and verified by BICR, or until any of these conditions are met:

- the start of new anticancer treatment
- pregnancy
- withdrawal of consent

- death
- or notification by the Sponsor

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response will not be verified by BICR in real time and no notification will be sent to sites for this purpose.

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

Treatment beyond centrally verified PD per RECIST 1.1 may be permitted at the discretion of the investigator after consulting with the Sponsor and receiving signed informed consent addendum from the participant (Figure 3). Participants who continue treatment beyond centrally verified PD must continue tumor imaging assessments as described in the SoA (Section 1.3). Investigator assessments are to be documented on the eCRF, but scans are not to be submitted to the iCRO. Further progression and discontinuation of study intervention are to be determined by the investigator.

In participants who do not have disease progression by central verification (investigator assessment of disease progression, however BICR assessment of disease progression per RECIST 1.1 = "No"), treatment can continue to be administered at investigator's discretion for clinically stable participants and after a new informed consent addendum is signed. Imaging should continue to be performed as per imaging schedule and must be submitted to the iCRO along with a VOP request until central verification of progression is received.

All investigator evaluations of tumor response will utilize the RECIST 1.1 criteria and should be entered into the appropriate electronic case report forms by the sites.

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

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

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment calculated from the date of randomization (see Section 8.2.1.2) until the start of a new anticancer treatment, disease

progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

Note: new anticancer treatment is defined as a different treatment than the anticancer therapy provided in this study.

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor scans must be performed within 28 days before restarting study intervention treatment with pembrolizumab.

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

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

Scans are to be performed until disease progression, the start of a new anticancer treatment, pregnancy, withdrawal of consent, death, completion of Second Course, or notification by the Sponsor, whichever occurs first.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, CCI [redacted], or notification by the Sponsor, whichever occurs first.

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

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

8.2.1.5 RECIST 1.1 Assessment of Disease

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

immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
  - continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired)
  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression
  - if subsequent scan(s) indicate progression, request verification from iCRO
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anti-cancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

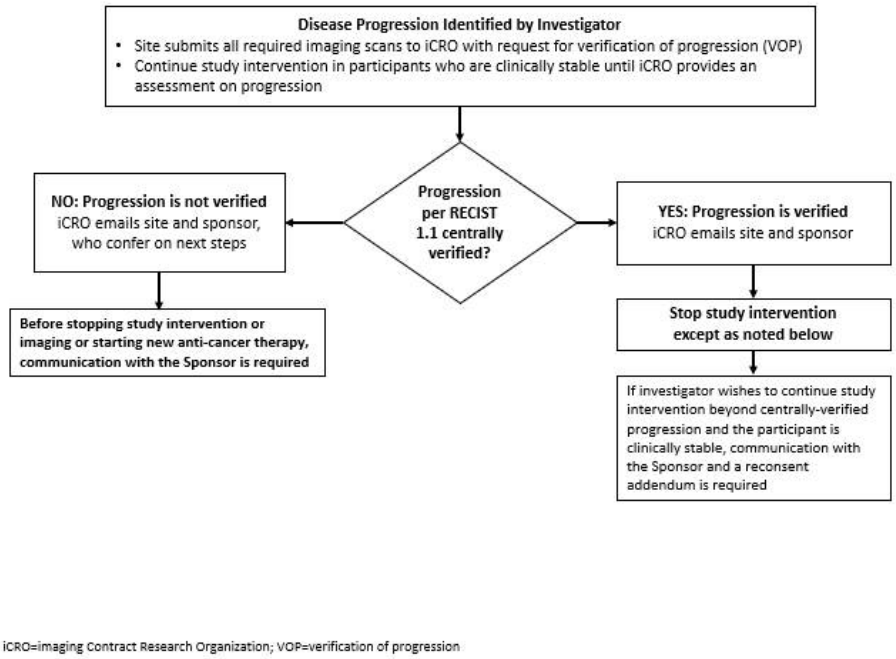
If disease progression is verified, the process continues as follows:

- investigator judgement will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

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

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

Figure 3 Study Intervention Decision Making Process When Progression per RECIST 1.1 is Observed by Investigator



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

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants. CCI [redacted] Additional assessment will occur at Treatment Discontinuation Visit and at 30-day Safety Follow-up Visit. Perform ePROs in the following order listed: EORTC QLQ-C30 followed by EQ-5D-5L. Note: ePROs will be assessed on scheduled cycle visits.

It is best practice and strongly recommended that ePROs are administered to randomized participants prior to 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 [redacted]

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

8.3.1 Physical Examinations

8.3.1.1 Complete Physical Examination

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

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

8.3.1.2 Directed Physical Examination

For cycles that do not require a complete 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.

Note: [redacted]

- [redacted]

CCI

[redacted]

8.3.2 Vital Signs

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

- Vital signs include temperature, heart rate, respiratory rate, and blood pressure. The same method of temperature measurement must be used for all participants and must remain the same for each participant. Height will be measured during the Screening Phase only. Weight will be measured during the Screening phase and at every treatment visit.

- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. The correct size of the blood pressure cuff and correct positioning of the participant's arm are essential to the accuracy of the blood pressure measurement.

- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital signs will be measured in a semi-supine position after 5 minutes rest.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECG is specified in the schedule of activities in Section 1.3. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Eastern Cooperative Oncology Group Performance Status

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

The investigator or qualified designee will assess ECOG status (see Appendix 10) at screening, prior to the administration of each dose of study intervention, and during the Follow-up period (Section 1.3).

8.3.5 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 [redacted] and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

8.3.6 Pregnancy Testing

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Pregnancy testing (urine or serum) should be conducted at every monthly intervals during intervention.

  - Pregnancy testing (urine or serum) should be conducted as per SoA for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for participant's contraception as noted in

Section 5.1. The length of time required to continue pregnancy testing for each study intervention is.

- Pembrolizumab 150 days
- Chemotherapy 210 days

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Refer to Appendix 7 for country-specific requirements.

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator, 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 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 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 randomization through 120 days, following cessation of pembrolizumab, 180 days following cessation of chemotherapy, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside 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 8.

Table 8 Reporting Time 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:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. 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 towards 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 SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born

with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

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

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

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

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

The Sponsor will monitor 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 progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

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

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

8.4.8 Medical Device and Drug-device Combination Products/Combination Medicinal Product - PQCs/Malfunctions

The method of documenting and reporting of such events complaints associated with medical devices, drug-device combination product/combination medicinal product including PQCs/malfunctions will occur as noted below and in Appendix 4.

To fulfill regulatory reporting obligations worldwide, medical device information (including device constituent part information) associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines. All associated person SAEs must be reported to the Sponsor in the same time frame as all other SAEs per Section 8.4.1 via CRF and as per data entry guidelines. All SAEs due to malfunction will be followed until resolution, stabilization, until the event is otherwise explained, or the participant or associated person is lost to follow-up.

PQCs/malfunctions including those that involve a participant or any user/associated person must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

8.5 Treatment of Overdose

CCI [redacted]

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.

8.6 Pharmacokinetics

8.6.1 Blood Collection for PK

Sample collection, storage, and shipment instructions for serum samples will be provided in the CCI [redacted]. PK samples should be drawn according to the PK collection schedule for all participants (Section 1.3). Every effort should be taken to collect samples at 30 days after end of study intervention.

8.6.2 Blood Collection for Antidrug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the CCI [redacted]. ADA samples should be drawn according to the ADA collection schedule for all participants (Section 1.3). Every effort should be taken to collect samples at 30 days after end of study intervention for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

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:

- Archival or newly obtained tumor tissue
- Blood for genetic analysis
- Blood for ctDNA analysis

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the CCI [redacted]

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 future biomedical research if the participant provides documented informed consent for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the CCI [redacted]

8.9 Future Biomedical Research Sample Collection

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

- Leftover samples listed in Section 8.8 (including any extracted material from samples)

CCI [redacted]

CCI

[redacted]

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

Approximately 28 days prior to intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Documented consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is hepatitis and HIV testing which may be done up to 28 days prior to the first dose of study intervention if required by the local health authority.

- Evaluation of ECOG is to be performed within 7 days prior to randomization.

- A WOCBP must have a negative highly sensitive pregnancy test (as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Additional pregnancy testing can be conducted if required by local regulations or clinically indicated.

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

8.11.2 Treatment Period (Intervention Phase)

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1. Unless otherwise specified, assessments/procedures are to be

performed prior to the first dose of study intervention for each cycle, and the window for each visit is ±1 day for Cycles 1 through 7 and ±3 days for Cycle 8+.

8.11.2.1 Optional Home Health Visits for PK Sampling

A global home health vendor is available to be utilized for participants in both the SC and IV arms who must have additional CCI [redacted].

If the visiting nurse service is utilized for any of the visits listed above, the nurse will be instructed to immediately contact the site if the participant reports any potential AE to the nurse. In addition to this, the investigator should contact the participant by phone on the same day as the nurse visit, or as soon as possible (if the home health visit occurred on a weekend or holiday) to perform an investigator AE assessment. Refer to the nursing manual for additional details.

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

Randomized participants who discontinue study intervention for reasons other than progressive disease will move into the Follow-up Phase (Section 8.11.4).

8.11.4 Post-Treatment (Post-Intervention) Visit

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

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

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

8.11.4.1 Safety Follow-up Visits

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

If a participant has a discontinuation visit ≥30 days after the last dose of study intervention, the Safety Follow-up Visit is not required.

Participants who are eligible for Second Course retreatment with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Intervention Phase and 1 after the Second Course Retreatment.

8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than documented disease progression will move into the Efficacy Follow-up Phase. Follow-up visits after treatment discontinuation must coincide with the imaging schedule until disease progression, death, or end of study. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Every effort must be made to collect imaging until the start of new anticancer therapy, confirmed PD, or death. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.3 will move from the Efficacy Follow-up Phase to the Second Course Retreatment Phase when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab.

8.11.4.3 Survival Follow-up Assessments

Participant survival follow-up status will be assessed 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.

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

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

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

8.11.5 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 time period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP. Other planned analyses (ie, those specific to the analysis of future biomedical research) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12. See Appendix 7 for country-specific information.

Study Design Overview	A Randomized, Phase 3, Open-label Study to Investigate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab versus Intravenous Pembrolizumab, Administered with Platinum Doublet Chemotherapy, in the First-Line Treatment of Participants with Metastatic Squamous or Nonsquamous Non-Small-Cell Lung Cancer
Treatment Assignment	Participants will be randomized CCI [redacted] • Arm B – Participants will receive up to 35 cycles of 200 mg pembrolizumab IV Q3W administered with platinum doublet chemotherapy CCI [redacted]
Analysis Populations	• PK (primary): Per-protocol Set • Efficacy: ITT • Safety: APaT • PRO: PRO FAS
Primary Endpoint(s)	CCI [redacted]

Secondary Endpoints	• ORR • CCI • Safety and tolerability • PFS • OS • DOR • ADA
Statistical Methods for Key Immunogenicity/ Pharmacokinetic Analyses	CCI
Statistical Methods for Key Safety Analyses	For Tier 2 endpoints, 95% CIs will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]
Interim Analysis	CCI
Multiplicity	CCI By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], if one hypothesis is rejected, the alpha will be shifted to the other hypothesis. The futility assessment at the IA1 is non-binding.

Sample Size and Power	The planned sample size is ~512 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 is being conducted as a randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment and randomization will be implemented by an IVRS vendor.

Although the trial is open label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented.

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

9.3 Hypotheses/Estimation

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

CCI [redacted]

9.4 Analysis Endpoints

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

9.4.1 Pharmacokinetics Endpoints

The methodological details for assessment of model-based PK parameters CCI [redacted] will be summarized in a separate MAP.

Primary

CCI

[redacted]

Secondary

CCI

[redacted]

9.4.2 Safety Endpoints

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

9.4.3 Efficacy Endpoints

Secondary

- Objective Response Rate (ORR)

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

- Progression-free survival (PFS)

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

- Overall Survival (OS)

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

- Duration of Response (DOR)

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

9.4.4 Immunogenicity Endpoint

Immunogenicity (ADA incidence) will be assessed by analyzing the development of ADAs following administration of pembrolizumab SC and pembrolizumab IV.

9.4.5 PRO Endpoints

The predefined PRO endpoints in this study are mean change from baseline in EORTC QLQ-C30 global health/QoL scale (Items 29 and 30) and physical functioning domain score (Items 1 through 5), role functioning domain scores (Items 6 and 7) and mean score change from baseline in EQ-5D VAS. Exploratory PRO endpoints as described in Section 4.2.1.4 will be evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Pharmacokinetics Analysis Populations

The PP population will be used for the analysis of PK data in this study.

CCI

[redacted]

CCI

[redacted]

Any participants or data values excluded from the analyses will be identified, along with the reasons for exclusion, in the CSR.

9.5.2 Safety Analysis Populations

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

At least one laboratory, vital sign, or ECG measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Efficacy Analysis Populations

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

9.5.4 PRO Analysis Populations

The PRO analyses are based on the PRO FAS population, defined for each PRO endpoint respectively as randomized participants who have at least one PRO assessment available and have received at least one dose of study medication. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

9.6.1 Statistical Methods for Pharmacokinetics Analyses

The primary objectives are to compare GMR between pembrolizumab SC and pembrolizumab IV based on CCI [redacted]. These objectives will be assessed via the following non-inferiority (NI) hypothesis:

$$H_0: GMR = \frac{GM_{SC}}{GM_{IV}} \leq 0.8$$

$$H_1: GMR = \frac{GM_{SC}}{GM_{IV}} > 0.8$$

CCI [redacted]

9.6.2 Statistical Methods for Safety Analyses

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

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

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) 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 special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen method (1985), an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985]. There are no safety events that are considered Tier 1 for this protocol.

Tier 2 Events

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

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

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3 to 5 AE, a drug-related

Grade 3 to 5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. 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, vital signs, and ECG parameters, 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 (incidence ≥10% of participants in one of the treatment groups)	X	X
	Any Serious AE (incidence ≥2% of participants in one of the treatment groups)	X	X
	Any Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3-5 AE		X
	Any serious AE		X
	Any drug-related AE		X
	Any serious and drug-related AE		X
	Any Grade 3-5 and drug-related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence > 0% of participants in all of the treatment groups)		X
	Change from Baseline Results (Lab Toxicity Grade, Vital Signs)		X
AE=adverse event; CI=confidence interval; SOC=system organ class.			

9.6.3 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the efficacy objectives (which are secondary objectives in the study). For this study, efficacy analyses are descriptive only. No type I error control is applied to efficacy analyses, so p-values, if provided, are nominal only and provided for descriptive purposes.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], stratified Cochran-Mantel-Haenszel method, the stratified log-rank

test, and stratified Cox model. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

The efficacy analyses for ORR, DOR, and PFS will include responses and documented progression events that occur prior to Second Course Retreatment.

9.6.3.1 Objective Response Rate

The stratified Miettinen and Nurminen's method will be used for comparison of the ORR between 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported.

Furthermore, the stratified Cochran-Mantel-Haenszel method will also be used for comparison of the ORR between 2 treatment groups. The ratio of ORR and its 95% CI using the normal approximation on the logarithmic scale will be reported as applicable.

The stratification factors used for randomization (see Section 6.3.2) will be applied to the stratified analysis specified above.

Additional sensitivity analyses will be conducted excluding all the participants enrolled from Russia and Ukraine. The details of the sensitivity analyses will be specified in the sSAP.

9.6.3.2 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. 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, hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a confirmed PD event.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy will be censored at the last disease assessment prior to the initiation of

new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, an additional sensitivity analysis with different sets of censoring rules will be performed. The sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analysis are summarized in Table 10.

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9.6.3.3 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 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 date the participant was last known to be alive.

9.6.3.4 Duration of Response

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

Censoring rules for DOR are summarized in Table 11.

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

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9.6.3.5 Analysis Strategy for Key Efficacy Variables

Efficacy will be assessed only once, at the time of FA. A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 12.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/ Variable	Statistical Method	Analysis Population	Missing Data Approach
ORR per RECIST 1.1 by BICR	P-value: stratified Miettinen and Nurminen method, CCI [redacted] Estimation: stratified Miettinen and Nurminen method, stratified CMH method	ITT	Participants with missing data are considered nonresponders
PFS per RECIST 1.1 by BICR	P-value: stratified log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 10
OS	P-value: stratified log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored at participant's last known alive date

BICR=blinded independent central review; CMH=Cochran-Mantel-Haenszel; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.

9.6.4 Statistical Methods for Patient-Reported Outcome Analyses

Changes from baseline in the following exploratory PRO endpoints will be assessed:

- Global health status/QoL score (QLQ C30 Items 29 and 30)
- Physical functioning domain score (QLQ C30 Items 1 through 5)
- Role functioning domain score (QLQ C30 Items 6 and 7)
- EQ-5D-5L VAS score

Treatment effect on PRO score change from baseline will primarily be evaluated at predefined timepoint or the latest time point where the overall completion/compliance rates are ~60%/~80%, respectively, and will be based on a constrained longitudinal data analysis model. The difference in the least square mean change from baseline between arms will be reported at the predefined primary analysis time point.

Descriptive analyses will assess the empirical mean change (with 95% CIs) from baseline across all time points for each endpoint.

The detailed analysis plan will be specified in sSAP.

9.6.5 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis

tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analysis

The eDMC will serve as the primary reviewer of the results of the interim analysis of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of the interim analysis will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Treatment-level results from the interim analysis will be provided to the eDMC 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 interim analysis.

Although the trial is open label, analyses or summaries generated by randomized treatment assignment, or actual treatment received, will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

9.7.1 Pharmacokinetics Interim Analysis

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[redacted]

9.7.2 Safety Interim Analysis

The eDMC will be responsible for periodic interim safety reviews as specified in the DMC charter. CCI

[redacted]

9.8 CCI

The study uses the graphical method of Maurer and Bretz [Maurer, W., et al 2011] to provide strong multiplicity control for multiple hypotheses as well as the interim analysis. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 4 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 shown in the boxes on the lines connecting hypotheses.

CCI

[redacted]

CCI

[redacted]

9.8.1 CCI [redacted]

CCI

[redacted]

9.8.2 CCI

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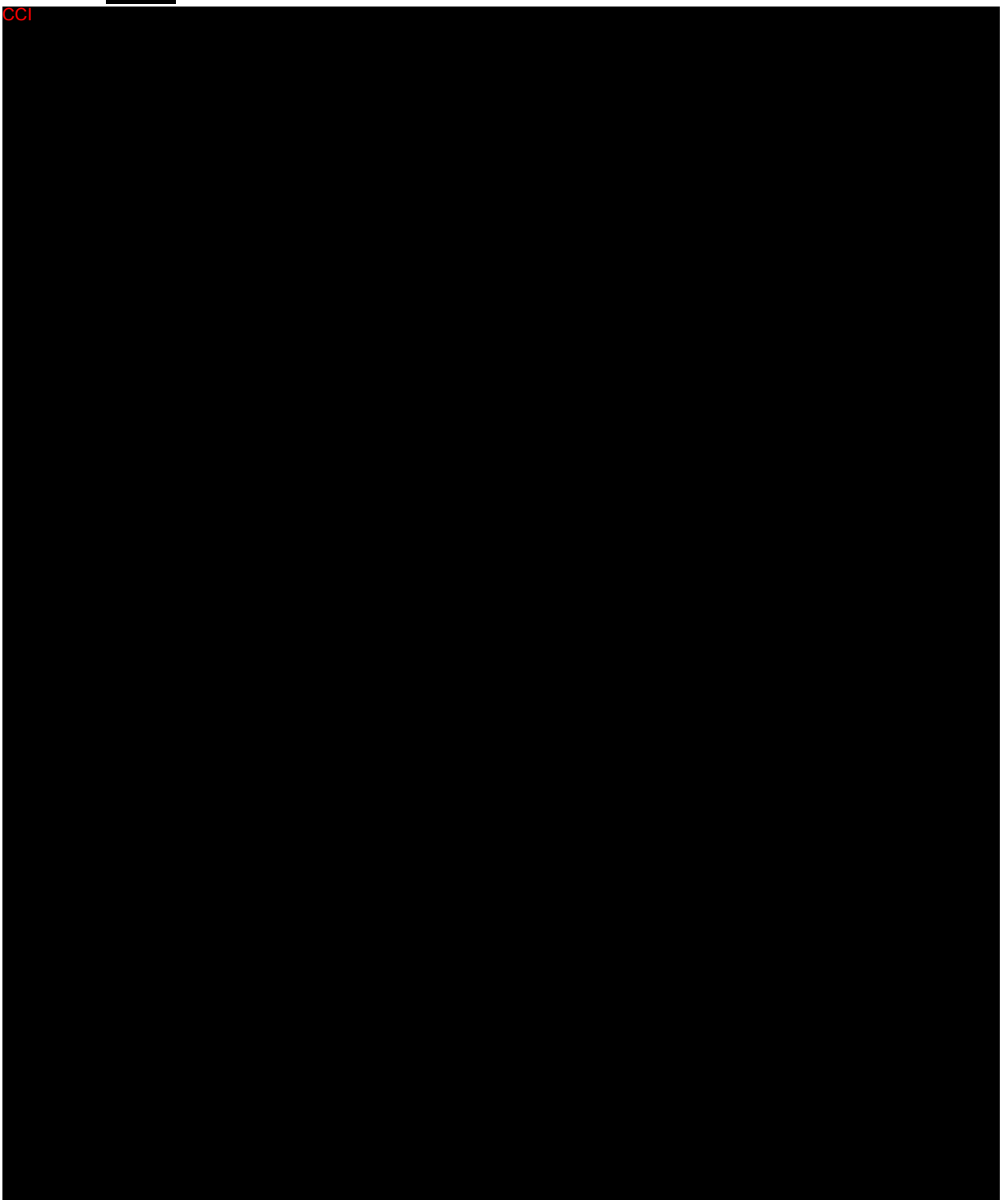

CCI [redacted]

9.9 Sample Size and Power Calculations

The study will randomize approximately 512 participants CCI [redacted] into the pembrolizumab SC and pembrolizumab IV arms. CCI [redacted] are primary endpoints for the study, with ORR as a secondary endpoint.

CCI [redacted]

The assumptions for the above sample size and power calculations are listed below. The assumptions come from PK modeling based on historical pembrolizumab IV data/reference PK model and KEYNOTE-555 Cohort A data for SC. To ensure robust SC dose selection, both mean level and stochastic simulations were performed using PK parameter estimates from the combined SC and IV PK model informed by the reference pembrolizumab IV PK dataset (including 2993 participants with melanoma or NSCLC, pooled from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024) and SC PK dataset KEYNOTE-555 Cohort A.

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[redacted]

The sample size and power calculations were performed using R.

9.10 Subgroup Analyses

Subgroup analysis will not be performed for CCI [redacted] given that historical data from Keytruda development program has consistently shown that there is no clinically relevant impact of covariates in PK.

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 the number of cycles in which the participant receives the study medication. Summary statistics will be provided on the Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. 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 (or individuals acting on behalf of MSD) 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 Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 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 prior to transmission to the Sponsor.

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

10.1.3.3 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 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

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

10.1.4.2 Executive Oversight Committee

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

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors 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 trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will

review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 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, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 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.

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. 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 16 will be performed by the local laboratory.
- All on-treatment samples will be collected prior to administration of study intervention.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 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 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN) or urea[a]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate)[b]	Chloride	Phosphorous
	Creatinine or creatinine clearance[c]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Lactate dehydrogenase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) as required by local health authority or institutional regulations. Refer to Appendix 7 for country-specific information. • Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. • Thyroid-stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3)			

Laboratory Assessments	Parameters
aPTT=activated partial thromboplastin time; FT4=free thyroxine; GFR=glomerular filtration rate; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC = red blood cell; T3 = triiodothyronine; TSH=thyroid-stimulating hormone; WBC=white blood cell; WOCBP=women of child bearing potential. NOTES: a. BUN is preferred; if not available, urea may be tested. b. Performed only if considered the local standard of care. c. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.	

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

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

10.3.1 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 (also referred to as Sponsor's product) 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
  Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose

without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

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

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the 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.

10.3.3 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

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

  Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

  Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

  Grade 4: Life threatening consequences; urgent intervention indicated.

  Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure**: Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course**: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause**: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge**: Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)
  - **Rechallenge**: Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

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

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

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

  Yes, there is a reasonable possibility of Sponsor's product relationship:
  - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  No, there is not a reasonable possibility of Sponsor's product relationship:
  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

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

- The causality assessment is 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the 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 e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device, Drug-Device Combination Product/Combination Medicinal Product: Definitions, Collection, and Documentation

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a participant according to the study protocol, that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use and/or drug-device combination product/combination medicinal product as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

Note: See Appendix 7 for country-specific information.

Definitions

Combination Product – A product composed of any combination of a drug, a device and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.

Complaint - Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. See also AE and PQC.

Note: A complaint does not necessarily need to involve a user or any other person.

Malfunction - The failure of a device constituent part or the device product as a whole to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device/device constituent part. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Medical Device – An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

PQC - Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Deterioration of Health/Serious Injury/Serious Illness

This includes:

- Life-threatening illness, even if temporary in nature
- Results in permanent impairment of a body function or permanent damage to a body structure
- Fetal distress, fetal death or any congenital abnormality or birth defects
- A condition necessitating medical or surgical intervention, including hospitalization or prolonged hospitalization, to prevent one of the above
- Cases that are considered medically significant

The specific definitions for Japan are described in Appendix 7, Country-specific requirements.

Recording

- When a complaint including PQC/malfunction occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug-device combination product/combination medicinal product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

- It is important that the investigator provides his/her assessment of causality (relationship) to the medical device/device constituent part) at the time of the initial report.

The specific recording of Malfunctions for Japan are described in Appendix 7, Country-specific requirements.

Assessing Causality

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

- The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

- Premenarchal

- Premenopausal female with 1 of the following:

  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

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

- Postmenopausal female

  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

    Females on HRT and whose menopausal status is in doubt will be required to use one of the 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 Contraception Requirements

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

Note: See Appendix 7 for country-specific requirements.

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

1. **Definitions**

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. **Biorepository Specimen Usage[3,4]**

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

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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. **Retention of Specimens**[3,4]

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

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

8. **Data Security**[3,4]

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

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

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

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

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

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

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

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

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

12. **Questions**

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

13. **References**

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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 Brazil

Section 4.1 Overall Design, Section 7.1 Discontinuation of Study Intervention, Section 8.2.1.2 Tumor Imaging During the Study, Section 8.2.1.5 RECIST 1.1 Assessment of Disease

All information regarding treatment beyond progression is documented in the Main ICF and signed by the participant at the start of screening. Informed consent addendum for treatment beyond progression will not be collected per local regulations.

10.7.2 Colombia

Section 1.3.1 Screening and Intervention Phase

HIV, Hepatitis B, and C testing during the screening is required to determine participant´s eligibility for the study.

10.7.3 France

Section 1.3.1 Screening and Intervention Phase

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

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

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

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

Section 5.2 Exclusion Criteria

Carboplatin / Paclitaxel only:

a. Participants who experience hemorrhage from tumor

b. Participants who use phenytoin or fosphenytoin

Cisplatin / Pemetrexed only:

a. Participants with a hearing impairment

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

c. Participants who are unable to tolerate use of phenytoin

Section 6.5 Concomitant Therapy

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

Section 6.6.2.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

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

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

Section 8.3.6 Pregnancy Testing

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

Section 10.5 Appendix 5: Contraceptive Guidance

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

10.7.4 Guatemala

Section 1.3.1 Screening and Intervention Phase

Prior to start in the study, a serum pregnancy test is required as per local regulations.

Additional evaluations/testing may be deemed necessary by the investigator and/or the Sponsor for reasons related to participant safety. In some cases, such evaluations/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.

Section 8.3.6 Pregnancy Testing

Prior to start in the study, a serum pregnancy test is required as per local regulations.

10.7.5 Japan

Section 1.3.1 Screening and Intervention Phase – footnotes

For the assistance to early diagnosis of pneumonitis/interstitial lung disease in study participants, the following items, such as pulse oximetry monitoring (peripheral capillary oxygen saturation [SpO2]), C-reactive protein (CRP), Krebs von den Lungen-6 (KL-6), and surfactant protein-D (SP-D), will be measured in this study. These items should be measured as follows:

SpO2 at the timing of vital sign assessment.

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

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

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

Section 5.1 Inclusion Criteria

In addition to Inclusion Criterion 8, patients who stop breastfeeding at the start of the study but wish to resume breastfeeding thereafter during participation in the study are not eligible.

Section 6.1 Study Intervention(s) Administered

Table 2 Study Interventions

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

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Section 10.4 Appendix 4: Medical Device, Drug-Device Combination Product/Combination Medicinal Product: Definitions, Collection, and Documentation

Definitions

Medical Device - Devices, etc, (other than regenerative medicine products) intended for use in the diagnosis, treatment or prevention of disease in humans or animals, or intended to affect the structure or functions of the body of humans or animals.

Combination Medicinal Product - A product comprised of 2 or more regulated components, ie, a drug and a device; a device and a cellular and tissue-based products; a cellular and tissue-based products and a drug; or a drug, a device, and a cellular and tissue-based products according to Japan regulations.

Malfunction - Failure of quality, safety and performance, etc, of investigational device in a broad sense such as damage or operational failure.

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[redacted]

Malfunction which may lead to Serious Adverse Events - Any malfunction of a medical device which might have led to the death of a participant and/or the associated person or to a serious deterioration in his/her state of health. “Which might have led to” means that there is the possibility that death or a serious deterioration might have occurred in a participant and/or the associated person, although these cases have not actually occurred.

Recording - Combination medicinal product malfunction which could have resulted in SAEs will be reported to the Sponsor within 5 calendar days of learning of the information via a paper reporting form.

10.7.6 Peru

Section 1.3.1 Screening and Intervention Phase

HIV, Hepatitis B, and C testing during the screening is required to determine participant´s eligibility for the study.

Pregnancy testing in WOCBP is required at screening and within 24 hours prior to administration of each cycle of study treatment. Urine or Serum β-HCG is acceptable; if urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

10.7.7 Romania

Section 1.3.1 Screening and Intervention Phase

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

Pregnancy testing must be performed monthly by WOCBP during treatment with study interventions and 30 days after last dose of study intervention.

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

Pregnancy testing must be performed monthly by WOCBP during treatment with study interventions and 30 days after last dose of study intervention.

Section 5.2 Exclusion Criteria

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

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

10.7.8 South Africa

Section 1.3.1 Screening and Intervention Phase

HIV testing at screening is mandatory.

Testing for active tuberculosis is required at screening and every 6 months during treatment as mandated by local regulation.

Section 5.2 Exclusion Criteria

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

Has known active tuberculosis (TB; *Bacillus* tuberculosis) infection requiring systemic therapy. Testing for active tuberculosis is required at screening and every 6 months during treatment as mandated by local regulation.

10.7.9 Spain

Section 1.3.1 Screening and Intervention Phase

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

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

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

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

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

Section 5.2 Exclusion Criteria

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

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

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

Section 6.5 Concomitant Therapy

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

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

Section 8.3.6 Pregnancy Testing

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

Section 10.2 Appendix 2: Clinical Laboratory Tests

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

Section 10.5 Appendix 5: Contraceptive Guidance

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

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Not applicable.

10.9 Appendix 9: Other Medical Device: Complaints Including Product Quality Complaints/Malfunction, Serious Injury, Death, Fetal Distress/Fetal Death and Congenital Anomaly: Definitions and Reporting

Not applicable.

10.10 Appendix 10: 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 (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

[ECOG ACRIN Cancer Research Group 2016]

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
1L	First Line
AE	Adverse event
ADA	Antidrug Antibodies
ADL	Activities of daily living
ALT	Alanine aminotransferase
ALK	Anaplastic lymphoma kinase
ANC	Absolute neutrophil count
APaT	All-participants-as-treated
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
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AST	Aspartate aminotransferase
β-HCG	Beta human chorionic gonadotropin
BCG	Bacillus Calmette-Guérin
BICR	Blinded independent central review
C_{avg}	Average concentration
CI	Confidence interval
C_{max}	Maximal concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
C_{trough}	Minimal concentration
CV	Coefficient of variation
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DOR	Duration of response
ECI	Events of clinical interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data collection
EGFR	epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30
ePRO	Electronic patient-reported outcome
FA	Final analysis
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
FSH	Follicle stimulating hormone

Abbreviation	Expanded Term
FT4	Free thyroxine
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GM	Geometric mean
GMR	Geometric mean ratio
HA	health authority
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IA1	Interim Analysis 1
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
INR	International normalized ratio
irAEs	Immune-related adverse events
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	intent-to-treat
IUD	Intrauterine device
IV	Intravenous
IVRS	Interactive voice response system
MAP	modeling analysis plan
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
Nab-paclitaxel	Nano particle albumin-bound paclitaxel
NCI	National Cancer Institute
NI	Non-Inferiority
NSCLC	Non-small cell lung cancer (NSCLC)
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Progressive disease
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
PP	Per protocol
PQC	Product quality complaint
PRO	Patient-reported outcome
PR	Partial response
PTT	Partial thromboplastin time

Abbreviation	Expanded Term
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors RECIST 1.1
RNA	Ribonucleic acid
CCI [redacted]	[redacted]
SAE	Serious adverse events
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of activities
SOC	Standard of care
sSAP	Supplementary statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TPS	Tumor proportion score
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

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[redacted]

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[redacted]

CCI

[redacted]

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