Official Protocol Title:	A Phase II Trial to Investigate Genetic Markers of Response to Pembrolizumab (MK-3475, SCH 900475) Combined with Chemotherapy as a First-line Treatment for Non-Small Cell Lung Cancer (KEYNOTE-782)
NCT number:	NCT03664024
Document Date:	20 AUG 2021

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Phase II Trial to Investigate Genetic Markers of Response to Pembrolizumab (MK-3475, SCH 900475) Combined with Chemotherapy as a First-line Treatment for Non-Small Cell Lung Cancer (KEYNOTE-782)

Protocol Number: 782-02

Compound Number: MK-3475

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	116833
EUDRACT	2018-002598-22
NCT	NCT03664024

Approval Date: 20 August 2021

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 2	20-AUG-2021	To include instruction allowing participants to be enrolled in a pembrolizumab extension study upon study completion, add final analysis in the statistical analysis plan, and update the Sponsor's branding information.
Amendment 1	02-APR-2019	To include direction for re-consenting participants upon disease progression, move the collection time point of one of the primary endpoint samples, and correct errors in the Schedule of Activities.
Original Protocol	12-JUL-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [782-02]

Overall Rationale for the Amendments:

To include instruction allowing participants to be enrolled in a pembrolizumab extension study upon study completion, add final analysis in the statistical analysis plan, and update the Sponsor's branding information.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title page	Added a copyright statement	To add clarification on copyrights
4.4 Beginning and End of Study Definition	Added text of "Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available."	To allow participants to be enrolled in a pembrolizumab extension study upon study completion for the medical benefit of the participants
9.1 Statistical Analysis Plan Summary	Added text "Final analysis will occur after all participants have received 35 administrations of pembrolizumab or discontinued study intervention."	To add final analysis to the summary of the statistical analysis plan
9.8 Final Analysis	Added a section for final analysis	To align with the update in Section 9.1

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase II Trial to Investigate Genetic Markers of Response to Pembrolizumab (MK-3475, SCH 900475) Combined with Chemotherapy as a First-line Treatment for Non-Small Cell Lung Cancer (KEYNOTE-782)

Short Title: Biomarkers of Response to Pembrolizumab Combined with Chemotherapy in Non-Small Cell Lung Cancer (KEYNOTE-782)

Acronym: KEYNOTE-782

Hypotheses, Objectives, and Endpoints:

Participants with Stage IV nonsquamous NSCLC without prior systemic treatment will be treated with standard of care pembrolizumab combined with platinum-doublet chemotherapy for 4 cycles, then pembrolizumab plus pemetrexed maintenance for up to 31 additional cycles. The platinum doublet would be pemetrexed plus the investigator's choice of either cisplatin or carboplatin.

Objectives/Hypothesis	Endpoints
Primary Objective	
• Objective: To evaluate if total baseline tumor mutation burden (TMB) in cfDNA is predictive of objective response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by the investigator by estimating the level of association.	• Objective response (OR): Complete response (CR) or partial response (PR)
Secondary Objectives	
• Objective: To evaluate if total baseline TMB in cfDNA is predictive of progression-free survival (PFS) per RECIST 1.1 by investigator review or overall survival (OS) by estimating the level of association.	• PFS is defined as the time from the start of treatment to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. • OS is defined as the time from the start of treatment to death due to any cause.
• Objective: To evaluate the safety and tolerability of pembrolizumab + investigator choice chemotherapy.	• Adverse events (AEs) • Discontinuations due to AEs.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Non-Small Cell Lung Cancer
Population	Male/Female participants with nonsquamous NSCLC who have not received prior systemic chemotherapy treatment for stage IV NSCLC, are at least 18 years of age, and in whom epidermal growth factor receptor (EGFR-), anaplastic lymphoma kinase (ALK-), c-ros oncogene 1 (ROS1), or B isoform of rapidly accelerated fibrosarcoma (B-RAF) -directed therapy is not indicated will be enrolled in this trial.
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 100 participants will be enrolled in this study as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period/	Use
1	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21 day cycle	SOC[a]
	Pemetrexed	500 mg/m^2	Q3W	IV infusion	Day 1 of each 21 day cycle	SOC
	Carboplatin OR Cisplatin	AUC 5 mg/mL/min 75 mg/m^2	Q3W	IV infusion	Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4)	SOC

Abbreviations: IV intravenous; Q3W every 3 weeks; SOC standard of care.
[a] May not be SOC in some countries.

Total Number	1
Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until disease progression is radiographically documented and , when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) for participants treated with pembrolizumab, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 , and confirmed by the site per iRECIST (for participants treated with pembrolizumab), initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Steering Committee	Yes
Executive Oversight Committee	No
Data Monitoring Committee	No
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 9.

1.2 Schema

The study design is depicted in Figure 1.

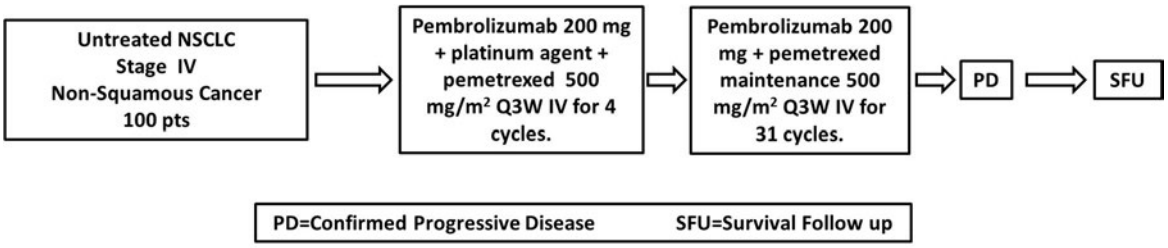

Figure 1 Trial Schema

1.3 Schedule of Activities (SoA)

Table 1 Study Schedule of Activities

Trial Period		**Treatment Cycles (3-week cycles)**								**Post Treatment**			**Notes**
Visit/Cycle	**Screening**	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**	**EOT**	**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Administrative Procedures													
Informed Consent	X									X			Additional consent is required at disease progression
Informed Consent for Future Biomedical Research (optional)	X												
Participant Identification Card	X												Update card once participant is allocated.
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior/Concomitant Medication Review (including any prebiotic or probiotic use)	X	X	X	X	X	X	X	X	X	X	X		Concomitant medications may need to be reported beyond 30 days if related to an SAE.
NSCLC Disease Details and Prior Treatment	X												
Obtain Allocation Number using IVRS		X											Request after eligibility is confirmed and prior to first treatment.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Subsequent Antineoplastic Therapy Status									X	X	X		
Survival Status	←											→	Participants may be contacted for survival status at any time during the course of the study.
Study Treatment Administration-													
Pembrolizumab 200 mg		X	X	X	X	X	X	X					Pembrolizumab dosed Q3W.
Pemetrexed 500 mg/m^2		X	X	X	X	X	X	X					Participants may receive maintenance pemetrexed at the discretion of the investigator if participant discontinues treatment with pembrolizumab during the study.
Carboplatin AUC 5 OR Cisplatin (75 mg/m^2)		X	X	X	X								Dosed Q3W for the first 4 cycles.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Clinical Procedures / Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X			Report non serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anticancer therapy is initiated, whichever is earlier.
Full Physical Examination	X								X				
Directed Physical Examination		X	X	X	X	X	X	X		X			
Vital Signs and Weight	X		X	X	X	X	X	X	X	X			Height at screening only.
Electrocardiogram	X												Additional ECGs may be performed as clinically indicated.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			For eligibility, assess within 10 days of the first dose.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory													
Pregnancy Test Urine or Serum β HCG [5]	X	X	X	X	X	X	X	X	X				WOCBP requires negative test within 72 hours prior to first dose in study. Pregnancy testing will be performed every cycle during the treatment period and at end of treatment as described in Section 10.5.3, and as required locally.
PT/INR and aPTT/PTT	X												Perform eligibility labs within 10 days prior to C1D1.
Hepatitis B & C Serology	X												Hepatitis B surface antigen, HBV DNA, HCV RNA (or HCV antibody if HCV RNA is not the local SOC). May use central lab only if local lab is not capable. Only required if mandated by local health authority.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
HIV Testing	X												Not required unless mandated by local health authority.
CBC with Differential	X		X	X	X	X	X	X	X	X			Perform eligibility labs within 10 days prior to C1D1. After C1D1, may collect Hematology Panel up to 3 days prior to dosing.
Comprehensive Chemistry Panel	X		X	X	X	X	X	X	X	X			Perform eligibility labs within 10 days prior to C1D1.
Urinalysis	X		X		X		X	X	X	X			Perform within 10 days prior to C1D1, then C2D1, C4D1, and C6D1, then every 6th cycle thereafter.
T3 or FT3, FT4, and TSH	X		X		X		X	X	X	X			Perform within 10 days prior to C1D1, then C2D1, C4D1, and C6D1, then every second cycle thereafter. May use central lab only if local lab is not capable.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Blood Samples for Analysis Performed by Central Laboratory													
Whole Blood for cfDNA Analyses	X		X	X	X	X			X				Blood for cfDNA [redacted] will be collected pretreatment at Screening, C2D1, C3D1, C4D1, and C5D1, on first radiographically confirmed Partial Response (PR), at second radiographically confirmed PR, at first radiographically confirmed Complete Response (CR), and at radiographically or clinically confirmed Progressive Disease (PD).

Trial Period		**Treatment Cycles (3-week cycles)**								**Post Treatment**			**Notes**
Visit/Cycle	**Screening**	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**	**EOT**	**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Serum for Cytokine Analysis		X	X		X			X	X				Blood to be collected pretreatment, pembrolizumab infusion for C1D1, C2D1, C4D1, and C12D1, on first radiographically confirmed Partial Response (PR), at second radiographically confirmed PR, at first radiographically confirmed Complete Response (CR), and at radiographically or clinically confirmed Progressive Disease (PD).

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Blood for Genetic Analysis		X											Collect pretreatment. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. Leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent.
Blood for RNA Analysis		X											Collect pretreatment.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Plasma for Metabolomics Analysis		X	X		X			X	X				Blood to be collected before infusion of pembrolizumab and after completing chemotherapy infusion at C1D1, C2D1, C4D1, and C12D1, on first radiographically confirmed Partial Response (PR), at second radiographically confirmed PR, at first radiographically confirmed Complete Response (CR), and at radiographically or clinically confirmed Progressive Disease (PD).

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Stool Samples for Analysis Performed by Central Laboratory													
Stool Microbiome Analysis		X	X		X			X	X				Collected by participant at home using a kit and returned to clinic at next study visit. Two separate stool collections within 1 week prior to first dose of therapy C1D1. A single stool collection within 5 days prior to each of the following study visits: C2D1, C4D1, C12D1, and at radiographically or clinically confirmed Progressive Disease (PD). Final collection may be returned to clinic at 30 day FU visit if it cannot be provided at progression.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
Tumor Tissue Collection													
Newly Obtained/Archival Tissue Sample or Biopsy for Biomarker Analysis, such as: WES, RNA, genetic analysis, and exploratory biomarkers	X												May use archival tissue sample that was obtained prior to screening period as part of the participant's standard care. If archived tissue of sufficient quality is not available, fresh core biopsy is required. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation. Fine needle aspiration (FNA) samples will not be accepted.
EGFR, ALK, B RAF, and ROS Molecular Status	X												May send tumor tissue to central lab for molecular testing if status is unknown and cannot be determined locally.

Trial Period	**Screening**	**Treatment Cycles (3-week cycles)**							**EOT**	**Post Treatment**			**Notes**
Visit/Cycle		**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**		**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	
PD L1 Molecular Status	X												Not required for eligibility, but collected as part of pre treatment biopsy analyses.
Tumor Imaging													
Imaging and RECIST Assessments (see Section 8.2.1)	X			X		X		See note	X		X		Perform imaging at Baseline, C3D1, C5D1, C8D1, , then Q9W through Week 48, then Q12W subsequently (all imaging after baseline has a ±7 day window). Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks prior to DC, scan at DC is not mandatory.

Trial Period		**Treatment Cycles (3-week cycles)**								**Post Treatment**			**Notes**
Visit/Cycle	**Screening**	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**Cycle 7 and beyond**	**EOT**	**Safety FU**	**Follow-up Visits**	**Survival FU**	
Scheduled Time Point and Window	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC±7**	**30 Days Post DC ±7**	**Q9W to Wk 48, then Q12W ± 14 days**	**Q12W ± 14 days**	

AE adverse events; ALK anaplastic lymphoma kinase; aPTT activated PTT; AUC area under the curve; β HCG beta human chorionic gonadotropin; C cycle; CBC complete blood count; cfDNA circulating free DNA; D day; DC discontinuation; DNA deoxyribonucleic acid; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR epidermal growth factor receptor; EOT end of treatment; FT3 free T3; FT4 free thyroxine; FU follow up; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; INR international normalized ratio; IVRS interactive voice response system; iRECIST modified Response Evaluation Criteria in Solid Tumors 1.1 for immune based therapeutics; KRAS a proto oncogene derived from Kirsten RAt Sarcoma virus; NSCLC non small cell lung cancer; PD L1 programmed cell death ligand 1; PI principal investigator; PT prothrombin time; PTT partial thromboplastin time; Q Every; RECIST Response Evaluation Criteria in Solid Tumors; RNA ribonucleic acid; ROS 1 c ros oncogene 1; SAE serious adverse event; SOC standard of care; T3 triiodothyronine; TSH thyroid stimulating hormone; W/Wk Week; WES whole exome sequencing; WOCBP women of childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

2.1.1 Rationale for the Trial and Selected Patient Population

Multiple programmed cell death 1 (PD-1) receptor/programmed cell death ligand 1 (PD-L1)-based combination therapies show promise in the clinic. However, it is not clear which patients are most likely to respond to which pembrolizumab-based combinations. This study will evaluate the value of TMB, as measured by cfDNA, in predicting the response to pembrolizumab and chemotherapy in NSCLC, assess the utility of cfDNA as an emerging technology that can allow exploration of the mechanisms of progression on and resistance to pembrolizumab and chemotherapy, and assess the role of the metagenomics (microbiome) and metabolomics in response to pembrolizumab + chemotherapy in NSCLC.

The global incidence of lung cancer was 1.8 million in 2012, resulting in an estimated 1.6 million deaths [World Health Organization 2012]. In the United States, the 2016 estimated incidence of new diagnoses was 224,400 and estimated number of deaths was 158,100 [National Cancer Institute 2016]. NSCLC represents approximately 80% to 85% of all lung cancers. Of the patients with NSCLC, tumor histology is approximately 46% adenocarcinoma, 16% squamous, 5% other (including neuroendocrine), and the rest, "not otherwise specified" [Sulpher, J. A., et al 2013].

The standard of care (SOC) for metastatic NSCLC has changed in recent years with the development of immunotherapy agents. Two important trials, KEYNOTE-024 and KEYNOTE-042, have demonstrated pembrolizumab monotherapy efficacy in the first-line setting versus chemotherapy. In the Phase 3 study KEYNOTE-024, pembrolizumab, a PD-1 receptor inhibitor, showed statistically significant increases in overall survival (OS) and progression-free survival (PFS) compared to SOC platinum-based chemotherapy for treatment-naïve participants with metastatic NSCLC whose tumors expressed high levels of PD-L1 (tumor proportion score [TPS] ≥50%) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, leading to regulatory approval for this indication in the US and other countries around the world. Approximately 30% of patients with newly diagnosed, advanced NSCLC have tumors that highly express PD-L1 to a TPS ≥50% [Reck, M., et al 2016].

KEYNOTE-042 is an international, open-label, Phase 3 study designed to compare OS between pembrolizumab and standard of care platinum-doublet chemotherapy as first-line therapy in patients with advanced or metastatic NSCLC that expresses PD-L1 in ≥1% of tumor cells. In 2018, an interim analysis conducted by the independent Data Monitoring Committee (DMC) demonstrated that treatment with pembrolizumab resulted in significantly longer OS than platinum-based chemotherapy (carboplatin plus paclitaxel or carboplatin plus pemetrexed) in patients with a PD-L1 TPS ≥1%. As part of a prespecified analysis plan, OS was sequentially tested and was significantly improved in patients with a TPS ≥50%, with a TPS ≥20%, and then in the entire study population with a TPS ≥1% [Lopes, G., et al 2018].

The safety profile of pembrolizumab in this trial was consistent with that observed in previously reported monotherapy studies involving patients with advanced NSCLC.

Prior to the approval of pembrolizumab, the SOC for first-line metastatic NSCLC has been platinum-doublet chemotherapy. Studies evaluating different pembrolizumab combinations in anti-PD-1/PD-L1 naïve participants have shown preliminary evidence of clinical activity in participants with recurrent and/or metastatic disease. To evaluate the activity of the combination of pembrolizumab and chemotherapy, 2 pivotal studies were initiated, KEYNOTE-021 and the follow-up study, KEYNOTE-189 (see Section 2.2.2). In the Phase 1/2 study KEYNOTE-021 Cohort G, pembrolizumab plus pemetrexed and carboplatin showed statistically significant increases in objective response rate (ORR) compared to pemetrexed and carboplatin alone in participants with nonsquamous advanced NSCLC, regardless of PD-L1 status, although the ORR was higher in the TPS ≥50% subgroup. These results established pembrolizumab plus chemotherapy as an efficacious option for first-line therapy in patients with NSCLC; these findings were further evaluated in the Phase 3 study KEYNOTE-189 (nonsquamous histology). In KEYNOTE-189, pembrolizumab plus investigator choice platinum agent and pemetrexed chemotherapy had a statistically significant increase in OS over the platinum agent and pemetrexed alone in advanced NSCLC [Lopes, G., et al 2018].

However, for these studies not all NSCLC patients have shown benefit from anti-PD-1 antibody therapy, either alone or in combination with chemotherapy, presumably due to multiple inherent or acquired immune-mediated resistance mechanisms that are active at the level of the host, including microbiome, or the tumor microenvironment. Moreover, many patients ultimately progress, indicating the need for identifying those mechanisms to increase and maintain benefit. Such resistance mechanisms are likely to be heterogeneous and multi-factorial; therefore, identifying new biomarkers of response to differentiate potential responders or non-responders will enable further development of more sophisticated patient selection criteria and potential combination therapies, either up front or upon progression. Furthermore, taking a more holistic approach, markers of a microbiome conducive or detrimental to PD-1 therapy may point to possible microbiome augmentation or modulation to enhance anti-PD-1 therapy and/or reduce associated drug toxicity. To elucidate this biology, it is best considered where PD-1 has established efficacy either alone or in combination with other agents.

PD-L1 has been established as a validated predictive biomarker for response to pembrolizumab monotherapy in first-line NSCLC [Reck, M., et al 2016]. We are interested in exploring other potential markers of PD-1 and chemotherapy activity.

Data from NSCLC studies have demonstrated that treatment with a combination of pembrolizumab and chemotherapy has clinical benefit over chemotherapy alone [Gandhi, L., et al 2018]. Chemotherapy adds another layer of complexity to PD-1 intervention due to its multitude of effects on the patient's physiology, tumor, and immune system.

In return, other elements may modulate chemotherapy function such as the microbiome, which comprises the eukaryote and prokaryote microorganisms that occupy distinct

ecological niches. Advances in the study of the microbiome have indicated a range of physiological effects are manifested by these organisms. The microbiome has been shown to modulate the function of a variety of chemotherapies through immune- and non-immune-mediated mechanisms.

Pembrolizumab has been combined with chemotherapy in several tumor types, yet little is known about the biological mechanisms of the interactions between these therapies. The deep interrogation of response and resistance mechanisms to pembrolizumab in combination with chemotherapy has the potential to establish tumor-agnostic markers of response and/or resistance.

Understanding the relationship between tumor genetics, the immune system, microbiome, and response to anti-PD-1 therapy is best determined in participants who have not received several lines of prior systemic therapy, surgery, or radiation due to potential detrimental effects on immune and microbiome compartment function when considered alone or the relationships between them. Furthermore, an appropriate treatment niche is where benefit of pembrolizumab combination therapy has been established. Consequently, a first-line NSCLC setting such as used for KEYNOTE-21 Cohort G and KEYNOTE-189 represents an appropriate population to undertake these exploratory genetic and biomarker analyses to further understand patient selection and mechanisms of drug action and resistance. Validated biomarkers may ultimately be needed to guide patients, physicians, and payers through an expanding armamentarium of combination options.

2.1.2 Tumor Mutation Burden

Tumor rejection antigens allow tumors sufficiently distinct from normal tissue to activate the immune system and induce an efficient antitumor response. Tumor-mutated specific antigens (neoantigens) are major tumor rejection antigens [Schumacher, T. N. 2015] [Castle, J. C., et al 2012]. The recent development of innovative deep sequencing technologies (at an affordable cost) along with advances in bioinformatics has enabled systemic analysis of nonsynonymous somatic TMB and identification of potentially immunogenic neoantigens. The genetic landscape and the full spectrum of genomic alterations in each individual tumor provide the guidance for personalized cancer immunotherapy [Yuan, J. 2016].

Two pilot studies in mouse models first demonstrated that whole exome sequencing is able to identify neoantigen-specific cluster of differentiation (CD)8+ T-cells associated with tumor response [Matsushita, H., et al 2012] [Castle, J. C., et al 2012]. Several clinical studies demonstrated the feasibility and importance of understanding the immunogenicity of neoantigens and their potential clinical application in patients treated with tumor-infiltrating lymphocyte adoptive cell therapy [Robbins, P. F., et al 2013] [Tran, E. 2014] [Linnemann, C., et al 2015]. Tumor mutational burden was associated with clinical outcome to immune checkpoint blockade cancer immunotherapy in patients with advanced melanoma and NSCLC [Snyder, A., et al 2014] [Rizvi, N. A., et al 2015] [Van Allen, E. M., et al 2015]. Patients with mismatch repair deficient tumors likewise had high rates of clinical response to PD-1 blockade [Le, D., et al 2015]. The recent 2017 FDA approval of pembrolizumab in

microsatellite instability (MSI)-high tumors highlights this relationship between DNA repair abrogation, neoantigens, and response to checkpoint inhibitors.

Recent data have shown a relationship between TMB and monotherapy response to pembrolizumab in NSCLC [Rizvi, N. A., et al 2015]. Checkmate 227 was a multi-arm randomized trial aimed at analysis of checkpoint inhibition in first-line NSCLC. The statistical design was modified during trial execution to include TMB for patient stratification independent of PD-L1-status. Selective trial data were presented at the 2018 annual American Association for Cancer Research meeting [Hellmann, M. D., et al 2018] and indicated that the combination of a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, ipilimumab, and the PD-1 inhibitor nivolumab had superior PFS compared to chemotherapy for participants with high TMB defined at >10 mutations per megabase of genomic DNA.

Data from KEYNOTE-189 have indicated that regardless of PD-L1 status, pembrolizumab and chemotherapy had superior OS compared to chemotherapy alone in the first-line nonsquamous NSCLC setting. TMB has not been prospectively interrogated in this population as an exploratory marker, and several significant questions remain around relationship between PD-L1 status, TMB, and whether TMB itself is predictive of response in the setting of an anti-PD-1/PD-L1 agent and chemotherapy.

This trial is intended to extend these studies to investigate TMB as one of several exploratory genetic markers for response to pembrolizumab in combination with chemotherapy in the first-line NSCLC setting.

2.1.3 Tumor Cell-Free DNA Analysis

Tumor genetics and TMB have been historically interrogated using next-generation sequencing technologies using formalin-fixed paraffin embedded tissue (FFPE), with DNA sequencing being whole genome, whole exome, or defined gene panels. For many tumor types, biopsies have inherent risk to the patient, notwithstanding patient logistical and financial costs. While biopsies for diagnosis do constitute a standard of care, for a variety of technical reasons, including having reliable tissue for DNA sequencing, blood-based markers offer a variety of advantages. Furthermore, biopsies are usually undertaken at diagnosis, whereas blood-based markers have the advantage of being interrogated over the course of therapy and importantly at progression.

Through mechanisms that are not well understood, small fragments of tumor DNA appear in systemic circulation. An increasing body of evidence demonstrates that these fragments, known as cell-free circulating tumor DNA (cfDNA), directly encode genetic features of the tumors from which they are derived (http://www.grail.com). cfDNA can be interrogated at the whole-genome level or using defined gene panels. The latter offers several advantages, including cost and reduced sequencing and analysis time, both of which are important in a clinical setting. Gene panels can be constructed to interrogate several features of a tumor's genetics and can obtain the same depth of genetic information as can be obtained from whole-genome analyses.

The complexity of tumors suggests that measurements that capture the breadth of the heterogeneous cancer genomes represent the best and most direct signature of disease biology. High-intensity sequencing assays can readily detect the low fraction of cfDNA in the bloodstream, which is very small compared to DNA from non-cancerous cells. This necessitates the ability to distinguish faint signals and tumor genetics of early-stage through advanced tumors from a background of wild-type genomic DNA. cfDNA technology represents a unique capability for deciphering tumor genetics without the need for invasive and potentially detrimental tumor biopsies.

Biopsy-dependent markers have the detriment of limited samplings over the course of therapy. Consequently, there is little temporal information that can be obtained to identify tumor genetic evolution over the course of therapy. Furthermore, the ability to predict response and/or progression is constrained by a defined time point analysis of the tumor-immune interaction, which is not relevant to the stochastic relationship between an evolving tumor and the immune system. Therefore, a blood-based cfDNA assay offers the advantage as a read-out of these temporal changes, with the prospect of kinetic assessment of tumor fraction cfDNA being predictive for early response and/or progression to immunotherapy. In addition, the ability to assess temporal changes in tumor genetics will give insight into tumor clonal evolution and immune editing of specific neoantigens.

Therefore, as cfDNA represents the genomic diversity of cancer throughout the body, cfDNA-based tests have the potential to deliver sensitive and specific tests for early cancer detection, analysis of TMB and tumor genetics, mechanisms of resistance to immunotherapy, and importantly, determination of tumor response to therapy. This trial will assess these exploratory genetic markers, including TMB, in collaboration with GRAIL Inc. (http://www.grail.com), a company specializing in tumor cfDNA analysis. These analyses will be performed using a proprietary gene panel and bioinformatics pipeline aimed at a focused assessment of NSCLC genetics and immune activity.

This study will investigate the utility of cfDNA technology to assess tumor genetics as predictive for response or resistance to pembrolizumab plus chemotherapy in study participants with stage IV NSCLC without prior systemic therapy. The study will also investigate other exploratory cellular and genetic markers of immune response.

2.1.4 Microbiome Modulation of the Immune System and Immunotherapy

The human body is host to large numbers of bacteria and other microorganisms, primarily colonizing epithelial surfaces with the highest densities within the lower GI tract. Microbiome components have both local and physiological effects that are mediated via microbiome-immune co-evolution and microbiome production of metabolites [Belkaid, Y. 2017]. These commensals play an important homeostatic role in a variety of human body systems, including the immune system and endocrine systems. The microbiota play a fundamental role in the induction, evolution, function, and modulation of the host immune system. Likewise, the host immune system has evolved mechanisms to maintain this symbiotic relationship with the microbiome. The maintenance of this communication allows the induction of protective responses to pathogenic organisms and the utilization of immune

regulatory pathways involved in the sustained tolerance to innocuous antigens. This ability of the microbiome components to set the systemic immunological tone requires complex feedback loops between innate and adaptive components of the immune system.

The largest component of the microbiome in numbers and biological complexity is within the gut environment. These commensals have systemic immune-stimulatory and immune-regulatory effects, which suggest the gut microbiome impacts the systemic immune system through a broad range of immune functions [Haase, S., et al 2018]. The lung is one such tissue impacted by this distant microbiome ecology [Shukla, S. D., et al 2017]. Chronic respiratory diseases, namely asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis, all have been demonstrated to be impacted by the gut microbiota (reviewed in [Shukla, S. D., et al 2017] [Lloyd, C. M. 2017]). The gut lung cross-talk is considered to be mediated by resident microbes, microbiome-generated metabolites, and patrolling immune cells. This relationship between the systemic effects of the gut microbiome and the immune system suggests a combined impact on the development of cancer and its evasion of the immune system.

The microbiome may modulate systemic T cell-mediated tumoricidal activity, as administration of antibiotics severely reduced the efficacy of adoptive T-cell transfer in several mouse models of cancer [Luo, A., et al 2017]. The microbiome-mediated modulation of the immune system impacts cancer at all of its developmental stages, including development, elimination, equilibrium, and escape [Zitvogel, L., et al 2018] [Kim, C. H. 2018] [Rea, D., et al 2018]. Some tumors themselves have been reported to have a resident microbiome population, suggesting that effects may sometimes be more direct [Hooper, S. J., et al 2007] [Chanudet, E., et al 2007] [Hubbard, A. L., et al 1998] [Silva-Valenzuela, C. A., et al 2016]. Microorganism presence in tumor tissue can be directly related to tumorigenesis, as exemplified by *Helicobacter pylori* in gastric cancer [Wroblewski, L. E., et al 2010], or may represent a coincidental infection.

However, our understanding of this biological interaction between microbiome and tumor immunology is limited. Evidence suggests for some cancers, such as GI cancer, that gut dysbiosis is a direct contributing factor to cancer development and immune evasion [Meng, C., et al 2018]. Identifying defined mechanisms of microbiome-induced immune evasion of cancer will help to determine how that microbiome may also be directed to be “pro-tumorigenic” versus “tumor-protective”. Furthermore, the microbiome has an additional cancer-related effect, which is modulation of the effectiveness of chemotherapy and immunotherapy. So, identifying how to alter microbiome elements to increase therapy effectiveness may be a new element in cancer therapy.

The recent advances in the use of immunotherapy in the first-line lung cancer space have indicated the rationale for combination of chemotherapy with immune agents. The concept that the microbiome may independently modulate these modalities individually and in combination indicates a need to understand these effects. Evidence from mouse models suggests links between the effectiveness of platinum-based cytotoxic compounds and the microbiome [Iida, N., et al 2013] [Alexander, J. L., et al 2017]. However, there are limited clinical data on microbiome and standard of care chemotherapies.

Recent work has indicated a possible involvement of microbiome in influencing the efficacy of checkpoint inhibitor treatment strategies for both CTLA-4- and PD-1-targeting checkpoint inhibitors. Mouse models indicated direct links between various bacterial genera and T-cell components associated with checkpoint inhibitors [Vetizou, M., et al 2015]. Three recent investigations into the microbiome and the PD-1/PD-L1 axis have provided clinical data that the gut microbiome modulates the response to inhibitors of PD-1/PD-L1 axis [Gopalakrishnan, V., et al 2018] [Matson, V., et al 2018] [Routy, B., et al 2018]. Overall, they indicated that a healthier, highly diverse microbiota and the presence of certain bacterial species favor the establishment of an anti-tumor immune response at baseline that may be enhanced by the anti-PD-1 axis treatment, leading to a more favorable clinical response.

These studies reported the importance of defined gut microbiota on response to PD-1 therapy, but highlighted different bacterial players between the studies. Many factors modulate microbiome composition, such as geographical location, socioeconomic factors, antibiotic or other drug use, early childhood exposure, stress, and diet. Furthermore, the taxonomic identification of bacterial species by shotgun metagenomics has several limitations, including incomplete databases of full bacterial genomic sequences and analysis pipelines. In addition, the effects of the microbiota on therapy are likely due to changes in the population ecology and metabolism of the gut microbiota that together affect cancer immunity. Presumably, the effects on the immune system may not be wholly dependent on the bacterial composition per se but more potentially on the metabolites they produce [Cummings, J. H., et al 1987] [Rooks, M. G. 2016] [Stockinger, B., et al 2014]. So, understanding the element of bacterial-produced metabolites through metabolomics analysis in conjunction with microbiome assessment will help us to further understand the relationship with response to anti-PD-1 therapy.

This trial will investigate, as exploratory markers, the role of the microbiome and metabolomics in response to pembrolizumab plus chemotherapy in treatment-naïve NSCLC participants. A first-line lung population is the more suitable niche, as prior lines of therapy are likely to have perturbed the microbiota due to the therapy itself, AEs such as GI toxicity, or the management of AEs such as use of antibiotics in infections.

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin (Ig)G4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (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 Investigator's Brochure (IB).

In this study, pembrolizumab will be administered in combination with pemetrexed and either cisplatin or carboplatin. Refer to the prescribing information for cisplatin, carboplatin, and pemetrexed.

2.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells to FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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

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

2.2.2 Completed Clinical Studies

Six completed, company-sponsored, clinical studies were conducted to evaluate the efficacy of pembrolizumab monotherapy and pembrolizumab combination therapy in the treatment of NSCLC: KEYNOTE-001, KEYNOTE-010, KEYNOTE-021, KEYNOTE-024, KEYNOTE-042, and KEYNOTE-189. Several additional studies are in progress. Refer to the current pembrolizumab IB for a description of KEYNOTE-001 and KEYNOTE-010. The results of KEYNOTE-010 indicate that in previously treated participants with NSCLC with PD-L1 TPS ≥1%, and disease progression following platinum-containing

chemotherapy, pembrolizumab provides a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy. Furthermore, the PD-L1 selection employed in KEYNOTE-010 identified participants more likely to benefit from pembrolizumab and resulted in favorable HR in OS compared to docetaxel.

Overall, the results from KEYNOTE-001 and KEYNOTE-010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. The 2 key clinical studies for this trial population are KEYNOTE-021 Cohort G and KEYNOTE-189.

KEYNOTE–021

In the Phase 1/2 Cohort A of KEYNOTE-021, 25 participants with treatment-naïve, advanced/metastatic NSCLC, regardless of PD-L1 expression and without treatable EGFR or ALK aberrations, were treated with 4 cycles of carboplatin, paclitaxel, and pembrolizumab (randomized 1:1 to 2 mg/kg or 10 mg/kg) followed by pembrolizumab Q3W [Langer, C. J., et al 2016]. The primary endpoint of the cohort was to determine the recommended Phase 2 dose for pembrolizumab in combination with chemotherapy in participants with unresectable or metastatic NSCLC.

No dose-limiting toxicities were observed, no treatment-related deaths occurred, and no treatment-related discontinuations occurred. Grade 3/4 AE were observed in 56% of participants and potential irAEs were observed in 16% of participants.

After a median duration of follow-up of 13 months (range, 2-21 months), the confirmed ORR was 52% (13/25; 95% CI: 31 to 72) per blinded independent central review (BICR). Median PFS was 10.3 months (95% CI: 3.7 to not reached [NR]) per BICR and OS was NR (95% CI: 11.0 to NR). Responses were seen in both PD-L1-positive and PD-L1-negative participants [Gadgeel, S., et al 2016]

In the Phase 2 Cohort G study KEYNOTE-021, pembrolizumab plus pemetrexed plus carboplatin demonstrated a statistically significant increase in ORR and PFS compared to pemetrexed plus carboplatin alone for participants with treatment-naïve advanced NSCLC in whom EGFR- or ALK-directed therapy is not indicated. The magnitude of benefit observed in this PD-L1 unselected nonsquamous NSCLC population has not been observed in randomized studies adding a third agent to standard chemotherapy and subsequently led to FDA-accelerated approval of the combination for the first-line treatment of participants with metastatic nonsquamous NSCLC, contingent upon verification and description of clinical benefit in a confirmatory study [Langer, C. J., et al 2016].

Cohort G included participants with treatment-naïve, nonsquamous, stage IIIB/IV NSCLC, irrespective of PD-L1 expression and without treatable EGFR mutations or ALK translocations, randomized 1:1 to receive pembrolizumab plus pemetrexed plus carboplatin OR pemetrexed plus carboplatin alone.

The cohort enrolled 123 participants, with 60 randomly assigned to the pembrolizumab plus chemotherapy arm and 63 to the chemotherapy alone group. For the primary endpoint of ORR, 33/60 participants (55%; 95% CI: 42 to 68) in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18/63 participants (29%; 95% CI: 18 to 41) in the chemotherapy-alone group (estimated treatment difference: 26% [95% CI: 9 to 42]; p 0.0016).

Progression-free survival was significantly longer with pembrolizumab plus chemotherapy compared with chemotherapy alone (HR 0.53 [95% CI: 0.31 to 0.91]; p 0.010). Median PFS was 13.0 months (95% CI: 8.3 to NR) for pembrolizumab plus chemotherapy and 8.9 months (95% CI: 4.4 to 10.3) for chemotherapy alone. At the time of data cutoff, no difference in survival was noted between treatment groups (HR 0.90 [95% CI: 0.42 to 1.91]), though the survival analysis may be premature and participants progressing on the chemotherapy-only arm were permitted to crossover to pembrolizumab monotherapy on study as well as receive immunotherapy subsequently.

Treatment-related AEs occurred in 55/59 (93%) participants in the as-treated pembrolizumab plus chemotherapy group and 56/62 (90%) participants in the as-treated chemotherapy alone group, including 23 (39%) and 16 (26%) participants, respectively, who had events of Grade 3 or worse severity. The rate of treatment discontinuation because of treatment-related AEs was similar between groups, with 6/59 (10%) participants in the pembrolizumab plus chemotherapy group and 8/62 (13%) participants in the chemotherapy-alone group.

The addition of pembrolizumab to carboplatin and pemetrexed significantly improved the proportion of participants who achieved an objective response compared with carboplatin and pemetrexed alone in participants with chemotherapy-naïve, advanced nonsquamous NSCLC. In addition, this combination significantly prolonged PFS in this population. These data suggest that the combination of pembrolizumab, carboplatin, and pemetrexed provides a significant and clinically relevant improvement in antitumor activity compared with chemotherapy alone for treatment-naïve, nonsquamous, advanced NSCLC. These results subsequently led to the FDA-accelerated approval of the combination for the first-line treatment of participants with metastatic nonsquamous NSCLC, contingent upon verification and description of clinical benefit in a confirmatory study KEYNOTE-189.

KEYNOTE-189

KEYNOTE-189 is a Phase 3, randomized, double-blinded, active-controlled, multicenter study of pembrolizumab plus pemetrexed and platinum (carboplatin or cisplatin) versus pemetrexed and platinum in participants with treatment-naïve, metastatic, nonsquamous NSCLC. The primary endpoint is PFS per RECIST 1.1 as assessed by BICR.

The results of the KEYNOTE-189 demonstrated an OS benefit of pembrolizumab plus platinum-based doublet chemotherapy to platinum-doublet chemotherapy alone [Gandhi, L., et al 2018]. After a median follow-up of 10.5 months, the estimated survival at 12 months was 69.2% (95% CI: 64.1 to 73.8) in the pembrolizumab-containing group versus 49.4% (95% CI: 42.1 to 56.2) in the placebo-combination group, with an HR for death 0.49 (95%

CI: 0.38 to 0.64; $p<0.001$). There was an improvement in OS seen across all PD-L1 groups that were evaluated. The median PFS was 8.8 months (95% CI: 7.6 to 9.2) in the pembrolizumab-containing group and 4.9 months (95% CI: 4.7 to 5.5) in the placebo-combination group, with an HR for disease progression or death 0.52 (95% CI: 0.43 to 0.64; $p<0.001$). The KEYNOTE-189 data indicate that the combination of a checkpoint inhibitor and chemotherapy is a viable therapeutic option for first-line NSCLC treatment.

The overall response rate assed by BICR was 47.6% (95 CI: 42.6 to 52.5) in the pembrolizumab-combination group and 18.9% 95% CI: 13.8 to 25.0) in the placebo-combination group ($p<0.001$). The disease control rate (the proportion of patients with a confirmed complete or partial response or stable disease) was 84.6% in the pembrolizumab combination group and 70.4% in the placebo-combination group. The median duration of response was 11.2 months (range, 1.1+ to 18.0+) in the pembrolizumab-combination group and 7.8 months (range, 2.1+ to 16.4+) in the placebo-combination group. The response rate in the pembrolizumab-containing arm was higher in all categories of PD-L1 tumor proportion score, with the greatest difference in patients with TPS ≥50% (61.4% vs 22.9%).

Adverse events of any cause regardless of attribution occurred in 99.8% of the patients in the pembrolizumab-combination group and in 99.0% of those in the placebo-containing group. The events were Grade 3 or higher in 67.2% and 65.8% of the patients, respectively. Discontinuation of all trials drugs because of AEs occurred in 13.8% of patients in the pembrolizumab-combination group and in 7.9% of the placebo-containing group. Discontinuation of pembrolizumab and placebo were 20.2% and 10.4%, respectively.

These results have confirmed that KEYNOTE-21 Cohort G and KEYNOTE-189 have demonstrated the increased clinical efficacy of pembrolizumab and platinum-containing doublet chemotherapy versus platinum-containing doublet across all categories of PD-L1 expression. The data from KEYNOTE-021 and KEYNOTE-189 demonstrate there is still a need to understand the biology of resistance to PD-1 inhibitors and exploratory markers of pembrolizumab and chemotherapy response.

2.2.3 Ongoing Clinical Studies

2.2.3.1 Pembrolizumab Studies

Pembrolizumab is under evaluation in participants with NSCLC as monotherapy and in combination with chemotherapy, immunotherapy, and targeted therapies. A full list of ongoing company-sponsored studies can be found in the current IB of pembrolizumab.

2.2.3.2 Ongoing Grail cfNA Biomarker Studies

There are 2 ongoing GRAIL-sponsored oncology studies using cfDNA to interpret tumor genetics. NCT02889978 titled “The Circulating Cell-free Genome Atlas Study (CCGA)” is a study aimed at mapping the cell-free tumor genome of early cancer patients. This study will collect biological samples from donors with a new diagnosis of cancer (blood and tumor tissue) and from donors who do not have a diagnosis of cancer (blood) in order to characterize the population heterogeneity in cancer and non-cancer participants and to

develop and validate models for distinguishing cancer from non-cancer. The purpose of the CCGA Study is to characterize the landscape of cell-free nucleic acid (cfNA) profiles in individuals with and without cancer, and develop an assay to detect early cancer in blood. The observational CCGA Study will enroll approximately 10,500 individuals with newly diagnosed cancer (treatment naïve) and approximately 4500 individuals without cancer, interrogating the biology of both tumor biopsy tissue samples and the circulating, tumor-derived nucleic acids in blood. cfNAs in the blood are an emerging biomarker for earlier cancer detection. Clinical outcomes data will be collected on the enrolled participants at least annually for up to 5 years. The result will be a detailed atlas of cancer genetics that GRAIL will use to support its product development goals. The database, upon analysis, may be expanded to enroll additional individuals with specific cancers or without cancer. Initial results from a substudy of approximately 1650 participants from CCGA were presented at the 2018 Annual American Association for Cancer Research Conference [Aravanis, A. A., et al 2018].

NCT03085888 is an observational breast cancer study titled “The STRIVE Study: Breast Cancer Screening Cohort for Development of Assays for Early Cancer Detection”. The aim of this study is to use high-intensity sequencing of circulating cfNAs to support the development of a test for detection of invasive breast cancer. STRIVE is a multi-center, longitudinal, prospective, observational study that will enroll approximately 120,000 women at the time of their screening mammogram.

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. Results from KEYNOTE-189 show that treatment with pembrolizumab plus platinum-doublet chemotherapy provides a substantial benefit in this patient population [Gandhi, L., et al 2018]. 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

Participants with Stage IV nonsquamous NSCLC without prior systemic treatment will be treated with standard of care pembrolizumab combined with platinum-doublet chemotherapy for 4 cycles, then pembrolizumab plus pemetrexed maintenance for up to 31 additional cycles. The platinum doublet would be pemetrexed plus the investigator’s choice of either cisplatin or carboplatin.

Objectives	Endpoints
Primary Objective	
• Objective: To evaluate if total baseline TMB in cfDNA is predictive of objective response per RECIST 1.1 by the investigator by estimating the level of association.	• Objective response (OR): Complete response (CR) or partial response (PR)
Secondary Objectives	
• Objective: To evaluate if total baseline TMB in cfDNA is predictive of PFS per RECIST 1.1 by investigator review or OS by estimating the level of association.	• PFS is defined as the time from the start of treatment to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. • OS is defined as the time from the start of treatment to death due to any cause.
• Objective: To evaluate the safety and tolerability of pembrolizumab + investigator choice chemotherapy	• AEs • Discontinuations due to AEs
Tertiary/Exploratory Objectives	
• Objective: To evaluate whether total baseline TMB in cfDNA or whole exome sequencing (WES) of tumor biopsy/sample is predictive of OR and PFS per iRECIST 1.1 by investigator review	• OR: Complete response (CR) or partial response (PR) • PFS is defined as the time from the start of treatment to the first documented PD or death due to any cause, whichever occurs first.
• Objective: To characterize kinetic profiles of tumor fraction in cfDNA and evaluate whether they are predictive of OR and PFS per RECIST 1.1 by investigator review and OS	• OR: Complete response (CR) or partial response (PR) • PFS is defined as the time from the start of treatment to the first documented PD or death due to any cause, whichever occurs first. • OS is defined as the time from the start of treatment to death due to any cause.
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamics activity, and/or the mechanism of action of chemotherapy or pembrolizumab	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry (IHC), and other blood-derived biomarkers

Objectives	Endpoints
• Objective: To estimate the concordance between baseline WES-based TMB of tumor biopsy or FFPE sample and baseline TMB in cfDNA	• Baseline TMB in cfDNA (blood) • WES-based TMB of tumor FFPE biopsy/sample
• Objective: To evaluate the impact of pre-treatment (baseline) and on-treatment gut microbiome signatures associated with OR and PFS per RECIST 1.1 by investigator review and OS	• OR: Complete response (CR) or partial response (PR) • PFS is defined as the time from the start of treatment to the first documented PD or death due to any cause, whichever occurs first. • OS is defined as the time from the start of treatment to death due to any cause.
• Objective: To evaluate whether metabolomics components are associated with OR and PFS per RECIST 1.1 by investigator review and OS	• OR: Complete response (CR) or partial response (PR) • PFS is defined as the time from the start of treatment to the first documented PD or death due to any cause, whichever occurs first. • OS is defined as the time from the start of treatment to death due to any cause.

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, multi-site, open-label study of pembrolizumab + platinum-doublet chemotherapy (pemetrexed plus investigator's choice of either cisplatin or carboplatin) as first-line treatment in participants with stage IV NSCLC who have not previously received systemic therapy for their metastatic disease and in whom EGFR-, ALK-, B-RAF-, or ROS1-directed therapy is not indicated. Treatment will include pembrolizumab combined with a platinum-doublet chemotherapy for 4 cycles then pembrolizumab plus pemetrexed maintenance for up to 31 additional cycles. The platinum-doublet will be pemetrexed plus the investigator's choice of either cisplatin or carboplatin.

Participants will be evaluated with radiographic imaging to assess response to treatment at 6 weeks (42 ± 7 days) and 12 weeks (84 ± 7 days) and then every 9 weeks (63 ± 7 days) for the first 48 weeks and every 12 weeks (84 ± 7 days) subsequently. Imaging will continue on this schedule until documented disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, or administrative reasons, or initiation of a new

anticancer regimen requiring cessation of treatment. All imaging obtained on the study will be assessed by the investigator using RECIST 1.1 and iRECIST 1.1 (see Section 8.2) for determination of objective response of complete or partial response (CR or PR, respectively) and PFS.

AE monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Study treatment will continue until 35 administrations of pembrolizumab (approximately 2 years), documented PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdrawal of consent, pregnancy of the participant, or administrative reasons requiring the cessation of treatment. Optionally, participants with a confirmed CR who have received at least 8 cycles of pembrolizumab may discontinue treatment (Section 7.1).

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

Specific procedures to be performed during the study, 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

This clinical trial will test the utility of TMB and other exploratory markers of response in a treatment-naïve nonsquamous NSCLC population. The treatment regimen of pembrolizumab in combination with platinum-doublet chemotherapy has been previously tested with positive efficacy results in a randomized, Phase 3 trial, KEYNOTE-189.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Efficacy Endpoints per RECIST 1.1

Objective response by RECIST 1.1 criteria is considered preliminary evidence of efficacy and is a reasonable endpoint in a Phase 2 study.

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

PFS is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities.

This study will use objective response based on RECIST 1.1 criteria as assessed by the investigator as the primary endpoint, and PFS, as assessed by the investigator, and OS as secondary endpoints. Objective response is defined a confirmed CR or confirmed PR per RECIST 1.1 as assessed by investigator recorded between the start of treatment and disease progression or death due to any cause, whichever occurs first.

RECIST 1.1 will be used when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.2.1.4). 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.

4.2.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

4.2.1.2 Biomarkers

4.2.1.2.1 Circulating Free DNA Mutation Burden

Circulating free (cf)DNA in plasma samples obtained over the course of the study will be assessed by high-intensity, next-generation genetic sequencing to identify genomic alterations in genes. [redacted]. Data acquired will be analyzed to characterize the association between these genetic elements, clinical response, and durability of responses.

4.2.1.2.2 Tumor Mutation Burden

The tumor mutation burden in tumor biopsy or FFPE samples will be assessed in order to determine concordance with the mutation burden in cfDNA.

4.2.1.2.3 Microbiome and Metabolomics

Gut microbiome populations over the course of the study will be identified by metagenomics and analyzed to characterize the association between bacterial population signatures of response or progression. Similarly, plasma metabolomics signatures will be assessed for association with clinical response and durability of responses. Probiotics and prebiotics will be monitored during the study, as none of these supplements have been clinically validated in a randomized Phase 3 study to modulate cancer therapy including immunotherapy. Furthermore, the understanding of the microbiome itself, let alone its role in pembrolizumab response in any tumor type including NSCLC, is highly limited and is one of the key translational goals of this study.

4.2.1.3 Safety Endpoints

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

4.2.1.4 Pharmacodynamic Endpoints

Pharmacodynamic markers will be interrogated to gain a better understanding of response and resistance biology. Tumor biopsies will be performed at baseline (archival FFPE tissue acceptable for this sample). Blood samples for exploratory biomarkers and planned genetic analysis will be collected at baseline, at selected time points while on therapy depending on the biomarker, on response, and at the end of treatment/progression as listed in the schedule of events. Detailed endpoints are described in the biomarker section (Section 8.10).

4.2.1.5 Planned Exploratory Biomarker Research

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

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. In addition to studying variation across the human genome, cfDNA-based technologies enable blood-based interrogation of tumor genetics, including total TMB, tumor immune-editing, and tumor evolution. cfDNA analysis represents a more complete snapshot of total tumor genetics of primary and metastatic lesions over single-site, biopsy-based analyses. cfDNA technologies allows interrogation of tumor genetics without the risk of invasive biopsies and being a blood marker enables routine tumor genetics assessment over the course of therapy. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other blood-derived biomarkers

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

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

Microbiome analysis of stool

Stool samples from this study will be collected to assess the microbiome associated with clinical activity. This research may help identify factors predictive of pembrolizumab response and resistance and novel targets for cancer immunotherapy.

Metabolomics

Blood samples from this study will be collected to assess the metabolomics profiles associated with clinical activity. This research may help identify factors predictive of pembrolizumab response and resistance and novel targets for cancer immunotherapy.

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

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

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

4.3 Justification for Dose

4.3.1 Pembrolizumab

Pembrolizumab 200 mg IV Q3W is the approved dose for the NSCLC indication per the current label.

4.3.2 Chemotherapy

This study will use SOC dosing for carboplatin at AUC 5 mg•min/mL ≤50 mg, cisplatin at 75 mg/m^2, and pemetrexed at 500 mg/m^2 in participants with NSCLC. Refer to the carboplatin, cisplatin, and pemetrexed prescribing information for more information.

4.4 Beginning and End of Study Definition

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

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

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/female participants with metastatic NSCLC who have received no systemic anticancer therapy for their metastatic NSCLC and who are at least 18 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Have a histologically-confirmed or cytologically confirmed diagnosis of stage IV (M1a, M1b, or M1c [AJCC 8th edition]) nonsquamous NSCLC.

2. Have confirmation that epidermal growth factor receptor (EGFR-), anaplastic lymphoma kinase (ALK-), c-ros oncogene 1 (ROS1), or B isoform of rapidly accelerated fibrosarcoma (BRAF) directed therapy is not indicated as primary therapy. Documentation of the absence of tumor activating EGFR mutations, BRAF mutations, ALK gene rearrangements, and ROS1 gene rearrangements is required.

3. Have measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

4. Have not received prior systemic treatment for their advanced/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.

5. Have provided sufficient evaluable Stage IV, archival, solid tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion (that was not previously irradiated) for biomarker analysis (Fine Needle Aspiration [FNA] samples will not be accepted). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. (See Procedures Manual for specific details.)

Demographics

6. Participant is ≥18 yearsof age inclusive, at the time of signing the informed consent.

7. Have an ECOG performance status of 0 or 1 within 10 days prior to the first dose of study treatment.

Male Participants

8. Agree to use a contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days, corresponding to time needed to eliminate any study intervention(s) (pembrolizumab and/or any active comparator/combination) plus an additional 90 days (a spermatogenesis cycle) for study interventions where there is risk of clinically relevant genotoxicity after the last dose of study intervention and refrain from donating sperm during this period.

Female Participants

9. Not be pregnant (Appendix 5) or breastfeeding, and at least 1 of the following conditions applies:

    a) Not be a woman of childbearing potential (WOCBP) as defined in Appendix 5.

    OR

    b) A WOCBP must agree to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days (corresponding to time needed to eliminate any study intervention(s) (pembrolizumab and or any active comparator/combination) after the last dose of pembrolizumab.

Informed Consent

13. The participant (or legally acceptable representative if applicable) provides written 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.

Laboratory Values

14. Have adequate organ function as indicated by the laboratory values in Table 2. Specimens must be collected and reviewed within 10 days prior to the start of study treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated CrCl [b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for participants with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin (serum)	≤1.5 ×ULN **OR** direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN. If there is no institutional ULN, then direct bilirubin must be <40% of total bilirubin to be eligible. Note: In no case can the total bilirubin exceed 3 x ULN.
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN or ≤5 × ULN for participants with liver metastases
Coagulation	
International normalized ratio or prothrombin time (PT) Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)[c]	≤1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within 2 weeks of the screening test. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

[b] CrCl should be calculated per institutional standard.

[c] PTT may be performed if the local lab is unable to perform aPTT.

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

15. Has provided blood for cfDNA analysis that has been received and determined to be of sufficient quality and quantity by the designated laboratory for the primary endpoint.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has predominantly squamous cell histology NSCLC. Mixed tumors will be categorized by the predominant cell type.

2. Has small cell elements present in NSCLC tumor.

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

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

4. Has clinically active diverticulitis, intra-abdominal abscess, GI obstruction, peritoneal carcinomatosis.

5. Has a known history of prior malignancy except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for 2 years since initiation of that therapy.

   Note: The time requirement for no evidence of disease for 2 years does not apply to the NSCLC tumor for which a participant is enrolled in the study. The time requirement also does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

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

Prior/Concomitant Therapy

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

8. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.

9. Has received prior therapy with a PD-1/PD-L1 receptor inhibitor.

10. Is expected to require any other form of antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).

11. Has received a live vaccine within 30 days prior to treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

12. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients or to another monoclonal antibody.

13. Has a known sensitivity to any component of cisplatin, carboplatin or pemetrexed.

14. Has 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.

15. Is on chronic systemic steroids. Participants with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.

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

Prior/Concurrent Clinical Study Experience

17. 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 as long as it has been 4 weeks after the last dose of the previous investigational agent.
    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

Diagnostic Assessments

18. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

19. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

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

20. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

21. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

22. Has an active infection requiring systemic therapy.

23. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

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

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

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

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

Other Exclusions

27. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study intervention.

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

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

During each dosing session, participants will abstain from alcohol from 24 hours before the start of dosing until after collection of the metabolomic sample. Ethanol and its metabolites are also products of bacterial metabolism and alcohol use may interfere with the translational metabolomics analyses.

5.3.3 Activity Restrictions

Participants will abstain from strenuous exercise (eg, swimming, running, or any gym workout) for 4 hours before each blood collection for cfDNA and metabolomics analysis. Participant may resume normal activity following blood draw, as per investigator's instructions. Participants should wait to have all blood samples collected at the visits before exercise. Participants may participate in light recreational activities during studies (eg, watching television, reading).

5.3.4 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.5 Pregnancy

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

Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.1.

5.3.6 Use in Nursing Women

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Centrally sourced Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment . These Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Locally sourced clinical supplies will be provided locally by the study site as described in Section 6.1.

6.1 Study Intervention(s) Administered

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

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP/ NIMP	Sourcing
NA	Other	pembrolizumab (MK-3475)	Biological/ Vaccine	Solution for Infusion	25 mg / mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	SOC	IMP	Central
NA	Other	pemetrexed	Drug	Lyophilized Powder	500 mg	500 mg/m2	IV Infusion	Day 1 of each 21-day cycle	SOC	NIMP	US: Local ex-US: Central
NA	Other	carboplatin	Drug	Solution for Infusion	10 mg / mL	AUC 5 mg/mL/ min	IV Infusion	Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4)	SOC	NIMP	US: Local ex-US: Central
NA	Other	cisplatin	Drug	Solution for Infusion	1 mg/ mL	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4)	SOC	NIMP	US: Local ex-US: Central

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) are based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. SOC = Standard of care.

The chemotherapy doublet must include pemetrexed plus the investigator's choice of either cisplatin or carboplatin. Upon IVRS allocation, the investigator will assign each participant to either cisplatin or carboplatin, as determined by the investigator.

All study interventions will be administered on an outpatient basis.

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

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

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

Interruptions from the protocol-specified treatment plan for ≥21 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

Below is a list of specifically prohibited medications or devices for this study:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol

  Note: denosumab is permitted.

- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab

- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion, provided the lesions were not previously defined by the site as target lesions.

- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study

  Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an AE, SAE, or ECI or for use as a premedication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of CT radiography. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered SOC (eg, for COPD exacerbation).

- Replacement doses of steroids (eg, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

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

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

All concomitant medications received within 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 events of clinical interest (ECIs) as defined in Section 8.4.7.

6.5.1 Probiotics and Prebiotics

Use of commercially available prebiotics and probiotic supplements will be monitored on study. Any prebiotic or probiotic use should be recorded in the concomitant medications eCRF. Examples of representative prebiotic and probiotics are listed below. The list is not comprehensive.

- Probiotics may include products containing any of the following:
  - *Bifidobacterium spp*.
  - *Saccharomyces boulardii*
  - *Lactobacillus spp.*

Prebiotics are dissacharide containing supplements including lactulose; oligosaccharides, including fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), isomalto-oligosaccharides, xylo-oligosaccharides, transgalacto-oligosaccharides (TGOS), and soybean oligosaccharides; and polysaccharides, such as the fructan inulin, reflux starch, cellulose, hemicellulose or pectin.

6.5.2 Rescue Medications and Supportive Care

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

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

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

6.6 Dose Modification (Escalation/Titration/Other)

If appropriate, the investigator may attribute each toxicity event to cisplatin/carboplatin, pemetrexed, or pembrolizumab alone or to the combination and use a stepwise dose modification according to Table 5 through Table 8. Dose modifications must be based on the maximum toxicity experienced during a cycle. Toxicity needs to resolve to Grade ≤1 or baseline prior to resuming subsequent cycle. For individual participants requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the participant.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any particular component will have that agent discontinued.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications. Participants may have chemotherapy discontinued and continue on pembrolizumab alone. Similarly, participants may discontinue pembrolizumab and continue on chemotherapy alone, if appropriate, through the duration of study participation (ie, up to 35 total cycles).

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

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 5 through Table 8.

Table 4 Dose Modifications for Trial Medications

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

6.6.1 Dose Modification

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug 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 v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

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

6.6.2 Dose Modification for Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 7 and Table 8. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Table 7 Recommended Dose Modifications for Chemotherapy Hematological Toxicity

		Pemetrexed	**Cisplatin/Carboplatin**
Platelets	**ANC**	**Dose level (DL) from** Table 3	
≥50,000/mcL AND	≥500/mcL	DL 0	DL 0
≥50,000/mcL AND	<500/mcL	DL -1	DL -1
<50,000/mcL without bleeding AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥2 bleeding AND	ANY	DL -2	DL -2
ANY	<1000/mcL + fever ≥38.5°C (101°F)	DL -1	DL -1

Table 8 Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

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

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. Study intervention (name, strength, or potency) 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 period will still continue to participate in the study as specified in Section 1.3 (SoA) and Section 8.12.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 12 consecutive weeks, unless approved with written documentation from Sponsor.
- 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.
- If the investigator performs a drug screen at his/her discretion and the participant has a positive urine drug screen at any time during the course of the study.

- Confirmed radiographic disease progression outlined in Section 8.2.1.2 (exception if the Sponsor approves treatment continuation)

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

- Noncompliance with study intervention or procedure requirements

- Recurrent Grade 2 pneumonitis

- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of pemetrexed beyond the date when the initial CR was declared.

- Completion of 35 treatments (approximately 2 years) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose.

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.

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 or trained 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 signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

8.1.1.1 General Informed Consent

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

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

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

The participant or his/her legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, 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 written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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 significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 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 starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. 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 allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. The assigned screening number will become the participants' treatment/randomization number. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Administration of IV study medication (pembrolizumab and chemotherapy) will be witnessed by the investigator and/or study staff.

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

8.1.8.1 Timing of Dose Administration

Study interventions will generally be administered in the following order: pembrolizumab, premedications, pemetrexed, and then carboplatin or cisplatin. Details of administering the individual components are discussed below.

8.1.8.1.1 Timing of Dose Administration of Pembrolizumab

Study treatment with pembrolizumab should be administered on Day 1 of each 21-day cycle after all procedures/assessments have been completed as detailed in the SoA (Section 1.3). All study treatments will be administered on an outpatient basis. Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each 21-day cycle due to administrative reasons except for Cycle 1 Day 1, where the window is +3 days from randomization.

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

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

8.1.8.1.2 Timing of Dose Administration of Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes on Day 1 of the 21-day cycle. All participants should be premedicated with steroids as per the approved label and local standard practices. In addition, all participants must take a folic acid

preparation or multivitamin with folic acid containing between 350 to 1000 µg daily. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

Participants must also receive 1 intramuscular injection of vitamin B12 1000 µg during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed.

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

8.1.8.1.3 Timing of Dose of Carboplatin or Cisplatin

8.1.8.1.3.1 Carboplatin

Carboplatin AUC 5 will be administered as an IV infusion over 30 to 60 minutes on Day 1 of every 21-day cycle following pemetrexed infusions, for a maximum of 4 administrations.

8.1.8.1.3.2 Cisplatin

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

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3) and Section 8.12.3.

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

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox [redacted]. 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 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

All imaging will be completed and read locally per clinical SOC.

Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Participant eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1.

Brain imaging is only required for participants with existing or suspected CNS metastases and/or carcinomatous meningitis. MRI is preferred; however, CT imaging with contrast will be acceptable, if MRI is medically contraindicated. Bone scans are also required for participants with a history of bone metastases and/or for those participants with new bone pain.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of allocation.

Tumor imaging performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation. If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from the date of randomization. The second on-study imaging assessment should be performed at 12 weeks (84 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) through Week 48 or more frequently if clinically indicated. After 48 weeks, participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the site PI elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death or notification by the Sponsor, whichever occurs first.

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 (ie, 9 or 12 weeks later) if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 8.2.1.5), disease progression in participants treated with pembrolizumab should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.1.5. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed disease progression, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.2.1.5.

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 if the investigator elects not to implement iRECIST.

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 (every 9 weeks in Year 1 or 12 weeks after Year 1) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 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.

8.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 (SoA).

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 9.

Table 9 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

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

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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height (at screening only) and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.1.1 Full Physical Examination

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

8.3.1.2 Directed Physical Examination

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

8.3.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Procedures Manual and the SoA.

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

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

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

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.4.2 Pregnancy Test

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

8.3.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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 as specified in the SoA (Section 1.3).

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

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

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

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

All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following cessation of study intervention, 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 drug-related.

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 10.

Table 10 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:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

Care will be taken not to introduce bias when detecting 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, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 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 wth 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

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

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

Efficacy endpoints, as described in Section 9.4.1, will not be reported to MSD.

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

MSD will monitor efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to MSD 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 (ECIs)

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

Events of clinical interest for this study include:

1) An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

8.5 Treatment of Overdose

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

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

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic markers will be evaluated to gain a better understanding of response and resistance biology. Blood samples for a variety of exploratory biomarkers and planned genetic analysis will be collected at baseline, prior to and/or following treatment per the SoA (Section 1.3), at response if it occurs, and at end of treatment/progression. Detailed endpoints are described below in the biomarker section (Section 8.10).

8.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover main study plasma from metabolomics analysis stored for future research
- Leftover main study serum from cytokine analysis stored for future research
- Leftover main study RNA
- Leftover main study tumor stored for future research
- Leftover main study stool stored for future research

8.9 Planned Genetic Analysis Sample Collection

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual.

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if participant signs the Future Biomedical Research consent.

8.10 Biomarkers

Collection of samples for biomarker analysis supports primary endpoint, secondary endpoints, and exploratory endpoints in this study, as shown below. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Whole blood for the following analyses:
  - cfDNA (**primary endpoint and secondary endpoint**)
  - Cytokine analysis (exploratory endpoint)
  - Genetic analysis (exploratory endpoint)
  - RNA analysis (exploratory endpoint)
  - Metabolomics analysis (exploratory endpoint)
- Archival or newly obtained Stage IV tumor tissue for the following analyses:
  - PD-L1 molecular status (exploratory endpoint)
  - WES for TMB (exploratory endpoint)
  - Other, eg: RNA, genetic, or other exploratory biomarkers
- Stool for microbiome analysis (exploratory endpoint)

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Merck Procedures Manual for this study.

8.10.1 Tissue Biomarkers

8.10.1.1 PD-L1 IHC

Although not required for determining eligibility, pre-treatment PD-L1 status of tumor tissue will be recorded for each participant. If PD-L1 results are not available from a participant's diagnostic biopsy, PD-L1 IHC must be performed. Analysis may be performed locally using PharmDx kit (Agilent, FDA approved for NSCLC), which uses the 22C3 antibody. Otherwise, adequate tumor tissue must be sent to the central tissue lab, Covance, for this analysis. Sample requirements, collection, storage, and shipment instructions are provided in the Procedures Manual.

8.10.1.2 Exploratory Biomarkers

To be eligible to participate in the study, participants must provide sufficient evaluable Stage IV, archival solid tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion (that was not previously irradiated) for biomarker analysis (Fine Needle Aspiration [FNA] samples will not be accepted). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. The

Merck Procedures Manual for this study specifies the definitions for what is considered sufficient and evaluable tissue. This sufficient and adequate tissue must be provided to the central lab prior to Randomization.

The planned Exploratory Biomarker tissue analyses will include the following:

- WES for TMB (exploratory endpoint)
- Other, eg: RNA, genetic, or other exploratory biomarkers

Tissue sample requirements, collection, storage, and shipment instructions are provided in the Merck Procedures Manual for this study.

8.10.2 Blood-based Biomarkers

Whole blood will be collected for primary and secondary endpoints, and exploratory biomarker analyses. These collections are shown in the SoA and include: whole blood for cfDNA analysis, serum for cytokine analysis, blood for genetic analysis, blood for RNA analysis, and plasma for metabolomics analysis.

The Merck Procedures Manual details the requirements for sample collection, processing, storage and shipment for each of the blood-based biomarkers.

The Screening cfDNA collection is required for analyzing the primary endpoint of this study. For this most critical sample, please ensure that the Merck Procedures Manual is followed exactly for the collection, processing, storage, and shipment of this sample. All cfDNA shipments must be shipped the same day of collection, via overnight expedited shipping in extreme ambient shipping kits.

8.10.3 Stool-based Biomarkers

Stool samples will be collected for microbiome analysis per the SoA. Of note, two (2) separate stool collections are required within 1 week prior to first dose of therapy on C1D1. A single stool collection is required within 5 days prior to each of the designated on-treatment study visits. Sites should provide the participant with adequate stool collection kits and instructions for at-home collection of stool *prior* to the designated study visit.

Stool sample collection, storage, and shipment instructions are provided in the Merck Procedures Manual.

8.11 Health Economics Medical Resource Utilization and Health Economics

Not applicable.

8.12 Visit Requirements

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

8.12.1 Screening

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 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 testing, which may be done up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 10 days prior to the first dose of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study intervention. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

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

8.12.2 Treatment Period

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

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

8.12.3.1 Safety Follow-up Visit

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

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. SAEs that occur within 90

days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

8.12.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 12 weeks to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or end of study as detailed in Section 1.3 (SoA). Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

8.12.3.3 Survival Follow-up

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

8.12.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report for the study. Details around the analysis approach for biomarker endpoints related to the exploratory objectives are deemed out of scope for this SAP, but may be the subject of sSAPs.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase II Trial to Investigate Genetic Markers of Immune Response to Pembrolizumab Combined with Chemotherapy in First-Line Non-Small Cell Lung Cancer (KEYNOTE-782)
Treatment Assignment	• Participants will receive: (1) Pembrolizumab 200 mg Q3W in combination with carboplatin AUC 5 mg/mL/min Q3W IV and pemetrexed 500 mg/m^2 Q3W IV for 4 cycles followed by pembrolizumab monotherapy 200 mg Q3W IV with pemetrexed maintenance 500 mg/m^2 Q3W IV. OR (2) Pembrolizumab 200 mg Q3W in combination with cisplatin 75mg/m^2 Q3W IV and pemetrexed 500 mg/m^2 Q3W IV for 4 cycles followed by pembrolizumab monotherapy 200 mg Q3W IV with pemetrexed maintenance 500 mg/m^2 Q3W IV.
Analysis Populations	All Subjects as Treated (ASaT)
Primary Efficacy Endpoint	1) Objective response (OR): Complete response (CR) or partial response (PR)
Primary Biomarker Endpoint	1) Baseline tumor mutation burden (TMB) in circulating cell-free DNA (cfDNA) (blood)
Key Secondary Endpoints	1) PFS is defined as the time from the start of treatment to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. 2) OS is defined as the time from the start of treatment to death due to any cause.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	For the primary objective, the posterior probability that the coefficient for baseline TMB in cfDNA is greater than zero in a logistic regression model of objective response (yes/no) will be used to estimate the level of association of baseline TMB in cfDNA and objective response in NSCLC participants treated with pembrolizumab + platinum-doublet chemotherapy.
Statistical Methods for Key Safety Analyses	Descriptive summary statistics will be provided.
Interim Analyses	A preliminary analysis of the primary objective: an evaluation of the level of association of TMB in cfDNA and objective response will occur approximately 16 weeks after last patient enrolled (LPE). Final analysis will occur after all participants have received 35 administrations of pembrolizumab or discontinued study intervention.
Multiplicity	No multiplicity adjustment
Sample Size and Power	This estimation study will enroll approximately 100 participants.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Early Clinical Development Statistics Department of the Sponsor.

This trial is being conducted as an unblinded, 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.

Biomarker assays used to assess the primary, secondary, and tertiary/exploratory objectives in this study will be performed by personnel blinded to participants' clinical outcome data.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

1) Objective Response: defined as confirmed CR or PR between the start of the study treatment and disease progression/recurrence (or death due to any cause, whichever occurs first) as assessed by the investigator using RECIST 1.1. A treated participant will be designated as a 'responder' if he/she achieves a confirmed CR or confirmed PR and designed as a 'non-responder' otherwise. Participants with missing response data are considered non-responders.

Secondary Efficacy Endpoints

2) Progression-Free Survival (PFS): defined as the time from start of treatment to the first documented PD (per investigator assessed RECIST 1.1) or death due to any cause, whichever occurs first.

3) Overall Survival (OS): defined as the time from start of treatment to death due to any cause.

9.4.2 Biomarker Endpoints

Primary and Secondary Biomarker Endpoints

The primary and secondary biomarker endpoint is baseline TMB in cfDNA from blood detailed in Section 4.2.1.1.1.

Exploratory Biomarker Endpoints

Details around other biomarker-related endpoints associated with the exploratory objectives, including additional genomic, metabolic, proteomic, radiomic, and microbiome endpoints, as well as details for the processing and normalization of these complex data sources, are deemed out of scope for this SAP, but may be the subject of supplementary SAPs.

9.4.3 Safety Endpoints

Refer to Section 4.2.1.3 for the description of safety measures.

9.5 Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of the primary, secondary, and exploratory objectives. The ASaT population consists of all subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of primary, secondary, and exploratory objectives using the ASaT population.

9.6 Statistical Methods

9.6.1 Statistical Methods for Biomarker/Efficacy Analyses

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

Those generating the biomarker data will remain blinded to a participant's clinical status as a responder or non-responder per RECIST 1.1 (investigator-assessed) in order to preserve an objective evaluation of the study objectives. Demographic and baseline characteristics of responders and non-responders will be tabulated.

Primary Objective

Logistic regression modeling of responders (CR or PR) and non-responders will be used to estimate the level of association of baseline TMB in cfDNA and objective response in NSCLC participants treated with pembrolizumab + investigator choice platinum-doublet chemotherapy (pemetrexed plus investigator choice of either cisplatin or carboplatin). The logistic regression model will include a term for independent variable: continuous $\log_{10}$ transformed TMB in cfDNA and dependent variable: objective response (yes/no). The posterior probability that the coefficient for cfDNA TMB is greater than zero in the logistic regression model will be reported. In addition, logistic regression models adjusting for ECOG performance status, smoking status, and other relevant clinical variables will be evaluated to assess the importance of these prognostic factors and support the robustness of TMB in cfDNA findings. Sensitivity analyses using raw scale and square root transformations of TMB in cfDNA will be explored to handle any zero-inflation in the TMB in cfDNA data. The association of baseline TMB in cfDNA with objective response will also

be evaluated using the area under the ROC curve (AUROC). The distribution of baseline TMB in cfDNA will be graphically displayed and summarized (mean, median, and standard deviation) by responders (CR or PR) versus non-responders.

Secondary Objectives

Cox regression modeling will be used to estimate the level of association of baseline TMB in cfDNA and survival (PFS or OS). The Cox regression models will include a term for the independent variable: continuous $\log_{10}$ transformed TMB in cfDNA and dependent variables: PFS or OS. Participants without documented progression or death at the time of analysis will be censored at the date of the last adequate assessment. The posterior probability that the coefficients for cfDNA TMB are less than zero in the Cox regression models will be reported. In addition, Cox regression models adjusting for ECOG performance status, smoking status, and other relevant clinical variables will be evaluated to assess the importance of these prognostic factors and support the robustness of TMB in cfDNA findings. Sensitivity analyses using raw scale and square root transformations of TMB in cfDNA will be explored to handle any zero-inflation in the TMB in cfDNA data.

Exploratory Objectives

Details around the analysis approach for biomarker endpoints related to the exploratory objectives are deemed out of scope for this SAP, but will be the subject of supplemental SAPs.

Table 11 summarizes the estimation strategy for the primary and secondary objectives detailed above.

Table 11 Analysis Strategy for Primary and Secondary Objectives

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[1]	Statistical Method[2]	Analysis Population	Missing Data Approach
Primary Objective				
Objective Response (OR)	P	Posterior probability of TMB coefficient in logistic regression[3]	ASaT	Study participants with missing data are considered non-responders.
Objective Response (OR)	S	AUROC	ASaT	Study participants with missing data are considered non-responders.
Secondary Objective				
Progression-free survival (PFS)	P	Posterior probability of TMB coefficient in Cox regression[4]	ASaT	Censored at the date of last adequate assessment
Overall survival (OS)	P	Posterior probability of TMB coefficient in Cox regression[4]	ASaT	Censored at the date of last follow-up

[1] ASaT All Subjects as Treated; cfDNA circulating free deoxyribonucleic acid; P Primary approach; PFS progression free survival; S Supportive approach; TMB tumor mutation burden.

[2] Statistical models are described in further detail below:

[3] Logistic regression model, including term for independent variable baseline cfDNA TMB and dependent variable OR (yes/no CR or PR). The posterior probability of the TMB coefficient in logistic regression models adjusting for ECOG performance status, smoking status, and other relevant clinical variables will be evaluated as a supportive approach.

[4] Cox regression model, including term for independent variable baseline cfDNA TMB and dependent variables PFS or OS. The posterior probability of the TMB coefficient in Cox regression models adjusting for ECOG performance status, smoking status, and other relevant clinical variables will be evaluated as a supportive approach.

9.6.2 Statistical Methods for Safety Analyses

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

Descriptive summary statistics will be provided for safety endpoints. For continuous measures such as changes from baseline in laboratory tests and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format. Additional safety endpoints may also be summarized as deemed clinically appropriate.

9.7 Interim Analyses

A preliminary analysis of the primary objective: an evaluation of the level of association of TMB in cfDNA and objective response will occur approximately 16 weeks after last patient enrolled (LPE).

9.8 Final Analysis

The final analysis of the primary objective will occur after all participants have received 35 administrations of pembrolizumab or discontinued study intervention.

9.9 Multiplicity

No multiplicity adjustment will be applied to the primary or secondary analyses.

9.10 Sample Size and Power Calculations

This study will enroll approximately 100 participants. This provides 80% power to detect a coefficient for cfDNA TMB greater than zero in a logistic regression model for objective response with type I error rate of 5% (one-sided) and with mean fold increase in median cfDNA TMB for responders versus non-responders of 1.78, assuming a 50% ORR. 50% ORR is consistent with data from KEYNOTE-021G and KEYNOTE-189, where in the same treatment setting response rates of 56.7% and 47.6%, respectively, were observed. Historically, an approximate 60% increase in the median WES TMB for responders compared to non-responders to pembrolizumab monotherapy has been observed in bladder and head and neck squamous cell carcinoma (HNSCC), indications which are most similar to NSCLC. Recent NSCLC pembrolizumab monotherapy-treated WES TMB data are in alignment with historical data. A linear relationship between WES TMB data and TMB in cfDNA data is assumed.

While historical data provide evidence of a 60% increase in the median WES TMB for responders compared to non-responders, it is important to note the fold increase is in reference to response to treatment with pembrolizumab monotherapy. The fold increase in the median TMB for responders versus non-responders treated with pembrolizumab plus chemotherapy may lessen from that expected for pembrolizumab monotherapy if chemotherapy generates objective responses independent of the level of the biomarker, TMB.

Table 12 shows the mean fold increase of median TMB in cfDNA for responders compared to non-responders from 10,000 simulated datasets with 80% and 90% power to detect a coefficient for TMB in cfDNA greater than zero with type I error rate of 5% (one-sided) for varying objective response rates (ORR). The simulations used to generate Table 12 make the following assumptions: TMB in cfDNA is normally distributed on the $\log_{10}$ scale with equal variance between responders and non-responders, the mean TMB in cfDNA of responders is a positive shift from the mean TMB in cfDNA of non-responders, and the variance of TMB in cfDNA is 0.24 on the $\log_{10}$ scale. First, the power was calculated as the proportion of 10,000 datasets with logistic regression coefficient for TMB in cfDNA Wald-test p-value less than or equal to one-sided α 0.05 using logistic regression models for objective response.

Then, the geometric mean of the paired fold-difference in median TMB in cfDNA for responders versus non-responders for the 10,000 datasets was estimated.

With limitations in the ability to detect a statistically significant association at one-sided α 0.05 with underlying fold-change (responders/non-responders) less than 1.78 (closer to the historical 1.60), an estimation approach to the primary and secondary study objectives was taken.

Table 12 Mean Fold Increase in the Total Tumor Mutation Burden (TMB) in Circulating Free DNA (cfDNA) for Responders Compared to Non-responders With 80% and 90% Power to Detect a Coefficient for cfDNA TMB Greater Than Zero for Varying Objective Response Rates (ORR)

N	Response Rate (%)	Mean Fold Increase in TMB in cfDNA Responders vs. Non-Responders with 80% Power[1]	Mean Fold Increase in TMB in cfDNA Responders vs. Non-Responders with 90% Power[1]
100	40	1.78	1.98
	45	1.78	1.97
	50	1.78	1.95
	55	1.78	1.95

[1]Based on 10,000 generated datasets; power evaluated from logistic regression models at α=0.05 (one-sided)

9.11 Subgroup Analyses

Not applicable.

9.12 Compliance (Medication Adherence)

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

9.13 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (eg, N, mean, median, standard deviation, etc.) for duration of treatment in cycles.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information 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 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee is composed of Sponsor personnel and representatives of GRAIL, Inc.

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

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

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

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

10.1.9 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) within 72 hours of first dose Thyroid panel: TSH, FT4, FT3/T3Serology			
NOTES:				

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, 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.

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

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

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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 Common Terminology for Adverse Events (CTCAE), version 4. 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 activities of daily living (ADL).

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

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Assessment of causality

Did the Sponsor's product cause the AE?

The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are

intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

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

Exposure: Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time Course: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

Dechallenge: Was the Sponsor' 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 IRB/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 CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

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

Yes, there is a reasonable possibility of Sponsor's product relationship:

There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

No, there is not a reasonable possibility of Sponsor's product relationship:

Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

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

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

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there are 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 electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

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

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception that has a low user dependency as described in Table 14 during the protocol-defined time frame in Section 5.1.

Table 14 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen only contraceptive implant[a,b] • Intrauterine hormone-releasing system (IUS)[b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [a] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [b] If hormonal contraception efficacy is potentially decreased due to interaction with study intervention, condoms must be used in addition to the hormonal contraception during the intervention period and for at least 120 days (corresponding to time needed to eliminate study intervention plus 30 days for study interventions with genotoxic potential) after the last dose of study intervention.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated a maximum of 72 hours before the first dose.

Following initiation of treatment, additional pregnancy testing will be performed at every study visit during the treatment period and at 180 days for study interventions with risk of evidence of genotoxicity at any dose, after the last dose of study intervention, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

- **Definitions**

1. 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]

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

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

4. DNA: Deoxyribonucleic acid.

5. RNA: Ribonucleic acid.

- **Scope of Future Biomedical Research**

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

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

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

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

- **Summary of Procedures for Future Biomedical Research.**

1. Participants for Enrollment

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

2. 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.

3. 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.

4. 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.

- **Confidential Participant Information for Future Biomedical Research**

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

- **Biorepository Specimen Usage**

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

- **Withdrawal From Future Biomedical Research**

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox [redacted]. 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.

- **Retention of Specimens**

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being

answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

- **Data Security**

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

- **Reporting of Future Biomedical Research Data to Participants**

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

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

- **Future Biomedical Research Study Population**

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

- **Risks Versus Benefits of Future Biomedical Research**

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

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

- **Questions**

Any questions related to the future biomedical research should be emailed directly to [redacted]

- **References**

3) National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid 45618

4) International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

5) 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/

6) 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

Not applicable.

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained using iRECIST for participant management (see Table 9). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits After Pseudo-progression Resolves

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

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
aPTT	activated partial thromboplastin time
ASaT	All Subjects as Treated
AUC	area under the time-concentration curve
BICR	blinded independent central review
B-RAF	B isoform of rapidly accelerated fibrosarcoma
C1D1	Cycle 1 Day 1
CBC	complete blood count
CCGA	Circulating Cell-free Genome Atlas Study
CD	cluster of differentiation
cfDNA	circulating free DNA
cfNA	cell-free nucleic acid
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	discontinuation
DILI	drug-induced liver injury
DL	dose level
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed paraffin embedded
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HR	hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin

Abbreviation	Expanded Term
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
KRAS	a proto-oncogene derived from Kirsten RAt Sarcoma virus
mAb	monoclonal antibody
MRI	magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	microsatellite instability
NR	not reached
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1 receptor
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TMB	tumor mutation burden
TPS	tumor proportion score
ULN	upper limit of normal
WES	whole exome sequencing
WOCBP	woman/women of childbearing potential

10.10 Appendix 10: Eastern Cooperative Oncology Group (ECOG) Performance Scale

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

11 REFERENCES

[Alexander, J. L., et al 2017]	Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. Nat Rev Gastroenterol Hepatol. 2017 Jun;14:356-65.	[04Y5MB]
[Aravanis, A. A., et al 2018]	Aravanis AA, Oxnard GR, Maddala T, Hubbell E, Venn O, Jamshidi A, et al. Development of plasma cell-free DNA (cfDNA) assays for early cancer detection: first insights from the Circulating Cell-free Genome Atlas study (CCGA) [abstract]. Presented at: 2018 American Association for Cancer Research (AACR) Annual Meeting; 2018 Apr 14-18; Chicago, IL. Abstract no. LB-343.	[04YCX5]
[Belkaid, Y. 2017]	Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity. 2017 Apr 18;46:562-76.	[04Y5M7]
[Castle, J. C., et al 2012]	Castle JC, Kreiter S, Diekmann J, Lower M, van de Roemer N, de Graaf J. et al. Exploiting the mutanome for tumor vaccination. Cancer Res. 2012 Mar 1;72(5):1081-91.	[04MLPX]
[Chanudet, E., et al 2007]	Chanudet E, Adam P, Nicholson AG, Wotherspoon AC, Ranaldi R, Goteri G, et al. Chlamydiae and Mycoplasma infections in pulmonary MALT lymphoma. Br J Cancer. 2007;97(7):949-51.	[04Y4GY]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Cummings, J. H., et al 1987]	Cummings JH, Pomare EW, Branch WJ, Naylor CPE, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut. 1987;28:1221-7.	[04Y5ZW]

[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Gadgeel, S., et al 2016]	Gadgeel S, Stevenson J, Langer C, Gandhi L, Borghaei H, Patnaik A, et al. Pembrolizumab plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C. Poster session presented at: The American Society of Clinical Oncology; 2016 Jun 3-7; Chicago, IL.	[04HX6N]
[Gandhi, L., et al 2018]	Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. In press 2018.	[04X2M4]
[Gopalakrishnan, V., et al 2018]	Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell. 2018 Apr 9;33:570-80.	[04Y63M]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Haase, S., et al 2018]	Haase S, Haghikia A, Wilck N, Muller DN, Linker RA. Impacts of microbiome metabolites on immune regulation and autoimmunity. Immunology. In press 2018.	[04Y643]

[Hellmann, M. D., et al 2018]	Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018 May 31;378(22):2093-104.	[04YCWH]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Hooper, S. J., et al 2007]	Hooper SJ, Crean SJ, Fardy MJ, Lewis MAO, Spratt DA, Wade WG, et al. A molecular analysis of the bacteria present within oral squamous cell carcinoma. J Med Microbiol. 2007;56:1651-9.	[04Y63B]
[Hubbard, A. L., et al 1998]	Hubbard AL, Harrison DJ, Moyes C, McOrist S. Direct detection of eae-positive bacteria in human and veterinary colorectal specimens by PCR. J Clin Microbiol. 1998 Aug;36(8):2326-30.	[04Y645]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Iida, N., et al 2013]	Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science. 2013 Nov 22;342:967-70.	[04Y5Y9]
[Kim, C. H. 2018]	Kim CH. Immune regulation by microbiome metabolites. Immunology. In press 2018.	[04Y5Y4]

[Langer, C. J., et al 2016]	Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Oct 9. [Epub ahead of print].	[04JNLW]
[Le, D., et al 2015]	Le D, Uram J, Wang H, Bartlett B, Kemberling H, Eyring A, et al. PD-1 blockade in tumours with mismatch repair deficiency. Poster session presented at The American Society of Clinical Oncology, 2015 May 30; Chicago, IL.	[04HGBM]
[Linnemann, C., et al 2015]	Linnemann C, van Buuren MM, Bies L, Verdegaal EME, Schotte R, Calis JJA, et al. High-throughput epitope discovery reveals frequent recognition of neo-antigens by CD4+ T cells in human melanoma. Nat Med. 2015 Jan;21(1):81-5. Erratum in: Nat Med. 2016 Oct 6;22(10):1192.	[04Y5Y0]
[Lloyd, C. M. 2017]	Lloyd CM, Marsland BJ. Lung homeostasis: influence of age, microbes, and the immune system. Immunity. 2017 Apr 18;46:549-61.	[04Y5XH]
[Lopes, G., et al 2018]	Lopes G, Wu Y, Kudaba I, Kowalski D, Cho BC, Castro G, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: open-label, phase 3 KEYNOTE-042 study [abstract]. Presented at: The American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(suppl). Abstract no. LBA4.	[04Y5G9]
[Luo, A., et al 2017]	Luo A, Leach ST, Barres R, Hesson LB, Grimm MC, Simar D. The microbiota and epigenetic regulation of T helper 17/regulatory T cells: in search of a balanced immune system. Front Immunol. 2017 Apr 10;8:417.	[04Y5XG]

[Matson, V., et al 2018]	Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018 Jan 5;359:104-8.	[04Y435]
[Matsushita, H., et al 2012]	Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012 Feb;482:400-4.	[04Y40R]
[Meng, C., et al 2018]	Meng C, Bai C, Brown TD, Hood LE, Tian Q. Human gut microbiota and gastrointestinal cancer. Genomics Proteomics Bioinformatics. 2018;16:33-49.	[04Y447]
[National Cancer Institute 2016]	National Cancer Institute. SEER Stat Fact Sheets: Lung and bronchus cancer [Internet]. Bethesda, MD: National Cancer Institute; 2016. Available from: http://seer.cancer.gov/statfacts/.	[04FJVR]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Rea, D., et al 2018]	Rea D, Coppola G, Palma G, Barbieri A, Luciano A, Del Prete P, et al. Microbiota effects on cancer: from risks to therapies. Oncotarget. 2018 Apr 3;9(25):17915-27.	[04Y5HM]

[Reck, M., et al 2016]	Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8. [Epub ahead of print].	[04JNM3]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Rizvi, N. A., et al 2015]	Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8.	[04Y4PT]
[Robbins, P. F., et al 2013]	Robbins PF, Lu YC, El-Gamil M, Li YF, Gross C, Gartner J, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells [manuscript]. Nat Med. 2013 Jun;19(6):747-52.	[04Y4LG]
[Rooks, M. G. 2016]	Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nat Rev Immunol. 2016 Jun;16:341-52.	[04Y4VK]
[Routy, B., et al 2018]	Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018 Jan 5;359:91-7.	[04Y66F]
[Schumacher, T. N. 2015]	Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015 Apr 3;348(6230):69-74.	[04Y4MS]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]

[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Shukla, S. D., et al 2017]	Shukla SD, Budden KF, Neal R, Hansbro PM. Microbiome effects on immunity, health and disease in the lung. Clin Transl Immunology. 2017 Mar 10;6:e133.	[04Y67J]
[Silva-Valenzuela, C. A., et al 2016]	Silva-Valenzuela CA, Desai PT, Molina-Quiroz RC, Pezoa D, Zhang Y, Porwollik S, et al. Solid tumors provide niche-specific conditions that lead to preferential growth of Salmonella. Oncotarget. 2016;7(23):35169-80.	[04Y6CV]
[Snyder, A., et al 2014]	Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014 Dec 4;371(23):2189-99.	[04Y6CW]
[Stockinger, B., et al 2014]	Stockinger B, Di Meglio P, Gialitakis M, Duarte JH. The aryl hydrocarbon receptor: multitasking in the immune system. Annu Rev Immunol. 2014;32:403-32.	[04Y5PH]
[Sulpher, J. A., et al 2013]	Sulpher JA, Owen SP, Hon H, Tobros K, Shepherd FA, Sabri E, et al. Factors influencing a specific pathologic diagnosis of non-small-cell lung carcinoma. Clin Lung Cancer. 2013 May;14(3):238-44.	[040565]
[Tran, E. 2014]	Tran E, Rosenberg SA. T-cell therapy against cancer mutations. Oncotarget. 2014 Jul 19;5(13):4579-80.	[04Y5PG]
[Van Allen, E. M., et al 2015]	Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015 Oct 9;350(6257):207-11. Erratum in: Science. 2015 Nov 13;350(6262):aad8366.	[04Y8N4]

[Vetizou, M., et al 2015]	Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015 Nov 27;350(6264):1079-84.	[04Y8N3]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[World Health Organization 2012]	Globocan 2012: Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 [Internet]. Lyon (FR): World Health Organization, International Agency for Research on Cancer (IARC). c2014 [updated 2014 Oct 3]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx	[0402K4]
[Wroblewski, L. E., et al 2010]	Wroblewski LE, Peek RM Jr, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 2010 Oct;23(4):713-39.	[04Y8N5]
[Yuan, J. 2016]	Yuan J. Circulating protein and antibody biomarker for personalized cancer immunotherapy. J Immunother Cancer. 2016;4:46.	[04Y8DN]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]
[Zitvogel, L., et al 2018]	Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science. 2018 Mar 23;359:1366-70.	[04Y8F0]