NCT03088540
EudraCT Number: 2016-004407-31
IND Number: 130787

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A GLOBAL, RANDOMIZED, PHASE 3, OPEN-LABEL STUDY OF REGN2810 (ANTI-PD-1 ANTIBODY) VERSUS PLATINUM-BASED CHEMOTHERAPY IN FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED OR METASTATIC PD-L1 + NON-SMALL CELL LUNG CANCER

Compound:	REGN2810 (cemiplimab)
Clinical Phase:	3
Protocol Number:	R2810-ONC-1624
Protocol Version:	R2810-ONC-1624 Amendment 9
Amendment 9 Date of Issue:	*See the appended electronic signature page*
Amendment 8 Date of Issue:	23 Oct 2019
Amendment 7 Date of Issue:	28 May 2019
Amendment 6 Admin Date of Issue:	06 Sep 2018
Amendment 6 Date of Issue:	22 Aug 2018
Amendment 5 Date of Issue:	05 Sept 2017
Amendment 4 Date of Issue:	17 Jul 2017
Amendment 3 Date of Issue:	15 Mar 2017
Amendment 2 Date of Issue:	19 Jan 2017
Amendment 1 Date of Issue:	29 Nov 2016
Original Date of Issue:	01 Nov 2016
Scientific/Medical Monitor:	[redacted] Oncology & Translational Sciences Global Development [redacted] Oncology & Translational Sciences Global Development

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

AMENDMENT HISTORY

Amendment 9

The table below summarizes the changes to the protocol and the affected sections.

Change	Rationale for Change	Sections Changed
Instituted provision to allow patients originally randomized to platinum doublet chemotherapy to be treated with cemiplimab instead.	The Independent Data Monitoring Committee (IDMC) has determined that the primary endpoint of overall survival (OS) has been met at a pre-specified interim analysis. Based on these findings the Sponsor has decided to allow patients on the chemotherapy doublet arm to cross-over to cemiplimab with immediate effect to ensure all patients on the study have access to the treatment that has been demonstrated to be superior for prolonging survival.	Clinical Study Protocol Synopsis: Study Design Section 3.2.6 Rationale for Crossover of all Patients to Cemiplimab (section added) Section 5.1 Study Description and Duration Figure 2 Study Flow Diagram Implemented in Amendment 9 (figure added) Section 7.1 Investigational and Reference Treatments
Confirmation that all pre-specified endpoints will be analyzed at the time of a positive outcome of OS.	When the primary endpoint has been achieved all patients randomized to chemotherapy will be offered cemiplimab. Thus new progression free survival (PFS) events in patients originally treated with chemotherapy will not be interpretable to contribute to this other primary endpoint, The other endpoints are secondary and will be sufficiently mature for analysis.	Section 10.6 Interim Analysis Section 10.7 Sensitivity Analyses Addressing PD-L1 Measure Issues (section added)
Updated language to allow patients to be contacted for follow-up at the time of pre-	To confirm patient survival if necessary before database lock	Section 7.9 Post-Study Treatments and Procedures

Change	Rationale for Change	Sections Changed
planned interim and final analyses		Table 6 Schedule of Events: Follow-up Period Assessments and Procedures
Updated the Introduction with relevant data from recent clinical trials.	To keep background and justification for study up to date with current data.	Section 1 Introduction Section 3.2.3 Rationale for Choice of PD-L1 Expression Level
Corrected an error in the follow-up assessments and procedures incorrectly indicating that samples will be collected for analysis of anti-drug antibodies (ADA) at follow-up visits 1 and 3.	An error was inadvertently introduced into Protocol Amendment 7. ADA samples have not been collected at follow-up visit 1 since before the implementation of Protocol Amendment 6.	Table 6 Schedule of Events: Follow-up Period Assessments and Procedures
Personnel changes	To reflect changes in study oversight	Title Page
Minor editorial and administrative updates	Correction of typographical, grammatical, formatting, and minor administrative errors.	Throughout the document

Amendment 8

The table below summarizes the changes to the protocol, and the affected sections.

Change	Section Changed
Added 4 additional time points for interim analyses and updated the alpha spending function under the originally specified O'Brien-Fleming alpha spending framework.	Clinical Study Protocol Synopsis, Statistical Plan Section 5.2 Planned Interim Analysis Section 5.3.2 Independent Data Monitoring Committee Section 10.2 Justification of Sample Size Section 10.5.2 Type I Error Control for Interim and Final Analyses of OS

Change	**Section Changed**
	Section 10.6 Interim Analysis
Modifications for consistency and clarity, and administrative updates.	Title Page Section 3.1 Hypotheses Table 6 Schedule of Events Follow-Up Period Assessments and Procedures (ADA sample row) Section 8.2.1 Procedures Performed only at Screening Visits

Amendment 7

The table below summarizes the changes to the protocol, and the affected sections.

Change	**Section Changed**
Changed Overall Survival (OS) to a primary objective and endpoint (from secondary) to provide more robust support for a registration application.	Clinical Study Protocol Synopsis: Objectives, Endpoints, Statistical Plan Section 1 Introduction Section 2.1 Primary Objectives Section 2.2 Secondary Objective Section 3.1 Hypotheses Section 3.2.2 Rationale of Endpoints/Objectives Section 4.2.1 Primary Endpoint Section 4.2.2 Key Secondary Endpoints Figure 1 Study Flow Diagram Section 10.1 Statistical Hypothesis Section 10.2 Justification of Sample Size Section 10.3.2 Safety Analysis Set Section 10.4.3 Medical History Section 10.4.4 Prior Medications/Concomitant Medications Section 10.4.5 Efficacy Analyses Section 10.4.5.1 Primary Efficacy Analysis

Change	**Section Changed**
	Section 10.4.5.2 Secondary Efficacy Analysis Section 10.4.7 Analysis of Drug Concentration Data Section 10.5 Multiplicity Considerations Section 10.5.1 Type I Error Control for Analyses of Primary Endpoints of OS and PFS (section added) Figure 2 α Reallocation Strategy Between Primary Endpoints of PFS and OS Section 10.5.2 Type I Error Control for Interim and Final Analyses of OS Table 7 Alpha Spending for Analysis of OS (table added) Table 7 Alpha Spending for Analysis of PFS (table deleted) Section 10.5.3 Type I Error for Analyses of Primary and Key Secondary Endpoints Section 10.6 Interim Analysis Table 8 Plan for Interim and Final Analyses of Primary Endpoints Section 21 References
Updated information related to cemiplimab and other PD-1 inhibitors based on emerging relevant data.	Section 1 Introduction Section 3.1 Hypotheses Section 3.2.4 Rationale for Cemiplimab Dose and Schedule Selection
Clarified changes made in Amendment 6.	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration Section 7.8.1 Disease Progression While Receiving Cemiplimab Section 7.10 Optional Treatment with Cemiplimab Plus Chemotherapy (section deleted)

Change	**Section Changed**
	Table 4 Schedule of Events: Screening Visit Assessments and Procedures Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Section 8.2.3.5 Laboratory Tests
Updated language per current protocol template.	Section 8.2.5 Future Biomedical Research Section 8.2.5.1 Genomic Sub-Study - Optional Section 9.3.2 Serious Adverse Events Section 9.4.1 Adverse Events Section 9.4.2 Serious Adverse Events Section 10.4.6.1 Adverse Events
Modifications for consistency and clarity, and administrative updates.	Title Page Clinical Study Protocol Synopsis: Study Design Section 2.3 Other Secondary Objectives Section 3.2.2 Rationale of Endpoints/Objectives Section 4.2.3 Other Secondary Endpoints Section 5.1 Study Description and Duration Table 2 Cemiplimab Dose Modifications Section 7.7 Concomitant Medications and Procedures Section 7.7.2 Permitted Medications and Procedures Section 7.8.2 Crossover Phase to Cemiplimab Table 6 Schedule of Events: Follow-up Period Assessments and Procedures Section 8.1.1 Footnotes for the Schedule of Events Tables Section 8.2.4.1 Drug Concentration Measurements and Samples Section 10.3.1 Efficacy Analysis Sets

Change	**Section Changed**
	Section 10.3.2 Safety Analysis Set Section 10.4.7 Analysis of Drug Concentration Data Section 10.4.11 Exposure-Response Analysis
Correction of typographical, grammatical, and formatting errors.	Throughout the document

Amendment 6 Admin

The table below summarizes the changes to the protocol, and the affected section.

Change	**Section Changed**
The numbering of the exclusion criteria was inadvertently changed in Amendment 6, and has been corrected	Section 6.2.2 Exclusion Criteria
A typographical error in Amendment 6, which incorrectly stated that the sample size for this study was 300, has been corrected to reflect the actual sample size of 700	Section 7.5 Method of Treatment Assignment

Amendment 6

The table below summarizes the changes to the protocol, and the affected sections.

Change	**Section Changed**
Increased enrollment from 300 to 700 patients to accommodate anticipated weaker effect on PFS due to emerging data from other studies exploring efficacy of anti-PD-1 in this population	Synopsis: Population Section 6.1 Number of Patients Planned
Added exclusion of patients with active or latent tuberculosis, per health authority request	Synopsis: Procedures and Assessments Section 6.2.2 Exclusion Criteria (#36) Section 8.2.1 Procedures Performed only at Screening Visits Table 4 Schedule of Events: Screening Visit Assessments and Procedures
Added clarification that all tumor assessments will be submitted to an Independent Review Committee (IRC) and that IRC will confirm disease progression	Synopsis: Study Design, Treatments Section 5.1 Study Description and Duration Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures

Change	**Section Changed**
Updated information from the phase 1 study 1423 as response assessments have now been obtained	Section 1 Introduction
Added EU drug approval information for pembrolizumab	Section 1 Introduction
Added description of Keynote-042 study and results to support the decision to increase enrollment from 300 to 700 patients	Section 1 Introduction Section 3.1 Hypothesis Section 3.2.3 Rationale for PD-L1 Expression Levels Section 10.2 Justification of Sample Size
Updated Radiographic Tumor Assessment Schedule to every 9 weeks until progression for all patients	Section 3.2.2 Rational of Endpoints/Objectives Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Section 8.2.2.1 Radiographic Tumor Assessments
Clarified enrollment and labs required for PD-L1 (IHC 22C3 pharmDx assay) expression and for ROS1 fusions, and clarified that labs should be confirmed by a central laboratory. Also clarified that testing does not need to be repeated if it has been done previously and the results are available from other Regeneron NSCLC immunotherapy studies	Section 3.2.3 Rationale for Choice of PD L1 Expression Levels Section 6.2 Study Population Section 6.2.2 Exclusion Criteria (#14) Section 8.2.1 Procedures Performed only at Screening Visits Section 8.2.4.3 Biomarker Procedures Table 4 Schedule of Events: Screening Visit Assessments and Procedures
Removed statement that initial radiographic disease progression must be determined by the investigator for Exploratory Efficacy Endpoint	Section 4.2.4 Exploratory Efficacy Endpoint
Removed “Total number of patients whose response in the ADA assay is negative at all times” from the Immunogenicity Assessment Variables	Section 4.4 Immunogenicity Assessment Variables

Change	**Section Changed**
Added option to crossover to cemiplimab with after initial disease progression on chemotherapy and specify when follow-up assessments occur	Section 5.1 Study Description and Duration
Updated population of patients eligible to receive retreatment with cemiplimab after discontinuing cemiplimab early	Section 5.1 Study Description and Duration
Specified which assessments are not required for patients who cross over to cemiplimab	Section 5.1 Study Description and Duration Section 7.8.2 Crossover Phase to Cemiplimab
Added option to continue cemiplimab with the addition of 4 cycles of histology-specific chemotherapy after initial disease progression on cemiplimab monotherapy, along with justification for this option based on Keynote-042 study results; remove option for patients randomized to cemiplimab monotherapy to continue cemiplimab monotherapy until further progression	Synopsis: Study Design Section 5.1 Study Description and Duration Section 7.8.1 Disease Progression While Receiving Cemiplimab Section 7.10 Optional Treatment with Cemiplimab plus Chemotherapy
Removed description of further progression, as it will no longer be assessed, with option to either crossover to cemiplimab or add chemotherapy to cemiplimab treatment	Section 5.1 Study Description and Duration Section 7.8.1 Disease Progression While Receiving Cemiplimab
Incorporated of health authority request to update language related to hepatitis B, hepatitis C, and human immunodeficiency virus.	Section 3.1 Hypothesis Section 5.1 Study Description and Duration Section 6.2.2 Exclusion Criteria (#9) Section 10.2 Justification of Sample Size
Modified target population to include patients with stage IIIC NSCLC who are not eligible for definitive Chemo/RT; stage IIIC is a new stage of NSCLC, added by AJCC in January 2018. This includes patients who were previously stage IV and does not alter the study population	Synopsis: Study Design Section 6.2 Study Population Section 6.2.1 Inclusion Criteria (#2)

Change	**Section Changed**
Targeted population has been modified to explain the exclusion criterion that excludes never-smokers from the trial	Synopsis: Population Section 6.2 Study Population
Permitted tumor tissue samples obtained from the primary site if it is not possible to obtain the biopsy from other sites and from archival tissue that is less than 5 months old	Section 6.2.1 Inclusion Criteria (#3a)
Updated timing of exclusion criterion based on the date of randomization instead of date of enrollment	Section 6.2.2 Exclusion Criteria (#2, #4, #6, #8)
Added clarification that in order for a history of radiation pneumonitis to be permitted, it must be resolved for ≥6 months prior to randomization	Section 6.2.2 Exclusion Criteria (#5)
Removed exclusion of patients with known allergy to doxycycline or other tetracycline antibiotics, as all patients will receive only C2 going forward.	Section 6.2.2 Exclusion Criteria (#18)
Added exclusion of recipients of organ transplants	Section 6.2.2 Exclusion Criteria (#24)
Clarified that all patients who discontinue from the study will not be replaced	Section 6.4 Replacement of Patients
Removed the vial fill size and temperature requirements for cemiplimab as this information is included and regularly updated in the lab manual	Section 7.1 Investigational and Reference Treatments Section 7.6.1 Packaging, Labeling, and Storage
Added clarification for guidelines that investigators should follow for patients treated with a combination of cemiplimab and chemotherapy	Section 7.3.2.2 Reasons for Permanent Discontinuation of Chemotherapy
Added note to clarify that CXR PA/Lateral should be obtained at screening	Table 4 Schedule of Events: Screening Visit Assessments and Procedures
Added timepoints at which TSH should be assessed	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures
Clarified that concomitant medications and adverse events will be collected continuously	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures

Change	**Section Changed**
Clarified that PK samples will be collected at the time of disease progression if patient progresses prior to completing 36 cycles of treatment	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures
Clarified that PK and ADA samples will be collected only from patients who are randomized to receive cemiplimab, not from those who crossover after progressing on chemotherapy	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures
Added pancreatic enzyme tests (Amylase/Lipase), per health authority request	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures Section 8.2.3.5 Laboratory Tests
Removed "every 6 weeks" from the Pregnancy Testing guidance to avoid confusion and complications with scheduling the test	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures Section 8.2.3.5 Laboratory Tests
Clarified that if local guidelines require pretreatment, the pretreatment should be administered within 3 days of randomization, followed by study treatment administration	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures
Added footnote that allows for PK samples and serum pregnancy test to be collected/performed up to 72 hours prior to infusion	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures
Updated time windows for follow-up visits 2 to 7 in Schedule of Events	Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures
Removed sentence stating that patients who withdraw from the study during the follow up period to return to the clinic to complete follow-up visits	Section 8.1.2 Early Termination Visit
Removed heart rate recording guidance from 12-Lead Electrocardiogram assessment	Section 8.2.3.4 12-Lead Electrocardiogram

Change	**Section Changed**
Updated text regarding substitution of venous testing of plasma CO2 for bicarbonate testing in centers where it is commonly used	Section 8.2.3.5 Laboratory Tests
Update to PK and ADA sampling schedules during treatment and follow- up periods	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures
Changed the definition of infusion reactions from 2 hours to 1 day after the infusion is completed, and clarify that infusion-related reactions have been observed in cemiplimab studies	Section 7.4.1 Acute Infusion Reactions Section 9.3.5 Infusion Reactions
Updated Obligations of Sponsor to clarify what adverse events will be considered unexpected	Section 9.2 Obligations of Sponsor
Updated timeframe for reporting a pregnancy of a study patient or a female partner of a study patient from within 90 days to within 180 days of the last dose of study drug	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Updated sample size justification and statistics sections with calculations based on increased enrollment	Synopsis: Statistical Plan Section 10.2 Justification of Sample Size Section 10.4.5.1 Primary Efficacy Analysis Section 10.4.5.2 Secondary Efficacy Analyses Section 10.5 Multiplicity Considerations
Added interim analysis plan and updated other sections for consistency	Synopsis: Statistical Plan Section 10.4.5.1 Primary Efficacy Analysis Section 10.4.5.2 Secondary Efficacy Analyses Section 10.5 Multiplicity Considerations Section 10.6 Interim Analysis
Updated Efficacy Analysis section for clarity	Section 10.4.1 Patient Disposition Section 10.4.4 Prior Medications/Concomitant Medications
Updated Safety Analysis section for clarity and to account for crossover treatment with	Section 10.4.6.1 Adverse Events

Change	**Section Changed**
cemiplimab and treatment with cemiplimab plus chemotherapy after disease progression	Section 10.4.6.4 Treatment Compliance
Updated Study Flow Diagram	Figure 1 Study Flow Diagram
Updated to Colitis AE management, requiring permanent discontinuation for grade 4 colitis	Appendix 3 Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific REGN2810 Drug-Related Adverse Events
Minor editorial clarifications and corrections	Throughout the protocol
REGN2810 replaced with cemiplimab	Throughout the protocol

Amendment 5

The following table outlines the changes made to the protocol and the affected sections.

Change	**Section Changed**
Appendix 3 was inadvertently removed from amendment 4. Appendix 3 has been reinserted.	Appendix 3: Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific REGN2810 Drug-Related Adverse Events
Minor edit: Amendment 3 date of issue changed to 15 Mar 2017	Title page
A 12-lead electrocardiogram (ECG) should be acquired prior to obtaining any blood samples. This sentence has been changed to the following: A 12-lead ECG should be acquired at screening.	Table 4 Schedule of Events: Screening Visits Assessments and Procedures
Added the following: The partial pressure of carbon dioxide (PCO2) test is an acceptable test at centers where this is commonly used instead of the bicarbonate test.	Section 8.2.3.5 Laboratory Tests

Amendment 4

The following table outlines the changes made to the protocol and the affected sections.

Change	**Sections Changed**
The following other secondary objectives added: • To assess immunogenicity (ADA/Nabs) to REGN2810 and any relationship with drug concentrations, efficacy and safety) • To conduct Exposure-Response analyses on efficacy endpoints, safety, and relevant exploratory biomarkers, as appropriate	Synopsis Section 2.3 Other Secondary Objectives
The following Exploratory Objectives added:	Synopsis

Change	Sections Changed
• To assess pharmacodynamic (PD) changes in putative serum biomarkers (which may include but are not limited to cytokines, circulating tumor nucleic acids, etc. • To conduct PK/PD analyses on exploratory biomarkers, as appropriate	Section 2.4 Exploratory Objectives
Definitions of immunogenicity variables updated to match other studies in REGN2810 program Section title was updated	Section 4.4 Immunogenicity Assessment Variables Section 10.3.3 Pharmacokinetic and ADA Analysis Sets
An exclusion criterion has been added for the following reason: Patients who have previously been treated with idelalisib will be excluded from treatment with REGN2810 as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of REGN2810 monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of REGN2810. In addition, following exclusion criterion added: Member of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor	Section 6.2.2 Exclusion Criteria (#23) Section 6.2.2 Exclusion Criteria (#24)
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 7.3.2 Study Drug Discontinuation
An adverse event of special interest (AESI) has been added to the list of AESIs:	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor

Change	Sections Changed
• An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.	
Two new subsections added: 10.4.10 PK/PD Analyses for Exploratory Biomarkers 10.4.11. Exposure-Response (E-R) Analysis	Section 10.4.10 PK/PD Analysis of Exploratory Biomarkers Section 10.4.11 Exposure- Response Analysis
Removed Appendix 3	Appendix 3 Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific REGN2810 Drug-Related Adverse Events Section 7.3.1 REGN2810 Monotherapy Section 7.3.1.2 Immune-Related Adverse Events Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor Table 2 REGN2810 Dose Modification footnotes
Figure 1 Study Flow Diagram updated Table 5 (“Cycle 28” added to comment section for Pharmacokinetic Sample and Anti-Drug Antibody Sample)	Figure 1 Table 5
Minor edits	Throughout the protocol

Amendment 3

The purposes of this amendment are to:

- Revise the protocol to incorporate feedback from the FDA and other health authorities
- Update the dose to 350 mg from 250 mg, and provide dose rationale for 350 mg dose
- Make minor editorial changes

The table below summarizes the changes to the protocol, and the affected sections.

Change	**Section Changed**
Updated number of patients treated with REGN2810.	Section 1 Introduction
Updated dose to 350 mg to 250 mg, and provided rationale for dose change.	Clinical Study Protocol Synopsis: Study Design, Treatments Section 3.1 Hypothesis Section 3.2.4 Rational e for REGN2810 Dose and Schedule Selection Section 5.1 Study Description and Duration Section 7.1 Investigational and Reference Treatment Section 7.8.1 Disease Progression while Receiving REGN2810 Section 7.8.2 Crossover Phase to REGN2810 Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures
Defined the end of the study.	Section 5.1.1 Study Description and Duration
Contraception language updated for exclusion criterion number 21	Section 6.2.2 Exclusion Criteria, #21
Removed ability to withdraw 10 mL at a concentration of 25 mg/mL from vial containing study drug.	Section 7.1 Investigational and Reference Treatment Section 7.6.1 Packaging, Labeling, and Storage

Change	**Section Changed**
Anti-drug antibody sample collection added at day 1 cycle 1, preinfusion on day 1 of cycle 3, day 1 of cycle 9, and day 1 of cycle 18 Anti-drug antibody sample visits added at follow-up visits 1 and 3.	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures
Brain scans during the treatment and follow-up periods should be performed every 12 weeks instead of 18 weeks.	Table 5 Schedule of Events: Treatment Period/On-Study Assessments and Procedures
Radiographic assessments for patients who have not experienced progressive disease should be performed every 9 weeks.	Table 6 Schedule of Events: Follow-up Period Assessments and Procedures
Removed requirement for a minimum of 10 slides for unstained slides of tumor sample.	Section 8.2.1 Procedures Performed only at Screening Visits Section 8.2.4.3 Biomarker Procedures
Clarified that a biopsy will be collected at screening or archival tissue if ≤5 months. Clarified that tumor tissue will be used for additional PD-L1 assays.	Section 8.2.4.3 Biomarker Procedures
Removed RNA from optional genomics sub-study.	Section 8.2.5.1 Genomics Sub-Study - Optional
Clarified all infusions reactions are to be recorded as an AE.	Section 9.3.5 Infusion Reactions
Statistical section updated by deleting the following text: Clarified that while the study is open-label, analyses or summaries generated by randomized treatment or treatment received will be limited and documented	Section 10 Statistical Plan
The primary analysis will now be called sensitivity analysis. Added reference	Clinical Study Protocol Synopsis: Statistical Plan Section 10.4.5.2 Secondary Efficacy Analysis

Amendment 2

The purposes of this amendment are to:

- Remove Appendix 2 and Appendix 3
- Change format of Appendix 3
- Add Asia to the geographical stratification
- Spell out EU as Europe

The table below summarizes the changes to the protocol, and the affected sections.

Amendment 1 (29 Nov 2016)

The purposes of this amendment are to:

- Respond to a Food and Drug Administration (FDA) request for revision of the protocol.
- Remove the United States (US) and Japan as study site locations
- Remove "IRB" since the study is not being conducted in the US
- Inserted generic PD-L1 assay description
- Make a minor editorial change

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Global, Randomized, Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1 + Non-Small Cell Lung Cancer
Site Locations	Patients will be randomized at approximately 250 sites in Europe, Asia, and Rest of World (ROW).
Objectives	The primary objectives of the study are to compare the overall survival (OS) and progression-free survival (PFS) of REGN2810 (cemiplimab) versus standard-of-care platinum-based chemotherapies in the first-line treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors express programmed cell death ligand-1 (PD-L1) in ≥50% of tumor cells. The key secondary objective of the study is to compare the objective response rate (ORR) of cemiplimab versus platinum-based chemotherapies. The other secondary objectives of the study are the following: • To compare the duration of response (DOR) of cemiplimab versus platinum-based chemotherapies • To assess quality of life (QOL) of patients treated with cemiplimab versus patients receiving platinum-based chemotherapies as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13). • To evaluate the safety and tolerability of cemiplimab versus platinum-based chemotherapies • To measure concentrations of cemiplimab in serum and characterize the pharmacokinetics (PK) of cemiplimab • To assess immunogenicity (anti-drug antibodies and neutralizing anti-drug antibodies) to cemiplimab and any relationships with pharmacokinetics (PK), efficacy and safety • To conduct Exposure-Response analyses on efficacy endpoints, and safety. Exploratory objectives: • To assess correlation between the level of PD-L1 expression at baseline and efficacy of study treatment • To assess time to new anti-tumor therapy • To assess pharmacodynamic (PD) changes in putative serum biomarkers (which may include but are not limited to cytokines, circulating tumor nucleic acids, etc)

	• To perform PK/PD analyses on exploratory biomarkers, as appropriate.
Study Design	This is a randomized, multicenter, open-label, pivotal phase 3 study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with stage IIIB, stage IIIC, or stage IV squamous or non-squamous NSCLC who are not candidates for treatment with definitive concurrent chemoradiation, whose tumors express PD-L1 in ≥50% of tumor cells, and who have received no prior systemic treatment for their advanced disease. The study will consist of the following 3 periods: screening, treatment, and follow-up. Patients will undergo a screening evaluation to determine their eligibility within 28 days prior to randomization. Eligible patients will be randomized to one of the following 2 treatment groups: cemiplimab 350 mg monotherapy or standard-of-care chemotherapy. Randomization will be stratified by histology (non-squamous versus squamous) and geographic region (Europe, Asia, or ROW). Patients with NSCLC randomized to chemotherapy may receive one of the following regimens: Paclitaxel + cisplatin or carboplatin Gemcitabine + cisplatin or carboplatin Pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance (it is strongly recommended that patients with squamous NSCLC do not receive pemetrexed-containing regimens) Patients assigned to the cemiplimab treatment group will receive cemiplimab 350 mg as an intravenous (IV) infusion on day 1 of every treatment cycle (every 3 weeks [Q3W]) for up to 108 weeks or until Response Evaluation Criteria in Solid Tumors (RECIST) 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. Patients who experience Independent Review Committee (IRC) assessed RECIST 1.1-defined progressive disease on therapy may continue treatment with cemiplimab 350 mg Q3W for up to 108 additional weeks, with the addition of histology-specific chemotherapy for 4 cycles, provided they meet specific criteria and the patient has not completed the 108-week treatment period. Histology specific chemotherapy is defined as paclitaxel + cisplatin or carboplatin for squamous cell NSCLC and pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance for non-squamous NSCLC. Patients assigned to chemotherapy will receive one of the protocol given options of platinum-doublet chemotherapy treatment for 4 to 6 cycles or until RECIST 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. Patients who experience disease progression while on, or after completion of chemotherapy will be offered the option to crossover to cemiplimab at the time of IRC confirmed progression to receive cemiplimab 350 mg Q3W for up to 108 weeks, provided they meet specific criteria. At the time of Amendment 9 finalization, the primary endpoint of OS has been reached. Based on the demonstrated improvement in OS in patients receiving cemiplimab, all patients randomized to receive platinum-based chemotherapy are

	permitted to cross over to receive treatment with cemiplimab 350 mg Q3W for up to 108 additional weeks prior to disease progression. Patients will have follow-up visits every 6 weeks for 6 months and then at 9 months and 12 months after the last dose of treatment.
Study Duration	The duration of the study will be approximately 48 months.
Population	
Sample Size:	Approximately 700 patients will be randomized.
Target Population:	Patients included in this study will be men and women ≥18 years of age, diagnosed with stage IIIB, IIIC, or stage IV squamous or non-squamous NSCLC, who are not eligible for definitive chemo/radiation, whose tumors express PD-L1 in ≥50% of tumor cells (using the PD-L1 IHC 22C3 pharmDx assay), and who have received no prior systemic treatment for their advanced disease. The study population will be limited to previous and current smokers as the benefit of PD-1 blockade has not been shown in never-smokers. Patients with actionable mutations will be excluded because they respond best to targeted therapy.
Treatments	
Study Drug Dose/Route/Schedule:	Cemiplimab will be administered at 350 mg as an IV infusion Q3W for up to 108 weeks or until IRC-assessed RECIST 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent.
Reference Drug Dose/Route/Schedule:	Standard-of-care chemotherapy (one of the protocol given options of platinum-doublet chemotherapy treatment) will be administered for 4 to 6 cycles or until IRC-assessed RECIST 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent.

Endpoints	
Primary:	The primary endpoints of the study are OS and PFS as assessed by a blinded independent review committee (IRC) using RECIST 1.1.
Secondary:	The key secondary endpoint in the study will be ORR. Other secondary endpoints will include DOR and QOL, as well as the safety and tolerability of cemiplimab.
Procedures and Assessments	Procedures performed at screening include informed consent; recording of medical, oncology, and concomitant medications histories; recording of demographics; collection of tumor tissue for PD-L1 assessment; testing of tumor tissue for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations and human homolog of the transforming gene v-ros of the avian sarcoma virus UR2 (ROS1) fusions; radiographic tumor assessment; tumor burden assessment; chest X-ray; serum pregnancy testing; 12-lead electrocardiogram (ECG); complete physical examination, including vital signs, height, and weight assessments; Eastern Cooperative Oncology Group (ECOG) performance status assessment; TB skin testing in high risk individuals at the discretion of the investigator; and laboratory testing. Samples for an optional genomic sub-study may also be obtained. During the treatment and follow-up periods, the following procedures will be performed to assess safety: physical examination; ECOG performance status assessment; vital signs; laboratory testing, including pregnancy testing for women of childbearing potential; ECG and chest X-ray (at the discretion of the investigator); and recording of adverse events (AEs) and concomitant medications. Computed tomography (CT) or magnetic resonance imaging (MRI) for tumor assessment will be performed at time points throughout the study. Quality of life will be measured using validated patient self-administered questionnaires (EORTC QLQ-C30 and EORTC QLQ-LC13). Other assessments will include samples for biomarker assessments, samples for cemiplimab concentration measurement, and samples for cemiplimab immunogenicity assessment.
Statistical Plan	**Statistical Hypothesis** The analyses of OS and PFS will be performed with an overall 2-sided α of 0.05 for the following null and alternative statistical hypotheses: <u>Overall Survival</u> • H0: The survival curve of OS for cemiplimab is the same as that for platinum-based chemotherapy • H1: The survival curve of OS for cemiplimab is not the same as that for platinum-based chemotherapy

Progression Free Survival

- H0: The survival curve of PFS for cemiplimab is the same as that for platinum-based chemotherapy
- H1: The survival curve of PFS for cemiplimab is not the same as that for platinum-based chemotherapy

Justification of sample size

Enrollment of 700 patients is assumed to occur over 38 months (3 patients per month for the first 4 months, 12 patients per month from month 5 to month 8, 23 patients per month from month 9 to month 16, 30 patients per month from month 17 to month 20, and 20 patients per month thereafter). The patients will be randomized at 1:1 ratio to cemiplimab arm or platinum-based chemotherapy arm. A dropout rate of 10% per year is assumed.

Overall Survival

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median OS has ranged from approximately 11.3 to 14.2 months. For PD-1 monotherapy, a delayed treatment effect in OS has been observed in Keynote-024, Keynote-042 and Checkmate 026. In these studies, during the first 6 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in OS when compared to treatment with chemotherapy.

The sponsor assumes without crossover effect a median OS of 13 months for patients treated with chemotherapy alone, and a non-proportional HR between cemiplimab and chemotherapy, with an HR of 1.05 for the first 6 months and an HR of 0.58 after 6 months.

With 5 planned interim analyses using Lan-DeMets O'Brien-Fleming spending function, and with 476 deaths at final analysis of OS, the study has approximately 86% power for detecting a significant OS effect at 2-sided α of 0.04 and approximately 88% power for detecting a significant OS effect at 2-sided α of 0.05.

Progression Free Survival

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median PFS has ranged from approximately 4.8 to 6.4 months. For PD-1 monotherapy, a delayed treatment effect in PFS has been observed, in Keynote-024, Keynote- 042 and Checkmate 026. In these studies, during the first 3 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in PFS when compared to treatment with chemotherapy.

The sponsor assumes a median PFS of 6.4 months for patients treated with chemotherapy alone, and a non-proportional HR between cemiplimab and chemotherapy, with an HR of 1.3 for the first 3 months and an HR of 0.5 after 3 months.

With 525 PFS events, the study has approximately 76% power for detecting a significant PFS effect at 2-sided α of 0.01 and approximately 90% power for detecting a significant PFS effect at 2-sided α of 0.05.

Statistical methods

The overall type I error rate for analyses of the primary endpoints of OS and PFS is controlled at a 2-sided α of 0.05 by the following α reallocation strategy: the 2-sided α of 0.05 is initially split between the analyses of OS and PFS, with 0.04 to OS analysis and 0.01 to PFS analysis; the α allocated to PFS (0.01) is subject to be reallocated to OS if the PFS test is positive; the α allocated to OS (0.04) is subject to be reallocated to PFS if the OS test is positive. The type I error rate for interim and final analyses of OS is controlled using the O'Brien-Fleming spending function. The type I error rate for the analyses of primary and key secondary endpoints are controlled by hierarchical testing procedure, that is ORR will only be tested if both analyses of OS and PFS are statistically significant.

The primary endpoint of OS will be analyzed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factor. The HR and its 95% CI will be estimated by a stratified Cox regression model using the treatment as covariate and status of histology as stratification factor.

The primary endpoint of PFS will be analyzed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factor. The HR and its 95% CI will be estimated by a stratified Cox regression model using the treatment as covariate and status of histology as stratification factor.

If both analyses of OS and PFS are statistically significant, the ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by status of histology (non-squamous versus squamous). An associated odds ratio and 95% CI will be calculated. Objective response rate and the corresponding 95% exact CI will be calculated by the Clopper-Pearson method for each treatment arm.

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 grading scale will be used.

Cemiplimab concentrations in serum will be reported over time as individual values with descriptive statistics. The immunogenicity assessment variables will be analyzed using descriptive statistics. Biomarker analyses in this study will be exploratory in nature and results will be summarized in a separate report.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BMS	Bristol-Myers Squibb
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CT	Computed tomography
CTLA-4	Anti-cytotoxic T-lymphocyte-associated antigen 4
CTX	Cyclophosphamide
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

Abbreviation	Definition of Term
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-Human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
hfRT	Hypofractionated radiation therapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
irAE	Immune-related adverse event
IRC	Independent review committee
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
mAB	Monoclonal antibody
MRI	Magnetic resonance imaging
NAb	Neutralizing anti-drug antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PD-1	Programmed cell death-1
PD-L1, PD-L2	Programmed cell death ligand-1, programmed death ligand-2
PE	Physical examination

Abbreviation	Definition of Term
PFS	Progression-free survival
PI 3-K	Phosphoinositol3-kinase
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PT	Preferred term
PTT	Partial prothrombin time
QOL	Quality of life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
ROS1	Human homolog of the transforming gene v-ros of the avian sarcoma virus UR2
RNA	Ribonucleic acid
ROW	Rest of World
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TPS	Tumor proportion score
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (Siegel 2016). In 2020, an estimated 228,820 new cases of lung cancer will be diagnosed in the United States (US) and 135,720 people will die from the disease (American Cancer Society 2020). Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (30%). The majority of patients with NSCLC are often found to have advanced cancer at the time of diagnosis.

Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy was until recently the standard first-line treatment for patients with advanced NSCLC whose tumors do not have an epidermal growth factor receptor (EGFR) mutation, an anaplastic lymphoma kinase (ALK) mutation, or a c-ros oncogene 1 receptor tyrosine kinase (ROS1) fusion (Besse 2014, Ettinger 2016, Reck 2014). This is still the standard of care for patients in countries where therapies with immune checkpoint inhibitors are not approved or available. Chemotherapy for metastatic NSCLC is not curative and despite optimal treatment, patients have a median overall survival (OS) of approximately 8 to 12 months, and a 5-year survival rate of approximately 18% (Siegel, 2016). Therefore, newer therapeutic approaches are needed that will improve long-term survival and quality of life (QOL) in patients with advanced NSCLC.

It is recognized that a complex cross-talk between cancer cells and the host immune system exists that can both inhibit and enhance tumor growth (Vinay 2015). Cancer modulates and evades the host immune response through a number of mechanisms, including formation of an immune-suppressive environment within the tumor. Programmed cell death-1 (PD-1) is an important co-receptor expressed on the surface of activated T-cells that mediates immunosuppression. The binding of PD-1 to one of its ligands, programmed cell death ligand-1 (PD-L1) or programmed cell death ligand-2 (PD-L2), results in inhibition of a cytotoxic T-cell response. Increased expression of PD-L1 in the tumor microenvironment facilitates escape from the immune-surveillance mechanism (T-cell-induced anti-tumor activity). In contrast, blockade of this interaction by using a new class of agents called immune checkpoint inhibitors results in an enhanced T-cell response with anti-tumor activity.

In NSCLC, PD-L1 expression levels in tumor cells range from 13% to 85% (D'Incecco 2015, Kerr 2015), and a high level of expression has been correlated with poor patient prognosis and resistance to treatment (Creelan 2014). In recent years, with the introduction of immunotherapy to metastatic NSCLC treatments, patients' prognosis has significantly improved. Pembrolizumab (KEYTRUDA®), atezolizumab (TECENTRIQ®), and nivolumab (OPDIVO®) are anti-PD-1 or PD-L1 agents currently approved by the US Food and Drug Administration (FDA) as first- or second-line treatment of advanced NSCLC as monotherapy and in combination with platinum-based chemotherapy.

Initial clinical trials demonstrated the efficacy of PD-1 inhibitors as monotherapy in second-line treatment of NSCLC after failure of platinum-based doublet regimens, generating great enthusiasm for these new agents and leading to approvals for both nivolumab (OPDIVO® [nivolumab] [package insert], 2020) and pembrolizumab (KEYTRUDA® [pembrolizumab] [package insert], 2020). Programmed cell death-1/PD-L1 inhibitors have subsequently been evaluated in the first-line treatment of NSCLC. The phase 3 CheckMate 026 trial investigated the

efficacy of first-line treatment with nivolumab as monotherapy compared to platinum-based doublet chemotherapy in patients with advanced NSCLC and PD-L1 positive tumors (defined as present in 1% or more tumor cells). A total of 541 patients were randomized 1:1 to nivolumab or chemotherapy. In 423 patients with 5% or greater PD-L1 expression, progression-free survival (PFS) was 4.2 months with nivolumab and 5.9 months with chemotherapy (hazard ration [HR]: 1.15 95%CI: 0.91 to 1.45, p=0.25). OS was 14.4 months for nivolumab versus 13.2 months for chemotherapy (HR: 1.02; 95% CI: 0.80 to 1.30). Among all treated patients, any serious treatment-related adverse events (AEs) were 71% and 18% with nivolumab, and 92% and 51% with chemotherapy, respectively (Socinski 2016).

In contrast to this negative trial, pembrolizumab was investigated as monotherapy in KEYNOTE-024, an open-label, phase 3 trial with 305 patients with previously untreated advanced NSCLC with PD-L1 tumor proportion score (TPS) of at least 50% (PD-L1 ≥50%). Patients were randomized to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks [Q3W]) or the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. Median PFS was 10.3 months (95% confidence interval [CI]: 6.7 months to not reached) in the pembrolizumab group versus 6.0 months (95% CI: 4.2 to 6.2 months) in the chemotherapy group (hazard ratio [HR] for disease progression or death: 0.50; 95% CI: 0.37 to 0.68; p=0.0015 (Reck 2016). Median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (HR: 0.63; 95% CI, 0.47 to 0.86) (Reck 2019). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% versus 27.8%), the median duration of response (DOR) was longer (not reached [range: 1.9+ to 14.5+ months] vs 6.3 months [range: 2.1+ to 12.6+]), and treatment-related AEs of any grade were less frequent (occurring in 73.4% vs 90.0% of patients), as were grade 3, 4, or 5 treatment-related AEs (26.6% vs 53.3%) (Reck 2016). In October 2016, the FDA approved pembrolizumab (KEYTRUDA® [pembrolizumab] [package insert], 2020) for the treatment of patients with metastatic NSCLC, whose tumors express PD-L1 ≥50% as determined by the PD-L1 IHC 22C3 pharmDx 22C3 assay (Dako, North America, Inc.). This was the first FDA approval of a checkpoint inhibitor for first-line treatment of advanced lung cancer. This approval also expanded the indication in second-line treatment of lung cancer to include all patients with PD-L1-expressing NSCLC.

The efficacy of pembrolizumab monotherapy in patients with PD-L1 tumor proportion score (TPS) of ≥1% was tested in the phase 3 trial KEYNOTE-042, in which, similarly to KEYNOTE-024, 1274 patients with previously untreated advanced NSCLC, without EGFR or ALK mutations were randomized to receive either pembrolizumab or the investigator's choice of platinum-based chemotherapy. Pembrolizumab did provide an OS benefit vs chemotherapy in the overall patient population (TPS ≥1%). Median OS was 16.7 months (95% CI: 13.9 to 19.7) in the pembrolizumab group versus 12.1 months (95% CI: 11.3 to 13.3) in the chemotherapy group (HR for disease progression or death: 0.81; 95% CI: 0.71 to 0.93; p=0.0018). However, the benefit was driven by the PD-L1 high population (TPS ≥50% expression, HR=0.69). Pembrolizumab did not provide a survival benefit in the 1% to 49% PD-L1 population (HR=0.92). In patients with TPS ≥50%, the median OS was 20.0 months (95% CI: 15.4 to 24.9) in the pembrolizumab group versus 12.2 months (95% CI:10.4 to 14.2) in the chemotherapy group (HR for disease progression or death: 0.69; 95% CI: 0.56 to 0.85;

p=0.0003). In patients with TPS ≥20%, median OS was 17.7 months (95% CI: 15.3 to 22.1) in the pembrolizumab group versus 13.0 months (95% CI: 11.6 to 15.3) in the chemotherapy group (HR for disease progression or death: 0.77; 95% CI: 0.64 to 0.92; p=0.0020). In patients with TPS ≥50%, median PFS was 7.1 months (95% CI: 5.9 to 9.0) in the pembrolizumab group versus 6.4 months (95% CI: 6.1 to 6.9) in the chemotherapy group (HR=0.81 [95% CI, 0.67-0.99]; p=0.0170), which did not meet protocol-specified significance boundary. The median DOR was 20.2 months (range: 2.1+ to 31.2+ months) in the pembrolizumab arm vs 8.3 months in the chemotherapy arm (range: 1.8+ to 28.1) for patients with TPS ≥50% (De Lima Lopes 2018).

It is worth noting that the results of KEYNOTE-042 in the subset of patients with TPS ≥50%, are different from those of KEYNOTE-024. In KEYNOTE-042, progression free survival and OS curves show that rapidly progressing patients (patients that progress or die within 6 months) treated with chemotherapy may have better outcomes than patients treated with immunotherapy. After 6 months, the curves cross and the benefit of the immunotherapy becomes apparent. The reasons for these differing outcomes are uncertain, and potentially reflect the inclusion of patients with more advanced or aggressive disease in KEYNOTE-042, but in both studies the clinical benefit of PD-1 inhibition was still demonstrated in the population with TPS ≥50%. It is also worth noting that median OS in the population of patients with TPS ≥50% treated with pembrolizumab in KEYNOTE-042 was shorter than that observed in the matching population in KEYNOTE-024 (20.0 months [95% CI: 15.4 to 24.9] vs 30.0 months [95% CI, 18.3 months to not reached]), thus supporting the hypothesis of clinically meaningful differences in the patients enrolled in the 2 trials.

Despite the differences between studies KEYNOTE-024 and KEYNOTE-042, they have shown that for patients with advanced NSCLC and PDL-1 TPS ≥50% a therapeutic strategy based on first-line monotherapy PD1 inhibition represents an opportunity to improve patients' outcome while avoiding the toxicity of chemotherapy.

More recently, results with pembrolizumab in combination with various platinum-containing regimens in chemotherapy-naive patients (KEYNOTE-021, phase 2, Cohort G [n=123]) have shown ORR of 57% with pembrolizumab with chemotherapy and 30% with chemotherapy (estimated difference, 26.4%; 95% CI, 8.9%–42.4%; p=0.0016). PFS was significantly improved with the combination vs chemotherapy (HR=0.53, 95% CI: 0.33–0.86, p=0.0049) with median (95% CI) PFS of 19.0 (8.5–Not Reported [NR]) months vs 8.9 (95% CI, 6.2–11.8) month. The HR for OS was 0.59 (95% CI, 0.34–1.05; p=0.0344). With a median follow-up of 23.9 months (range, 0.8–29.0 months), median (95% CI) OS was not reached (22.8 months –NR) for pembrolizumab with chemotherapy and 20.9 (14.9–NR) months in the chemotherapy arm. Eighteen-month OS rate was 70% with pembrolizumab with chemotherapy and 56% with chemotherapy (Borghaei 2018). These results led to the accelerated approval of pembrolizumab in combination with carboplatin and pemetrexed as first-line treatment in patients with non-squamous NSCLC in the US in 2017 (KEYTRUDA® [pembrolizumab] [package insert], 2020). In a subsequent confirmatory double-blind phase 3 study, KEYNOTE-189, 616 patients with non-squamous NSCLC who were treatment-naive for metastatic disease were randomly assigned to receive platinum-based chemotherapy with or without pembrolizumab. After a median follow-up of 10.5 months, the estimated rate of OS at 12 months was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab with chemotherapy arm versus 49.4% (95% CI, 42.1 to 56.2) in the chemotherapy arm (HR for death, 0.49; 95% CI, 0.38 to 0.64; p<.001). Improvement in

OS was seen across all PD-L1 categories that were evaluated (PD-L1 tumor proportion score <1%, 1% to 49%, and ≥50%). Median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab with chemotherapy arm versus 4.9 months (95% CI, 4.7 to 5.5) in the chemotherapy arm (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; p<0.001). The addition of pembrolizumab to chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone in non-squamous NSCLC patients with metastatic disease (Gandhi 2018, KEYTRUDA® [pembrolizumab] [package insert], 2020). In August 2018, pembrolizumab in combination with pemetrexed and carboplatin was approved by the FDA as first-line treatment of patients with metastatic non-squamous NSCLC.

Atezolizumab (TECENTRIQ®) is an anti-PD-L1 monoclonal antibody that has been evaluated in combination with the anti-angiogenic agent bevacizumab and with first-line platinum-based chemotherapy. In the randomized, phase 3, IMpower150 trial, 1202 patients with non-squamous NSCLC, were equally randomized to receive atezolizumab plus carboplatin/paclitaxel (Arm A), atezolizumab plus carboplatin/paclitaxel plus bevacizumab (Arm B), or carboplatin/paclitaxel plus bevacizumab (Arm C). IMpower 150 met the co-primary endpoints of PFS and OS, and demonstrated a statistically significant and clinically meaningful benefit with the atezolizumab/bevacizumab/chemotherapy regimen versus bevacizumab/chemotherapy regimen. Median OS reached 19.4 months for Arm B versus 14.7 months for Arm C (HR 0.780, 95% CI [0.636, 0.956]; p=0.0164), and an analysis of PFS showed a median duration of 8.3 months for Arm B versus 6.8 months for Arm C (HR 0.592, 95% CI [0.499, 0.703]; p<0.0001). The OS benefit of atezolizumab/bevacizumab/chemotherapy regimen was maintained across all key subgroups evaluated, including all PD-L1 subgroups, although the results were not always statistically significant (Socinski 2016). In December 2018, the FDA approved atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in patients with metastatic non-squamous NSCLC (TECENTRIQ® [atezolizumab] [package insert], 2018).

Squamous NSCLC

In parallell with non-squamous advanced NSCLC, the efficacy of pembrolizumab and atezolizumab was also tested in the treatment of squamous NSCLC. KEYNOTE-407, a randomized, blinded, phase 3 study of pembrolizumab plus platinum-based chemotherapy improved OS, PFS, response rates, and duration of response in treatment-naïve patients with advanced squamous cell NSCLC compared with chemotherapy alone irrespective of PD-L1 status. Patients were randomized to receive pembrolizumab plus carboplatin and paclitaxel or nanoparticle albumin-bound paclitaxel versus the same chemotherapy plus placebo. At the second interim analysis, with a median follow-up of 7.8 months, OS was significantly improved in the pembrolizumab-containing arm: median OS of 15.9 months versus 11.3 months in the chemotherapy arm (p=0.0008). PFS also favored pembrolizumab with chemotherapy: median of 6.4 months vs 4.8 months with chemotherapy (p<0.0001). PFS was better with the addition of pembrolizumab in all levels of PD-L1expression, but the reduction on the rate of disease progression was proportional to PD-L1 expression in tumor. The ORR was significantly higher in the pembrolizumab/chemotherapy arm: 59.4% vs 38%, respectively (p=0.0004). The median duration of response was 7.7 months vs 4.8 months, respectively (Paz-Ares 2018). In October 2018, FDA Approved pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of patients with metastatic squamous NSCLC (KEYTRUDA® [pembrolizumab] [package insert], 2020).

IMpower131 is a phase 3, open-label, randomized study evaluating atezolizumab in combination with carboplatin and nanoparticle albumin-bound -paclitaxel or atezolizumab in combination with carboplatin and paclitaxel versus chemotherapy (carboplatin and nanoparticle albumin-bound paclitaxel) alone in treatment-naïve patients with stage IV squamous NSCLC. The study enrolled 1021 patients who were randomized equally to receive atezolizumab plus carboplatin and paclitaxel (Arm A), or atezolizumab plus carboplatin and nanoparticle albumin-bound paclitaxel (Arm B), or carboplatin and nanoparticle albumin-bound paclitaxel (Arm C, control arm). Outcomes for only 2 of the study arms, however, were reported at ASCO 2018: atezolizumab plus chemotherapy (carboplatin and nanoparticle albumin-bound paclitaxel), 343 patients; and chemotherapy (carboplatin and nanoparticle albumin-bound paclitaxel), 340 patients. In this study, 29% of all patients, regardless of PD-L1 expression, had a reduced risk of disease worsening or death, compared with those who received chemotherapy alone. There was a doubling of PFS benefit with this combination: At 12 months, cancer had not worsened in 24.7% patients receiving atezolizumab and chemotherapy, compared to 12% of those receiving chemotherapy alone. Improved PFS was observed in all groups of patients who received atezolizumab and chemotherapy, including those with PD-L1–negative tumors. OS data are not yet mature (Jotte 2018).

It is possible that in first-line NSCLC, tumors expressing low-level PD-L1 will require combination therapy, rather than monotherapy with an anti-PD1, to treat their lung cancer. Therefore, Regeneron is limiting our monotherapy trial to patients whose tumors express PD-L1 in ≥50% of tumor cells.

Cemiplimab (the INN for REGN2810) is a human IgG4 monoclonal antibody (mAb) to the PD-1 receptor that blocks PD-1/PD-L1-mediated T-cell inhibition. LIBTAYO® (cemiplimab) 350 mg as an IV infusion over 30 minutes Q3W is approved in the US, Europe, Canada, and Brazil for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation. In the US, it is approved with a suffix as cemiplimab-rwlc.

Cemiplimab is currently being evaluated in more than 20 phase 1 through phase 3 clinical studies. Regeneron Pharmaceuticals, Inc. (hereafter, referred to as Regeneron) believes that cemiplimab will prove to be as effective as any of the other approved anti-PD-1 antibodies, based on ongoing cemiplimab studies, and in addition to its expected activity as a monotherapy.

Cemiplimab has been generally well tolerated, and the reported AEs have been similar to what have been observed with other PD-1 inhibitors. The most common treatment-emergent adverse events (TEAEs) occurring in 10% or more of patients were fatigue, nausea, anemia, decreased appetite, arthralgia, constipation, cough, vomiting, and abdominal pain. No protocol-defined dose limiting toxicities have been observed. Preliminary efficacy has been observed in several tumor types, including NSCLC. These data provided preliminary evidence that cemiplimab has anti-tumor activity in patients with advanced NSCLC and provided the rationale for the design of Study R2810-ONC-1624.

A total of 20 patients previously treated with chemotherapy for their advanced NSCLC were enrolled in the phase 1 study R2810-ONC-1423 and received with monotherapy cemiplimab. Of the 20 patients,1 had a complete response (CR), 7 had a partial response (PR), and 4 had stable

disease (SD). The overall response rate per central independent review was 40.0% (n=8/20). Disease control rate was 60.0% (n=12/20).

These data provided preliminary evidence that cemiplimab has anti-tumor activity in patients with advanced NSCLC. Additional background information on cemiplimab and the development program can be found in the Investigator's Brochure.

The current study is a randomized, global, open-label, phase 3 study of cemiplimab monotherapy versus standard-of-care, platinum-based, doublet chemotherapies in patients with advanced or metastatic, squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells and who have received no prior systemic treatment for their advanced disease. The main objectives of the study will be to determine if cemiplimab improves OS and/or PFS over standard-of-care platinum doublet chemotherapy in this patient population. Additional objectives include further characterization of tumor responses, patient-reported outcomes, safety, and pharmacokinetics (PK).

2. STUDY OBJECTIVES

The overall goal of the study is to assess safety and efficacy of cemiplimab as first-line treatment in patients with advanced or metastatic NSCLC whose tumors highly express PD-L1.

2.1. Primary Objectives

The primary objectives of the study are:

- To compare the OS of cemiplimab versus standard-of-care platinum-based chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumors express PD-L1 in ≥50% of tumor cells.
- To compare the PFS of cemiplimab versus standard-of-care platinum-based chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumors express PD-L1 in ≥50% of tumor cells.

2.2. Secondary Objective

- The key secondary objective of the study is to compare the ORR of cemiplimab versus platinum-based chemotherapies.

2.3. Other Secondary Objectives

The other secondary objectives of the study are the following:

- To compare the DOR of cemiplimab versus platinum-based chemotherapies
- To assess QOL of patients treated with cemiplimab versus patients receiving platinum-based chemotherapies as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13)

- To evaluate the safety and tolerability of cemiplimab versus platinum-based chemotherapies
- To measure concentrations of cemiplimab in serum and characterize the PK of cemiplimab.
- To assess immunogenicity (ADA/Nabs) to cemiplimab and any relationship with drug concentrations, efficacy and safety.
- To conduct Exposure-Response analyses on efficacy endpoints and safety.

2.4. Exploratory Objectives

- To assess correlation between the level of PD-L1 expression at baseline and efficacy of study treatment
- To assess time to new anti-tumor therapy
- To assess pharmacodynamic (PD) changes in putative serum biomarkers (which may include but are not limited to cytokines, circulating tumor nucleic acids, etc)
- To conduct PK/PD analyses on exploratory biomarkers, as appropriate.

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

The hypotheses of this study are that:

- Cemiplimab prolongs OS as compared with standard of care platinum-based chemotherapies in the first line treatment of patients with advanced or metastatic NSCLC whose tumors PD-L1 in ≥50% of tumor cells
- Cemiplimab prolongs PFS as compared with standard of care platinum-based chemotherapies in the first line treatment of patients with advanced or metastatic NSCLC whose tumors PD-L1 in ≥50% of tumor cells

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median OS has ranged from approximately 11.3 to 14.2 months (Reck 2016, Lopes 2018, Carbone 2017, Gandhi 2018, Paz-Ares 2018). For PD-1 monotherapy, a delayed treatment effect in OS has been observed in Keynote-024, Keynote-042 and Checkmate 026. In these studies, during the first 6 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in OS when compared to treatment with chemotherapy.

Historically, median PFS in patients with stages IIIB, IIIC or IV squamous and non-squamous NSCLC treated with platinum-based doublet chemotherapy has ranged from approximately 4.8 to 6.4 months (Reck 2016, Lopes 2018, Carbone 2017, Gandhi 2018, Paz-Ares 2018). With the emergence of immunotherapy and the recognition that NSCLC tumors express PD-L1, the effects of a variety of PD-1/PD-L1 inhibitors as monotherapy and in combination with chemotherapy are under investigation. Accumulating clinical data suggest that anti-PD-1

monotherapy may prolong PFS and OS in NSCLC, with the greatest clinical benefit observed in tumors expressing PD-L1, especially at high levels.

An uncontrolled study of nivolumab monotherapy in 52 chemotherapy-naïve patients with advanced NSCLC describes a response rate of 23%, including 4 patients with ongoing CRs. Reductions in tumor burden were reported, regardless of histology. Median OS was 19.4 months for the overall population and 16.8 months and NR for patients with squamous and non-squamous histology, respectively. Median PFS was 3.6 months. Of the 46 patients with tumor specimens evaluable for PD-L1 expression, the confirmed ORR was 31% for patients with ≥5% PD-L1 expression and 50% for patients with ≥50% PD-L1 expression. Median PFS for patients with ≥50% PD-L1 expression was 8.3 months with an 18-month survival of 83%. However, clinical activity was observed regardless of the degree of PD-L1 expression, with higher ORRs in patients whose tumors overexpressed PD-L1 compared with patients whose tumors had low PD-L1 expression across all expression levels. The regimen was extremely well tolerated with mostly low-grade AEs (Gettinger 2016).

Similarly, pembrolizumab has been investigated as monotherapy in a group of patients with mixed histology NSCLC and shown to have anti-tumor activity (Garon 2015). Specifically, in the treatment-naïve cohort (n=101), an ORR of 24.8% was observed, along with a median PFS of 6.0 months (range: 4.1 to 8.6 months) and median OS of 16.2 months (range: 16.2 months to NR). In the PD-L1 high expressing (≥50%) treatment-naïve group (n=62), the ORR was 50.5%, median PFS was 12.5 months (range: 2.4 to 12.5 months), and median OS was not reached.

Keynote-024, an open-label, phase 3 trial with 305 patients with previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumors were randomized to receive either pembrolizumab (at a fixed dose of 200 mg Q3W) or the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. Median OS was 30.0 months (95% CI, 18.3 months to not reached) in the pembrolizumb group versus 14.2 months (95% CI, 9.8 to 19.0 months) in the chemotherapy group (hazard ratio [HR], 0.63; 95% CI, 0.47 to 0.86). Median PFS was 10.3 months (95% CI: 6.7 months to not reached) in the pembrolizumab group versus 6.0 months (95% CI: 4.2 to 6.2) in the chemotherapy group (HR for disease progression or death: 0.50; 95% CI: 0.37 to 0.68; p=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response (DOR) was longer (not reached [range: 1.9+ to 14.5+ months] vs. 6.3 months [range: 2.1+ to 12.6+]), and treatment-related AEs of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related AEs (26.6% vs. 53.3%) (Reck 2016). The results of this study led to the US FDA approving pembrolizumab (KEYTRUDA, Merck & Co., Inc.) on October 24, 2016, for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 ≥50%, as determined by the PD-L1 IHC pharmDx 22C3 assay (Dako, North America, Inc.).

Keynote-042 is an open-label, phase 3 trial in which 1274 patients with previously untreated advanced NSCLC, without EGFR or ALK mutations and with a PD-L1 tumor proportion score (TPS) of ≥1% were randomized to receive either pembrolizumab (at a fixed dose of 200 mg Q3W) or the investigator's choice of platinum-based chemotherapy.

The primary endpoint of the study was OS. Pembrolizumab did provide a survival benefit vs. chemotherapy in the overall patient population, TPS ≥1%, median OS was 16.7 months (95% CI: 13.9 to 19.7) in the pembrolizumab group versus 12.1 months (95% CI: 11.3 to 13.3) in the chemotherapy group (HR for disease progression or death: 0.81; 95% CI: 0.71 to 0.93; p=0.0018). However, the benefit was driven by the PD-L1 high population (≥50% expression, HR=0.69). Pembrolizumab did not provide a survival benefit in the 1-49% PD-L1 population (HR=0.92). In patients with TPS ≥50%, the median OS was 20.0 months (95% CI: 15.4 to 24.9) in the pembrolizumab group versus 12.2 months (95% CI: 10.4 to 14.2) in the chemotherapy group (HR for disease progression or death: 0.69; 95% CI: 0.56 to 0.85; p=0.0003). In patients with TPS ≥20%, median OS was 17.7 months (95% CI: 15.3 to 22.1) in the pembrolizumab group versus 13.0 months (95% CI: 11.6 to 15.3) in the chemotherapy group (HR for disease progression or death: 0.77; 95% CI: 0.64 to 0.92; p=0.0020). In patients with TPS ≥50%, median PFS was 7.1 months (95% CI: 5.9 to 9.0) in the pembrolizumab group versus 6.4 months (95% CI: 6.1 to 6.9) in the chemotherapy group (HR=0.81 [95% CI, 0.67-0.99]; p=0.0170), which did not meet protocol-specified significance boundary.

The median DOR was 20.2 months (range: 2.1+ to 31.2+ months) in the pembrolizumab arm vs. 8.3 months in the chemotherapy arm (range: 1.8+ to 28.1) for patients with TPS ≥50%. Treatment-related AEs of any grade were less frequent in the pembrolizumab arm (occurring in 62.7% vs. 89.9% of patients), as were grade 3, 4, or 5 treatment-related AEs (17.8% vs. 41.0%) despite longer exposure (De Lima Lopes 2018).

Because of the relatively stronger effect of non-proportional hazard in PFS and in OS seen in Keynote-042 for the patients with TPS ≥50% compared to that seen in Keynote-024, the statistical assumptions for PFS in this study have been modified in Amendment 6, and required an increase in study size.

The phase 3 CheckMate 026 trial investigated the efficacy of first-line treatment with nivolumab compared to platinum-based doublet chemotherapy in patients with advanced NSCLC and PD-L1 positive tumors (defined as present in 1% or more tumor cells). A total of 541 patients were randomized 1:1 to nivolumab or chemotherapy. Patients who progressed on chemotherapy could crossover to nivolumab as second-line treatment. In the 423 patients with 5% or greater PD-L1 expression, PFS was 4.2 months with nivolumab and 5.9 months with chemotherapy (HR: 1.15; 95% CI: 0.91 to 1.45, p=0.25). Overall survival was 14.4 months for nivolumab versus 13.2 months for chemotherapy (HR: 1.02; 95% CI: 0.80 to 1.30). Among all treated patients, any and serious treatment-related AEs were 71% and 18% with nivolumab, and 92% and 51% with chemotherapy, respectively (Socinski 2016).

Cemiplimab is a mAb to the PD-1 receptor that blocks PD-1/PD-L1-mediated T-cell inhibition, whose mechanism of action is similar to other PD-1 inhibitors in development. Early clinical data from study R2810-ONC-1423 suggest that cemiplimab has anti-tumor activity in patients with NSCLC. Moreover, in preclinical models, the anti-tumor activity of cemiplimab was similar to that observed with antibodies that were generated based on the publicly available genetic sequences of pembrolizumab and nivolumab, anti-PD-1 antibodies approved for the treatment of melanoma, NSCLC, and renal cell carcinoma (see the Investigator's Brochure for further details of preclinical pharmacology and anti-tumor activity of cemiplimab). These data support that first-line cemiplimab administered as monotherapy at 350 mg Q3W is likely to

prolong PFS in patients with advanced or metastatic, squamous or non-squamous NSCLC whose tumors express PD-L1.

3.2. Rationale

3.2.1. Rationale for Study Design and Population

This study is a randomized, global, open-label, phase 3 study comparing cemiplimab monotherapy with standard-of-care chemotherapy in patients with advanced or metastatic, squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells and who have received no prior systemic treatment for their advanced disease. The population selected for inclusion in this study represents a large proportion of the patients with newly diagnosed advanced lung cancer for whom the first-line, standard-of-care treatment option is chemotherapy. Despite available therapies, the disease often progresses. Subsequent treatment options have been limited, and the 5-year survival is low with few apparent cures. Non-small cell lung cancer tumors express PD-L1, and preliminary data suggest that use of PD-1/PD-L1 inhibitors in first-line treatment either as monotherapy or in combination with chemotherapy may benefit patients whose tumors express high levels of PD-L1 (compared with those that either do not express PD-L1 or express low levels of PD-L1); hence, the focus on including only patients whose tumors express PD-L1 in ≥50% of tumor cells. The study is open-label because chemotherapy is administered for a limited timeframe compared with cemiplimab, which is intended to be given for up to 2 years. Imposing a double-blind design would require patients in the chemotherapy treatment group to receive placebo until the time of disease progression, and this was not viewed as acceptable given the nature of the disease. Patients in the chemotherapy treatment group will be given the option to crossover to cemiplimab monotherapy at the time of disease progression given that use of PD-1 inhibitor is now the standard-of-care for second-line treatment of NSCLC (Ettinger 2016).

3.2.2. Rationale of Endpoints/Objectives

The primary objective of this study is to compare the primary endpoints of OS and PFS in patients treated with cemiplimab to patients treated platinum-based chemotherapy. Overall survival has been recognized as the gold standard for demonstrating benefit of antineoplastic therapies in randomized clinical trials.

Progression-free survival, the time to tumor progression (based on Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1] criteria [Eisenhauer 2009]) or death, was chosen as a primary endpoint because PFS is recognized as a marker of clinical benefit. Based on data released for another PD-1 antibody, PFS would be expected to be prolonged in patients with NSCLC whose tumors express PD-L1 in ≥50% of tumor cells. Disease progression will be determined based on the RECIST 1.1 criteria (Eisenhauer 2009). The first radiographic tumor assessment will occur after 9 weeks of study treatment and every 9 weeks thereafter. Further, to diminish bias in the assessment of disease progression in this open-label study, an independent review committee (IRC), which will be blinded to treatment assignment, will be utilized to adjudicate tumor responses.

Efficacy responses to be assessed will also include assessment of ORR and DOR to treatment. From a patient perspective, preservation of QOL is important; therefore, QOL will be assessed through the use of 2 validated questionnaires.

3.2.3. Rationale for Choice of PD-L1 Expression Levels

Preliminary data suggest that tumor cell PD-L1 expression may correlate with anti-PD-1 clinical activity in both squamous and non-squamous NSCLC (Gadgeel 2016, Gettinger 2015). In an exploratory analysis of an ongoing study, nivolumab monotherapy in chemotherapy-naïve patients with advanced NSCLC resulted in higher response rates and more prolonged PFS and 1-year OS rates as the level of PD-L1 expression increased (1%, 5%, 10%, 25%, 50%) (Gettinger 2015). Merck & Co. recently reported that pembrolizumab was superior compared with chemotherapy for both the primary endpoint of PFS and the secondary endpoint of OS in the KEYNOTE-024 trial (Reck 2016) (Reck 2019). The KEYNOTE-024 trial included 305 treatment-naïve patients with advanced NSCLC whose tumors expressed PD-L1 in ≥50% of tumor cells (as measured with the PD-L1 IHC 22C3 assay [Dako, North America, Inc.]), and led to the approval by the US FDA of pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the first-line treatment of patients with metastatic NSCLC, whose tumors express PD-L1 ≥50% (De -Lima Lopes 2018).

The Keynote-042 trial included 1274 treatment-naïve patients with advanced NSCLC whose tumors had a TPS ≥1% and were negative for EGFR and ALK mutations. While patients receiving pembrolizumab experienced improved OS regardless of the level of PD-L1 expression, significant improvement in OS was observed only in those with TPS ≥50%.

Bristol-Meyers Squibb reported that their first-line lung cancer trial had failed because the primary endpoint of PFS was not met. The trial was designed to assess the benefit of nivolumab monotherapy in a patient population whose tumors expressed PD-L1 in ≥5% of tumor cells (as measured with the PD-L1 IHC 28-8 assay [Dako, North America, Inc.]) (Socinski 2016). Therefore, in this study, only patients whose tumors express PD-L1 in ≥50% of tumor cells (as measured with the PD-L1 IHC 22C3 pharmDx) will be eligible to participate.

The use of the PD-L1 IHC 22C3 pharmDx assay for decisions regarding treatment with cemiplimab is considered investigational.

3.2.4. Rationale for Cemiplimab Dose and Schedule Selection

In the ongoing first-in-human (FIH) study, the 3 mg/kg Q2W intravenous (IV) dose has shown anti-tumor activity and acceptable safety in the FIH study, including in NSCLC patients; efficacy was also observed at 1 mg/kg Q2W. As many standard chemotherapy treatments for NSCLC are dosed on a Q3W schedule, the clinical development strategy of cemiplimab coalesced around a Q3W treatment interval. The ongoing clinical development of cemiplimab also seeks to incorporate a flat dosing paradigm. As such, a Q3W flat dose regimen has been selected that is expected to provide a similar clinical efficacy and safety profile to that observed for the 3mg/kg Q2W regimen.

A flat IV cemiplimab dose of 350 mg Q3W was selected, based on population PK modeling and simulation, as it is expected to provide exposure that closely replicates that observed in patients (mean weight - 80 kg) for the 3 mg/kg Q2W IV regimen in the ongoing FIH study R2810-ONC-

1423 (NCT02383212). Simulations of cemiplimab exposure in 1000 patients using population PK analyses indicated that: 1) a 350 mg Q3W dose in patients resulted in similar (≤20% difference) C_{trough}, AUC_{12W}, and C_{max} as compared to the 3 mg/kg Q2W dose in the FIH patient population (80 kg), and exceeded those observed at the 1 mg/kg Q2W dose, and 2) the variability in cemiplimab exposure (CV%) was similar for body-weight adjusted doses as compared to flat doses. A similarity in cemiplimab exposure with 350 mg Q3W compared to 3 mg/kg Q2W has been confirmed in Study R2810-ONC-1540. Given the similar exposure at 350 mg Q3W when compared to the 3 mg/kg Q2W regimen, a similar efficacy/safety profile is also expected. Therefore, the 350 mg Q3W IV dose of cemiplimab is being proposed for phase 3 studies in patients with NSCLC, and across the cemiplimab program.

3.2.5. Rationale for Standard-of-Care Chemotherapy as Comparator

Platinum-based doublet chemotherapy is currently recommended as first-line treatment for advanced or metastatic NSCLC (Reck 2014, Ettinger 2016), and will therefore serve as the active comparator in this study. There is no single "best" platinum-based doublet standard chemotherapy for squamous or non-squamous NSCLC. Randomized studies that have compared various regimens have not shown any difference in survival (Fossella 2003, Scagliotti 2002, Schiller 2002). Pemetrexed-based doublets are restricted to non-squamous NSCLC (ALIMTA® US PI, ALIMTA European Union Summary of Product Characteristics).

The PARAMOUNT study is a recent large study of pemetrexed in advanced non-squamous NSCLC (Paz-Ares 2013). In this study, 939 patients with advanced non-squamous NSCLC were given 4 cycles of pemetrexed-cisplatin induction therapy. Of these patients, 539 patients with no disease progression and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were then randomly assigned in a 2:1 ratio to receive maintenance pemetrexed (500 mg/m^2 on day 1 of 21-day cycles; n=359) or placebo (n=180). The results demonstrated that maintenance pemetrexed resulted in a statistically significant 22% reduction in the risk of death (HR: 0.78; 95% CI: 0.64 to 0.96; p=0.0195; median OS: pemetrexed, 13.9 months, placebo, 11.0 months). Survival on pemetrexed was consistently improved for all patient subgroups, including the induction response subgroups: complete/partial responders (n=234) OS HR: 0.81; 95% CI 0.59 to 1.11 and stable disease (n=285) OS HR: 0.76; 95% CI, 0.57 to 1.01. However, drug-related grade 3 to 4 toxicities of anemia, fatigue, and neutropenia were significantly higher in pemetrexed-treated patients. As such, the investigator in this study will decide, in consultation with the patient, whether or not to include pemetrexed maintenance in the treatment regimen. A decision not to include pemetrexed maintenance will be documented in the case report form (CRF).

Both cisplatin and carboplatin are used, although carboplatin may be associated with fewer side effects. Given this and that clinical practice preferences will vary in this global study, investigators will be given the option to choose from several approved treatment regimens.

Randomized, controlled studies of patients with stage IV disease and good performance status have shown that cisplatin-based chemotherapy improves survival and palliates disease-related symptoms (Weick 1991).

Administration of 4 cycles of chemotherapy is standard, but up to 6 cycles may be given in non-progressing patients that are tolerating treatment. For this study, patients will be administered

chemotherapy for at least 4 cycles and up to 6 cycles, depending on patient tolerability and disease assessment.

3.2.6. Rationale for Crossover of All Patients to Cemiplimab

The pre-specified interim analysis, performed according to Table 8, demonstrated that patients treated with cemiplimab monotherapy had a significant increase in OS. Cemiplimab decreased the risk of death by 32.4% (HR=0.676; CI:0.525-0.870 p=0.002) compared to platinum-doublet chemotherapy. Median OS was 22.1 months (95% CI: 17.7, NE) in the cemiplimab arm and 14.3 months (95% CI: 11.7, 19.2) in the chemotherapy arm. Additionally, no new cemiplimab safety signal was identified.

As a statistically significant and clinically meaningful benefit of cemiplimab over platinum-based chemotherapy has been demonstrated in first-line, PD-L1 ≥50% NSCLC, the Sponsor has decided to allow patients on the chemotherapy doublet arm to cross-over to cemiplimab with immediate effect to ensure all patients on the study have access to the treatment that has been demonstrated to be superior for prolonging survival.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, and height) and disease characteristics, including PD-L1 status as well as medical and oncology history.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoints are OS and PFS as assessed by a blinded IRC using RECIST 1.1 (Eisenhauer 2009; see Appendix 2).

Overall survival will be defined as the time from randomization to the date of death. A patient who has not died will be censored at the last known date of contact.

Progression-free survival will be defined as the time from randomization to the date of the first documented tumor progression, as determined by the IRC (using RECIST 1.1) or death due to any cause. Patients will be censored according to rules listed below:

1. Patients who do not have a documented tumor progression or death will be censored on the date of their last evaluable tumor assessment.
2. Patients who do not have a documented tumor progression or death before initiation of new anti-tumor therapy will be censored on the date of their last evaluable tumor assessment prior to or on the date of new anti-tumor therapy.
3. Patients who withdraw consent before taking any study treatment, and as a consequence have no post-baseline tumor assessment, will be censored at the date of randomization.
4. Patients who do not have any evaluable tumor assessments after randomization and do not die will be censored on the date of randomization.

4.2.2. Key Secondary Endpoints

The key secondary endpoint in the study will be ORR.

Objective response rate will be defined as the number of patients with a best overall response (BOR) of confirmed CR or PR divided by the number of patients in the efficacy analysis set.

Best overall response will be defined as the best overall response, as determined by the IRC per RECIST 1.1, between the date of randomization and the date of the first objectively documented progression or the date of subsequent anti-cancer therapy, whichever comes first.

4.2.3. Other Secondary Endpoints

Other secondary endpoints will include DOR and QOL. Duration of response will be defined as the time between the date of first response (CR or PR) to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Quality of life will be measured by EORTC QLQ-C30 and EORTC QLQ-LC13.

Other secondary endpoints will also include the safety and tolerability of cemiplimab. To evaluate the safety and tolerability of cemiplimab versus platinum-based chemotherapies, safety and tolerability will be measured by the incidence of AEs, serious adverse events (SAEs), deaths, and laboratory abnormalities. To assess immunogenicity (ADA/Nabs) to cemiplimab and any relationship with drug concentrations, efficacy and safety. To conduct Exposure-Response analyses on efficacy endpoints and safety.

4.2.4. Exploratory Efficacy Endpoint

Time to new anti-tumor therapy will be an exploratory endpoint. Time to new anti-tumor therapy is defined as the time between the date of randomization and the first date of initiation of new anti-tumor therapy. To assess pharmacodynamic (PD) changes in putative serum biomarkers (which may include but are not limited to cytokines, circulating tumor nucleic acids, etc). To conduct PK/PD analyses on exploratory biomarkers, as appropriate.

4.3. Pharmacokinetic Variables

Cemiplimab concentrations in the serum of patients randomized to the cemiplimab treatment group will be assessed at multiple time points throughout the treatment and follow-up periods.

Pharmacokinetic variables may include, but are not limited to, the following:

- C_{eoi} – concentration at end of infusion
- C_{trough} – pre-infusion concentration
- t_{eoi} – time of end of infusion

4.4. Immunogenicity Assessment Variables

Immunogenicity assessment will include the assessment of anti-drug antibody (ADA) and the assessment of neutralizing ADA (NAb). Anti-drug antibody variables will be measured in samples from patients randomized to the cemiplimab treatment group and will include status (positive or negative) and titer as follows:

- Treatment emergent – defined as any positive response in the ADA assay post-first infusion when baseline results are negative
- Treatment boosted – defined as any post-treatment positive ADA assay response that is at least 9-fold over the baseline titer level when baseline is positive in the ADA assay
- Titer category is defined based on values as (titer value category):
  - Low (titer <1000)
  - Moderate (1000≤ titer ≤10,000)
  - High (titer >10,000)

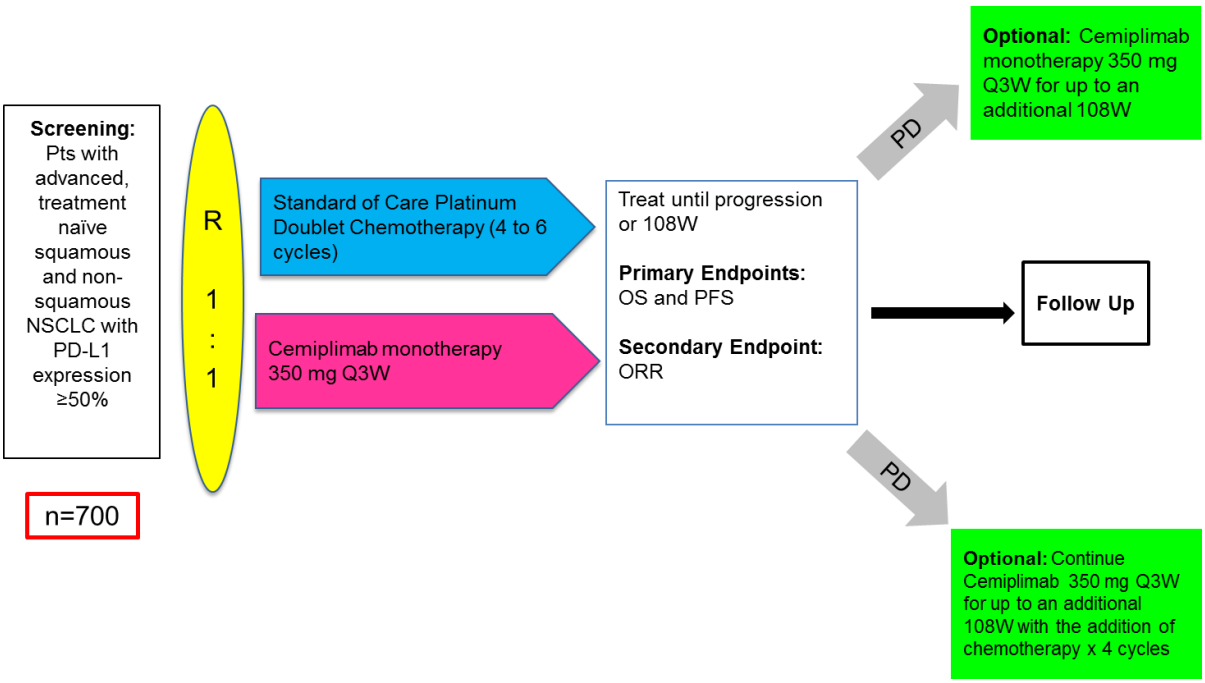
If a sample is confirmed positive in the ADA assay, the presence or absence of neutralizing activity of the ADA in the sample will be assessed.

5. STUDY DESIGN

5.1. Study Description and Duration

This is a randomized, multicenter, open-label, pivotal phase 3 study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with stage IIIB or IIIC, or stage IV squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells and who have received no prior systemic treatment for their advanced disease. The study will consist of the following 3 periods: screening, treatment, and follow-up. A study flow diagram is presented in Figure 1.

Figure 1: Study Flow Diagram



Abbreviations: ORR=objective response rate; OS=overall survival; PD=progressive disease; PD-L1=programmed death ligand 1; PFS=progression-free survival; Q3W=every 3 weeks; R=randomized; W=weeks

Screening Visit

Patients will undergo a screening evaluation to determine their eligibility within 28 days prior to randomization (see Table 4). Programmed cell death ligand-1 expression in tumor tissue (archival or recently obtained biopsy collected; refer to laboratory manual) will be assessed using a validated PD-L1 IHC assay that reports 50% positivity by a central laboratory (see Section 8.2.4.3). Patients whose tumors express PD-L1 in ≥50% of tumor cells will continue in screening. Patients whose tumors express PD-L1 in <50% of tumor cells will be excluded from the study. Tumor tissue will also be tested for mutations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) and for human homolog of the transforming gene v-ros of the avian sarcoma virus UR2 (ROS1) fusions.

Baseline radiographic tumor assessments should also be performed within 28 days prior to randomization (see Table 4). These assessments will not be reviewed by IRC for eligibility assessment.

Treatment Period

Eligible patients will be randomized to one of the following 2 treatment groups:

- Cemiplimab 350 mg monotherapy
- Standard-of-care chemotherapy

Randomization will be stratified by histology (non-squamous versus squamous) and geographic region (Europe, Asia, or Rest of World [ROW]). Treatment should begin within 3 days of randomization. Details of the treatment regimens are provided in Section 7.1.

Patients with NSCLC randomized to chemotherapy may receive one of the following regimens:

- Paclitaxel + cisplatin or carboplatin
- Gemcitabine + cisplatin or carboplatin
- Pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance (it is strongly recommended that patients with squamous NSCLC do not receive pemetrexed-containing regimens)

The choice of chemotherapy from the above options will be at the discretion of the investigator and is to be decided and documented prior to randomization.

For the purposes of this study, a treatment cycle will be defined as 21 days or 3 weeks.

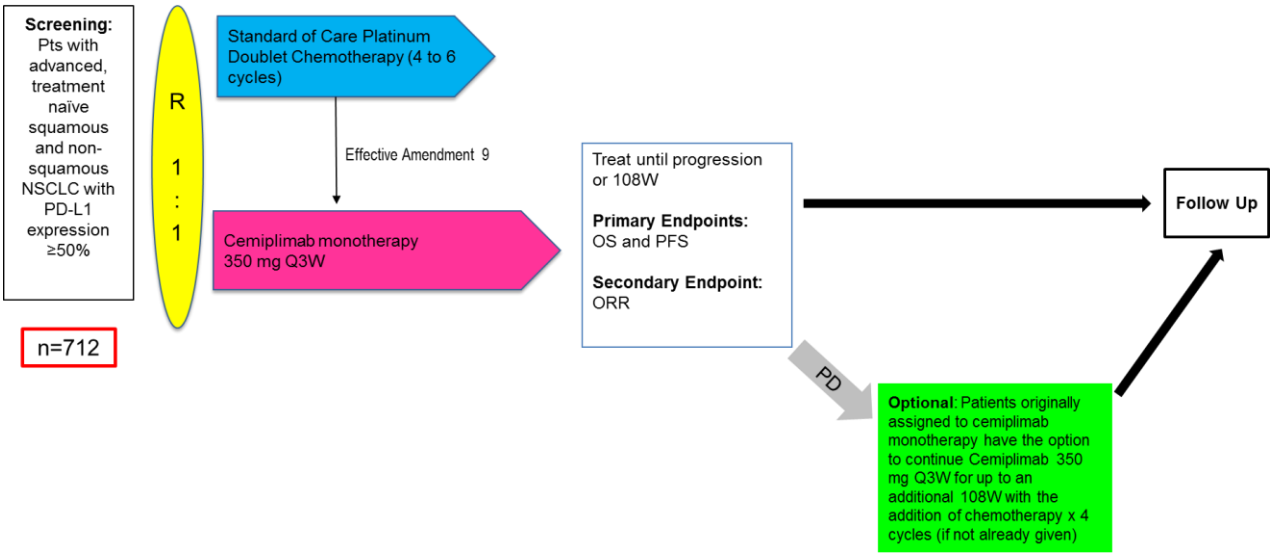
Laboratory results for safety assessments must be available prior to dosing of cemiplimab or chemotherapy on day 1 of each dosing cycle (Table 5).

At the time of Amendment 9 finalization, the primary endpoint of OS has been reached. Based on the demonstrated improvement in OS in patients receiving cemiplimab, all patients randomized to receive platinum-based chemotherapy are permitted to cross over to receive treatment with cemiplimab 350 mg Q3W for up to 108 additional weeks (36 cycles) prior to disease progression (Figure 2). Patients eligible to cross over to cemiplimab include the following:

- Patients who are actively being treated with chemotherapy
- Patients who have completed chemotherapy and are in follow-up, but whose disease has not yet progressed
- Patients who have discontinued chemotherapy and have progressed, but have not yet crossed over to cemiplimab for any reason

The timing of the crossover for each patient will be decided by the treating physician. All other patients will continue study treatment as outlined in the protocol until either their disease progresses or they complete 108 weeks of treatment with cemiplimab.

Figure 2: Study Flow Diagram Implemented in Amendment 9



Treatment Period: Cemiplimab Patients

Patients assigned to the cemiplimab treatment group will receive cemiplimab 350 mg as an IV infusion on day 1 of every treatment cycle for up to 108 weeks or until RECIST 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent.

Radiographic tumor assessments will be obtained in all patients every 3 cycles beginning at week 9 (day 63 ±5 days), until disease progression, loss to follow-up, withdrawal of consent, death, or initiation of another anti-cancer treatment. Disease progression determined by the investigator will be used for clinical management of the patient. IRC-assessed RECIST 1.1-defined progressive disease is required to declare progression of the purposes of PFS, ORR, and DOR endpoints, and for the purpose of receiving extended treatment of chemotherapy in addition to cemiplimab.

Safety will be assessed through the occurrence of TEAEs, vital sign evaluation, physical examination, and laboratory analyses (Table 5). Blood samples will be collected to measure serum concentrations of cemiplimab and ADA and NAb titers; for all patients, blood samples will be collected to measure exploratory biomarkers (Table 5). To assess disease-related

symptoms, patients will be asked to complete QOL questionnaires at time points specified in Table 5.

Treatment Period: Chemotherapy Patients

Patients assigned to chemotherapy will receive one of the protocol-specified options of platinum-doublet chemotherapy treatment for 4 to 6 cycles or until IRC-assessed RECIST 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. The choice of chemotherapy must be documented prior to randomization of the patient. At the discretion of the investigator, patients with non-squamous NSCLC treated with pemetrexed and cisplatin or carboplatin may receive pemetrexed maintenance therapy until disease progression. The investigator will decide in consultation with the patient whether or not to include pemetrexed maintenance in the treatment regimen. A decision not to include pemetrexed maintenance will be documented in the CRF.

Radiographic tumor assessments will be obtained in all patients beginning at week 9 (day 63 ±5 days) every 3 cycles until disease progression, loss to follow-up, withdrawal of consent, death, or initiation of another anti-cancer treatment. Disease progression will be defined using RECIST 1.1 criteria (Appendix 2). Investigators and the IRC (Section 5.3.1; who will be blinded to treatment assignment) will assess response to therapy using RECIST 1.1 criteria. Disease progression determined by the investigator will be used for clinical management of the patient. Disease progression and BOR determined by the blinded IRC will be used for endpoint assessments.

Safety will be assessed through the occurrence of TEAEs, vital sign evaluation, physical examination, and laboratory analyses (Table 5). To assess disease-related symptoms, patients will be asked to complete QOL questionnaires at time points specified in Table 5.

Effective in Amendment 9, all patients are permitted to cross over to receive cemiplimab 350 mg Q3W for up to 108 additional weeks prior to disease progression.

Follow-Up Period

Patients will have follow-up visits every 6 weeks for approximately 6 months and then at 9 months and 12 months after the last dose of treatment.

The study will end when the survival analysis is complete. The last patient last visit is 48 months from the enrollment of the last patient. The duration of the study for each patient will be approximately 48 months.

Follow-up Period: Cemiplimab Patients

- Patients in the cemiplimab treatment group will enter the follow-up period after completion of the 108-week treatment period or when the decision is made to discontinue cemiplimab therapy.
- Patients who discontinued cemiplimab treatment early due to CR or PR, who then have disease progression while in follow-up may be offered the option to begin retreatment with cemiplimab 350 mg Q3W for up to 108 weeks. Study assessments for these patients will be performed as specified in Table 5.

- Follow-up study assessments will be performed as specified in Table 6. Patients assigned to the cemiplimab treatment group will have blood samples taken for PK and ADA testing as specified in Table 6.

Follow-up Period: Chemotherapy Patients

- Patients in the chemotherapy treatment group will enter follow-up after completion of 4 to 6 cycles, at the time of initial IRC-assessed, RECIST 1.1-defined progressive disease while on therapy, or early termination (Section 8.1.2).
- Effective in Amendment 9, all patients are permitted to cross over to receive cemiplimab 350 mg Q3W for up to 108 additional weeks prior to disease progression.
- Patients that opt to be treated with anti-cancer treatments including cemiplimab, other than chemotherapy, will be expected to complete all follow-up assessments as specified in Table 6.

Follow-up Period: Chemotherapy Crossover Patients

- Patients who experience IRC-assessed RECIST 1.1-defined progressive disease while on chemotherapy or after completion of chemotherapy will be offered the option at the time of progression to receive cemiplimab 350 mg Q3W for up to 108 weeks, provided they meet the criteria for cemiplimab therapy (Section 6.2).
- Patients who crossover to receive cemiplimab 350 mg Q3W for up to 108 weeks will enter follow-up after completion of up to 108 weeks of treatment, at the time of progression while on therapy, or early termination. Follow-up assessments for these patients will be performed as specified in Table 6.
- NOTE: Effective in Amendment 9, all patients are permitted to crossover to receive cemiplimab 350 mg Q3W for up to 108 additional weeks (36 cycles) prior to disease progression.

Extended Treatment: Cemiplimab Continuation plus Chemotherapy Patients

- Patients originally assigned to receive cemiplimab, who experience IRC-assessed RECIST 1.1-defined progressive disease on therapy may continue treatment with cemiplimab 350 mg Q3W for up to 108 additional weeks, along with the addition of histology-specific chemotherapy for 4 cycles, provided they meet specific criteria and the patient has not completed the 108-week treatment period (Section 7.8.1). Alternatively, these patients may opt to initiate a new anti-cancer treatment.
- Histology-specific chemotherapy is defined as paclitaxel plus cisplatin or carboplatin for squamous cell NSCLC and pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance for non-squamous NSCLC.
- Patients who are treated with cemiplimab plus histology-specific chemotherapy beyond the initial determination of progressive disease will enter follow-up after completion of up to 108 additional weeks of treatment, at the time of further progression while on therapy, or early termination. Follow-up assessments for these patients will be performed as specified in Table 6.

5.1.1. End of Study Definition

The study will end when the survival analysis is complete.

5.2. Planned Interim Analysis

Five interim analyses are planned. Refer to Section 10.6 for details.

5.3. Study Committees

Two independent study committees will be utilized, an IRC and an Independent Data Monitoring Committee (IDMC).

5.3.1. Independent Review Committee

A blinded IRC composed of members who are independent from the sponsor and the study investigators will review all available (de-identified) radiographic tumor assessments to determine tumor response using RECIST 1.1 criteria. The IRC-determined tumor response will be used in the analysis of the PFS, ORR, and DOR endpoints. Details of the IRC responsibilities and procedures will be specified in the IRC charter.

5.3.2. Independent Data Monitoring Committee

An IDMC composed of members who are independent from the sponsor and the study investigators will monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will also monitor and review the efficacy interim analyses for OS.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC will be described in the IDMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 700 patients will be randomized at approximately 250 global sites. Of the 700 patients, it is estimated that approximately two-thirds of the patients will have non-squamous histology and one-third will have squamous histology. It is estimated that approximately 20% to 25% of all NSCLC patients will have tumors that express PD-L1 in ≥50% of tumor cells.

6.2. Study Population

Patients included in this study will be men and women ≥18 years of age, diagnosed with stage IIIB or IIIC or stage IV squamous or non-squamous NSCLC, who are not candidates for definitive chemotherapy and radiation, whose tumors express PD-L1 in ≥50% of tumor cells (using the PD-L1 IHC 22C3 pharmDx assay) and who have received no prior systemic treatment for their advanced disease. The use of the PD-L1 IHC 22C3 pharmDx assay for decisions regarding treatment with cemiplimab is considered investigational.

The study population will be limited to previous and current smokers as the benefit of PD-1 blockade has not been shown in never-smokers. Patients with actionable mutations will be excluded because they respond best to targeted therapy.

6.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Men and women ≥18 years of age
2. Patients with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or stage IIIC disease who are not candidates for treatment with definitive concurrent chemoradiation or patients with stage IV disease who received no prior systemic treatment for recurrent or metastatic NSCLC.
    a. Patients who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease more than 6 months after completing therapy are eligible
3. Archival or newly obtained formalin-fixed tumor tissue from a metastatic/recurrent site, which has not previously been irradiated.
    a. Tissue may be obtained from the primary site if it is still in place and the other metastatic sites are either not accessible (ie, brain), cannot be used (ie, bone), or the biopsy would put the patient at undue risk.
    b. If an archival biopsy is used, it must be less than 5 months old
4. Tumor cells expressing PD-L1 in ≥50% of tumor cells by IHC performed by the central laboratory
5. At least 1 radiographically measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria (see Appendix 2). Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site.
6. ECOG performance status of ≤1

7. Anticipated life expectancy of at least 3 months
8. Adequate organ and bone marrow function as defined below:
    a. Hemoglobin ≥9.0 g/dL
    b. Absolute neutrophil count ≥1.5 × 10^9/L
    c. Platelet count ≥100,000/mm^3
    d. Glomerular filtration rate (GFR) >30 mL/min/1.73m^2
    e. Total bilirubin ≤1.5 × upper limit of normal (ULN) (if liver metastases ≤3 × ULN), with the exception of patients diagnosed with clinically confirmed Gilbert's syndrome
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN or ≤5 × ULN, if liver metastases
    g. Alkaline phosphatase ≤2.5 × ULN (or ≤5.0 × ULN, if liver or bone metastases)
    h. Not meeting criteria for Hy's law (ALT >3 × ULN and bilirubin >2 × ULN)
9. Willing and able to comply with clinic visits and study-related procedures
10. Provide signed informed consent
11. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Patients that have never smoked, defined as smoking ≤100 cigarettes in a lifetime
2. Active or untreated brain metastases or spinal cord compression. Patients are eligible if central nervous system (CNS) metastases are adequately treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. Patients must be off (immunosuppressive doses of) corticosteroid therapy.
3. Patients with tumors tested positive for EGFR gene mutations, ALK gene translocations, or ROS1 fusions (Section 8.2.1). All patients should have tumor evaluations for EGFR mutations, ALK rearrangement, and ROS1 fusions confirmed by a central laboratory.
4. Encephalitis, meningitis, or uncontrolled seizures in the year prior to randomization.
5. History of interstitial lung disease (eg, idiopathic pulmonary fibrosis, organizing pneumonia) or active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management. A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved ≥6 months prior to randomization.
6. Patients with active, known, or suspected autoimmune disease that has required systemic therapy in the past 2 years. Patients with vitiligo, type I diabetes mellitus, and hypothyroidism (including hypothyroidism due to autoimmune thyroiditis) only requiring hormone replacement are permitted to be randomized.
7. Patients with a condition requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of randomization. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being

administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.

8. Another malignancy that is progressing or requires treatment, with the exception of nonmelanomatous skin cancer that has undergone potentially curative therapy, or in situ cervical carcinoma or any other tumor that has been treated, and the patient is deemed to be in complete remission for at least 2 years prior to randomization, and no additional therapy is required during the study period.
9. Uncontrolled infection with hepatitis B or hepatitis C or human immunodeficiency virus; or diagnosis of immunodeficiency
    a. Patients with hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted.
    b. Patients who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.
    c. Patients with HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted.
10. Exclusion criterion removed
11. Active infection requiring systemic therapy within 14 days prior to randomization.
12. Prior therapy with anti-PD-1 or anti-PD-L1. Prior exposure to other immunomodulatory or vaccine therapy such as anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies is permitted, but the last dose of such an antibody should have been at least 3 months prior to the first dose of study drug.
13. Treatment-related immune-mediated AEs from immune-modulatory agents (including but not limited to anti-PD1/PD-L1 mAbs, anti-CTLA4 mAbs, and phosphoinositol 3-kinase [PI 3-K]-δ inhibitors) that have not resolved to baseline at least 3 months prior to initiation of treatment with study therapy. Patients are excluded from treatment with cemiplimab if they experienced immune-mediated AEs related to prior treatment with a blocker of the PD-1/PD-L1 pathway that were grade 3 or 4 in severity and/or required discontinuation of the agent, regardless of time of occurrence.
14. Receipt of an investigational drug or device within 30 days of screening or within 5 half-lives of the investigational drug (whichever is longer)
15. Receipt of a live vaccine within 30 days of planned start of study medication
16. Major surgery or significant traumatic injury within 4 weeks prior to first dose
17. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments
18. Exclusion criterion removed
19. Known psychiatric or substance abuse disorder that would interfere with participation with the requirements of the study, including current use of any illicit drugs
20. Pregnant or breastfeeding women.

21. Women of childbearing potential* or men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include:

    - stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    - intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    - bilateral tubal ligation
    - vasectomized partner (provided that partner is the sole sexual partner of the WOCBP patient and that the vasectomized partner has received medical assessment of the surgical success)
    - and/or sexual abstinence†, ‡.
    - Women of child bearing potential is defined as women who are fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

      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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

      Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

      † 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 drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

      ‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

22. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded from this study
23. Prior treatment with idelalisib
24. Member of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor
25. Recipients of organ transplants

26. Active or latent tuberculosis. Latency should be ruled out by purified protein derivative (PPD)/QuantiFERON testing according to local guidelines in high risk individuals at the discretion of the investigator

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.2 and Table 6.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Patients

Patients who discontinue from the study will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Cemiplimab (REGN2810) will be supplied as a liquid in sterile, single-use vials. Each vial will contain cemiplimab at a concentration of 50 mg/mL.

Cemiplimab will be administered in an outpatient setting as a 30-minute (±10 minutes) IV infusion.

Instructions on dose preparation are provided in the pharmacy manual. Instructions on management of acute infusion reactions are provided in Section 7.4.1.

Study treatment (cemiplimab or chemotherapy) will be administered by the investigator or other designated study personnel. Patients will be randomized to receive one of the following treatment regimens:

- Cemiplimab at 350 mg as an IV infusion
- Platinum-based doublet chemotherapy (with or without maintenance therapy)

Cemiplimab will be administered Q3W for up to 108 weeks or until disease progression, unacceptable toxicity, death, or withdrawal of consent. Chemotherapy will be administered for 4 to 6 cycles as outlined in Table 1 and according to the local prescribing information and practice guidelines, or until disease progression, unacceptable toxicity, death, or withdrawal of consent.

The choice of chemotherapy will be one of the regimens shown in Table 1. The investigator may choose from one of these regimens provided that it is consistent with the local standard-of-care (Table 1). Assignment of chemotherapy choice must be made prior to randomization. Chemotherapy should be procured by the study sites as local commercial products in some countries and where allowed by local regulations; for other countries, Regeneron may provide the chemotherapy to the study sites. Preference should be given to regimens that are allowed by local regulations.

Implemented in Amendment 9, all patients are permitted to receive cemiplimab 350 mg IV per the recommendation of the IDMC (See Section 3.2.6).

Table 1: Guidelines for Platinum-Based Doublet Chemotherapy Regimens

Option	Chemotherapy Regimen	Dosing Frequency	Maintenance Therapy
1	Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days for 4 to 6 cycles	Optional pemetrexed 500 mg/m^2 IV day 1 every 21 days
2	Pemetrexed 500 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days for 4 to 6 cycles	Optional pemetrexed 500 mg/m^2 IV day 1 every 21 days
3	Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days for 4 to 6 cycles	No maintenance
4	Paclitaxel 200 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days for 4 to 6 cycles	No maintenance
5	Gemcitabine 1250 mg/m^2 IV plus cisplatin 100 mg/m^2 IV	Day 1 and day 8 (gemcitabine only) every 21 days for 4 to 6 cycles	No maintenance
6	Gemcitabine 1250 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 and day 8 (gemcitabine only) every 21 days for 4 to 6 cycles	No maintenance

Abbreviations: AUC=area under the curve; IV=intravenous; N/A=not applicable

These are general guidelines. The dosages should be according to the local prescribing information and practice guidelines.

Note that patients with GFR <50 mL/min/1.73m^2 may NOT receive cisplatin-containing regimens.

7.2. Pretreatments

Premedications should be procured by the study sites as local commercial products in some countries and where allowed by local regulations; for other countries, Regeneron may provide the premedications. Preference should be given to regimens that are allowed by local regulations.

No premedications are to be administered prior to the first administration of cemiplimab. Premedications will be allowed at subsequent doses depending on the need to manage any observed low-grade infusion reactions.

For standard-of-care chemotherapy, premedications should be administered in accordance with the local prescribing information and practice guidelines. In general, it is recommended that patients receive corticosteroids, diphenhydramine, and an H_2-receptor blocker prior to receipt of paclitaxel. It is recommended that patients receiving pemetrexed receive vitamin supplementation (folic acid and vitamin B12) and corticosteroids. Patients receiving cisplatin should be adequately hydrated prior to infusion of therapy and receive highly effective combination antiemetic therapy.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modifications of Study Treatments

7.3.1.1. Cemiplimab Monotherapy

Dose modification of cemiplimab will not be permitted.

Cemiplimab treatment may be held upon occurrence of a treatment-related AE at any time on the study. Resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the investigator and sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories:

- Patients with events that require cemiplimab to be discontinued permanently or held for more than 84 days from the last scheduled dose.
- Patients with grade ≥2 uveitis. Patients with grade 2 uveitis will generally be discontinued from cemiplimab treatment, unless there is resolution to grade ≤1 outlined in Appendix 3 AND discussion with and approval by the medical monitor. All patients with grade ≥3 uveitis will be permanently discontinued from cemiplimab.

Guidelines for cemiplimab temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in Table 2.

Table 2: Cemiplimab Dose Modifications

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to grade ≤1 or baseline	Same dose and schedule	Toxicity does not resolve within 84 days of last infusion. *Permanent discontinuation should be considered for any severe or life-threatening event.*

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to grade ≤1 or baseline	Same dose and schedule	Toxicity does not resolve within 84 days of last infusion. *Permanent discontinuation should be considered for any severe or life-threatening event.*
Nonhematological toxicity **Note:** Exceptions to be treated as for grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Clinically insignificant laboratory abnormality not meeting AE criteria	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to grades 0 to 1 or baseline	*Clinical AE resolves within 84 days*: Same dose and schedule	Toxicity does not resolve within 84 days of last infusion.
	3	Yes	Toxicity resolves to grades 0 to 1 or baseline	Same dose and schedule	Toxicity does not resolve within 84 days of last infusion.
	4	Yes	N/A	N/A	Patient must be discontinued.

Abbreviations: AE=adverse event; irAE=immune-related adverse event; N/A=not applicable
For additional information regarding AEs with a potential for irAEs, see Table 3 and Appendix 3.

7.3.1.2. Immune-Related Adverse Events

Investigators must be extremely vigilant and be ready to intervene early in the management of immune-related AE (irAEs) because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. General guidance for irAEs is provided in Table 3. The recommendations in Table 3 and Appendix 3 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 3: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold/Discontinue Cemiplimab Treatment?	Supportive Care
Grade 1	No action.	Provide symptomatic treatment.
Grade 2	May withhold treatment.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3 Grade 4	Withhold treatment. Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity.	For any severe (grade 3-4) immune-related adverse event, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine, and mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

7.3.1.3. Chemotherapy

Dose modification/reduction or temporary cessation of a given chemotherapy should be managed in accordance with the regional standard-of-care and guidelines.

7.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug (cemiplimab or chemotherapy) and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule in Table 6.

Patients who permanently discontinue from study drug (cemiplimab or chemotherapy) and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

Any patient currently receiving cemiplimab who was previously treated with a PI 3-K inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these patients, the Sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

7.3.2.1. Reasons for Permanent Discontinuation of Cemiplimab

Cemiplimab dosing will be permanently stopped in the event of pregnancy.

In addition, cemiplimab for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the investigator or sponsor. A patient may choose to discontinue cemiplimab or study participation at any time for any reason.

After at least 6 months (24 weeks) of treatment, a patient with confirmed CR may choose to stop treatment early and be followed for the duration of the study. A patient with a PR that has stabilized after 6 months and is no longer changing after 3 successive tumor assessments may also choose to stop treatment early and be followed for the duration of the study.

A patient who permanently discontinues cemiplimab treatment should continue follow-up in the study without additional treatment until disease progression, completion of all study assessments, or closure of the study (Section 6.3).

7.3.2.2. Reasons for Permanent Discontinuation of Chemotherapy

Chemotherapy should be permanently discontinued for safety reasons, compliance issues, intolerance due to toxicity, or other reasons as provided by regional guidelines and standard-of-care.

A patient who permanently discontinues from chemotherapy should continue follow-up in the study without additional treatment until disease progression, completion of all study assessments, or closure of the study (see Section 6.3).

Investigators should follow the guidelines for cemiplimab and for chemotherapy when treating patients with the combination of cemiplimab and chemotherapy.

7.4. Management of Acute Reactions

7.4.1. Acute Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

Acute infusion reactions are defined as any AE that occurs during the infusion or within 1 day after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading scale (Section 9.5.1).

In the event of an infusion reaction of grade 3 or greater severity during or directly following cemiplimab infusion, dosing should be stopped and the patient must be permanently discontinued from cemiplimab treatment. Infusion reactions are defined in Section 9.3.5.

7.4.1.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

For patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment, premedication will be required for re-treatment.

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions.

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated ≤24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

7.4.1.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- any other symptom or sign that, in the opinion of the investigator, warrants discontinuation of the infusion

7.5. Method of Treatment Assignment

Each patient who signs the informed consent form (ICF) will be assigned a patient number and tracked centrally as described in the interactive voice response system (IVRS)/interactive web response system (IWRS) manual. Approximately 700 patients will be randomized in a 1:1 ratio according to a central randomization scheme provided by an IVRS/IWRS to the designated study pharmacist (or qualified designee). Patients will be randomized after providing informed consent, after completing screening assessments, and after the investigator has verified patient eligibility. Randomization will be stratified by histology (non-squamous versus squamous) and geographic region (Europe, Asia, or ROW).

Patients with squamous NSCLC will be randomized 1:1 to receive cemiplimab monotherapy or standard-of-care chemotherapy. Patients with non-squamous NSCLC will be randomized 1:1 to cemiplimab monotherapy or standard-of-care chemotherapy. The choice of chemotherapy will be at the discretion of the investigator. The stratification of geographic region is for the purpose of balancing the treatment assignment within the region only and will not be included analysis of efficacy endpoint as some of stratification category may have a few patients.

7.5.1. Blinding

This is an open-label study. To reduce bias, endpoint assessments will be performed by an IRC blinded to treatment assignment.

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

Open-label cemiplimab will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. Each vial will contain cemiplimab at a concentration of 50 mg/mL. Cemiplimab will be refrigerated at the site at a temperature of 2°C to 8°C, and refrigerator temperature will be logged daily. Further storage instructions will be provided in the pharmacy manual.

A pharmacist or other qualified individual will be identified at each site to prepare cemiplimab for administration. Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

7.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.6.4. Treatment Compliance

Cemiplimab will be administered at the study site, and administration will be recorded on the electronic CRF. All dosing records for each patient will be kept by the site.

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.7. Concomitant Medications and Procedures

Any procedure performed, or treatment administered from the time of informed consent until 90 days after the last study treatment (cemiplimab or chemotherapy) will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study, as well as any therapies started in the follow-up period to treat a study-drug-related

AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

7.7.1. Prohibited Medications

While participating in this study, a patient may not receive any investigational agent for treatment of a tumor other than cemiplimab as monotherapy or the study's specified chemotherapy regimens.

Treatment with bevacizumab or necitumumab is not one of the protocol–defined treatment options. If the treating physician believes that treatment with one of these 2 medications is required for a patient considering enrollment to the study and study-specified treatment options are not sufficient, they should not enroll in the study.

Any other medication that is considered necessary for the patient's welfare and is not expected to interfere with the evaluation of the cemiplimab may be given at the discretion of the investigator.

7.7.2. Permitted Medications and Procedures

It is recommended that patients do not receive concomitant systemic corticosteroids such as hydrocortisone, prednisone, prednisolone, or dexamethasone at any time throughout the study, except in the case of a life-threatening emergency and/or to treat an irAE.

Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Treatments for bone metastases (bisphosphonates, denosumab) are permitted.

Pemetrexed maintenance therapy is permitted for non-squamous NSCLC.

Radiation therapy with palliative intent is permitted.

7.8. Treatment with Cemiplimab Beyond Disease Progression

7.8.1. Disease Progression While Receiving Cemiplimab

It is recognized that a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Additionally, the results of the Keynote-042 study suggest that there is a group of patients with NSCLC who rapidly progress on anti-PD-1 therapy, who may not have experienced the full benefit from anti-PD-1 therapy at initial progression, and who may benefit from continuing cemiplimab with the addition of histology-specific chemotherapy.

Patients randomized to receive cemiplimab 350 mg who experience RECIST 1.1-defined progressive disease during cemiplimab monotherapy will be permitted to continue cemiplimab treatment with the addition of 4 cycles of histology-specific chemotherapy until further progression is observed, provided, the patient has not completed the 108-week treatment period and the following criteria are met:

- IRC confirms investigator assessment of disease progression

- Investigator assesses use of a PD-1/chemotherapy combination as an appropriate second-line treatment
- Patient continues to meet all other study eligibility criteria, as defined in the inclusion/exclusion criteria (Section 6.2)
- Patient is tolerant of cemiplimab and has a stable performance status.

Imaging should be performed within 9 weeks of the initial assessment of progressive disease to determine whether there has been a decrease in the original tumor size or continued progressive disease. Subsequent imaging frequency will be at the discretion of the investigator.

Other anti-cancer therapy should be considered at this time, if appropriate.

Patients should continue with assessments according to Table 5 at the discretion of the investigator. The following efficacy assessments do not need to be completed:

- Biomarker testing
- PK/ADA collection
- QOL questionnaire

In the case of clinical deterioration suspected to be due to progressive disease, confirmatory imaging should be obtained.

7.8.2. Crossover Phase to Cemiplimab

Patients treated with chemotherapy and who experience IRC-assessed RECIST 1.1-defined progressive disease either during or after completion of chemotherapy, will be permitted to crossover to cemiplimab 350 mg Q3W for up to 108 weeks, provided that they meet the following criteria:

- IRC confirms investigator assessment of disease progression
- Investigator assesses use of a PD-1 inhibitor as an appropriate second-line treatment
- Patient continues to meet all other study eligibility criteria, as defined in the inclusion/exclusion criteria (Section 6.2)

Patients should continue with assessments according to Table 5 at the discretion of the investigator. The following efficacy assessments do not need to be completed:

- Biomarker testing
- PK/ADA collection
- QOL questionnaire

Intolerance to chemotherapy is not a reason for crossover to cemiplimab.

7.9. Post-Study Treatments and Procedures

Patients will be contacted quarterly by telephone for survival status, if available, until death, loss to follow-up, or study termination by the sponsor. Survival assessments and their respective

entry into the database may be required more frequently than quarterly around the time of projected analyses.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented in Table 4 for screening, in Table 5 for the on-study period, and in Table 6 for the follow-up period.

Table 4: Schedule of Events: Screening Visit Assessments and Procedures

Study Procedure	Notes
Eligibility Assessments	
Informed Consent	Additional safety testing may be required by the investigator and/or the sponsor. Results of some of these tests (including but not limited to HIV, hepatitis C, and hepatitis B) may be sensitive. In these cases, testing will be performed according to local regulatory requirements and additional informed consent may be required.
Inclusion/Exclusion Criteria	
Tumor Tissue for PD-L1 Assessment (Archival or On-Study Biopsy)	Samples should be collected as described in the laboratory manual. Samples (archival tissue, if ≤5 months old, or recently obtained on-study biopsy collected during screening) will be tested for PD-L1 by a central laboratory. Randomization will be based on local confirmation of histology; histology may be confirmed by a central laboratory. Tumor tissue will also be tested for mutations in EGFR and ALK and for ROS1 fusions by a central laboratory.
Medical/Oncology History	
Demographics	
Efficacy Assessments	
Radiographic Tumor Assessment	• Contrast enhanced CT or MRI should be performed within 28 days prior to randomization (unless contrast is strictly contraindicated). • CT or MRI of the brain with contrast (unless contraindicated) should be performed in patients with a known history of treated brain metastasis, unless performed in the prior 60 days. Additional sites of known disease (including CNS) should be imaged at screening. • The same imaging modality should be used throughout the study.
Tumor Burden Assessment	Tumor burden assessment per RECIST 1.1 criteria
Safety Assessments	
Complete Physical Examination	
ECOG Performance Status	
Weight	
Height	
Vital Signs	Vital signs include temperature, seated BP, heart rate, and respiratory rate. BP and heart rate should be measured prior to obtaining any blood samples.
12-Lead ECG	A 12-lead ECG should be acquired at screening.

Study Procedure	Notes
Laboratory Tests: Hematology (CBC with differential) Serum Chemistry Prothrombin Time/PTT TSH	Measure free T4 if TSH is outside the local normal range.
Serum Pregnancy Test	Women of childbearing potential must have a serum pregnancy test performed within 72 hours prior to administration of the first dose of study treatment.
Concomitant Medications	
Adverse Events	
Chest X-Ray	A CXR PA/Lateral should be obtained at screening
TB skin testing at baseline for patients considered to be high-risk in the opinion of the investigator	Purified protein derivative (PPD)/QuantiFERON testing should be conducted according to local guidelines. Testing should be repeated if there is a history of BCG.
Biomarker Assessments	
Genomics Sub-Study Consent (Optional)	DNA consent should be obtained during the screening visit but may be obtained on study.

Abbreviations: AST/ALT=aspartate aminotransferase/alanine aminotransferase; BP=blood pressure; BUN=blood urea nitrogen; CBC=complete blood count; CNS=central nervous system; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HIV=human immunodeficiency virus; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PD-L1=programmed death ligand 1; PT=prothrombin time; PTT=partial thromboplastin time; RECIST=Response Evaluation Criteria in Solid Tumors; TSH=thyroid-stimulating hormone
Note: The screening evaluation is to occur within 28 days prior to randomization.

Table 5: Schedule of Events: Treatment Period/On-Study Assessments and Procedures

Study Procedure	Year 1			Year 2		Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks [63 Days] ±5 Days)	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks ±5 Days)	
Randomization	X					
Study Treatment Administration (One of the Following)						Treatment should be initiated within 3 days of randomization. If, per local guidelines and standard of care, pretreatment should be administered, pretreatment should be initiated within 3 days of randomization, followed by study treatment administration. At the time of Amendment 9, patients who are actively receiving chemotherapy are eligible to crossover to cemiplimab. See Section 5.1 for more details.
Cemiplimab 350 mg	X	X		X		Record start and stop infusion times. Administer Q3W for up to 108 weeks or until disease progression. Refer to pharmacy manual for further details regarding cemiplimab preparation.
Paclitaxel	X	X				Administer 4 to 6 cycles.
Carboplatin	X	X				Administer 4 to 6 cycles.
Cisplatin	X	X				Administer 4 to 6 cycles.
Gemcitabine	X	X				Gemcitabine is administered on days 1 and 8 of each 21-day cycle.
Pemetrexed	X	X				Pemetrexed maintenance is optional. Administer on day 1 every 21 days until disease progression.

Study Procedure	Year 1			Year 2		Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks [63 Days] ±5 Days)	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks ±5 Days)	
Efficacy Assessments						
Radiographic Tumor Assessment			X		X	• Radiographic evaluations will be performed beginning at week 9 (day 63 ±5 days) and every 9 weeks thereafter. Image with contrast (unless contraindicated) the chest/abdomen/pelvis and other areas being monitored. • Weeks are in reference to the calendar week and should not be adjusted due to dosing delays/interruptions. • Brain scans during the treatment and follow-up periods should be performed as clinically indicated except for patients with a history of metastases, who should have surveillance imaging approximately every 18 weeks for year 1 and every 24 weeks for year 2 or sooner, if indicated. • For patients who receive cemiplimab plus chemotherapy after initial disease progression, imaging will be performed within 9 weeks of the original tumor progression. Subsequent imaging frequency will be at the discretion of the investigator. • For patients who crossover to cemiplimab from chemotherapy, frequency of imaging will be at the discretion of the investigator. • All tumor assessments will be submitted to an Independent Review Committee (Section 5.3.1)
Tumor Assessment/Measurement			X		X	Tumor assessment per RECIST 1.1 criteria
Quality-of-Life Questionnaires	X	X		X		Complete prior to any study procedures. Complete on day 1 of every cycle for the first 6 doses and then on day 1 every 3 cycles (9 weeks). This assessment is not required after

Study Procedure	Year 1			Year 2		Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks [63 Days] ±5 Days)	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks ±5 Days)	
						disease progression if the patient continues on cemiplimab with the addition of chemotherapy, or if the patient crosses over to cemiplimab.
Safety Assessments						
Physical Examination	X	X		X		PE may be performed ≤72 hours prior to dosing on the day 1 visit of each cycle. A complete PE is to be performed prior to the first dose. A limited PE should be performed at all other visits, but a complete PE may be performed, if indicated. PE definitions are provided in Section 8.2.3.1.
Performance Status	X	X		X		
Vital Signs	X	X		X		Vital signs will be assessed and documented prior to infusion of treatment. In cemiplimab-treated patients, vital signs should be taken approximately 15 minutes (±10 minutes) after completion of the cemiplimab infusion.
12-Lead ECG						A 12-lead ECG should be acquired as clinically indicated, per the discretion of the investigator.
Hematology (CBC with Differential)	X	X		X		• Blood samples may be collected ≤72 hours prior to dosing on the day 1 visit of each cycle. • Results must be obtained/reviewed prior to dosing. • Screening laboratory examinations performed within 7 days of cycle 1 day 1 do not need to be repeated for this visit unless clinically indicated.
Serum Chemistry	X	X		X		• Blood sample may be collected ≤72 hours prior to dosing on the day 1 visit of each cycle. • Results must be obtained/reviewed prior to dosing.

Study Procedure	Year 1			Year 2		Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks [63 Days] ±5 Days)	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks ±5 Days)	
						• Screening laboratory examinations performed within 7 days of cycle 1 day 1 do not need to be repeated for this visit unless clinically indicated.
Pregnancy Test[a]	X	X		X		Women of childbearing potential must have a negative serum pregnancy test prior to study treatment administration on cycle 1 day 1 and a negative urine pregnancy test prior to study treatment administration on day 1 of each subsequent treatment cycle or more frequently per local standard.
TSH	X		X			May be obtained, as clinically indicated. Measure free T4 if TSH is abnormal.
Concomitant Medications	X	X		X		Continuous collection of concomitant medication information. For detail see Section 7.7.
Adverse Events	X	X		X		Continue collection of AE information. Assess using current version of NCI-CTCAE. See Section 9.4.1.

Study Procedure	Year 1			Year 2		Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks [63 Days] ±5 Days)	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks ±5 Days)	
PK Drug Concentration/ Anti-Drug Antibody Samples						
Pharmacokinetic Sample[a]	X	X				Collect predose[1] and at the end of infusion[2] on day 1 of cycle 1 and pre-infusion[3] and the end of infusion on day 1 of cycles 2 through 4, and day 1 of cycles 9, 18, and 36 or at the time of disease progression. PK samples are to be obtained only from patients randomized to receive cemiplimab initially, not from patients who crossover to cemiplimab after progression
Anti-Drug Antibody Sample	X	X				Collect predose[1] day 1 of cycle 1 and pre-infusion[3] on day 1 of cycles 9, 18, and 36 or at the time of disease progression. ADA samples, including NAb titers, are to be obtained only from patients initially randomized to receive cemiplimab.

Study Procedure	Year 1			Year 2		Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks [63 Days] ±5 Days)	Day 1, Each Cycle (Every 21 Days ±3 Days)	Every 3 Cycles (9 Weeks ±5 Days)	
Biomarker Samples						
Serum Biomarker Sample	X					Samples will be collected prior to drug administration on day 1 of cycle 1, cycle 2, and cycle 4, and at the time of disease progression. This assessment is not required after disease progression if the patient continues on cemiplimab with the addition of chemotherapy, or if the patient crosses over to cemiplimab.
Plasma Biomarker Sample	X					Samples will be collected prior to drug administration on day 1 of cycle 1, cycle 2, and cycle 4, and at the time of disease progression. This assessment is not required after disease progression if the patient continues on cemiplimab with the addition of chemotherapy, or if the patient crosses over to cemiplimab.
Blood Sample for Germline DNA (Optional)	X					Collect the DNA sample at cycle 1 day 1. If consent is not obtained during screening, it can be obtained at any other visit prior to collection of the DNA sample.
Tumor Biopsy						
Tumor Biopsy (Optional)						A tumor biopsy should be collected at the time of disease progression (optional) as described in the laboratory manual.

[a] This can be done at any time prior to infusion within a 72-hour period.

Abbreviations: ADA=anti-drug antibody; AST/ALT=aspartate aminotransferase/alanine aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; DNA=deoxyribonucleic acid; ECG=electrocardiogram; LDH=lactate dehydrogenase; NAb=neutralizing ADA; NCI-CTCAE=National Cancer Institute Common Terminology Criteria; PE=physical examination; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; TSH=thyroid-stimulating hormone; Q3W=every 3 weeks.

Table 6: Schedule of Events: Follow-Up Period Assessments and Procedures

Study Procedure	Follow-Up Visit 1	Follow-Up Visits 2 to 7	Notes
Day	14 to 30 days after the last study treatment administration (cemiplimab or chemotherapy) if discontinued due to progressive disease, toxicity, or other reason **OR** last cycle visit +14 to 30 days (±7 days) for completion of chemotherapy or cemiplimab	Prior follow-up visit + 6 weeks (±7 days) for follow-up visit 2, and prior follow-up visit + 9 weeks (±7 days) for follow-up visits 3, 4, 5, 6 and 7	
Efficacy Assessments			
Radiographic Tumor Assessment		X	• For patients who discontinue study drug (cemiplimab or chemotherapy) for reasons other than progressive disease, follow-up scans should be performed according to the on-study assessment schedule (Section 8.1) until progressive disease, withdrawal of consent, death, or loss to follow-up. o At the time of Amendment 9, patients who have completed chemotherapy and are in follow up, but whose disease has not yet progressed are eligible to crossover to cemiplimab. See Section 5.1 for more details. • Radiographic assessments for patients who have not experienced progressive disease should be performed every 9 weeks until disease progression, loss to follow-up, withdrawal of consent, death, or initiation of another anti-cancer treatment. • All tumor assessments will be submitted to an Independent Review Committee.
Tumor Assessment/Measurement		X	Tumor assessment per RECIST 1.1 criteria.
Tumor Biopsy (Optional)			A tumor biopsy should be collected at the time of disease progression (optional) as described in the laboratory manual.
Quality of Life Questionnaire	X		
Safety Assessments			
Physical Examination	X	X	A limited PE may be performed, but a complete PE should be performed when clinically indicated.

Study Procedure	Follow-Up Visit 1	Follow-Up Visits 2 to 7	Notes
Performance Status	X	X	
Vital Signs	X	X	
Hematology (CBC with Differential)	X		Collect at visits 2 to 7 as clinically indicated, per discretion of the investigator.
Serum Chemistry	X		Collect at visits 2 to 7 as clinically indicated, per discretion of the investigator.
Pregnancy Test	X	X	Urine pregnancy tests at each clinic visit, or more frequently per local standard.
Concomitant Medications	X	X	
Adverse Events	X	X	During follow up, AE collection should occur from the time the informed consent is signed until 90 days after the last dose of study drug, or until the patient commences another anti-cancer systemic therapy, whichever is earlier.
Survival Data Collection	X	X	• After follow-up visit 7, vital status information will continue to be collected every 3 months until death, loss to follow-up, or withdrawal of study consent. • Updated survival status may be requested by the sponsor at any time during the course of the study. Upon sponsor notification, all patients 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 and its respective entry into the database (excluding patients who have a death event previously recorded). • May be performed by phone contact or office visit.
PK Drug Concentration/ Anti-Drug Antibody Samples			
Pharmacokinetic Sample	X	X	Samples will be collected at follow-up visits 1, 2, and 3. Only for patients randomized to receive cemiplimab (eg, not patients who receive crossover cemiplimab or chemotherapy). This assessment is not required after disease progression if the patient continues on cemiplimab with the addition of chemotherapy.
Anti-drug Antibody Sample		X	Samples will be collected at follow-up visit 3. Only for patients initially randomized to receive cemiplimab.

Study Procedure	Follow-Up Visit 1	Follow-Up Visits 2 to 7	Notes
			This assessment is not required after disease progression if the patient continues on cemiplimab with the addition of chemotherapy.
Biomarker Samples			
Serum Biomarker Sample	X		Samples will be collected at follow-up visit 1 and at the time of progressive disease.
Plasma Biomarker Sample	X		Samples will be collected at follow-up visit 1 and at the time of progressive disease.

Abbreviations: ADA=anti-drug antibody; CBC=complete blood count; PE=physical examination; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

8.1.1. Footnotes for the Schedule of Events Tables

1. Predose is defined as within 15 minutes before the start of the first cemiplimab infusion (specific to PK drug concentration and ADA samples in Table 5).
2. End of infusion is defined as within 15 minutes after the end of infusion (specific to PK drug concentration and ADA samples in Table 5).
3. Pre-infusion is defined as within 15 minutes before the start of subsequent cemiplimab infusions (specific to PK drug concentration and ADA samples in Table 5).

8.1.2. Early Termination Visit

Patients who withdraw from the study treatment will be asked to return to the clinic to complete visit 1 of the follow-up period for study assessments as indicated in Table 6.

8.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. Procedures Performed only at Screening Visits

The following procedures will be performed at the screening visit (Table 4) for the sole purpose of determining study eligibility or characterizing the baseline population:

- Collection of tumor tissue for PD-L1 assessment
  - A formalin-fixed, paraffin-embedded tissue block or unstained slides of tumor sample (archival or recent) must be provided. Biopsies should be of sufficient size to ensure an adequate amount of tissue for analysis (excisional or incisional; fine needle aspirates are not acceptable). Complete instructions on the collection, processing, handling, and shipment of all samples will be provided in the laboratory manual.
  - PD-L1 testing will be done by central laboratory.
  - Tumor tissue will also be tested for mutations in EGFR and ALK and for ROS1 fusions at a central laboratory. Randomization will be based on local confirmation of histology and may be confirmed by a central laboratory.
  - The use of the PD-L1 IHC 22C3 pharmDx assay for decisions regarding treatment with cemiplimab is considered investigational.
- Baseline radiographic tumor assessment of the chest, abdomen, pelvis, and all other known or suspected sites of disease by CT or MRI.
- Chest X-ray PA/Lateral

- Serum pregnancy test in women of childbearing potential within 72 hours prior to administration of the first study treatment administration
- TB testing for high risk individuals at the discretion of the investigator using purified protein derivative (PPD)/QuantiFERON testing according to local guidelines

8.2.2. Efficacy Procedures

8.2.2.1. Radiographic Tumor Assessments

High-resolution CT with contrast and contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. In patients in whom contrast is strictly contraindicated, non-contrast scans will suffice. The chest, abdomen, and pelvis must be imaged along with any other known or suspected sites of disease. If more than 1 imaging modality is used at screening, the most accurate imaging modality according to RECIST 1.1 should be used when recording data. The same imaging modality used at screening should be used for all subsequent assessments.

Radiographic tumor assessments will be obtained in all patients at every 3 cycles, at week 9 (day 63 ±5 days) and every 9 weeks thereafter, until disease progression, loss to follow-up, withdrawal of consent, death, or initiation of another anti-cancer treatment. Tumor assessments should be performed per schedule even if dosing is interrupted. Tumor measurements will be made in accordance with RECIST 1.1 criteria (Eisenhauer 2009, Appendix 2) and should be performed by the same investigator or radiologist for each assessment, to the extent feasible.

The investigator assessment of changes in tumor measurements (per RECIST 1.1) will be used to guide clinical management. All radiographic tumor assessments performed for study purposes will be submitted to the IRC for adjudication of the study endpoints.

8.2.2.2. Survival Data Collection

Every effort will be made to collect survival data on all patients, including patients that withdraw from the study for any reason but have not withdrawn consent to collect survival information. If the death of a patient is not reported, the date of the last patient contact in this study will be used in the determination of the patient's last known date of alive.

8.2.2.3. Quality of Life Questionnaires

Patient-reported outcomes will be measured at a frequency indicated in Table 5 and Table 6 using the following validated patient self-administered questionnaires: EORTC QLQ-C30 and EORTC QLQ-LC13 (Bergman 1994, Bjordal 2000). Patients will be asked to complete these questionnaires prior to any study procedures being performed at a given study visit (during the on-study/treatment and follow-up periods).

8.2.3. Safety Procedures

8.2.3.1. Physical Examination

A complete or limited physical examination will be performed at the visits specified in Table 4, Table 5 and Table 6. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination.

Limited physical examination will include the lungs, heart, abdomen, and skin.

8.2.3.2. Weight and Height

Body weight measurements will be obtained at screening according to Table 4. Weight should be obtained with the patient wearing undergarments or very light clothing, with no shoes, and with an empty bladder. The same scale should be used throughout the study. The use of calibrated balance scales is recommended, if possible. Self-reported weights are not acceptable.

Height should be measured; self-reported heights are not acceptable.

8.2.3.3. Vital Signs

Vital signs, including temperature, seated blood pressure, heart rate, and respiratory rate, will be collected at time points according to Table 4, Table 5 and Table 6. Vital signs should be performed before blood is drawn during visits requiring blood draws.

Blood pressure should be measured in the same arm at all study visits (when feasible) and after the patient has been resting quietly in the seated position for at least 5 minutes.

At cycle 1 day 1 and on all subsequent treatment days, vital signs will be collected prior to infusion of treatment. In cemiplimab-treated patients, vital signs must also be obtained approximately 15 minutes (±10 minutes) after completion of the infusion.

8.2.3.4. 12-Lead Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening and when clinically indicated while on study (Table 4 and Table 5).

The patient should be relaxed and in a recumbent position for at least 5 minutes before recording an ECG. The ECG will be reviewed by the investigator or qualified designee at the site and will be available for comparison with subsequent ECGs. The ECG tracing will be retained with the source.

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

8.2.3.5. Laboratory Tests

Hematology, chemistry, and pregnancy testing samples will be analyzed by the site's local laboratory.

Samples for laboratory testing will be collected at time points according to Table 4, Table 5 and Table 6. Tests will include the following:

Blood Chemistry

Sodium	Phosphorus	ALT
Potassium	Glucose	AST
Chloride	Albumin	Total bilirubin
Bicarbonate*	Creatinine	Alkaline phosphatase
Calcium	BUN**	LDH
Magnesium	Uric acid	Total protein

*Venous testing of plasma CO2 is acceptable at centers where this is commonly used instead of bicarbonate.
**The urea test is acceptable instead of BUN at centers where this is commonly used instead of the BUN.

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells	Lymphocytes
White blood cells	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Other Laboratory Tests

Coagulation Tests: Prothrombin time/partial thromboplastin time will be analyzed by the site's local laboratory.

Thyroid Function Tests: Thyroid-stimulating hormone (TSH) will be analyzed by the site's local laboratory. If TSH is abnormal, a free T4 should be measured at the investigative site's local laboratory.

Pregnancy Testing

Women of childbearing potential must have a negative serum pregnancy test prior to study treatment administration on cycle 1 day 1 and a negative urine pregnancy test prior to study treatment administration on day 1 of each subsequent treatment cycle, or more frequently per local standard.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.4. Pharmacokinetic and Immunogenicity Measurements and Procedures

8.2.4.1. Drug Concentration Measurements and Samples

Cemiplimab concentrations in the serum from patients randomized to the cemiplimab treatment group will be measured using a validated enzyme-linked immunosorbent assay method at visits and time points indicated in Table 5 and Table 6. Actual time of each blood draw must be recorded. Predose samples may be collected ≤72 hours prior to day 1 dosing. "Predose" is defined as within 15 minutes before the start of the first cemiplimab infusion. "Pre-infusion" is defined as within 15 minutes before the start of subsequent cemiplimab infusions. "End of infusion" is defined as within 15 minutes after the end of the infusion.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research.

8.2.4.2. Anti-Drug Antibody Measurements and Samples

Serum samples for immunogenicity (ADA and NAbs) assessments will be collected from patients randomized to the cemiplimab treatment group prior to dosing at time points listed in Table 5 and Table 6. Any unused samples collected for immunogenicity assessments may be used for exploratory biomarker research.

8.2.4.3. Biomarker Procedures

For biomarker assessments, a formalin-fixed, paraffin-embedded tissue block or unstained slides of tumor samples (archival or recent) must be provided. Tumor biopsies should be of sufficient size to ensure an adequate amount of tissue for analysis (excisional, incisional, or core needle; fine needle aspirates are not acceptable). Complete instructions on the collection, processing, handling, and shipment of all samples will be provided in the laboratory manual.

With the use of the collected tumor tissue, the following biomarker-based eligibility and stratification strategies will be implemented in this study to determine eligibility and allow for stratified analysis based on tumor PD-L1 expression.

A validated PD-L1 IHC assay will be utilized to assess PD-L1 expression levels in recently obtained tumor tissue (biopsy collected at screening visit or archival tissue if ≤5 months old) in

order to qualify patients for enrollment. The ≥50% PD-L1 positivity cutoff will be used as an inclusion criterion for this study.

Tumor tissue biopsy samples will also be tested for EGFR mutations, ALK translocations, and for ROS1 fusions for determination of study eligibility by a central laboratory. This testing does not need to be repeated if it has been done previously and the results are available from other Regeneron NSCLC immunotherapy studies.

Tissue permitting, additional testing may be employed to determine PD-L1 expression levels in the same tissue specimens. This approach may provide a better understanding of the performance of PD-L1 expression level as a predictive biomarker of response to cemiplimab. Of special interest is PD-L1 expression across different cell types including tumor cells, stroma cells, and infiltrating immune cells.

Tumor tissue will also be used for validation of the additional PD-L1 assays.

After completion of PD-L1 expression analysis, the remaining tumor tissue may be used to study the biomarkers associated with clinical response to cemiplimab.

Biomarker serum and plasma samples will be collected from all patients enrolled in this study at multiple time points to study the potential pharmacodynamics or predictive biomarkers of response to cemiplimab (refer to the laboratory manual).

8.2.5. Future Biomedical Research

The biomarker samples unused for study-related research (serum, plasma, and tumor tissues), as well as unused PK and immunogenicity samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future exploratory biomarker assessments, future biomedical research of lung carcinoma and other diseases. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the Clinical Study Report (CSR).

8.2.5.1. Genomics Sub-Study - Optional

Germ-line DNA will be collected as optional to enable analysis of tumor mutational burden as well as exploratory analysis of variants potentially associated with efficacy and/or safety signals.

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study. Samples for deoxyribonucleic acid (DNA) extraction should be collected on cycle 1 day 1 (baseline/predose) but may be collected at any study visit.

DNA samples for the genomics sub-study will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of other diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic

markers related to the study treatment or other diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number, may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic sub-study will not be reported in the CSR.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Ethics Committee (EC) all unanticipated problems involving risks to the patient per local EC requirements.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, ECs as appropriate, and to the investigators.

Any SAE not listed as expected in the Reference Safety Information table of cemiplimab Investigator's Brochure or in the reference safety document of assigned chemotherapy will be considered as unexpected.

In addition, the sponsor will report any other SAEs to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and ECs as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in Section 9.3.2.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, 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).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE.

Criteria for reporting SAEs must be followed for these events. See Section 9.4.2 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (See Section 9.4.3 for the list of AESIs specific to this study).

9.3.4. Immune-Related Adverse Events

Case report forms for this study are designed to capture AEs that may be suggestive of potential irAEs. Attribution of AEs in the CRFs will require the investigator's assessment regarding not

only whether the AE was related to cemiplimab but also whether the AE was an irAE. See the CRF completion guidelines for information about attribution of irAEs.

Detailed guidance of management of irAEs is provided in Section 7.3.1.2 and Appendix 3.

Note regarding irAEs: For any AE that is of a type known to be potentially immune-related (eg, rash, colitis, elevated transaminases, or endocrine) but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

9.3.5. Infusion Reactions

Infusion-related reactions are known to occur with infusions of therapeutic proteins and have been observed in cemiplimab studies.

Infusion-related reactions are defined as any AE that occurs during the infusion or within 1 day after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1 .

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 90 days after the last dose of study drug, or until the patient commences another anti-cancer systemic therapy, whichever is earlier. Prior to initiation of study drug, only the following categories of AEs should be reported on the AE CRF:

- SAEs
- Non-SAEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

Other AEs that occur prior to first treatment should be reported on the medical history CRF.

All AEs after initiation of study treatment and until 90 days after the last dose of study treatment, regardless of relationship to study treatment, will be reported on the AE CRF. Additionally, any SAE or AE that the investigator believes may be related to study drug and that occurs later than 90 days after last dose of study drug, or after the patient has commenced another anti-cancer systemic therapy (whichever is earlier) should be reported.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE that occurs 90 days after the last dose of study drug, or after the patient commences another anti-cancer systemic therapy (whichever is earlier), only those SAEs or AEs deemed by the investigator to be related to study drug will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered resolved, chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient or female partner of a male study patient, during the study or within 180 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Adverse events of special interest for this study include the following:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or greater irAEs
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with cemiplimab exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an AE as an irAE. Detailed guidance of management of irAEs are provided in Section 7.3.1.2 and Appendix 3. The recommendations in Section 7.3.1.2 and Appendix 3 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient. For any AE that is of a type known to be potentially immune-related (eg, rash, colitis, elevated transaminases, or endocrine) but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study manual for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-Up

Information for any non-SAE that starts during the treatment period or within 90 days after last dose of study treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered resolved, chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the NCI-CTCAE, version 4.03 grading system. Adverse events not listed in the NCI-CTCAE will be graded according to the following scale:

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

2 (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

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

4 (Life–threatening): Life-threatening consequences; urgent intervention indicated.

5 (Death): Death related to AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semicolon indicates "or" within description of the grade):

- **Mild**: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- **Moderate**: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.
- **Severe**: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

A list of factors to consider when assessing the relationship of AEs to study drug is provided in Appendix 1.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs to study conduct will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related:	There is no reasonable possibility that the event may have been caused by study conduct
Related:	There is a reasonable possibility that the event may have been caused by study conduct

A list of factors to consider when assessing the relationship of AEs to study conduct is provided in Appendix 1.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Infusion Procedure or Study Procedure:

The relationship of AEs to infusion procedure or study procedures will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the infusion procedure or study procedure?

The possible answers are:

Not Related:	There is no reasonable possibility that the event may have been caused by the infusion procedure or study procedure
Related:	There is a reasonable possibility that the event may have been caused by the infusion procedure or study procedure

A list of factors to consider in assessing the relationship of AEs to infusion procedure or study procedure is provided in Appendix 1.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

9.6. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

10.1. Statistical Hypotheses

The analyses of OS and PFS will be performed with an overall 2-sided α of 0.05 for the following null and alternative statistical hypotheses:

Overall Survival

- H0: The survival curve of OS for cemiplimab is the same as that for platinum-based chemotherapy
- H1: The survival curve of OS for cemiplimab is not the same as that for platinum-based chemotherapy

Progression Free Survival

- H0: The survival curve of PFS for cemiplimab is the same as that for platinum-based chemotherapy
- H1: The survival curve of PFS for cemiplimab is not the same as that for platinum-based chemotherapy

10.2. Justification of Sample Size

Enrollment of 700 patients is assumed to occur over 38 months (3 patients per month for the first 4 months, 12 patients per month from month 5 to month 8, 23 patients per month from month 9 to month 16, 30 patients per month from month 17 to month 20, and 20 patients per month thereafter). The patients will be randomized at 1:1 ratio to cemiplimab arm or platinum-based chemotherapy arm. A dropout rate of 10% per year is assumed.

Overall Survival

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median OS has ranged from approximately 11.3 to 14.2 months (Reck 2016, Lopes 2018, Carbone 2017, Gandhi 2018, Paz-Ares 2018). For PD-1 monotherapy, a delayed treatment effect in OS has been observed in Keynote-024, Keynote-042 and Checkmate 026. In these studies, during the first 6 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in OS when compared to treatment with chemotherapy.

The sponsor assumes without crossover effect a median OS of 13 months for patients treated with chemotherapy alone, and a non-proportional HR between cemiplimab and chemotherapy, with an HR of 1.05 for the first 6 months and an HR of 0.58 after 6 months.

With 5 planned interim analyses using Lan-DeMets O'Brien-Fleming spending function (detailed in Section 10.5), and with 476 deaths at final analysis of OS, the study has approximately 86% power for detecting a significant OS effect at 2-sided α of 0.04 and approximately 88% power for detecting a significant OS effect at 2-sided α of 0.05.

Progression Free Survival

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median PFS has ranged from approximately 4.8 to 6.4 months (Reck 2016, Lopes 2018, Carbone 2017, Gandhi 2018, Paz-Ares 2018). For PD-1 monotherapy, a delayed treatment effect in PFS has been observed in Keynote-024, Keynote-042 and Checkmate 026. In these studies, during the first 3 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in PFS when compared to treatment with chemotherapy.

The sponsor assumes a median PFS of 6.4 months for patients treated with chemotherapy alone, and a HR between cemiplimab and chemotherapy, with an HR of 1.3 for the first 3 months and an HR of 0.5 after 3 months.

With 525 PFS events, the study has approximately 76% power for detecting a significant PFS effect at 2-sided α of 0.01 and approximately 90% power for detecting a significant PFS effect at 2-sided α of 0.05.

The EAST v6.0 software was used for sample size calculation for OS and PFS.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients. This is the intention to treat population. The FAS is based on the treatment allocated (as randomized). All efficacy endpoints will be analyzed using the FAS by treatment group.

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug. This population is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF by treatment group.

10.3.3. Pharmacokinetic and ADA Analysis Sets

The PK population includes all randomized patients (safety population) who received cemiplimab and who had at least 1 non-missing cemiplimab concentration following the first dose of cemiplimab up to the end of the study.

The ADA analysis set includes all treated patients who received any study medication and had at least 1 non-missing post-baseline ADA assay result following the first dose of study drug.

The biomarker analysis set includes all treated patients who had at least 1 sample assayed.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25% percentile and 75% percentile may be provided if needed.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

The descriptive summary of time-to-event data will include median time to event and its 95% CI using the Kaplan-Meier method.

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients
- The total number of randomized patients: received a randomization number
- The total number of patients in the FAS
- The total number of patients in the SAF
- The total number of patients who discontinued treatment and the reasons for treatment discontinuation
- The total number of patients who discontinued the study and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment and study, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and by all patients combined.

10.4.3. Medical History

Medical history will be summarized by primary system organ class (SOC) and preferred term (PT) for each treatment group.

10.4.4. Prior Medications/Concomitant Medications

Number and proportion of patients taking prior/concomitant medication will be summarized by anatomical therapeutic chemical (ATC) level 2 and ATC level 4 according to the current version of the World Health Organization Drug Dictionary.

Listings of pretreatment medication and concomitant medications include generic name, ATC levels 2 and 4, indication, start date, end date, ongoing status, dose, frequency, and route.

10.4.5. Efficacy Analyses

10.4.5.1. Primary Efficacy Analysis

Overall Survival Analysis:

The primary endpoint of OS will be analyzed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factor. The HR and its 95% CI will be

estimated by a stratified Cox regression model using the treatment as covariate and status of histology as stratification factor.

Restricted Mean Survival Time (RMST) method may be conducted as a sensitivity analysis for OS to account for the possible non-proportional hazards effect.

Since patients in the control arm are allowed cemiplimab treatment after progressive disease and patients in the cemiplimab arm are allowed cemiplimab plus chemotherapy treatment after progressive disease, sensitivity analyses with adjustment for the effect of these additional treatments on OS may be performed based on recognized methods, eg, the Rank Preserving Structural Failure Time (RPSFT) model (Robins 1991).

Progression Free Survival Analysis:

The primary endpoint of PFS will be analyzed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factor. The HR and its 95% CI will be estimated by a stratified Cox regression model using the treatment as covariate and status of histology as stratification factor.

Three sensitivity analyses will be performed using different censoring rules and progressive disease event definitions. The first sensitivity analysis is the same as the primary analysis except that it considers initiation of new anti-cancer treatment as a progressive disease event for patients without documented progressive disease or death prior to initiation of new anti-tumor treatment. The second sensitivity analysis is the same as the primary analysis except that for the second sensitivity analysis, a patient who has progressive disease or death after missing ≥2 tumor assessments will be censored at the last tumor assessment prior to missing ≥2 tumor assessments. The third sensitivity analysis will be performed based on investigator-determined progressive disease events.

Further details of sensitivity analyses will be described in SAP as needed.

10.4.5.2. Secondary Efficacy Analysis

If both analyses of OS and PFS are statistically significant, the ORR will be analyzed using Cochran-Mantel-Haenszel test stratified by status of histology (non-squamous versus squamous). An associated odds ratio and 95% CI will be calculated. Objective response rate and the corresponding 95% exact CI will be calculated by Clopper-Pearson method for each treatment arm.

10.4.5.3. Quality of Life Analysis

The change in EORTC QLQ-C30 and EORTC QLQ-LC13 scores from first assessment to the end of the study will be summarized descriptively at each post-baseline time point and compared using a mixed effect model, if appropriate.

10.4.5.4. Exploratory Efficacy Endpoint Analysis

The exploratory efficacy endpoint of time to new anti-tumor therapy will be analyzed using methods similar to those used in the analysis of the primary endpoint. The relationship between efficacy endpoints and PD-L1 expression levels may be assessed.

10.4.5.5. Subgroup Analyses

To determine the consistency of treatment effect across various demographic and baseline subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary and secondary endpoints will be estimated and plotted within each category of the following subgroup variables:

- Age category (≤65 versus >65 years)
- Gender (female, male)
- Race (white, non-white)
- ECOG status (0 versus 1)
- Geographic region of enrolling site

10.4.6. Safety Analysis

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

10.4.6.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the time from the day of first dose of study drug to the day of the last dose of study drug plus 90 days or to 1 day before patients receive their first dose of cemiplimab as crossover treatment or treatment of chemotherapy plus cemiplimab, or another anti-cancer systemic therapy, whichever is earlier.
- The post-treatment period is defined as the time starting one day after the end of on-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period but prior to start of crossover treatment or treatment of chemotherapy plus cemiplimab.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities. The verbatim text, the PT, and the primary SOC will be listed.

Summaries of TEAEs by treatment group will include the following:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (NCI-CTCAE, version 4.03), presented by SOC and PT
- TEAEs by outcome

- TEAEs led to treatment discontinuation, presented by SOC and PT
- TEAEs related to study drug, presented by SOC and PT
- AESI, presented by SOC and PT
- irAE, presented by SOC and PT
- IRR, presented by SOC and PT

Deaths and SAEs will be listed and summarized by treatment group.

Events of NCI-CTCAE grade 3 and grade 4 severity will be summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.6.2. Other Safety

Vital Signs

Vital signs (temperature, heart rate, seated blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be listed, and the number and percentage of patients with NCI-CTCAE grade 3 or grade 4 laboratory values will be summarized by laboratory test. Shift tables may be generated if applicable.

10.4.6.3. Treatment Exposure

Treatment duration, dose intensity, and number of cycles administered will be summarized by treatment group.

10.4.6.4. Treatment Compliance

Treatment compliance, which is defined as (Number of doses of study treatment administered during treatment period) / (Number of doses of study treatment planned to be administered during treatment period) × 100%, will be summarized by treatment group.

10.4.7. Analysis of Drug Concentration Data

Cemiplimab concentrations in serum will be reported over time as individual values with descriptive statistics. The PK data in this study may be included in a population PK analysis that will be presented in a separate report.

10.4.8. Analysis of Immunogenicity Data

The immunogenicity assessment variables described in Section 4.4 will be analyzed using descriptive statistics. Plots of drug concentrations will be examined, and the influence of treatment-emergent or treatment boosted positive ADA responses in the assay on individual PK profiles will be evaluated. Assessment of impact of treatment-emergent positive or treatment boosted ADA responses in the assay on safety and efficacy may be provided.

10.4.9. Analysis of Biomarker Data

Biomarker analyses in this study will be exploratory in nature and results will be summarized in a separate report. Detailed description of statistical methods that will be used for biomarker data analyses will be provided in a separate Biomarker Analytical Plan.

10.4.10. Pharmacokinetic/Pharmacodynamic Analyses for Exploratory Biomarkers

Exploratory PK/PD analyses may be conducted on exploratory biomarkers, as appropriate.

10.4.11. Exposure-Response Analysis

Exposure-Response (E-R) analyses will be conducted on efficacy endpoints and safety.

10.4.12. Sensitivity Analyses Addressing PD-L1 Measure Issues

Sensitivity analyses will be performed for primary endpoints of OS and PFS for patients whose tumors express PD-L1 in ≥50% of tumor cells based on PD-L1 assay in accordance with assay instructions, including using results from the retesting.

A listing will be provided including qualitative PD-L1 results from the retesting with PD-L1 assay in accordance with assay instructions. Quantitative results may also be listed.

10.5. Multiplicity Considerations

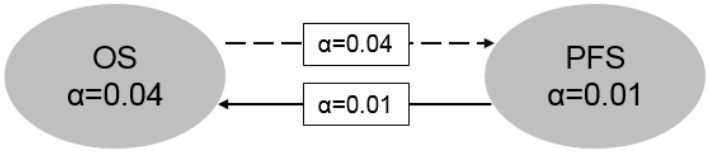
The familywise type I error rate for the study is strictly controlled at 2-sided α of 0.05.

The overall type I error rate for analyses of the primary endpoints of OS and PFS is controlled at a 2-sided α of 0.05 by the following α reallocation strategy detailed below (Figure 3). The type I error rate for interim and final analyses of OS is controlled using the O'Brien-Fleming spending function. The type I error rate for the analyses of primary and key secondary endpoints are controlled by hierarchical testing procedure, that is ORR will only be tested if both analyses of OS and PFS are statistically significant.

10.5.1. Type I Error Control for Analyses of Primary Endpoints of Overall Survival and Progression Free Survival

The 2-sided α of 0.05 is initially split between the analyses of OS and PFS, with 0.04 to OS analysis and 0.01 to PFS analysis. The α allocated to PFS (0.01) is subject to be reallocated to OS if the PFS test is positive. The α allocated to OS (0.04) is subject to be reallocated to PFS if the OS test is positive.

Figure 3: α Reallocation Strategy Between Primary Endpoints of PFS and OS



10.5.2. Type I Error Control for Interim and Final Analyses of OS

The OS hypothesis will be tested at overall 2-sided α of 0.04. If PFS analysis is significant, the OS hypothesis will be tested at overall 2-sided α of 0.05 (re-allocated α). The Lan-DeMets O'Brien-Fleming spending function will be used for analysis of OS. Table 7 demonstrates an example alpha spending boundary for OS interim analyses. For each interim and final OS analysis, the alpha spending function will be updated based on the actual number of deaths at the time of analysis and the outcome of final PFS analysis for alpha re-allocation if applicable.

Table 7: Example Alpha Spending Function for Analysis of OS

OS Information Time	Value	Overall α for OS analysis =0.04[c]	Overall α for OS analysis =0.05
33.4% (~159 deaths)	Z	3.8591	3.7063
	α (2-sided[a])	0.00011	0.00021
50% (~238 deaths)	Z	3.0954	2.9698
	α (2-sided)	0.00197	0.00298
60% (~286 deaths)	Z	2.8255	2.7126
	α (2-sided)	0.00472	0.00668
OS interim analysis at PFS final analysis Estimated # deaths[b]=308 64.7% information time	Z	2.7504	2.6428
	α (2-sided)	0.00595	0.00822
75% (~357 deaths)	Z	2.5163	2.4161
	α (2-sided)	0.01186	0.01569
OS final analysis # deaths = 476	Z	2.1066	2.0186
	α (2-sided)	0.03515	0.04353

[a] As a 2-sided test is used at interim, the superiority or futility of cemiplimab treatment will be claimed if the statistical boundary is crossed.
[b] This interim analysis will be performed when 525 PFS events are observed.
[c] The actual overall alpha spending for analysis of OS may change to 0.05 if final analysis of PFS is significant at 0.01 level. The critical z-value and nominal alpha for interim and final analysis of OS at the time or after final analysis of PFS may be adjusted pending the outcome of analysis of PFS.

10.5.3. Type I Error Control for Analyses of Primary and Key Secondary Endpoints

For the key secondary endpoint of ORR, the type I error rate is controlled by hierarchical testing procedure, that is, ORR will only be tested if both analyses of OS and PFS are statistically significant.

All other statistical comparisons will be exploratory in nature and, therefore, not controlled for multiplicity and should be interpreted accordingly.

10.6. Interim Analysis

Five interim analyses for OS are planned in addition to the final analysis.

Example efficacy boundaries and type I error control for the interim and final analyses are described in Section 10.5. The analyses planned and numbers of driving events are described in Table 8 below.

Table 8: Plan for Interim and Final Analyses of Primary Endpoints

Analysis in this study	Analyses to be conducted	Timing
Interim Analysis 1	Interim analysis of OS only	When approximately 1/3 of OS events are observed (~159 deaths)
Interim Analysis 2	Interim analysis of OS only	When approximately 50% of OS events are observed (~238 deaths)
Interim Analysis 3	Interim analysis of OS only	When approximately 60% of OS events are observed (~286 deaths)
Interim Analysis 4	Final analysis of PFS Interim analysis of OS	When approximately 525 PFS events are observed. 308 deaths are expected, which is ~64.7% OS information time.
Interim Analysis 5	Interim analysis of OS only	When approximately 75% of OS events are observed (~357 deaths)
Final Analysis	Final analysis of OS	When approximately 476 deaths are observed

Two hundred and forty-nine deaths had been observed for the second OS interim analysis. The critical z-value and nominal alpha for the second interim analysis of OS was updated based on this actual information fraction using the Lan-DeMets O'Brien-Fleming spending function (critical z-value = 3.02; nominal alpha = 0.00255).

The pre-specified second interim analysis demonstrated that patients treated with cemiplimab monotherapy had a significant increase in OS. Cemiplimab decreased the risk of death by 32.4% (HR=0.676; CI:0.525-0.870 p=0.0022) compared to platinum-doublet chemotherapy. Additionally, no new cemiplimab safety signal was identified.

As a statistically significant and clinically meaningful benefit of cemiplimab over platinum-based chemotherapy has been demonstrated in first-line, PD-L1 ≥50% NSCLC, the Sponsor has decided to allow patients on the chemotherapy doublet arm to cross-over to cemiplimab. All pre-specified endpoints will be analysed on the data collected up to the same data cutoff for this positive OS interim analysis. The remaining α allocated to OS will be reallocated to PFS analysis.

10.7. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of cemiplimab will be considered the baseline evaluation.

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data.
- The pattern of missing data and potential prognostic factors for missing data (QOL, clinical neurologic assessment, and mental status) will be examined to guide the use of proper statistical models.
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study drug except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study drug date, then the start date by the study drug intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol-defined clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not by visit summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries, and all observations will be presented in listings.

10.8. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, and medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System – statistical review, analysis, and reporting
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate EC. A copy of the EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient

in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

14.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.4. Ethics Committee

An appropriately constituted EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the EC approval letter with a current list of the EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an EC-approved amendment. Regulatory approvals will also be sought as required by regulatory guidance.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRFs that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

ALIMTA [package insert]. Indianapolis, IN: Eli Lilly and Company; 2013.

ALIMTA [SmPC]. Indianapolis, IN: Eli Lilly and Company; 2013.

American Cancer Society. Key Statistics for Lung Cancer. https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Published 2020. [Accessed] 06 May 2020

Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol. 2014;25(8):1475-84.

Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H;N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer. 2000;36(14):1796-807.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627-39.

Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017; 276(25):2415-26.

Creelan BC. Update on immune checkpoint inhibitors in lung cancer. Cancer Control. 2014;21(1):80-9.

D'Incecco A, Andreozzi M, Ludovini V, Rossi E, Capodanno A, Landi L, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer. 2015;112(1):95-102.

De Lima Lopes G, Wu Y, Sadowski S, Zhang J, Rangwala R, et al. P2.43: Pembrolizumab vs platinum-based chemotherapy for PD-L1+ NSCLC: phase 3, randomized, open-label KEYNOTE-042: track: immunotherapy. J Thorac Oncol. 2018;11(10S): S244-S245.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN Guidelines insights: non-small cell lung cancer, Version 4.2016. J Natl Compr Canc Netw. 2016;14(3):255-64.

Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003;21:3016–3024.

Gadgeel SM, Stevenson J, Langer C, Gandhi L, Borghaei H, Patnaik A, et al. Pembrolizumab (pembro) plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C. J Clin Oncol. 2016;34(Suppl); abstract 9016.

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. 2018; 278(22):2078-92.

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-28.

Gettinger SN, Hellmann MD, Shepherd FA, Antonia SJ, Brahmer JR, Man Chow LQ, et al. First-line monotherapy with nivolumab (NIVO; anti-programmed death-1 [PD-1]) in advanced non-small cell lung cancer (NSCLC): safety, efficacy and correlation of outcomes with PD-1 ligand (PD-L1) expression. J Clin Oncol. 2015;33(Suppl); abstract 8025.

Gettinger S, Rizvi NA, Chow LQ, Borghaei H, Brahmer J, Ready N, et al. Nivolumab onotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2016;34(25):2980-7.

Jotte RM, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Abreu DR, Hussein MA, et al. IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. Journal of Clinical Oncology 2018; 36(18_suppl):LBA9000-LBA.

Kerr KM, Tsao MS, Nicholson AG, Yatabe Y, Wistuba II, Hirsch FR; IASLC Pathology Committee. Programmed death-ligand 1 immunohistochemistry in lung cancer: in what state is this art? J Thorac Oncol. 2015;10(7):985-9.

KEYTRUDA [package insert]. Whitehouse Station, NY: Merck & Co, 2020.

Lopes G, Wu Y-L, 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. J Clin Oncol. 2018; 36(18_suppl):LBA4-LBA.

OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013;31(23):2895-902.

Paz-Ares L, Luft A, Vincente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018; 379(21):2040-51.Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii27-39.

Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3(iii27-39.

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp 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]

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019; 37(7):537-46.

Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communications in Statistics – Theory and Methods 1991; 20(8):2609-31.

Scagliotti GV, De Marinis F, Rinaldi M, Crinò L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 2002;20(21):4285-91.

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346(2):92-8.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.

Socinski M, Creelan B, Horn L, Reck M, Paz-Are L, Steins M, et al. CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage IV/recurrent programmed death ligand 1 (PD-L1)−positive NSCLC. Annals of Oncology. 2016;27(supplement 6):LBA7_PR.

TECENTRIQ® [atezolizumab] [package insert]. 2018. In: Genentech, Inc., South San Francisco, CA.

Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, et al. Immune evasion in cancer: mechanistic basis and therapeutic strategies. Semin Cancer Biol. 2015;35:S185-98.

Weick JK, Crowley J, Natale RB, Hom BL, Rivkin S, Coltman CA Jr, et al. A randomized trial of five cisplatin-containing treatments in patients with metastatic non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol. 1991:9(7):1157-62.

22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Global, Randomized, Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1 + Non-Small Cell Lung Cancer, Amendment 9, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO REGN2810 OR INFUSION PROCEDURE, STUDY CONDUCT, STUDY PROCEDURE, OR COMBINATION TREATMENT

Is there a reasonable possibility that the event may have been caused by the study drugs, study conduct, or infusion procedure, study procedure, or concomitant treatment?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of cemiplimab or study procedure
- do not reappear or worsen when dosing with cemiplimab or study procedure is resumed
- are not a known response to cemiplimab, infusion procedure, or study procedure based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of cemiplimab
- resolve or improve after discontinuation of cemiplimab or study procedure
- reappear or worsen when dosing with cemiplimab or study procedure
- are known to be a response to cemiplimab or the infusion procedure or study procedure based upon preclinical data or prior clinical data

Note: This list is not exhaustive.

APPENDIX 2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

This appendix has been excerpted from the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; Eisenhauer 2009). For full details pertaining to the RECIST 1.1 criteria, please refer to the publication.

1. Assessment of Tumor Burden Measurable Disease at Baseline

Overall tumor burden must be assessed at baseline and will be used as comparator for subsequent measurements. Tumor lesions will be characterized as measurable or non-measurable as follows:

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

1.1. Measurable disease

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of

- 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

1.2. Nonmeasurable disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered nonmeasurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT, MRI, or PET) are considered as nonmeasurable.

1.2.1. Special Considerations

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.3. Methods of Assessment

All measurements must be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **CT and MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

1.4. Baseline Documentation of Target and Non-Target Lesions

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or, in rare cases, unequivocal progression of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

1.5. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target and non-target lesions.

1.5.1. Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (**Note:** the appearance of one or more new lesions is also considered progressions).
- **Stable Disease:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- Target lesions that become 'too small to measure': All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm. However, when such a lesion becomes difficult to assign an exact measure to then: (i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. (ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).
- Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

1.5.2. Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response:** Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease:** Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "nontarget" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or investigator).

1.6. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

1.7. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account any requirement for confirmation. The patient's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009) is summarized in Table 9.

Table 9: Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1) in Patients with Target (and Non-Target) Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response*
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/non-PD/not evaluated	No	PR
SD	Non-CR/non-PD/not evaluated	No	SD
PD	Any	Yes or no	PD
Any	PD*	Yes or no	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

1.8. Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

1.9. Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

2.0. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

APPENDIX 3. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC CEMIPLIMAB DRUG-RELATED ADVERSE EVENTS

Section 7.3.1 provides the dose level reductions.

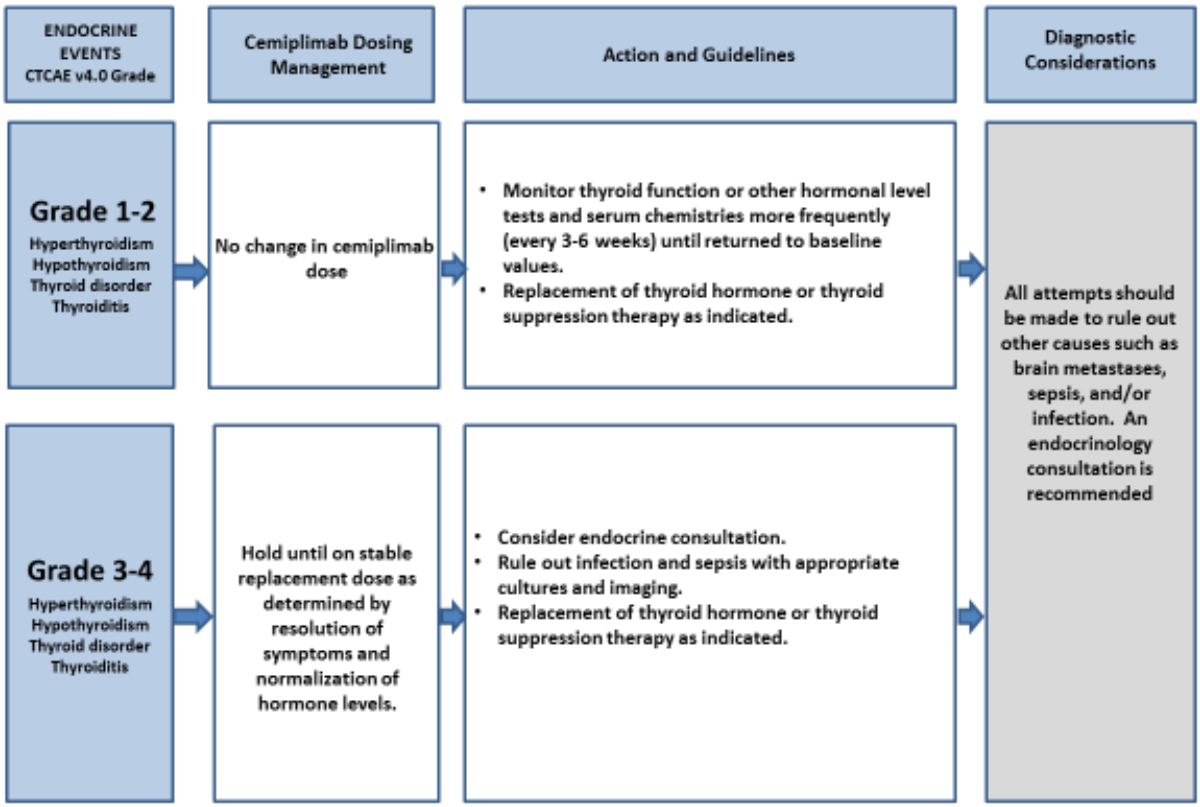
Colitis Adverse Event Management

COLITIS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1	No change in cemiplimab dose	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer If symptoms are persistent And/or severe, endoscopic evaluation should be considered
Grade 2	Hold until ≤Grade 1. Resume cemiplimab at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	• GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, cemiplimab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.	

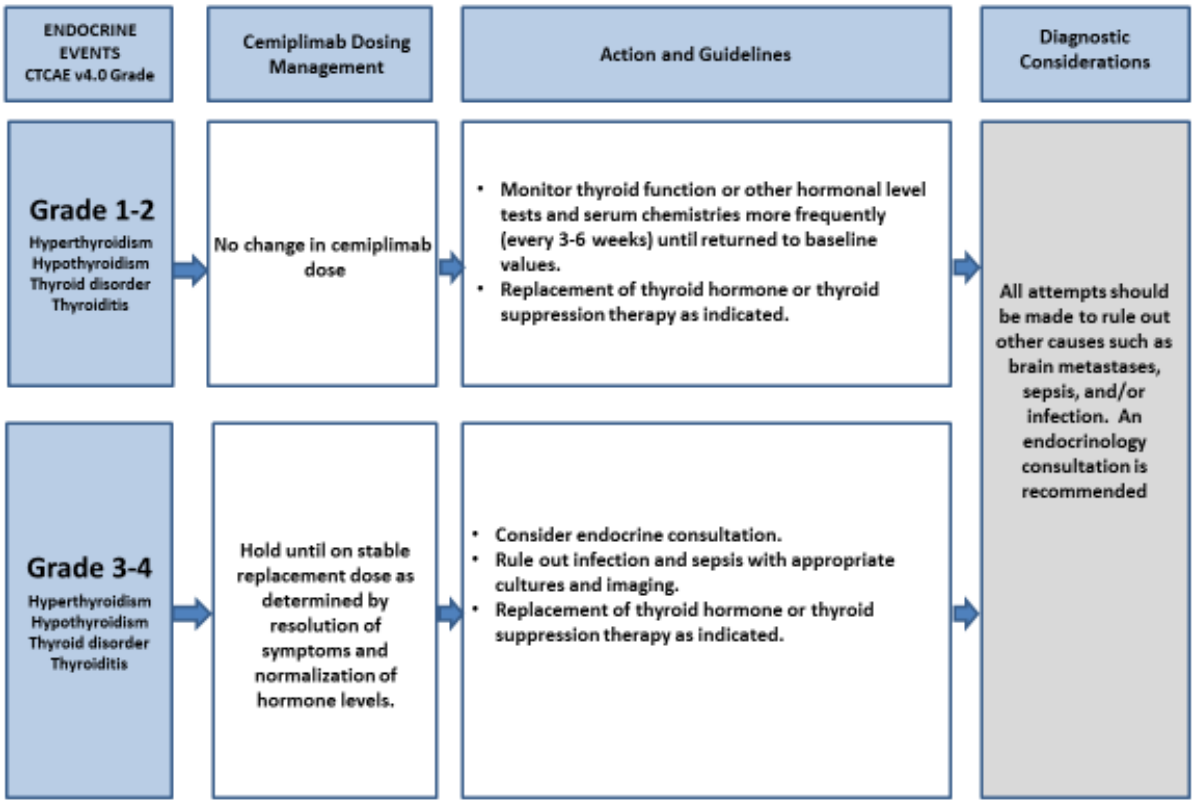
Colitis Adverse Event Management

COLITIS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3-4	Discontinue cemiplimab	• Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis. • If symptoms persist despite the above treatment a surgical consult should be obtained. • Permanent discontinuation of cemiplimab for grade 4 colitis	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer If symptoms are persistent And/or severe, endoscopic evaluation should be considered

Endocrine Adverse Event Management



Endocrine Adverse Event Management



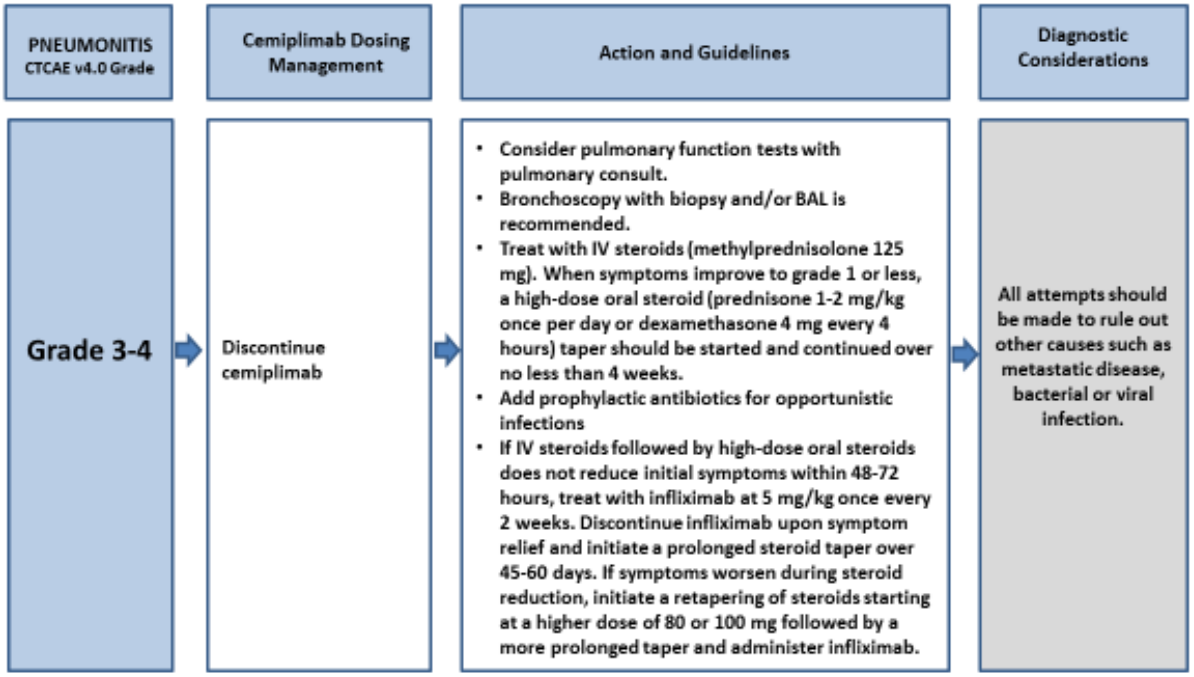
Endocrine Adverse Event Management (Cont)

ENDOCRINE EVENTS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1-4 Adrenal insufficiency Hypophysitis Hypopituitarism Pan-hypopituitarism	Hold until on stable replacement dose as determined by resolution of symptoms and normalization of hormone levels	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended

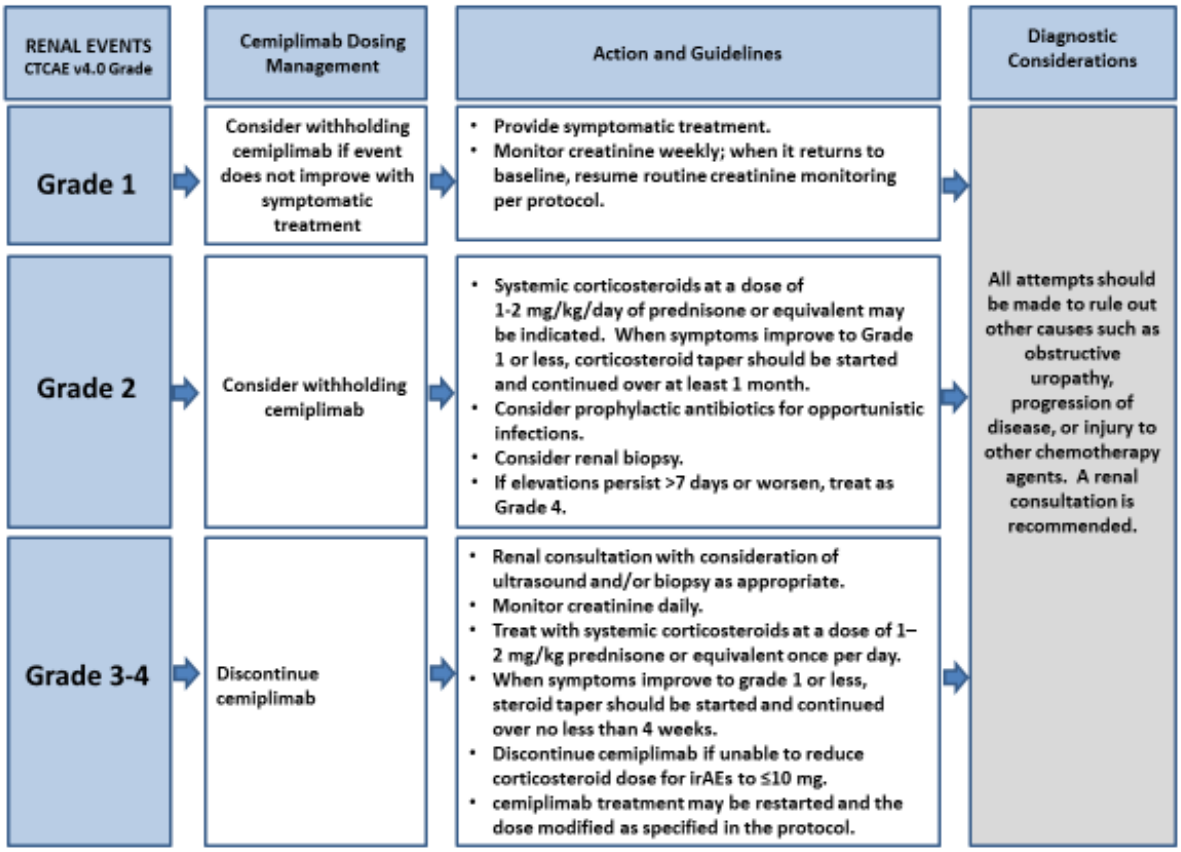
Pneumonitis Adverse Event Management

PNEUMONITIS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1	**Consider hold of therapy. cemiplimab may be continued with close monitoring.**	• **Radiologic findings should be followed on serial imaging studies at least every 3 weeks.** • **Monitor for symptoms every 2–3 days.** • **Consider pulmonary consultation and/or bronchoscopy if clinically indicated.**	**All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.**
Grade 2	**Hold cemiplimab**	**To rule out other causes such as infection:** • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1-3 days **If the patient is determined to have study drug associated pneumonitis:** • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with cemiplimab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. **For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply:** • First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles. • Second episode of pneumonitis: Discontinue cemiplimab if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis.	

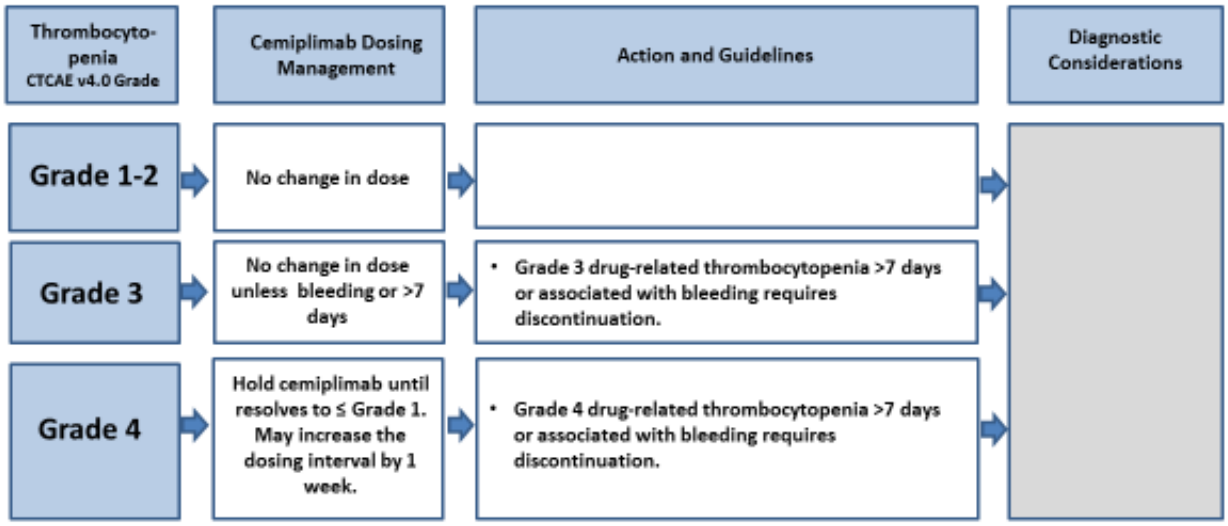
Pneumonitis Adverse Event Management (Cont)



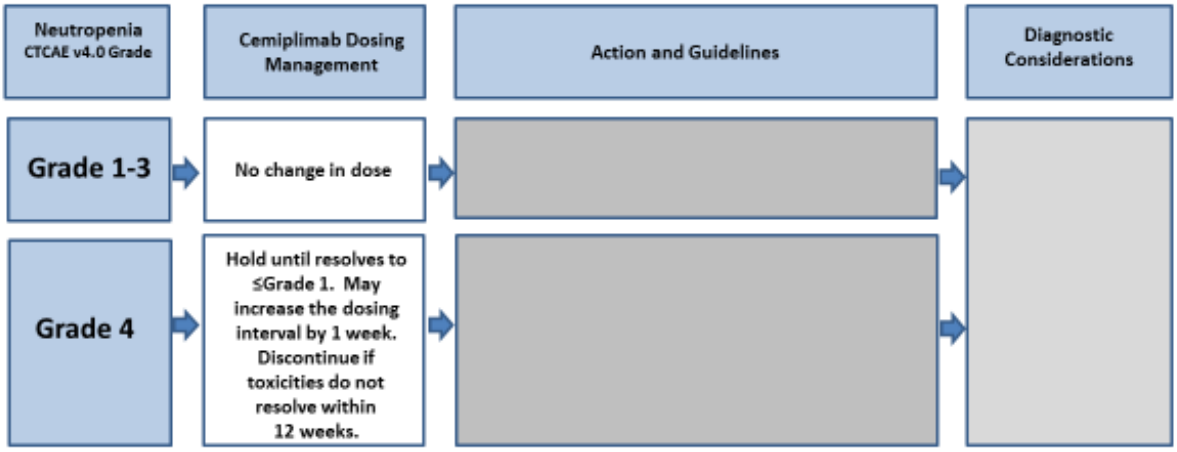
Renal Adverse Event Management



Hematologic Adverse Event Management



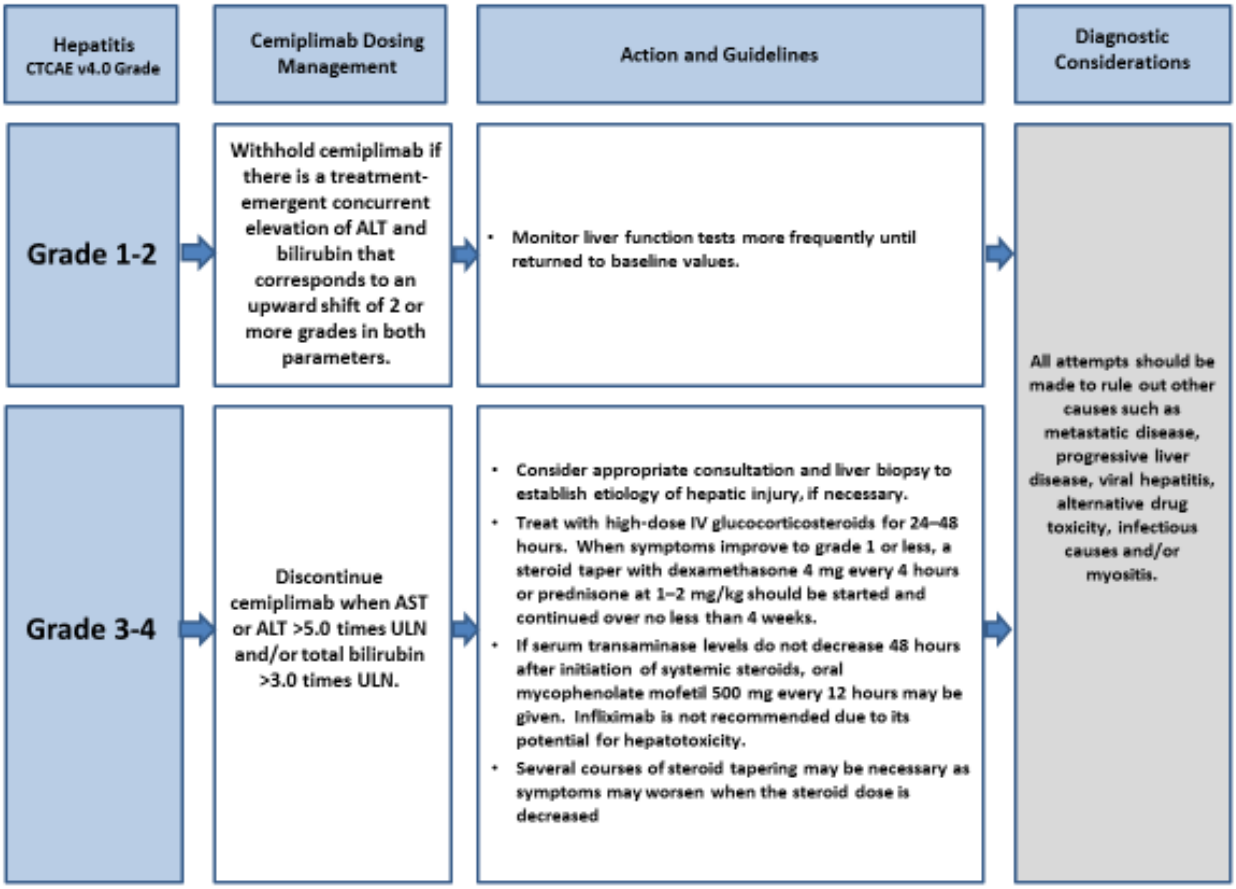
Hematologic Adverse Event Management (Cont)



Dermatologic Adverse Event Management

SKIN EVENTS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1-2	No change in dose	• Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events.	All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
Grade 3	hold cemiplimab	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	
Grade 4	Permanently discontinue cemiplimab	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1-2 mg/kg prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	

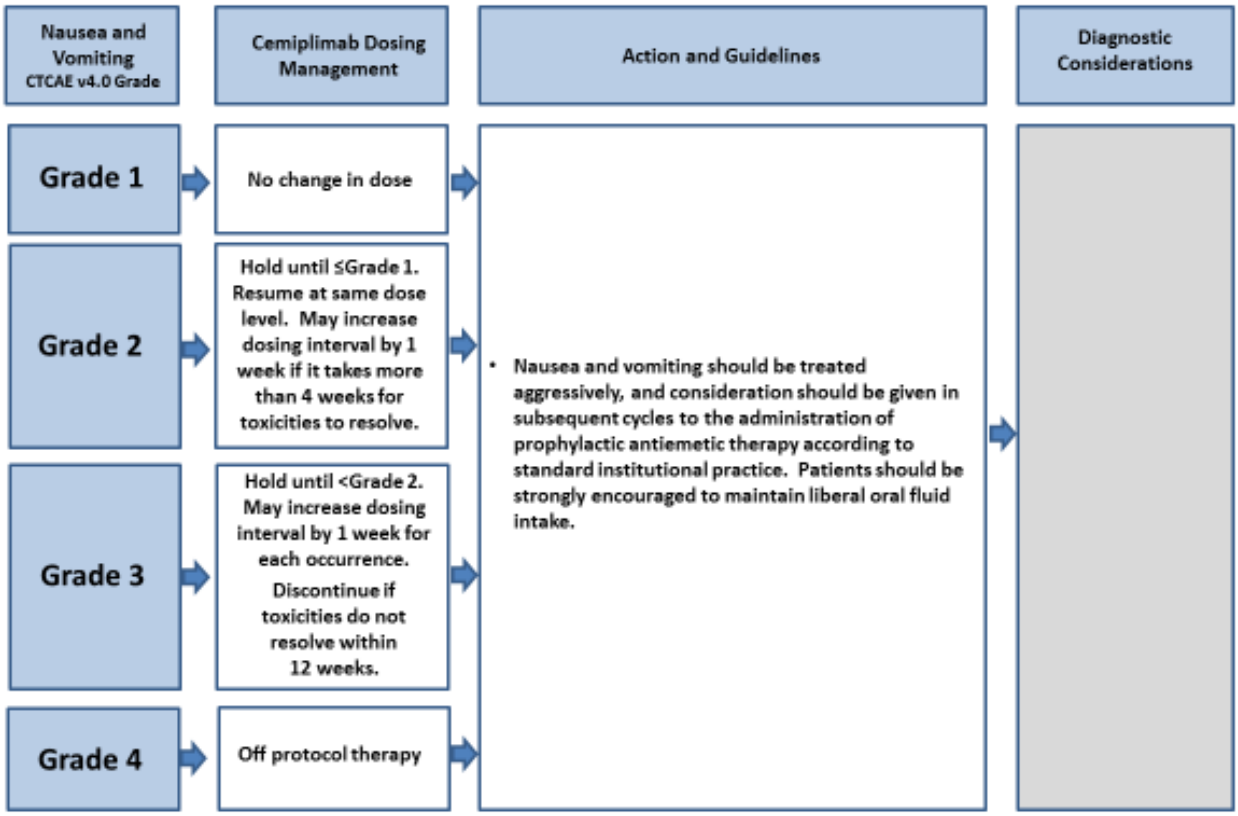
Hepatitis Adverse Event Management



Ophthalmologic (Uveitis) Adverse Event Management

Uveitis CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1	Discontinue cemiplimab if symptoms persist despite treatment with topical immunosuppressive therapy	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (*e.g.*, glaucoma or cataracts).
Grade 2	Discontinue cemiplimab if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	
Grade 3-4	Discontinue cemiplimab	• Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks	

Nausea and Vomiting Adverse Event Management



SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study and the data generated.

Study Title:	A Global, Randomized, Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1 + Non-Small Cell Lung Cancer
Protocol Number:	R2810-ONC-1624
Protocol Version:	R2810-ONC-1624 Amendment 9

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00110257 v1.0

ESig Approval	[redacted] 13-May-2020 15:49:20 GMT+0000
ESig Approval	[redacted] 13-May-2020 16:10:54 GMT+0000
ESig Approval	[redacted] 13-May-2020 18:35:38 GMT+0000
ESig Approval	[redacted] 13-May-2020 18:52:09 GMT+0000

Signature Page for VV-RIM-00110257 v1.0 Approved