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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, PHASE 3, OPEN-LABEL STUDY OF COMBINATIONS OF REGN2810 (CEMIPLIMAB, ANTI-PD-1 ANTIBODY), PLATINUM-BASED DOUBLET CHEMOTHERAPY, AND IPILIMUMAB (ANTI-CTLA-4 ANTIBODY) VERSUS PEMBROLIZUMAB MONOTHERAPY IN FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WITH TUMORS EXPRESSING PD-L1 ≥50%

Compound:	REGN2810 (Cemiplimab) (anti-PD-1 mAb)
Clinical Phase:	3
Protocol Number:	R2810-ONC-16111
Protocol Version:	R2810-ONC-16111 Amendment 3 Global
Amendment 3 Global Date of Issue:	*See appended electronic signature page*
Amendment 2 VHP Date of Issue:	16 March 2018
Amendment 2 Date of Issue:	23 February 2018
Amendment 1 Date of Issue:	21 November 2017
Original Date of Issue:	25 August 2017

Scientific/Medical Monitor:

[redacted]

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AMENDMENT HISTORY

Amendment 3 Global

Change	Sections Changed
Clarified that for patients on treatment Arm C, pemetrexed maintenance is not allowed.	Synopsis Study Design
Clarified that patients in follow-up may be offered retreatment up to an additional 108 week and patients may be required to sign a separate ICF per local regulatory requirements.	Section 5.1.3 Follow-up Period Section 7.8 Disease Progression While Receiving Cemiplimab or Pembrolizumab
Revised the following secondary endpoint text as: To assess the predictive utility of baseline PD L1 tumor expression levels on-clinical response. Clarified the following in the list of Other Secondary Objectives: Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel, sample permitting	Synopsis Objectives Section 2.2.2 Other Secondary Objectives
Inclusion criterion revised to add stage IIIC patient eligibility for the study and clarified that histologic diagnosis of NSCLC may be confirmed by the central laboratory.	Synopsis Study Design and Population Section 5.1 Study Description and Duration Section 6.2 Study Population Section 6.2.1 Inclusion Criteria #2
Gemcitabine options for platinum based doublet is deleted and chemotherapy cycles are changed from 4-6 cycles to 4 cycles. Following text deleted: 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. PK/ADA sample collection time points revised. Pharmacokinetics and immunogenicity of	Section 8.2.2.1 Radiographic Tumor Assessments Table 1 Guidelines for Platinum-Based Doublet Chemotherapy Regimens (Treatment Arm C) Table 5 Schedule of Events: Treatment Period Assessments and Procedures Table 6 Schedule of Events: Follow-up Period Assessments and Procedures Appendix 4 Cemiplimab Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedule Clarified that, if possible, a tumor biopsy should be collected at the time of

cemiplimab are now well understood and described by a linear population PK model in more than 500 patients from various studies. PK/ADA sampling can be reduced, as population PK modeling approaches are used to describe PK characteristics in individual patients and in the overall population of patients with NSCLC. Clarified that, if possible, a tumor biopsy should be collected at the time of progressive disease (optional) as described in the laboratory manual	progressive disease (optional) as described in the laboratory manual
Clarified that all patients will have tumor evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions confirmed by a central laboratory. Clarified that tuberculosis testing is for potential patients in TB endemic areas. Exclusion criteria added based on a health authority feedback: #24. History of previous organ transplant, including stem cell allograft #25. Meeting the comparator products contraindicated criteria as listed in local labeling. Investigators should review the current label in their local database.	Section 6.2.2 Exclusion Criteria #3, #23, #24, and #25
Clarified that: Tumor tissue samples will also be tested for EGFR mutations and ALK translocations as well as for ROS1 fusions by a central laboratory, unless these testing has already been performed and the results are available from other Regeneron NSCLC immunotherapy studies. Following text deleted: Biomarker procedures will include the use of tumor tissue samples for validation of additional PD-L1 assays. Following text deleted: Additional testing may be employed to determine PD-L1 expression levels by utilizing another PD-L1 IHC assay 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	Synopsis Procedures and Assessments Section 8.2.1 Procedures Performed only at Screening/baseline Visit Section 8.2.5 Biomarker Procedures Table 4 Schedule of Events: Screening Visit Assessments

REGN2810. Of special interest is PD-L1 expression across different cell types including tumor cells, stroma cells, and infiltrating immune cells. Following text revised as: If possible a tumor tissue biopsy sample should be obtained at the time of RECIST 1.1 defined progressive disease. to obtain information on mechanism of resistance.	
Electrocardiogram text revised to delete: Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR, QT, and QT corrected for Bazett's formula intervals will also be recorded.	Section 8.2.3.5 Electrocardiogram
Following text added, based on request by regulatory authority to evaluate ADA in ipilimumab, as follows: If necessary, these samples may also be used for ADA assessments of ipilimumab.	Section 8.2.4.2 Anti-Drug Antibody Measurements and Samples
The current text "Each vial will contain a volume sufficient to withdraw 5 mL of REGN2810 at a concentration of 50 mg/mL" is revised to "Each vial will contain withdrawable cemiplimab at a concentration of 50 mg/mL	Section 7.1.1 Cemiplimab Section 7.6.1 Packaging, Labeling, and Storage
Clarified that premedications are not required prior to the first administration of cemiplimab. And pretreatment with vitamin supplementation is to start within 3 days of randomization for patients with non-squamous NSCLC. Following text added: Pemetrexed maintenance therapy should be given according to local prescribing information and practice guidelines.	Section 7.2 Pretreatments Section 7.8 Disease Progression While Receiving Cemiplimab or Pembrolizumab Section 7.7.2 Permitted Medications and Procedures
Deleted "standard-of-care" wording from when mentioned in regards to platinum based chemotherapy(ies)."	Throughout the protocol
Changed REGN2810 to the generic name, cemiplimab and minor editorial changes	Throughout the protocol

Amendment 2 VHP

Change	Section Changed
The following text added to the exclusion criterion #10 “patients with HIV or hepatitis must have their disease reviewed by the specialist (e.g., infectious disease or hepatologist) managing this disease prior to commencing and throughout the duration of their participation in the trial” following European Union (EU) regulatory review.	Section 6.2.2 Exclusion Criteria, #10

Amendment 2

Change	Sections Changed
The current text of Key Secondary Endpoint “A patient who has not died will be censored at the last known date of contact" has been revised to "A patient who is lost to follow-up will be censored at the last date that the patient was known to be alive", following European Union (EU) regulatory review.	Section 4.2.2 Key Secondary Endpoint
Revised the exclusion criteria concerning human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) to clarify that patients with uncontrolled infection are excluded, but patients with controlled infection are permitted, as requested following EU regulatory review.	Section 6.2.2 Exclusion Criteria (combined criteria #10 and #11, and deleted previous #11)
The current text: “REGN2810 C2P1 drug product is supplied as a sterile liquid solution of 5.6 or 7.4 mL in a 10 or 20 mL glass vial for IV administration.” is revised to “REGN2810 C2P1 drug product is supplied as a sterile liquid solution of 5.6 mL in a 10 mL glass vial for IV administration.” as requested following EU regulatory review.	Section 7.1.1 REGN2810
The current text “Each vial will contain a volume sufficient to withdraw 5 mL or 7 mL of REGN2810 at a concentration of 50 mg/mL” is	Section 7.1.1 REGN2810 Section 7.6.1 Packaging, Labeling, and

Change	Sections Changed
revised to "Each vial will contain a volume sufficient to withdraw 5 mL of REGN2810 at a concentration of 50 mg/mL" as requested following EU regulatory review.	Storage
The inclusion of the text "or 4-6 cycles" as an option in Table 1 is deleted as requested following EU regulatory review. The current text "REGN2810 will be administered in combination with either platinum-based doublet chemotherapy (administered Q3W for 4 to 6 cycles; REGN2810/ipi or with platinum-based doublet chemotherapy (administered Q3W for 2 cycles) and ipilimumab (administered Q6W for up to 4 doses; REGN2810/chemo/ipi) and then alone for the remainder of the treatment period." is revised to "REGN2810 will be administered in combination with either ipilimumab (administered Q6W for up to 4 doses; REGN2810/ipi) or with platinum-based doublet chemotherapy (administered Q3W for 2 cycles) and ipilimumab (administered Q6W for up to 4 doses; REGN2810/chemo/ipi) and then alone for the remainder of the treatment period."	Table 1 Guidelines for Platinum-Based Doublet Chemotherapy Regimens (Treatment Arm C) Section 7.1.1 REGN2810.
Added tuberculosis screening, as requested following EU regulatory review.	Section 6.2.2 Exclusion Criteria (new criterion number 23) Table 4 Schedule of Events: Screening Visit Assessments and Procedures Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.3.6 Laboratory Testing
Added testing for amylase and lipase, as requested following EU regulatory review.	Table 4 Schedule of Events: Screening Visit Assessments and Procedures Table 5 Schedule of Events: Treatment Period Assessments and Procedures Section 8.2.3.6 Laboratory Testing
Revised the protocol to include regular thyroid function testing for Arm B as requested following EU regulatory review.	Table 5 Schedule of Events: Treatment Period Assessments and Procedures Section 8.2.3.6 Laboratory Testing

Amendment 1

Change	Sections Changed
The redesigned study is a phase 3, randomized, global, open-label, pivotal, study of the efficacy and safety of REGN2810/ipilimumab versus REGN2810/chemotherapy/ipilimumab versus pembrolizumab monotherapy in patients with stage IIIB 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. In the redesigned study, the study arms A and C remain the same; arm B will evaluate REGN2810 in combination with ipilimumab instead of chemotherapy. Rationale revised to reflect the new study design. Because this is the first study to evaluate the combination of REGN2810 and ipilimumab, and the combination or platinum doublet chemotherapy and ipilimumab, there will be an early review of data to ensure patient safety after the first 10 patients in the REGN2810/ipilimumab and the first 10 patients in the REGN2810/chemo/ipilimumab treatment arm have completed 4 weeks of follow-up following the first dose of REGN2810/ipilimumab or REGN2810/chemo/ ipilimumab respectively. An additional safety review will be performed by the IDMC after the first 10 patients in the REGN2810/ ipilimumab and REGN2810/chemo/ ipilimumab regimen have received all 4 doses of ipilimumab and have been followed for at least 6 weeks after the last dose. This analysis will include all patients who have been exposed to the combination treatment. Enrollment to Arm C does not need to be halted pending the results of the additional safety evaluation, but stopping criteria related to this evaluation was incorporated into the protocol. Rationale for combination of REGN2810 and ipilimumab has been revised to reflect the new study design. Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel, sample permitting	Clinical Study Protocol Synopsis: Objectives, Study Design, Treatments, Endpoints, Statistical Plan Section 1 Introduction Section 2.1 Primary Objectives Section 2.2.1 Key Secondary Objectives Section 2.2.2 Other Secondary Objectives Section 3.1 Hypothesis Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Endpoints and Objectives Section 3.2.4 Rational for Combination of REGN2810 and Ipilimumab Section 3.2.5 Rationale for Combination of REGN2810 and Ipilimumab and Limited (2 Cycles) Platinum-Based Doublet Chemotherapy Section 4.2.3 Other Secondary Endpoints Section 5 Study Design Figure 1 Study Flow Diagram Section 5.1 Study Description and Duration Section 5.1.1 Screening Section 5.1.2 Treatment Period Section 5.1.4 Description of Study Stopping Rules Section 5.1.5 Dose Limiting Toxicities Section 5.1.6 Maximum Tolerated dose Section 7.5 Method of Treatment Assignment Section 10.1 Statistical Hypothesis Table 5 Schedule of Events: Treatment Period Assessment and Procedures

Change	Sections Changed
Because this is the first study to evaluate the combination of REGN2810 and ipilimumab, and the combination or platinum doublet chemotherapy and ipilimumab description of study stopping rules revised. Description of dose limiting toxicities revised. The following changes were implemented: • Revised AST or ALT >5 times upper limit of normal (ULN) and/or total bilirubin >3 times ULN as a DLT criterion. • Added Grade 4 anemia DLT criteria include all Grade 3 immune-related AEs (irAEs). Any Grade 3 irAE which would result in permanent discontinuation of the REGN2810/ipilimumab or REGN2810/ipilimumab/chemo (or permanent discontinuation of ipilimumab), as outlined in the "Dosing Discontinuation" subsection of Section 7.3.1 of the protocol, or which would result in permanent discontinuation of REGN2810, as outlined in the guidelines in Appendix 3 of the protocol, will be considered a DLT. This specifically includes the following Grade 3 irAEs: pneumonitis, colitis/diarrhea, nephritis.	
The following statement added: The use of the PD-L1 IHC 22C3 pharmDx assay for decisions regarding treatment with REGN2810 is considered investigational.	Section 3.2.3 Rationale for Choice of Patient Population Based on the ≥50% Programmed death Death-1 Expression Cut-off Section 5.1.1 Screening
Due to a new statistical design, enrollment of approximately 585 subjects is needed to generate enough progression free survival (PFS) events. Therefore, the approximate number of planned subjects is reduced to 585 from 675.- An interim analysis for secondary endpoint of OS will be performed at the time of primary analysis for PFS.	Clinical Study Protocol Synopsis: Population, Statistical Plan Section 5.2 Planned Interim Analysis Section 6.1 Number of Patients Planned Section 7.5 Method of Treatment Assignment Section 10.2 Justification of Sample Size Section 10.6 Interim Analysis
Age limit requirements for the Japanese patients revised in Inclusion Criterion #1 as follows: Men	Section 6.2.1 Inclusion Criteria #1, #2, and #3

Change	Sections Changed
and women ≥18 years of age (≥21 years of age for Japanese patients) Based on the health authority feedback, inclusion criterion #2 revised to specify the following patient eligibility as follows: Patients with stage IV disease if they have not received prior systemic treatment for recurrent or metastatic NSCLC are eligible to participate in the study. Following guidance on biopsy sites provided: • Archival or fresh biopsies are acceptable • If an archival biopsy is used, it has to be less than 5 months old • The biopsy should be from a metastatic or recurrent site which has not previously been irradiated • Exception: the primary lung tumor is still in place and the other metastatic sites are either not accessible (brain) or cannot be used (bone) or the biopsy would put the patient at risk	
Exclusion criterion #3 modified to add a statement indicating that all patients should have tumor evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions. Exclusion criterion #5 revised to add the following: A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved ≥6 months prior to enrollment. Exclusion criterion #10 updated to add additional description of infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency Exclusion criterion #20 updated to include men of childbearing potential.	Section 6.2.2 Exclusion Criteria #3, #5, #10, and #20 Table 4 Schedule of Events: Screening Visit Assessments and Procedures
Study treatment for Arm B revised Guidelines for Platinum-based chemotherapy for treatment Arm C revised to remove the maintenance column from the table.	Section 7.1 Investigational and Reference Treatments Section 7.1.4 Platinum-Based Doublet Chemotherapy Table 1 Guidelines for Platinum-Based

Change	Sections Changed
	Doublet Chemotherapy Regimens (Treatment Arm C)
Because of study design revisions, the dose modification and treatment discontinuation rules have been updated.	Section 7.3.1 REGN2810 Plus Ipilimumab Combination Therapy Dosing Delay Rules Section 7.3.2 REGN Plus Ipilimumab and Chemotherapy Combination Therapy Dosing Delay Rules Section 7.3.3 REGN2810 as Combination Therapy
Following text added: irAEs of any grade in patients previously treated with PI3-K inhibitor	Section 9.3.3 Adverse Events of Special Interest
Acute infusion reactions are defined as any AE that occurs during the infusion or within one day after the infusion is completed, instead of within 2 hours.	Section 7.4.1 Acute Infusion Reactions Section 9.3.4 Infusion Reactions
Any treatment administered from the time of informed consent until 90 days (instead of 30 days) after the last study treatment will be considered concomitant medication.	Section 7.7 Concomitant Medications
Disease progression while Receiving REGN2810 or pembrolizumab description revised.	Section 7.8 Disease Progression While Receiving REGN2810 or Pembrolizumab
The following sentence deleted: This testing does not need to be repeated if it has been done previously and the results are available.	Section 8.2.5 Biomarker Procedures
Justification of the sample size was revised. Definitions of primary, secondary, and other analysis sets revised to reflect the new statistical design for the study. Multiplicity considerations revised due to hierarchical testing. An interim analysis for secondary endpoint of OS will be performed at the time of primary analysis for PFS.	Clinical Study Protocol Synopsis: Statistical Plan Section 10.2 Justification of sample size Section 10.3.3 Other Analysis Set Section 10.4.5.1 Primary Efficacy Analyses Section 10.4.5.2 Secondary Efficacy Analyses Section 10.5 Multiplicity Considerations Section 10.6 Interim Analysis
A written informed consent should be obtained for treatment beyond radiologic disease progression, acknowledging that this practice is not considered standard in the treatment of	Section 14.2 Informed Consent

Change	Sections Changed
cancer.	
The diagram for colitis adverse event management in Appendix 3 has been modified to require permanent discontinuation of cemiplimab for grade 4 colitis	Appendix 3 Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific REGN2810 Drug Related Adverse
ADA sample collection time points revised	Appendix 4 REGN2810 Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedule
Concomitant Medication Recording during follow-up added	Table 6 Schedule of Events: Follow-Up Period Assessments and Procedures
Data Quality Assurance section added	Section 18 Data Quality Assurance
Minor editorial changes	Throughout the protocol

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Phase 3, Open-Label Study of Combinations of REGN2810 (Cemiplimab, Anti-PD-1 Antibody), Platinum-based Doublet Chemotherapy, and Ipilimumab (Anti-CTLA-4 Antibody) Versus Pembrolizumab Monotherapy in First-Line Treatment of Patients With Advanced or Metastatic Non-Small Cell Lung Cancer With Tumors Expressing PD-L1 ≥50%
Site Locations	Patients will be randomized at approximately 200 global study sites.
Objectives	The primary objective of the study is to compare the progression-free survival (PFS) of cemiplimab plus ipilimumab combination therapy (hereinafter referred to as cemiplimab/ipi) and cemiplimab plus 2 cycles only of platinum-based doublet chemotherapy plus ipilimumab combination therapy (hereinafter referred to as "cemiplimab/chemo/ipi") with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC) whose tumors express programmed death ligand 1 (PD-L1) in ≥50% of tumor cells. The key secondary objectives of the study are the following: • To compare the overall survival (OS) of cemiplimab/ipi and cemiplimab/chemo/ipi with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells • To compare the objective response rate (ORR) of cemiplimab/ipi and cemiplimab/chemo/ipi with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells The other secondary objectives are the following: • To evaluate the safety and tolerability of cemiplimab/ipi and cemiplimab/chemo/ipi compared to pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells • To compare the OS at 12 and 18 months of cemiplimab/ipi or cemiplimab/chemo/ipi with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells • To compare quality of life (QOL) in patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of

	tumor cells receiving cemiplimab/ipi or cemiplimab/chemo/ipi with QOL in those patients receiving pembrolizumab monotherapy • To assess immunogenicity as measured by anti-drug antibodies (ADAs) for cemiplimab • To assess the predictive utility of baseline PD-L1 tumor expression levels on clinical response • To characterize the pharmacokinetics (PK) of cemiplimab when administered in combination with platinum-based doublet chemotherapy and/or ipilimumab • To conduct exposure-response (E-R) analyses for relevant biomarkers (exploratory PK/pharmacodynamic analyses) and E-R analyses for safety and efficacy endpoints, as appropriate
Study Design	This is a phase 3, randomized, global, open-label, pivotal study of the efficacy and safety of cemiplimab/ipi versus cemiplimab/chemo/ipi versus pembrolizumab monotherapy in patients with stage IIIB, 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. Patients will undergo a screening evaluation to determine their eligibility within 28 days prior to randomization. Eligible patients will be randomized 1:1:1 to one of the following treatment arms: • Treatment Arm A: pembrolizumab monotherapy 200 mg every 3 weeks (Q3W) for 108 weeks • Treatment Arm B: cemiplimab 350 mg Q3W for 108 weeks plus ipilimumab 50 mg every 6 weeks (Q6W) for up to 4 doses • Treatment Arm C: cemiplimab 350 mg Q3W for 108 weeks plus platinum-based doublet chemotherapy Q3W for 2 cycles and ipilimumab 50 mg every 6 weeks (Q6W) for up to 4 doses. Patients in this arm will not be permitted to receive pemetrexed maintenance. Patients will receive their assigned treatment for the 108-week treatment period. Treatment may be discontinued early due to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)-defined progressive disease, unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment, or, for patients in Treatment Arms B and C, in specific instances of confirmed complete response (CR) or partial response (PR). Patients who experience RECIST 1.1-defined progressive disease on therapy may continue treatment if the investigator judges the patient to be experiencing clinical benefit and if the patient has not completed the 108-week treatment period. If further progressive disease (defined as an

additional 10% increase in tumor burden from the time of initial progressive disease) is confirmed, treatment must be discontinued and other anti-cancer therapy considered, if appropriate. A similar approach to treatment beyond first evidence of progression may be offered to patients receiving pembrolizumab in Treatment Arm A.

After discontinuing study treatment, patients will enter the follow-up period.

Each patient will have the first follow-up visit 14 to 30 days after the last study treatment if treatment is discontinued early due to progressive disease, toxicity, or for another reason, or 14 to 30 days after the last cycle visit. Follow-up visit 2 through follow-up visit 7 will occur 28 days (±7 days) from the previous visit. Survival data will then be collected by phone or at an office visit every 3 months, until death, loss to follow-up, or withdrawal of study consent.

More than 353 patients have been dosed as of April 2017 with cemiplimab with no DLTs observed. Because this is the first study of the cemiplimab/ipi and cemiplimab/chemo/ipi combinations, safety data from the first 10 patients treated with cemiplimab/ipi in Treatment Arm B and the first 10 patients treated with cemiplimab/chemo/ipi in Treatment Arm C will be reviewed after these patients complete 4 weeks of follow-up following the first dose of cemiplimab/chemo/ipi. The data will be reviewed at a meeting of the IDMC. If 2 or more DLTs occur in the first 10 patients treated with cemiplimab/ipi or in the first 10 patients treated with cemiplimab/chemo/ipi, enrollment for the respective treatment arm will be stopped temporarily. Enrollment in Treatment Arms B and C will only be restarted after a formal safety review.

An additional safety review will be performed by the IDMC after the first 10 patients in the cemiplimab/ipi and the first 10 patients in the cemiplimab/chemo/ipi regimen have received all 4 doses of ipilimumab and have been followed for at least 6 weeks after the last dose. This analysis will include all patients who have been exposed to the combination treatment.

After this evaluation is performed, occurrence of drug related adverse events causing treatment discontinuation in ≥25% of treated patients will lead to a pause in further enrollment to Arm B or C pending review with the IDMC and the study steering committee.

The outcomes of these safety reviews will be a decision to do one of the following:

- Continue the study as planned after discussions with investigators and regulatory authorities
- Continue the study without the second cycle of chemotherapy
- Increase the interval for ipilimumab administration from 6 to 12 weeks in Treatment Arm B or C
- Discontinue Treatment Arm B or C

Study Duration	The approximate duration of the active study assessments for each patient, excluding screening, will be 32 months. This encompasses 25 months of study treatment plus 7 months of follow-up visits. After the active study assessments are complete, all patients will be followed for survival.
End of Study Definition	The end of study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 585 patients will be randomized.
Target Population:	Patients in this study will include men and women ≥18 years of age, diagnosed with stage IIIB, or IIIC NSCLC who are not eligible for definitive chemo/radiation therapy or patients with or stage IV non-squamous or squamous NSCLC, whose tumors express PD-L1 in ≥50% of tumor cells (measured using the PD-L1 immunohistochemistry 22C3 pharmDx assay [Dako, North America, Inc.]) and who have received no prior systemic treatment for their advanced disease.
Treatments	
Study Drug: **Dose/Route/Schedule:**	Cemiplimab administered at 350 mg as an intravenous (IV) infusion Q3W for 108 weeks in combination with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.
Study Drug: **Dose/Route/Schedule:**	Cemiplimab administered at 350 mg as an IV infusion Q3W for 108 weeks in combination with platinum-based doublet chemotherapy administered IV Q3W for 2 cycles and with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.
Reference Drug **Dose/Route/Schedule:**	Pembrolizumab administered at 200 mg as an IV infusion Q3W for 108 weeks.
Endpoints	
Primary:	The primary endpoint is PFS as assessed by a blinded Independent Review Committee (IRC) based on RECIST 1.1 assessments.
Secondary:	The key secondary endpoints will be OS and ORR. Other secondary endpoints will include the following: • The safety and tolerability of cemiplimab/ipi and cemiplimab/chemo/ipi measured by the incidence of treatment-emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), serious adverse events (SAEs), deaths, and laboratory abnormalities • Overall survival at 12 months and 18 months • Quality of life as measured by the European Organization for Research

	and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) • Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel, sample permitting
Procedures and Assessments	Procedures to be performed at screening will include informed consent; assessment of inclusion/exclusion criteria; recording of medical, oncology, and concomitant medications histories; recording of demographics; collection and testing of tumor tissue samples for PD-L1 assessment and for epidermal growth factor receptor and anaplastic lymphoma kinase mutations and C-ros oncogene receptor tyrosine kinase fusions; baseline radiographic tumor assessment and tumor burden assessment; chest X-ray; serum pregnancy testing; 12-lead electrocardiogram; complete physical examination including vital signs, height, and weight assessments; Eastern Cooperative Oncology Group (ECOG) performance status assessment; adverse event (AE) recording; and laboratory testing. Samples for an optional genomic sub-study may also be obtained. During the treatment period, the following procedures will be performed to assess efficacy and safety: QOL measurement using validated patient questionnaires, physical examination, ECOG performance status assessment; vital signs; laboratory testing, including pregnancy testing for women of childbearing potential; recording of AEs and concomitant medications. Computed tomography or magnetic resonance imaging (or positron emission tomography) for radiographic tumor burden assessment and tumor burden assessment based on RECIST 1.1 criteria will be performed at pre-specified time points throughout the study. Other assessments will include cemiplimab concentration measurement, cemiplimab ADA assessment, and biomarker assessments. . Survival data will then be collected by phone or at an office visit every 3 months, until death, loss to follow-up, or withdrawal of study consent.
Statistical Plan	The primary statistical hypothesis is that cemiplimab/ipi or cemiplimab/chemo/ipi will prolong PFS as compared with standard-of –care pembrolizumab monotherapy in treatment-naïve patients with squamous and non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells. The secondary hypothesis is that cemiplimab/ipi or cemiplimab/chemo/ipi will improve OS in the study patients whose tumors express PD-L1 in ≥50% of tumor cells. This study assumes a median PFS of 10 months for patients treated with pembrolizumab monotherapy and a median PFS of 15 months for patients treated with each of the cemiplimab combination therapies. The assumptions correspond to a 50% increase in median PFS and a hazard ratio (HR) of

0.6667. Under these assumptions, and for each cemiplimab combination treatment arm versus the pembrolizumab comparison, 256 PFS events are needed to yield an approximately 90% power to detect statistical significance at a 2-sided 0.05 level.

Considering a uniform enrollment rate and a combined enrollment, and PFS follow-up duration of approximately 36 months (24 months for enrollment and approximately 12 months follow-up for PFS), and a 10% dropout rate per year, enrollment of approximately 585 randomized patients (195 patients per arm) is needed to generate enough PFS events for each cemiplimab combination treatment arm versus the pembrolizumab comparison with 90% power. Under the enrollment assumption and the alternative hypothesis, it is estimated that at the time when not less than142 PFS events are observed in the pembrolizumab arm, each of the cemiplimab combination treatment arms plus the pembrolizumab arm will yield 256 PFS events in total. In order to harmonize the timing of the primary analysis for the 2 comparisons, the primary endpoint of PFS will be performed after 142 PFS events are observed in the pembrolizumab treatment arm.

Assuming a median OS of 18 months for patients treated with pembrolizumab monotherapy and a median OS of 24 months for patients treated with each of the cemiplimab combination therapies, a corresponding HR of 0.75 is anticipated if OS is distributed exponentially in each treatment arms. If the final analysis of OS is performed 12 months after the analysis of PFS, enrollment of 585 patients will yield approximately a power of 59% for the analysis of OS at a 2-sided alpha level of 0.05.

For PFS, it is projected that an observed HR of 0.78 or lower, corresponding to an increase in median PFS of 2.8 months or more (10 versus 12.8 months), would result in a statistically significant improvement in PFS. For OS, it is also projected that an observed HR of 0.77 or lower, corresponding to an increase in median OS of 5.4 months or more (18 versus 23.4 months), would result in a statistically significant improvement in OS.

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

For the 2 cemiplimab combinations versus pembrolizumab comparisons, and the test of primary endpoint of PFS, secondary endpoints of OS and ORR, a familywise type-I error rate of 0.05 is controlled by the hierarchical gatekeeping approach with the order of tests listed below:

1. PFS for cemiplimab/chemo/ipi vs. pembrolizumab
2. PFS for cemiplimab/ipi vs. pembrolizumab
3. OS for cemiplimab/chemo/ipi vs. pembrolizumab
4. OS for cemiplimab/ipi vs. pembrolizumab
5. ORR for cemiplimab/chemo/ipi vs. pembrolizumab
6. ORR for cemiplimab/ipi vs. pembrolizumab

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. Cemiplimab concentrations in serum will be reported over time as individual values with descriptive statistics.

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. Baseline characteristics and AEs will be summarized using descriptive statistics.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	Adrenocorticotropic hormone
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
Anti-CTLA-4	Anti-cytotoxic T-lymphocyte-associated antigen 4
Anti-PD-1	Anti-programmed death-1
Anti-PD-L1	Anti-programmed death ligand 1
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BOR	Best overall response
BP	Blood pressure
C2P1	Cell Line 2 Process 1
CBC	Complete blood count
CD	Cluster of differentiation
C_{eoi}	Concentration at end of infusion
CHO	Chinese hamster ovary
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
C_{trough}	Pre-infusion concentration
CTX	Cyclophosphamide
CV%	Variability in exposure
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response

EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
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
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer: Quality of Life Questionnaire Lung Cancer 13
E-R	Exposure-response
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HCV	Hepatitis C virus
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
ipi	Ipilimumab
IRB	Institutional Review Board
IRC	Independent Review Committee
irTEAE	Immune-related treatment-emergent adverse event
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system

LAM	Lactational amenorrhea method
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
n	Number of patients reflected in the calculation
N/A	Not applicable
NAb	Neutralizing anti-drug antibody
NCI-CTCAE	National Cancer Institute: Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death-1
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PR	Partial response
PT	Preferred term
PT/PTT	Prothrombin time/partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q9W	Every 9 weeks
Q12W	Every 12 weeks
Q18W	Every 18 weeks
Q24W	Every 24 weeks
QOL	Quality of life
R	Randomized
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid

ROS1	C-ros oncogene 1 receptor tyrosine kinase
RR	Respiratory rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SOC	System organ class
T4	Thyroxine
TEAE	Treatment-emergent adverse event
t_{eoi}	Time of end of infusion
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States

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1. INTRODUCTION

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (Siegel 2016, Bray 2013). 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 found to have advanced cancer at the time of diagnosis (Leighl 2012). With chemotherapy, these patients have a median overall survival (OS) of up to 12 to 18 months and a 5-year survival rate of approximately 18% (Leighl 2012, Siegel 2016).

Systemic treatment with platinum-based doublet regimens, with or without maintenance treatment, has been, until recently, the standard first-line treatment for all 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). Despite initial treatment with platinum-based doublet regimens, the disease often progresses, and additional treatment options have been limited.

In recent years, immunotherapies have been investigated as potential therapeutic approaches that will improve long-term survival and quality of life (QOL) in patients with advanced NSCLC. A complex cross-talk between cancer cells and the host immune system that can both inhibit and enhance tumor growth has recently been clarified (Vinay 2015). Tumors modulate and evade the host immune response through a number of mechanisms, including formation of an immune-suppressive environment within the tumor. Programmed death-1 (PD-1) is a co-receptor expressed on the surface of activated T cells that mediates immunosuppression. The binding of PD-1 to one of its ligands, programmed death ligand 1 (PD-L1) or programmed 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 results in an enhanced T-cell response with anti-tumor activity.

A number of diagnostic PD-L1 assays have been developed to inform treatment decisions (reviewed in Ratcliffe 2017). The assays demonstrate that there is a broad range of PD-L1 expression levels in tumor cells from NSCLC tumor samples (D'Incecco 2015, Kerr 2015). A high level of expression has been correlated with poor patient prognosis and resistance to standard-of-care chemotherapy (Creelan 2014). Blockade of the PD-1/PD-L1 T-cell checkpoint pathway has been shown to be an effective and well-tolerated approach to stimulating the immune response and has achieved significant objective responses in patients with NSCLC (Topalian 2012). Among patients with advanced, previously treated squamous and non-squamous NSCLC, OS was significantly improved in patients treated with the PD-1 inhibitor nivolumab compared to the OS in patients treated with docetaxel, regardless of PD-L1 expression (Borghaei 2015, Brahmer 2015). Similarly, patients with previously treated PD-L1-positive NSCLC who were treated with the PD-1 inhibitor pembrolizumab had improved OS compared to those treated with docetaxel (PD-L1 expression on at least 1% of tumor cells) (Herbst 2016). These data established the use of PD-1 inhibitors in the second-line treatment paradigm of patients with NSCLC (KEYTRUDA® [pembrolizumab] Package Insert,

KEYTRUDA European Union [EU] Summary of Product Characteristics [SmPC], OPDIVO® [nivolumab] Package Insert, OPDIVO EU SmPC, Ettinger 2016).

A third PD-L1 inhibitor, TECENTRIQ® (atezolizumab), was recently approved in the US for the treatment of metastatic NSCLC in patients with disease progression during or after treatment with platinum-based chemotherapy. Approval was based on 2 studies that demonstrated improved efficacy over docetaxel (Fehrenbacher 2016, Rittmeyer 2017).

Programmed cell death-1/ programmed death ligand 1 inhibitors are currently being investigated both as monotherapy (eg, KEYNOTE-024 and CheckMate 026) and in combination with standard-of-care chemotherapy regimens (eg, Rizvi 2016, Antonia 2014, Gadgeel 2016) or other immunotherapies (eg, CheckMate 012 [Hellmann 2017]) in the first-line treatment of patients with advanced NSCLC. Results from clinical studies, described in detail below, have been encouraging, and results of KEYNOTE-024 led to approval of pembrolizumab as first-line treatment in metastatic NSCLC patients whose tumors express PD-L1 in ≥50% of tumor cells.

In the phase 1 multicohort study, CheckMate 012, 56 patients with advanced squamous or non-squamous, treatment-naïve NSCLC received nivolumab in combination with 4 cycles of platinum-based chemotherapy. Response rates ranged from 33% to 47% with 1-year OS rates of 50% to 87% (Rizvi 2016). In patients treated with a PD-1/PD-L1 inhibitor in combination with chemotherapy, response rates ranging from 33% to 77% and median progression-free survival (PFS) ranging from 4.8 to 10 months have been observed in PD-L1 unselected tumors (Antonia 2014, Langer 2016). In tumors expressing high levels of PD-L1, even greater anti-tumor responses have been observed with response rates of 44% to 75% (Langer 2016, Gadgeel 2016) and a median PFS of 15 months (Gadgeel 2016). These limited data suggest that while monotherapy may be effective in the tumors with high PD-L1 expression, combination chemotherapy may be equally or more effective in patients with any degree of PD-L1 expression.

KEYNOTE-024 was an open-label, phase 3 study that included 305 patients with previously untreated, advanced NSCLC whose tumors expressed PD-L1 in ≥50% of tumor cells. The patients were randomized to receive either pembrolizumab 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 progression-free survival (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 <0.001). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% versus 27.8%). Furthermore, compared to the chemotherapy group, for the pembrolizumab group the median duration of response (DOR) was longer (not reached [range: 1.9+ to 14.5+ months] versus 6.3 months [range: 2.1+ to 12.6+ months]) and treatment-related adverse events (AEs) of any grade and of grades >3, 4, or 5 were less frequent (occurring in 73.4% versus 90.0% and 26.6% versus 53.3%, respectively) (Reck 2016). The results of this study led to approval of pembrolizumab in the United States (US), Japan, and some European countries for first-line treatment of advanced NSCLC in patients whose tumors express PD-L1 in ≥50% of tumor cells as determined by the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay (Dako, North America, Inc., PD-L1 IHC 22C3 pharmDx Package Insert; Roach 2016). This was the first Food and Drug Administration (FDA) approval of a checkpoint inhibitor for

first-line treatment of lung cancer. This approval also expanded the pembrolizumab indication for second-line treatment of lung cancer to include all patients with NSCLC expressing PD-L1 ≥1%.

In contrast to KEYNOTE-024, the phase 3 CheckMate 026 study, investigating the efficacy of first-line treatment with nivolumab compared to platinum-based doublet chemotherapy in patients with advanced PD-L1-positive NSCLC (defined as present in 1% or more tumor cells), did not meet its primary endpoint (Socinski 2016). Even in a subset analysis of those patients with PD-L1 expression in ≥50% of tumor cells, nivolumab failed to demonstrate any improvement over chemotherapy. There is currently no proven explanation for this discrepancy between the 2 studies. A total of 541 patients were randomized 1:1 to the nivolumab or chemotherapy treatment group. Patients who progressed on chemotherapy could cross over to nivolumab as second-line treatment. In the 423 patients whose tumors express PD-L1 in ≥5% of tumor cells, 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).

Programmed cell death-1/PD-L1 inhibitors have also been investigated in combination with standard-of-care chemotherapy regimens. Most recently, results with pembrolizumab in chemotherapy-naïve patients with non-squamous NSCLC in combination with carboplatin and pemetrexed (KEYNOTE-021, Cohort G [n=123]) have shown a median PFS of 10 months and median OS that was not reached (Langer 2016). Mean confirmed response rates ranged from 54% (PD-L1 expression ≥1% to 49%) to 60% (PD-L1 expression ≥50%), and median PFS ranged from 14 to 15 months. Patients whose tumors expressed PD-L1 <1% showed a median PFS of 6 months, which is historically observed with first-line chemotherapy regimens alone. These results led to the approval of pembrolizumab in combination with carboplatin and pemetrexed as first-line treatment in patients with non-squamous NSCLC (KEYTRUDA Package Insert).

A second type of immuno-oncology agent, anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4), has also been demonstrated to be clinically active in advanced cancers. Ipilimumab, a fully human monoclonal anti-CTLA-4 immunotherapy, has demonstrated clinical activity as monotherapy in melanoma (Wolchok 2010, O'Day 2010) and prostate cancer (Slovin 2013) and is now approved in the US and EU for treatment of unresectable or metastatic melanoma and for the adjuvant treatment of melanoma (YERVOY® Package Insert, YERVOY EU SmPC).

In addition to immuno-oncology agents as monotherapy, the potentially additive or synergistic effects of immuno-oncology therapeutics with different mechanisms of action are now being evaluated in NSCLC (reviewed in Buchbinder and Desai 2016). Nivolumab as combination immunotherapy with ipilimumab was evaluated in CheckMate 012, a phase 1 study in treatment-naïve patients with advanced NSCLC (Hellmann 2017). Patients received nivolumab plus ipilimumab at one of 3 dose regimens or nivolumab monotherapy (monotherapy treatment group results not reported in Hellmann 2017). Confirmed response rates were 47% (95% CI: 31% to 64%) in patients receiving nivolumab every 2 weeks (Q2W) plus ipilimumab every 12 weeks (Q12W) and 38% (95% CI: 23% to 55%) in patients receiving nivolumab Q2W plus ipilimumab every 6 weeks (Q6W). Median DOR was not reached in either treatment group (median follow-up times of 12.8 months in the patients receiving nivolumab Q2W plus

ipilimumab Q12W and 11.8 months in the patients receiving nivolumab Q2W plus ipilimumab Q6W. The greatest percentage of responses was noted in patients with tumors that expressed PD-L1. In patients whose tumors expressed PD-L1 in ≥1% of tumor cells, confirmed objective responses were achieved in 12 of 21 (57%) patients in the ipilimumab Q12W treatment group and 13 of 23 (57%) patients in the ipilimumab Q6W treatment group (Hellmann 2017). The 1-year survival rate in patients treated with nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W or Q12W was 100% in patients with tumors that expressed PD-L1 in ≥50% of tumor cells (n=13) and was 76% in all-comers (all patients regardless of PD-L1 status [n=77]), compared to 73% for patients receiving nivolumab monotherapy (n=52). One-year survival in patients with tumors that expressed PD-L1 in >1% of tumor cells was 91% in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q12W treatment group and 83% in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q6W treatment group (n=23 in each treatment group) compared to 73% in the nivolumab monotherapy treatment group (n=32) (Gettinger 2016). The improved efficacy in NSCLC patients whose tumors expressed PD-L1 contrasts to the phase 3 study in patients with melanoma (Larkin 2015), where addition of anti-CTLA-4 to anti-PD-1 provided benefit predominantly to those patients whose tumors had low baseline PD-L1 expression.

Combination immunotherapy with durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4) is currently being evaluated in multiple cancer types, including urothelial carcinoma (NCT02516241), squamous cell carcinoma of the head and neck (NCT02551159), and renal cell carcinoma (RCC) (NCT02762006). In patients with NSCLC, the durvalumab plus tremelimumab combination demonstrated clinical activity, regardless of PD-L1 expression levels. Investigator-reported confirmed responses occurred in 23% of patients (95% CI: 9% to 44%) in the durvalumab plus tremelimumab combination therapy group, including 22% (95% CI: 3% to 60%) of patients with PD-L1-positive tumors (tumors that expressed PD-L1 on ≥25% of tumor cells) and 29% (95% CI: 8% to 58%) of patients with PD-L1-negative tumors (tumors that expressed PD-L1 on <25% of tumor cells) (Antonia 2016). Recently, however, a phase 3 trial of durvalumab in combination with tremelimumab failed to significantly improve PFS over standard-of-care chemotherapy in PD-L1-positive patients with advanced NSCLC (AstraZeneca Press Release, 27 July 2017).

Ipilimumab plus chemotherapy also demonstrated improved median OS over chemotherapy alone (12.2 versus 8.3 months; p=0.23) in previously untreated patients with NSCLC when chemotherapy was given first followed by ipilimumab ("phased ipilimumab"). Median immune-related PFS, the primary endpoint, was significantly improved in patients receiving phased ipilimumab over chemotherapy alone (5.7 versus 4.6 months; p=0.05) (Lynch 2012).

Cemiplimab is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. Additional studies underway with cemiplimab are described in the Investigator's Brochure. Pre-clinical data indicate that cemiplimab has similar efficacy to other approved anti-PD-1 antibodies; clinical data to date confirm the pre-clinical data. Regeneron Pharmaceuticals, Inc. (Regeneron) is developing cemiplimab as a foundational immuno-oncology agent to be combined with maximal flexibility with other anti-cancer immunotherapies currently in pre-clinical development.

Please refer to the latest edition of the Investigator's Brochure for an overview of relevant safety data (including patient exposure and immune-related adverse events [irAEs]) and efficacy data from clinical studies with cemiplimab.

Study R2810-ONC-16111 is a randomized, open-label, phase 3 study of cemiplimab plus ipilimumab combination therapy (cemiplimab/ipi) or cemiplimab plus 2 cycles of platinum based doublet chemotherapy and ipilimumab combination therapy (cemiplimab/chemo/ipi) versus pembrolizumab monotherapy 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 objective of the study is to determine if cemiplimab/ipi or cemiplimab/chemo/ipi improves PFS over standard-of-care pembrolizumab in this patient population. Additional objectives include further characterization of OS, objective response rate (ORR), safety, pharmacokinetics (PK), and QOL.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare the progression-free survival (PFS) of cemiplimab (cemiplimab) plus ipilimumab combination therapy (hereinafter referred to as cemiplimab/ipi) and cemiplimab plus 2 cycles only of platinum-based doublet chemotherapy plus ipilimumab combination therapy (hereinafter referred to as "cemiplimab/chemo/ipi") with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC) whose tumors express programmed death ligand 1 (PD-L1) in ≥50% of tumor cells.

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

The key secondary objectives of the study are the following:

- To compare the OS of cemiplimab/ipi and cemiplimab/chemo/ipi with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells
- To compare the ORR of cemiplimab/ipi and cemiplimab/chemo/ipi with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells

2.2.2. Other Secondary Objectives

The other secondary objectives are the following:

- To evaluate the safety and tolerability of cemiplimab/ipi and cemiplimab/chemo/ipi compared to pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells
- To compare the OS at 12 and 18 months of cemiplimab/ipi and cemiplimab/chemo/ipi with pembrolizumab monotherapy in the first-line treatment of patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells
- To compare QOL in patients with advanced squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells receiving cemiplimab/ipi or cemiplimab/chemo/ipi with QOL in those patients receiving pembrolizumab monotherapy
- To assess immunogenicity as measured by anti-drug antibodies (ADAs) for cemiplimab
- To assess the predictive utility of baseline PD-L1 tumor expression levels on clinical response
- To characterize the PK of cemiplimab when administered in combination with platinum-based doublet chemotherapy and/or ipilimumab
- To conduct exposure-response (E-R) analyses for relevant biomarkers (exploratory PK/pharmacodynamic analyses) and E-R analyses for safety and efficacy endpoints, as appropriate
- Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel, sample permitting

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

The hypothesis of this study is that cemiplimab and ipilimumab for up to 4 cycles of combination therapy (cemiplimab/ipi) or cemiplimab plus platinum-based doublet chemotherapy for 2 cycles and ipilimumab for up to 4 cycles of combination therapy (cemiplimab/chemo/ipi) will prolong median PFS compared with pembrolizumab monotherapy in the first-line treatment of patients with advanced or metastatic NSCLC whose tumors express PD-L1 in ≥50% of tumor cells.

Historically, median PFS in patients with stage IIIB/IV squamous and non-squamous NSCLC treated with platinum-based doublet chemotherapy has ranged from approximately 2.7 to 6.4 months (El-Shenshawy 2012, Kelly 2001, Rosell 2002, Scagliotti 2002, Schiller 2002, Shimizu 2013, Reck 2016). 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 being investigated. 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.

Anti-PD-1 monotherapy as first-line treatment in patients with advanced NSCLC has demonstrated efficacy (Gettinger 2016, Garon 2015) and a significant improvement in PFS compared to chemotherapy (Reck 2016). Combination immunotherapies for NSCLC have also demonstrated clinical activity (Hellmann 2017).

Cemiplimab clinical study data (see Section 1) in addition to the demonstrated clinical activity of ipilimumab in combination with nivolumab support the hypothesis that the combination of cemiplimab/ipi or cemiplimab/chemo/ipi may prolong PFS in patients with advanced or metastatic, squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is a randomized, open-label, phase 3 study evaluating the efficacy of cemiplimab/ipi or cemiplimab/chemo/ipi compared with pembrolizumab monotherapy 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. This study will be open-label because the differences in administration and known distinct toxicities of the therapies do not lend themselves to blinding.

Because this is the first study to evaluate the combination of cemiplimab and ipilimumab and the combination or platinum doublet chemotherapy and ipilimumab, there will be an early review of data to ensure patient safety after the first 10 patients in the cemiplimab/ipi and the first 10 patients in the cemiplimab/chemo/ipi treatment arm have completed 4 weeks of follow-up following the first dose of cemiplimab/ipi or cemiplimab/chemo/ipi respectively. An additional safety review will be performed by the Independent Data Monitoring Committee (IDMC) after the first 10 patients in the cemiplimab/ipi and cemiplimab/chemo/ipi regimen have received all 4 doses of ipilimumab and have been followed for at least 6 weeks after the last dose. This analysis will include all patients who have been exposed to the combination treatment.

The study population is limited to previous and current smokers as the benefit of PD-1 blockade has not been shown to the same extent in non-smokers likely due to the lower mutational burden in this population (Reck 2016).

3.2.2. Rationale for Endpoints and Objectives

The primary objective of this study is to compare the PFS of cemiplimab/ipi or cemiplimab/chemo/ipi to pembrolizumab monotherapy. Based on data released for another PD-1 antibody, prolongation of PFS is expected in patients with NSCLC whose tumors express PD-L1 in ≥50% of tumor cells. Overall survival is clearly the ultimate endpoint of benefit, but an improvement in OS may be obscured due to patients who progress and elect to begin second-line treatment with pembrolizumab, nivolumab or atezolizumab as recommended in the recent National Comprehensive Cancer Network recommendations (Ettinger 2016). Therefore, OS will be a secondary endpoint. This approach is consistent with the 2015 FDA Guidance for Industry on Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and

Biologics (FDA 2015) and the December 2015 European Medical Agency Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA 2015), which contains specific guidance on NSCLC.

Progression-free survival, defined as 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 the primary endpoint because PFS is recognized as a marker of clinical benefit. Progression-free survival is an approvable endpoint in the US and is also acceptable in the EU for studies where the experimental treatment is likely to be well tolerated. Progressive disease 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 subsequent assessments will occur every 9 weeks (Q9W) during year 1, Q12W during year 2, and Q12W in follow-up or until RECIST 1.1-defined progressive disease or early treatment discontinuation for another reason. Further, to diminish bias in the assessment of progressive disease in this open-label study, an Independent Review Committee (IRC), which will be blinded to treatment assignment, will be utilized to adjudicate tumor responses. Overall survival at 12 months, 18 months, and end of treatment will be assessed as secondary endpoints, despite the acknowledged limitations. Additionally, efficacy responses to be assessed will include assessment of ORR. 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 Patient Population Based on the ≥50% Programmed Death-1 Expression Cut-off

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, Hellmann 2017). In an exploratory analysis of an ongoing study, nivolumab monotherapy in chemotherapy-naïve patients with advanced NSCLC resulted in higher response rates, more prolonged PFS, and higher 1-year OS rates as the level of PD-L1 expression increased (1%, 5%, 10%, 25%, and 50%) (Gettinger 2015).

The KEYNOTE-024 study included 305 treatment-naïve patients with advanced NSCLC whose tumors expressed PD-L1 in ≥50% of tumor cells (as measured by the PD-L1 IHC 22C3 pharmDx assay [Dako, North America, Inc.]), which led to the US FDA approval of pembrolizumab (KEYTRUDA, Merck & Co., Inc.) as first-line treatment in this patient population (Reck 2016).

Bristol-Meyers Squibb, Inc. recently reported that their first-line NSCLC study of nivolumab monotherapy had failed because the primary endpoint of PFS was not met. The study 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 pharmDx) (Socinski 2016). Therefore, in this study, only patients whose tumors express PD-L1 in ≥50% of tumor cells (measured using the PD-L1 IHC 22C3 pharmDx assay) 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 Combination of Cemiplimab and Ipilimumab

Combination immunotherapies that include an anti-CTLA-4 agent and an anti-PD-1/PD-L1 agent have the potential for additive or synergistic effects (reviewed in Buchbinder and Desai 2016).

Clinical activity of the combination of anti-PD-L1 and anti-CTLA-4 has been demonstrated in studies of durvalumab plus tremelimumab combination therapy (Antonia 2016; Section 1) and nivolumab plus ipilimumab combination therapy (described in detail below).

Ipilimumab has shown promise in multiple tumor types and is approved as monotherapy and in combination with nivolumab for advanced melanoma. Ipilimumab plus nivolumab combination therapy was approved for the treatment of advanced melanoma based on the results of CheckMate 067 that demonstrated significantly improved PFS in patients treated with the combination (11.5 months; 95% CI: 8.9 to 16.7 months) compared with ipilimumab monotherapy (2.9 months; 95% CI: 2.8 to 3.4 months; HR for death or disease progression, 0.42; 99.5% CI: 0.31 to 0.57; $p<0.001$) and nivolumab monotherapy (6.9 months; 95% CI: 4.3 to 9.5 months; HR for the comparison with ipilimumab, 0.57; 99.5% CI: 0.43 to 0.76; $p<0.001$) (Larkin 2015).

Ipilimumab plus nivolumab combination therapy has also demonstrated clinical activity in NSCLC (see Section 1) as first-line treatment in advanced NSCLC. In the CheckMate 012 study, confirmed response rates were 47% (95% CI: 31% to 64%) in patients receiving nivolumab Q2W plus ipilimumab Q12W and 38% (95% CI: 23% to 55%) in patients receiving nivolumab Q2W plus ipilimumab Q6W. The greatest percentage of responses was noted in patients with tumors that expressed PD-L1 (Hellmann 2017), which is in contrast with the phase 3 study in melanoma (Larkin 2015), in which addition of anti-CTLA 4 to anti PD-1 provided benefit predominantly in those patients with low baseline PD-L1 positivity. The 1 year survival rate in patients with tumors that expressed PD-L1 in ≥50% of tumor cells (n=13) was 100% and in all-comers (n=77) was 76%, compared to 73% for patients receiving nivolumab monotherapy (n=52) (Gettinger 2016; see Section 1 for additional details). Cemiplimab and ipilimumab are immuno-oncology agents with different mechanisms of action. Cemiplimab is a monoclonal antibody to the PD-1 receptor that blocks PD-1/PD-L1-mediated T-cell inhibition, whereas ipilimumab is an inhibitor of CTLA-4. Based on the unique mechanisms of action, the anti-PD-1/anti-PD-L1 action of cemiplimab and the anti-CTLA-4 action of ipilimumab have the potential for additive or synergistic effects (Buchbinder and Desai 2016). This effect may be particularly pronounced in the population of patients whose tumors express PD-L1 in ≥50% of tumor cells.

3.2.5. Rationale for Combination of Cemiplimab and Ipilimumab and Limited (2 Cycles) Platinum-Based Doublet Chemotherapy

Recent unpublished data have indicated that administration of 2 preliminary cycles of platinum-based doublet chemotherapy before the introduction of a secondary anti-CTLA-4 and/or anti-PD-1/PD-L1 agent may improve the overall efficacy; therefore, this regimen has also been adopted in this study.

Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well-tolerated approach to stimulating the immune response and has achieved significant objective responses in advanced melanoma, RCC, and NSCLC (Topalian 2012). However, optimal therapy will likely

require combining immuno-oncology agents with conventional therapies and/or novel immunotherapy approaches. Combinatorial approaches of immuno-oncology agents plus chemotherapy have demonstrated encouraging results in NSCLC (reviewed in Gainor 2016). For example, KEYNOTE-021, described in Section 1, evaluated pembrolizumab in combination with carboplatin and pemetrexed. Response rates ranged from 54% (PD-L1 expression ≥1% to 49%) to 60% (PD-L1 expression ≥50%), and median PFS ranged from 14 to 15 months (Langer 2016). Evaluation of the combination of cemiplimab plus platinum-based doublet chemotherapy will allow comparison of the safety and potential benefits in the population of NSCLC patients whose tumors express PD-L1 in ≥50% of tumor cells.

The recent trial of durvalumab in combination with tremelimumab failed to achieve statistically significant improvement in PFS over standard-of-care chemotherapy in PD-L1-positive patients with advanced NSCLC (AstraZeneca Press Release, 27 July 2017). This raises some concern whether the initial promising results of the combination of nivolumab and ipilimumab seen in CM-012 (Hellmann 2017) will bear out in larger trials. The time required to mobilize an effective anti-tumor response may sometimes take weeks to months and, in the setting of a rapidly growing tumor, may not arise before progression has occurred. As the recent data studying various combinations of immunotherapy and chemotherapy have shown, concomitant chemotherapy may not appreciably interfere with immunotherapy benefit. Therefore, in this study the combination of cemiplimab and ipilimumab will be accompanied by administration of the first 2 cycles of standard platinum doublet chemotherapy (on an every 3 weeks [Q3W] schedule). The rationale is that initial tumor control mediated by chemotherapy will provide more time for an effective immune response to mature, and may, in fact, be enhanced by chemotherapy-induced cell death, and augmented antigen presentation. The rationale for limiting the chemotherapy to 2 cycles is to limit the risk of triple combination-related toxicities and to limit the interference of longer administration of the cytotoxic regimens with the immuno-oncology combination therapy.

3.2.6. Rationale for Cemiplimab Dose Selection

The proposed cemiplimab dose of 350 mg Q3W given by the intravenous (IV) route was selected in this study for patients with NSCLC to better align with the dosing schedule of planned concurrent treatment with ipilimumab (50 mg Q6W for 4 doses). The cemiplimab dose of 350 mg Q3W was also selected for an ongoing pivotal phase 3 study in patients with NSCLC.

In the ongoing first-in-human (FIH) study (study R2810-ONC-1423), the 3 mg/kg Q2W IV dose has shown anti-tumor activity and acceptable safety in NSCLC patients among other patient types; efficacy was also observed at the 1 mg/kg Q2W dose. 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.

The preference of a flat dose over a body weight adjusted dose for anti-PD-1 monoclonal antibodies is supported by a wide safety margin (no maximum tolerated dose [MTD] observed), a flat E-R relationship for safety and efficacy over the therapeutic dosing range, and similar variability in exposure (CV%) after flat and body weight adjusted dose (Freshwater 2017, Zhao 2017a). In fact, pembrolizumab and nivolumab were initially approved at a body-weight adjusted dose of 2 mg/kg Q3W and 3 mg/kg Q2W, respectively, and were recently approved by

US FDA at flat doses of 200 mg Q3W and 240 mg Q2W, respectively, for the treatment of melanoma and NSCLC (KEYTRUDA Package Insert, OPDIVO Package Insert). The European Medicines Agency have also approved a flat dose of 200mg Q3W of pembrolizumab for NSCLC that has not been previously treated with chemotherapy.

A flat IV cemiplimab dose of 350 mg Q3W was selected based on population PK modeling and simulation, since this dose is expected to provide exposure that closely replicates the exposure observed in patients (mean weight: 80 kg) for the 3 mg/kg Q2W IV regimen in study R2810-ONC-1423 (NCT02383212). Simulations of cemiplimab exposure in 1000 patients using population PK analyses have demonstrated the following:

1. The variability in cemiplimab exposure was similar for body weight-adjusted doses as compared to flat doses, therefore supporting flat dose selection.
2. A 350 mg Q3W dose in patients with an expected mean body weight of 80 kg resulted in similar (≤20% difference) C_{trough}, area under the curve from time 0 to week 12 (AUC_{12W}), and peak concentration (C_{max}) as compared to the 3 mg/kg Q2W dose used in the FIH study. Cemiplimab concentrations with 350 mg Q3W exceeded those observed with 1 mg/kg Q2W, a dose that demonstrated clinical efficacy in the FIH study, and C_{trough} values with 350 mg Q3W exceeded concentrations of ~5 to 20 mg/L, above which saturation of PD-1 target occupancy is expected to occur based on linearity assessment on single-dose pharmacokinetics in cynomolgus monkeys.

The 350 mg Q3W dose of cemiplimab is, therefore, being proposed as the optimal dose in the phase 3 studies in patients with NSCLC and across the cemiplimab program.

There are some populations (eg, in Japan or other countries in Asia-Pacific Rim, where on average, the body weight in the population is slightly lower as compared to Western patients (with body weight distribution around a mean of 60 kg versus 80 kg) (Shimizu 2016), and body weight is a known covariate of exposure for monoclonal antibodies. The average body weight of the patient population in the FIH study R2810-ONC-1423 was approximately 80 kg. As supported by population PK modeling and simulation of cemiplimab exposure in 1000 patients, when cemiplimab is administered as a flat dose, a small (approximately 16%) but clinically unimportant increase in exposure of cemiplimab in serum is predicted on average in Asian and/or Japanese patients versus the existing data in Western patients. With the lack of any added safety signal in the existing clinical data at doses up to 10 mg/kg, the existing data support the use of the 350 mg Q3W treatment regimen for the global development of cemiplimab.

3.2.7. Rationale for Ipilimumab Dose Selection

Recent data presented by Bristol-Meyers Squibb, Inc. demonstrated higher tumor shrinkage in patients treated with nivolumab at 3 mg/kg Q2W plus ipilimumab at 1 mg/kg Q6W or Q12W compared to nivolumab monotherapy (Zhao 2017b). The incidence of AEs was similar for nivolumab monotherapy and nivolumab plus ipilimumab at 1 mg/kg Q6W or Q12W, but was higher in treatment groups with more frequent and/or higher ipilimumab dosing. Based on the presented risk-benefit assessment (Zhao 2017b) and E-R analyses, the recommended dose of ipilimumab in NSCLC is 1 mg/kg Q6W, which is equivalent to approximately 50 mg, the dose proposed in the present study.

3.2.8. Rationale for Pembrolizumab as Comparator

Pembrolizumab is currently recommended as first-line treatment for advanced or metastatic NSCLC in patients whose tumors express PD-L1 in ≥50% of tumor cells (Ettinger 2016) and will, therefore, serve as the active comparator in this study.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

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

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint is PFS as assessed by a blinded IRC based on RECIST 1.1 assessments. 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 (based on RECIST 1.1 assessments [Eisenhauer 2009; see Appendix 2]) or death due to any cause. Patients will be censored according to the 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 any evaluable tumor assessments after randomization and did not die will be censored on the date of randomization.

Rationale for PFS as the primary endpoint is provided in Section 3.2.2.

4.2.2. Key Secondary Endpoints

The key secondary endpoints in the study will be OS and ORR.

Overall survival will be defined as the time from randomization to the date of death. A patient who is lost to follow-up will be censored at the last date that the patient was known to be alive.

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

Best overall response will be defined as the BOR, 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 the following:

- The safety and tolerability of cemiplimab/ipi and cemiplimab/chemo/ipi measured by the incidence of treatment-emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), serious adverse events (SAEs), deaths, and laboratory abnormalities
- Overall survival at 12 months and 18 months
- Quality of life as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13)
- Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel, sample permitting

See Section 4.4 for immunogenicity variables.

4.3. Pharmacokinetic Variables

Cemiplimab concentrations in the serum of patients randomized to the cemiplimab/ipi or cemiplimab/chemo/ipi groups (Treatment Arms B and C, respectively) 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. Anti-Drug Antibody Variables

Anti-drug antibody variables will be measured in samples from patients randomized to the cemiplimab/ipi or cemiplimab/chemo/ipi groups (Treatment Arms B and C, respectively). Anti-drug antibody variables include status of ADA response and titer as follows:

- Treatment-boosted ADA response - defined as a positive response in the ADA assay after the first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive
- Treatment-emergent ADA response - defined as a positive response in the ADA assay after the first dose when baseline results are negative or missing

The treatment-emergent responses will be further categorized into persistent, indeterminate, and transient responses.

- Titer category is defined based on values as (titer value category):
  - Low (titer <1000)
  - Moderate (1000 ≤ titer ≤10,000)
  - High (titer >10,000)

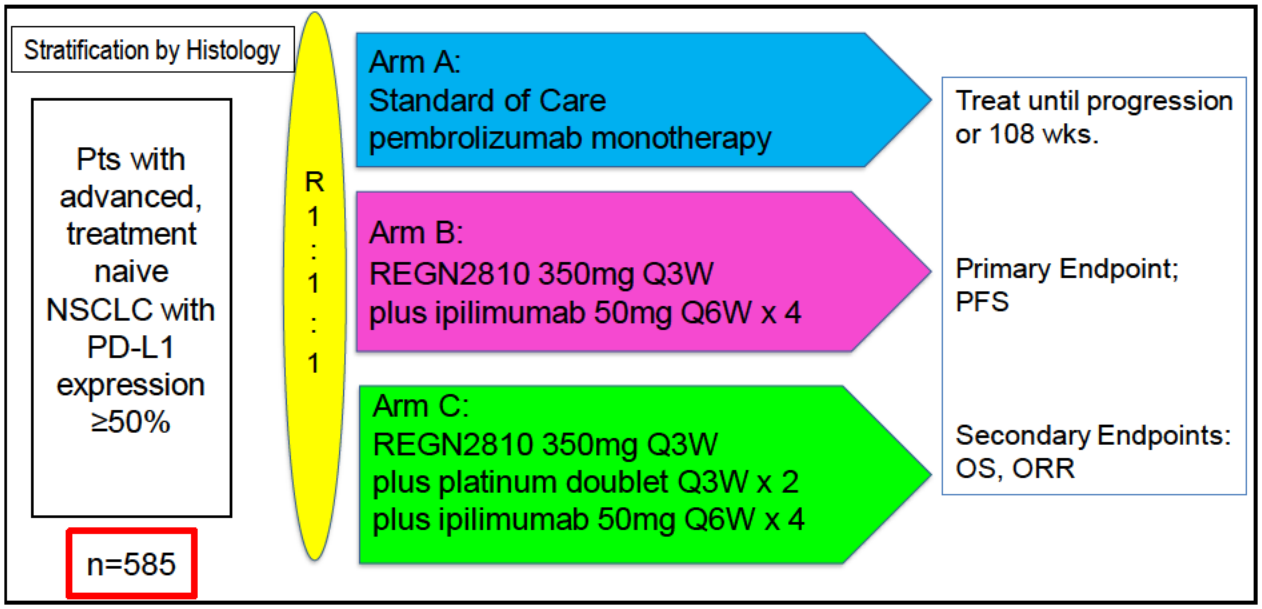
- Neutralizing anti-drug antibody (NAb) activities for samples that are confirmed positive in the ADA assay

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 3, randomized, global, open-label, pivotal, study of the efficacy and safety of cemiplimab/ipi versus cemiplimab/chemo/ipi versus pembrolizumab monotherapy 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. A study flow diagram is presented in Figure 1.

Figure 1: Study Flow Diagram



Abbreviations: NSCLC=non-small cell lung cancer; n=number; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; Pts:=patients; Q3W=every 3 weeks; Q6W=every 6 weeks; R=randomized; W=weeks

The study will consist of the following 3 periods: screening, treatment, and follow-up. After screening, eligible patients will be randomized to Treatment Arm A (pembrolizumab monotherapy), Treatment Arm B (cemiplimab/ipi) or Treatment Arm C (cemiplimab/chemo/ipi). The treatment period will be 108 weeks unless treatment is discontinued early. Treatment may be discontinued early due to RECIST 1.1-defined progressive disease, unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment, or, for patients in Treatment Arms B and C, in specific instances of confirmed CR or PR (see below). Patients receiving cemiplimab in combination with chemotherapy and/or ipilimumab who experience RECIST 1.1-defined progressive disease on therapy may continue treatment with cemiplimab if the investigator judges the patient to be experiencing clinical benefit and if the patient has not completed the 108-week treatment period. If further progressive disease (defined as an additional 10% increase in tumor burden from the time of initial progressive disease) is

confirmed, cemiplimab must be discontinued and other anti-cancer therapy considered, if appropriate.

After discontinuing study treatment, patients will enter the follow-up period.

The approximate duration of the active study assessments for each patient, excluding screening, will be 32 months. This encompasses 25 months of study treatment plus 7 months of follow-up visits. After the active study assessments are complete, all patients will be followed for survival.

5.1.1. Screening

Patients will undergo a screening evaluation to determine their eligibility within 28 days prior to randomization (Table 4). PD-L1 expression in a tumor tissue sample (archival tissue, if ≤5 months old, or recently obtained on-study biopsy collected during screening; for collection instructions, refer to the laboratory manual) will be assessed using the PD-L1 IHC 22C3 pharmDx assay that reports 50% positivity, as determined by a central laboratory (Section 8.2.5). 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. Of note the use of the PD-L1 IHC 22C3 pharmDx assay for decisions regarding treatment with cemiplimab is considered investigational.

Tumor tissue samples will also be tested for EGFR and ALK mutations as well as for ROS1 fusions in a central laboratory. Patients whose tumors are positive for any of these mutations/fusions (by testing at screening or by previous result) will not be eligible for the study.

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

Informed consent must be obtained prior to any study-related procedures. Assessments performed as part of standard-of-care that fall within the screening window (28 days prior to randomization) but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility.

5.1.2. Treatment Period

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

Treatment Period: Treatment Arm A

- Treatment Arm A: pembrolizumab monotherapy 200 mg Q3W for 108 weeks

Patients randomized to Treatment Arm A will receive pembrolizumab 200 mg as an IV infusion on day 1 of every treatment cycle (Q3W) for 108 weeks or until RECIST 1.1-defined progressive disease or early treatment discontinuation for another reason, including unacceptable toxicity, withdrawal of consent, death, or initiation of another anti-cancer treatment. Details of study treatment discontinuation criteria are discussed in Section 7.3.

Treatment Period: Treatment Arm B

- Treatment Arm B: cemiplimab 350 mg Q3W for 108 weeks plus ipilimumab 50 mg Q6W for up to 4 doses (cemiplimab/ipi)

Patients randomized to Treatment Arm B will receive the following treatments in combination:

- Cemiplimab 350 mg as an IV infusion on day 1 of every treatment cycle (Q3W) for 108 weeks or until RECIST 1.1-defined progressive disease or early treatment discontinuation for another reason, including unacceptable toxicity, withdrawal of consent, death, or initiation of another anti-cancer treatment, or in specific instances of confirmed CR or PR
- Ipilimumab 50 mg flat dose administered IV on day 1 of every other treatment cycle (ie, every 42 days or Q6W) for up to 4 doses.

Treatment Period: Treatment Arm C

- Treatment Arm C: Cemiplimab 350 mg Q3W for 108 weeks plus platinum-based doublet chemotherapy Q3W for 2 cycles and ipilimumab 50 mg Q6W for up to 4 doses (cemiplimab/chemo/ipi)

Patients randomized to Treatment Arm C will receive the following treatments in combination:

- Cemiplimab 350 mg as an IV infusion on day 1 of every treatment cycle (Q3W) for 108 weeks or until RECIST 1.1-defined progressive disease or early treatment discontinuation for another reason, including unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment, or in specific instances of confirmed CR or PR
- Platinum-based doublet chemotherapy Q3W for 2 cycles (depending on patient tolerability and disease assessment)
  - The choice of platinum-based doublet chemotherapy will be at the discretion of the investigator from one of the options listed in Section 7.1.4 and is to be decided and documented prior to randomization.
  - Patients in this arm will not be permitted to receive pemetrexed maintenance.
- Ipilimumab 50 mg flat dose administered IV on day 1 of every other treatment cycle (ie, every 42 days or Q6W) for up to 4 doses.

Treatment Period: All Treatment Arms

Details of the treatment regimens are provided in Section 7.1, and details of dose modifications and study drug permanent and temporary discontinuation criteria are discussed in Section 7.3.

Randomization will be stratified by histology (non-squamous versus squamous).

Treatment should begin within 3 days of randomization. Details of the treatment regimens are provided in Section 7.1. Treatment period length will depend on the treatment arm to which a patient is randomized.

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 on day 1 of each dosing cycle (Table 5).

Radiographic tumor assessments will be obtained in all patients Q9W beginning at week 9 (day 63 ± 5 days) during year 1 and Q12W beginning at week 55 (first radiographic

tumor assessment in year 2 performed at end of week 54) during year 2, until IRC-assessed RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment. See Section 8.2.2.1 for detailed timing of radiographic tumor assessments. Patients who discontinue for reasons other than progression who are not attending treatment visits may have radiographic tumor assessments between Q9W and Q12W until RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment.

Progressive disease will be defined using RECIST 1.1 criteria (Appendix 2). Investigators and the blinded IRC (Section 5.3.1) will assess response to therapy using RECIST 1.1 criteria. RECIST 1.1-defined progressive disease determined by the investigator will be used for clinical management of the patient. RECIST 1.1-based tumor burden assessments by the blinded IRC will be used for evaluation of efficacy endpoints.

Patients that experience RECIST 1.1-defined progressive disease on therapy may continue treatment if the investigator judges the patient to be experiencing clinical benefit and if the patient has not completed the 108-week treatment period (Section 7.8). Alternatively, these patients may opt to initiate a new anti-cancer treatment. If a patient continues treatment beyond the initial determination of progressive disease, study assessments should continue as per Table 5. If on the next scheduled radiographic tumor assessment, RECIST 1.1-defined further progressive disease is confirmed (Section 7.8), therapy will be discontinued. Further progression will be defined as an additional 10% increase in tumor burden from the time of initial progressive disease.

Safety will be assessed through the occurrence of AEs, recording of concomitant medications, vital sign evaluation, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, 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.

Blood samples will be collected from patients in Treatment Arms B and C to measure serum concentrations of cemiplimab and cemiplimab ADA titers. Blood samples will be collected to measure biomarkers associated with clinical response to cemiplimab including cytokines, circulating tumor nucleic acids, and other potential biomarkers of interest (Table 5).

After at least 6 months (24 weeks) of treatment, a patient with confirmed CR may choose to stop cemiplimab 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 cemiplimab treatment early and be followed for the duration of the study.

5.1.3. Follow-up Period

Patients who discontinue study treatment due to progressive disease should return to the clinic 14 to 30 days after the last study treatment to complete the end of study assessments (follow-up visit 1).

Patients who discontinue study treatment for reasons other than progressive disease should return to the clinic 14 to 30 days (±7 days) after the last cycle visit for follow-up visit 1 and then continue with follow-up visit 2 through follow-up visit 7.

Survival data will then be collected by phone or at an office visit every 3 months, until death, loss to follow-up, or withdrawal of study consent.

Follow-up procedures are outlined in Table 6.

Follow-up Period: All Treatment Arms

- Patients will enter follow-up after completion of the 108-week treatment period, when the decision is made to discontinue pembrolizumab monotherapy or cemiplimab combination therapy, or at the time of initial RECIST 1.1-defined progressive disease while on study treatment.
- Patients who completed the treatment period without RECIST 1.1-defined progressive disease or who discontinued study treatment early for reasons other than RECIST 1.1-defined progressive disease should continue to have radiographic tumor assessments Q12W.
- Patients who opt to be treated with other anti-cancer treatments will be expected to complete all follow-up assessments as specified in Table 6.

Follow-up Period: Treatment Arms B and C only

- Patients who discontinued cemiplimab treatment early (but after at least 6 months [24 weeks] of treatment) due to CR, PR, and entered follow-up at that time who then have RECIST 1.1-defined progressive disease while in follow-up may be offered the option of retreatment with cemiplimab 350 mg Q3W for an additional 108 weeks(see Section 7.8). 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 Treatment Arms B and C will have blood samples taken for PK and ADA testing as specified in Table 6.

5.1.4. Description of Study Stopping Rules

More than 353 patients have been dosed as of April 2017 with cemiplimab with no DLTs observed. Because this is the first study of the cemiplimab/ipi and cemiplimab/chemo/ipi combination, safety data from the first 10 patients treated with cemiplimab/ipi in Treatment Arm B and the first 10 patients treated with cemiplimab/chemo/ipi in Treatment Arm C will be reviewed after these patients complete 4 weeks of follow-up following the first dose of cemiplimab/chemo/ipi. The data will be reviewed at a meeting of the IDMC. If 2 or more DLTs occur in the first 10 patients treated with cemiplimab/ipi or in the first 10 patients treated with cemiplimab/chemo/ipi, enrollment for the respective treatment arm will be stopped temporarily. Enrollment in Treatment Arms B and C will only be restarted after a formal safety review.

An additional safety review will be performed by the IDMC after the first 10 patients in the cemiplimab/ipi and the first 10 patients in the cemiplimab/chemo/ipi regimen have received all 4 doses of ipilimumab and have been followed for at least 6 weeks after the last dose. This analysis will include all patients who have been exposed to the combination treatment.

After this evaluation is performed, a frequency or severity of drug related adverse events causing discontinuation of treatment in ≥25% of treated patients will lead to a pause in further enrollment to Arm B or C pending review with the IDMC and the study steering committee.

The outcomes of these safety reviews will be a decision to do one of the following:

- Continue the study as planned after discussions with investigators and regulatory authorities
- Continue the study without the second cycle of chemotherapy
- Increase the interval for ipilimumab administration from 6 to 12 weeks in Treatment Arm B or C
- Discontinue Treatment Arm B or C

5.1.5. Dose-Limiting Toxicities

The DLT observation period for determination of safety is defined as 28 days starting with cycle 1 day 1, with the intent to monitor safety and tolerability of cemiplimab/ipi and cemiplimab/chemo/ipi.

Any of the below outlined events occurring during the DLT observation period and considered to be at least possibly related to cemiplimab/ipi or cemiplimab/chemo/ipi will qualify as a DLT.

A DLT is defined as the following:

Nonhematologic Toxicity

1. Grade ≥2 uveitis (considered as a potential irAE)
2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal (ULN) and/or total bilirubin >3 times ULN
3. Any grade ≥3 nonhematologic toxicity, with the exception of the following:
   a. Grade 3 nausea, vomiting, or diarrhea unless persistent (>7 days of duration) despite maximal supportive care measures, as prescribed by the treating physician
   b. Grade ≥3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE
   c. Grade 3 infusion-related reactions that respond to medical management
   d. Any Grade 3 irAE (as defined by experience with other immunomodulatory drugs; see Section 7.3.4 for the description of common irAEs) other than uveitis that improves within 14 days to grade 2 or lower with medical management (including treatment with steroids).
   e. Any Grade 3 irAE which would result in permanent discontinuation of the cemiplimab/ipi/chemo (or permanent discontinuation of ipilimumab), as outlined in Section 7.3.1, or which would result in permanent discontinuation of cemiplimab, as outlined in the guidelines in Appendix 3, should be considered a DLT. This specifically includes the following Grade 3 irAEs: pneumonitis, colitis/diarrhea, nephritis.

Hematologic Toxicity

1. Grade 4 neutropenia lasting more than 7 days
2. Grade 4 thrombocytopenia
3. Grade 3 thrombocytopenia with bleeding
4. Grade ≥3 febrile neutropenia (fever ≥38.5°C with absolute neutrophil count $<1.0 \times 10^9$/L) or grade ≥3 neutropenia with documented infection
5. Grade 4 anemia

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays (Section 7.3.1), will be analyzed to determine if a given toxicity should be considered a DLT. Both irAEs and non-irAEs that meet the definition of a DLT will be considered to be DLTs.

In general, because there is no clinical experience with cemiplimab/ipi and cemiplimab/chemo/ipi, any AE that has been clearly described for other agents that block the PD-1/PD-L1 and/or CTLA-4 pathways or the combination will be treated initially as unexpected in this study. Such TEAEs will be monitored and especially considered on an ongoing basis to assess expectedness, including possible differences in event frequency or severity from that observed with other PD-1/PD-L1 and CTLA-4 blockers.

The TEAEs that appear to meet the DLT definition will be discussed between the sponsor and the investigator. The final decision of whether or not the TEAE meets the DLT definition will be based on a careful review of all relevant data and consensus between the Medical Monitor, Clinical Development Lead, and the designated Risk Management Lead from the Pharmacovigilance and Risk Management department. The investigator may also be consulted.

Regardless of whether a patient remains on study treatment and/or continues to participate in study procedures, such an event will count as a DLT, if the event occurs during the DLT observation period.

5.1.6. Maximum Tolerated Dose

If 2 or more of the first 10 patients from Treatment Arm B who are dosed with cemiplimab/ipi experience a DLT during the DLT monitoring period, the dosing interval for ipilimumab could be increased from Q6W to Q12W. If 2 or more DLTs occur in the first 10 patients treated in Treatment Arm B, enrollment to this treatment arm will be stopped temporarily and will be restarted only after the formal early safety review.

If 2 or more of the first 10 patients from Treatment Arm C who are dosed with cemiplimab/chemo/ipi experience a DLT during the DLT monitoring period, the dosing interval for ipilimumab could be increased from Q6W to Q12W or the number of cycles of platinum doublet chemotherapy reduced from 2 to 1. If 2 or more DLTs occur in the first 10 patients treated in Treatment Arm C, enrollment to this treatment arm will be stopped temporarily and will be restarted only after the formal early safety review.

An additional safety review will be performed by the IDMC after the first 10 patients in the cemiplimab/ipi and cemiplimab/chemo/ipi regimen have received all 4 doses of ipilimumab and

have been followed for at least 6 weeks after the last dose. This analysis will include all patients who have been exposed to the combination treatment.

The MTD is defined as the dose level immediately below the level at which dosing is stopped due to the occurrence of 2 or more DLTs. If the study is not stopped due to the occurrence of a DLT, it will be considered that the MTD has not been determined.

Based on data with cemiplimab and other anti-PD-1 investigational compounds, it is possible that an MTD may not be defined in this study.

5.1.7. End of Study Definition

The end of study is defined as the last visit of the last patient.

5.2. Planned Interim Analysis

An interim analysis for secondary endpoint of OS will be performed at the time of primary analysis for PFS. There will be an early safety review by the IDMC as detailed in Section 5.1.4.

5.3. Study Committees

Two independent study committees will be utilized: an IRC (Section 5.3.1) and an IDMC (Section 5.3.2).

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 based on RECIST 1.1 criteria. The IRC-determined tumor response will be used in the analysis of the PFS and ORR 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 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 are described in the IDMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 585 patients will be randomized at approximately 200 global sites. Of the 585 patients, it is estimated that approximately two-thirds of the patients will have non-squamous histology and one-third will have squamous histology.

6.2. Study Population

Patients in this study will include men and women ≥18 years of age, who are diagnosed with stage IIIB, or IIIC NSCLC who are not eligible for definitive chemo/radiation therapy or patients with or stage IV non-squamous or squamous NSCLC, 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.

To be eligible for the study, patients must meet all of the inclusion criteria (Section 6.2.1) and none of the exclusion criteria (Section 6.2.2).

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 (≥21 years of age for Japanese patients)
2. Patients with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB, or IIIC disease who are not candidates for treatment with definitive concurrent chemo/radiation or patients with stage IV disease if they have not received prior systemic treatment for recurrent or metastatic NSCLC. The histologic diagnosis of NSCLC may be confirmed by the central laboratory.
   - 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. Availability of an archival or on-study obtained formalin-fixed, paraffin-embedded tumor tissue sample
   - Guidance on biopsy sites:
     a. Archival or fresh biopsies are acceptable
     b. If an archival biopsy is used, it has to be less than 5 months old
     c. The biopsy should be from a metastatic or recurrent site which has not previously been irradiated
     d. Exception: the primary lung tumor is still in place and the other metastatic sites are either not accessible (brain) or cannot be used (bone) or the biopsy would put the patient at risk
4. Expression of PD-L1 in ≥50% of tumor cells determined by the commercially available PD-L1 IHC 22C3 pharmDx assay performed by the central laboratory.

5. At least 1 radiographically measureable 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) RECIST 1.1-defined progressive disease 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 ≥10.0 g/dL
    b. Absolute neutrophil count ≥1.5 × 10^9/L
    c. Platelet count ≥100,000/mm^3
    d. Glomerular filtration rate >30 mL/min/1.73 m^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 who 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 enrollment. Patients must be off (immunosuppressive doses of) corticosteroid therapy (see exclusion criterion 7 for details on timing of discontinuation of corticosteroid therapy).
3. Patients with tumors tested positive for EGFR and ALK gene mutations or ROS1 fusions. All patients should have tumor evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions confirmed by a central laboratory.
4. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
5. History of interstitial lung disease (eg, idiopathic pulmonary fibrosis, organizing pneumonia), active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management, or of pneumonitis within the last 5 years. A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved ≥6 months prior to enrollment.

6. Ongoing or recent evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related treatment-emergent adverse events (irTEAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
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. Previous treatment with idelalisib at any time (ZYDELIG®).
9. Another malignancy that is progressing or requires treatment, with the exception of nonmelanomatous skin cancer that has undergone potentially curative therapy, in situ cervical carcinoma, or any other localized tumor that has been treated, and the patient is deemed to be in complete remission for at least 2 years prior to enrollment, and no additional therapy is required during the study period.
10. Known active hepatitis B (known positive result) or hepatitis C (known positive result) and known quantitative HCV RNA results greater than the lower limits of detection of the assay). Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; or diagnosis of immunodeficiency:

    Exceptions:

    a. Patients with HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable anti-viral regimen) are permitted.
    b. Patients with hepatitis B (hepatitis B surface antigen positive) 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.
    c. 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.

    Patients with HIV or hepatitis must have their disease reviewed by the specialist (eg, infectious disease or hepatologist) managing this disease prior to commencing and throughout the duration of their participation in the trial.
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-CTLA-4 antibodies is permitted, but the last dose of such an antibody should have been at least 6 months prior to the first dose of study treatment.
13. Treatment-related immune-mediated AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 monoclonal antibodies, anti-CTLA-4 monoclonal antibodies, and PI3K-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 or therapy being studied (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 in general or to agents specifically used in the study.
18. Known psychiatric or substance abuse disorder that would interfere with participation and/or with the requirements of the study, including current use of any illicit drugs.
19. Pregnant or breastfeeding women.
20. Women of childbearing potential* and 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; and or sexual abstinence†, ‡.

    * Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. 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 treatments.

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

    Sexually active men and their partners must use highly effective contraception as described above. Contraception is not required for men with documented vasectomy.

21. 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.
22. Member of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor.
23. Active or latent tuberculosis. Latency should be confirmed by purified protein derivative (PPD)/QuantiFERON testing according to local guidelines in potential patients from tuberculosis-endemic areas.

24. History of previous organ transplant, including stem cell allograft
25. Meeting the comparator products contraindicated criteria as listed in local labeling. Investigators should review the current label in their local database.

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 has 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.

Rules for discontinuation of study treatment (permanent) are discussed in Section 7.3.8.

6.4. Replacement of Patients

Patients prematurely discontinued from the study or study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Eligible patients will be randomized to receive one of the following treatment arms:

- Treatment Arm A: pembrolizumab monotherapy 200 mg Q3W for 108 weeks
- Treatment Arm B: cemiplimab 350 mg Q3W for 108 weeks plus ipilimumab 50 mg Q6W for up to 4 doses (cemiplimab/ipi)
- Treatment Arm C: cemiplimab 350 mg Q3W for 108 weeks plus platinum-based doublet chemotherapy Q3W for 2 cycles and ipilimumab 50 mg Q6W for up to 4 doses (cemiplimab/chemo/ipi)

Patients will receive their assigned treatment for the 108-week treatment period or until RECIST 1.1-defined progressive disease or until early treatment discontinuation for another reason.

Study treatment will be administered by the investigator or other designated study personnel.

7.1.1. Cemiplimab

Cemiplimab is a covalent heterotetramer consisting of 2 disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kDa based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The cemiplimab heavy chain possesses an

IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody.

Cemiplimab is manufactured by Regeneron Pharmaceuticals, Inc.

Cemiplimab (50 mg/mL) is manufactured with Cell Line 2 Process 1 (C2P1) and formulated in an aqueous buffered solution at pH 6.0 containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80. Cemiplimab C2P1 drug product is supplied as a sterile liquid solution of 5.6 mL in a 10 mL glass vial for IV administration.

Cemiplimab will be supplied as a liquid in sterile, single-use vials. Each vial will contain withdrawable cemiplimab at a concentration of 50 mg/mL. See Section 7.6 for details on packaging, labeling, and storage.

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.

Cemiplimab will be administered in combination with either ipilimumab (administered Q6W for up to 4 doses; cemiplimab/ipi) or platinum-based doublet chemotherapy (administered Q3W for 2 cycles) and ipilimumab (administered Q6W for up to 4 doses; cemiplimab/chemo/ipi) and then alone for the remainder of the treatment period.

When administered in combination with ipilimumab and chemotherapy, infuse chemotherapy, then cemiplimab, then ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

When administered in combination with ipilimumab, infuse cemiplimab first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

When administered in combination with platinum-based chemotherapy doublet agents, the chemotherapy agents should be infused first, followed by cemiplimab, on the same day. Use separate infusion bags and filters for each infusion.

7.1.2. Ipilimumab

Ipilimumab 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 ipilimumab to the study sites. See Section 7.6 for details on packaging, handling, and storage.

Ipilimumab 50 mg flat dose will be administered IV over approximately 90 minutes on day 1 every 42 days (Q6W) for up to 4 doses in combination with cemiplimab. Administration should adhere to the local prescribing information and practice guidelines.

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

Ipilimumab should be infused after cemiplimab on the same day. Separate infusion bags and filters will be used for each infusion.

7.1.3. Pembrolizumab

Pembrolizumab 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 pembrolizumab to the study sites. See Section 7.6 for details on packaging, handling, and storage.

Pembrolizumab 200 mg will be administered IV over approximately 30 minutes on day 1 every 21 days (Q3W) for 108 weeks, until RECIST 1.1-defined progressive disease or until early treatment discontinuation for another reason. Administration will be according to the local prescribing information and practice guidelines.

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

7.1.4. Platinum-Based Doublet Chemotherapy

Chemotherapy will be administered Q3W in combination with cemiplimab as outlined in Table 1 for 2 cycles (depending on randomized treatment arm, patient tolerability, and disease assessment) or until RECIST 1.1-defined progressive disease or early treatment discontinuation for another reason. Chemotherapy will be administered according to local prescribing information and practice guidelines.

The choice of chemotherapy will be one of the regimens shown in Table 1. The investigator may choose from one of these regimens provided (Table 1). Assignment of the 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.

The sequence of drug administration is platinum-based chemotherapy doublet agents followed by cemiplimab.

Table 1: Guidelines for Platinum-Based Doublet Chemotherapy Regimens (Treatment Arm C)

Option	Chemotherapy Regimen	Dosing Frequency
1	Paclitaxel 200 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days (Q3W) for 2 cycles Calculate dose of carboplatin using the Calvert formula.
2	Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days (Q3W) for 2 cycles
3	Pemetrexed 500 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days (Q3W) for 2 cycles Calculate dose of carboplatin using the Calvert formula.
4	Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days (Q3W) for 2 cycles

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 glomerular filtration rate (GFR) <50 mL/min/1.73 m^2 may NOT receive cisplatin-containing regimens.

7.2. Pre-treatments

Pre-medications 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 pre-medications. Preference should be given to regimens that are allowed by local regulations.

Pre-medications are not required prior to the first administration of cemiplimab. Pre-medications will be allowed at subsequent doses depending on the need to manage any observed low-grade infusion reactions (See Section 7.4.1.1).

For chemotherapy, pre-medications 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 B_{12}) and corticosteroids. Pre-treatment with vitamin supplementation is to start within 3 days of randomization for patients with non-squamous NSCLC. Patients receiving cisplatin should be adequately hydrated prior to the infusion of therapy and receive highly effective combination antiemetic therapy.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Cemiplimab Plus Ipilimumab Combination Therapy Dosing Delay Rules

Patients in Treatment Arm B who experience protocol-defined DLTs (see Section 5.1.5; either during or outside of the DLT observation period) will be required to temporarily discontinue treatment with cemiplimab/ipi.

In addition to DLTs, during the cemiplimab/ipi treatment period, administration of cemiplimab (and of ipilimumab, if an AE occurred on the day of a planned ipilimumab dosing) must be delayed due to the following AEs:

- Either febrile neutropenia or neutropenia <500 cells/mm³ for >1 week despite the use of growth factors
- Any grade ≥2 non-skin, drug-related AE, except for fatigue and laboratory abnormalities and except for AEs that require study treatment discontinuation (as listed below)
- Any grade 3 drug-related laboratory abnormality (except for lymphopenia, AST, ALT, or total bilirubin or asymptomatic lipase or amylase)
  - Grade 3 lymphopenia will not require a dose delay
  - If the patient had a baseline AST, ALT, or total bilirubin level that was within normal limits, dosing should be delayed for a drug-related grade ≥2 toxicity
  - If the patient had a baseline AST, ALT, or total bilirubin level that was within the grade 1 toxicity range, dosing should be delayed for a drug-related grade ≥3 toxicity
  - Any grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis will not require a dose delay
- Any grade 3 skin drug-related AE
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study treatment

Resumption of treatment may be at the initial dose regimen or the dosing interval for ipilimumab could be increased from Q6W to Q12W, based upon the discretion of the investigator and the sponsor. Dose modification of cemiplimab will not be permitted.

A repeat occurrence of the same DLT after resumption of treatment will require permanent discontinuation of cemiplimab/ipi or cemiplimab/chemo/ipi respectively.

Criteria for Restarting Cemiplimab Plus Ipilimumab Dosing

Patients may resume treatment with cemiplimab/ipi when the drug-related AE(s) resolve to grade ≤1 or baseline value, with the following exceptions:

- Patients may resume study treatment in the presence of grade 2 fatigue.

- Patients who have not experienced a grade 3 drug-related skin AE may resume study treatment in the presence of grade 2 skin toxicity.
- Patients with baseline grade 1 AST, ALT, or total bilirubin level who require dose delays for reasons other than a 2-grade shift in AST, ALT, or total bilirubin may resume study treatment in the presence of grade 2 AST, ALT, OR total bilirubin.
- Patients with AST, ALT, and/or total bilirubin values meeting discontinuation criteria should have study treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must resolve to baseline before study treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume study treatment.
- Any AE that meets the discontinuation rules below requires that the patient discontinue study treatment.

Dosing Discontinuation Rules

The following categories require permanent discontinuation of cemiplimab/ipi:

- Any grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within the re-treatment period or that requires systemic treatment, require study treatment discontinuation.
- Any grade 3 non-skin, drug-related AE lasting >7 days require study treatment discontinuation, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, colitis, diarrhea, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, colitis, diarrhea, hypersensitivity reaction, or infusion reaction of any duration require study treatment discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require study treatment discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require study treatment discontinuation except for the following:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires study treatment discontinuation
    - Any drug-related liver function test abnormality that meets the following criteria requires study treatment discontinuation:
      - AST or ALT >5 to 10 × ULN for >2 weeks
      - AST or ALT >10 × ULN
      - Total bilirubin >5 × ULN

  - Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN

- Any grade 4 drug-related AE or laboratory abnormality requires study treatment discontinuation, except for the following events, which do not require study treatment discontinuation:
  - Grade 4 neutropenia ≤7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of onset
  - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyperthyroidism, hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, as applicable, may not require study treatment discontinuation per approval from the Medical Monitor
- Any study treatment delay resulting in no dosing for >6 weeks (cemiplimab), >12 weeks (ipilimumab Q6W), or >18 weeks (ipilimumab Q12W, if dose was revised to Q12W due to a toxicity or another reason) requires study treatment discontinuation, with the exception of dosing delays to manage drug-related AEs, such as prolonged steroid tapers and with the exception of delays noted in the next bulleted item
- Study treatment delays resulting in no dosing for >6 weeks (cemiplimab), >12 weeks (ipilimumab Q6W), or >18 weeks (ipilimumab Q12W, if dose was revised to Q12W due to a toxicity or another reason) that occur for non-drug-related reasons are permitted and may not require study treatment discontinuation, if approved by the Medical Monitor
- Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the investigator, presents a substantial clinical risk to the patient with continued cemiplimab or ipilimumab dosing requires study treatment discontinuation.

If the investigator determines that an AE is definitely related to ipilimumab based on the Reference Safety Information in the Investigator's Brochure or based on local prescribing information and practice guidelines, the patient may discontinue treatment with ipilimumab and continue treatment with only cemiplimab.

Additional guidelines for discontinuation of ipilimumab are provided in Section 7.3.5.

7.3.2. Cemiplimab Plus Ipilimumab and Chemotherapy Combination Therapy

Dosing Delay Rules

Patients in Treatment Arm C who experience protocol-defined DLTs (see Section 5.1.5; either during or outside of the DLT observation period) will be required to temporarily discontinue treatment with cemiplimab/chemo/ipi.

In addition to DLTs, during the cemiplimab/chemo/ipi therapy period, administration of cemiplimab (and of ipilimumab, if an AE occurred on the day of a planned ipilimumab dosing), must be delayed due to the following AEs:

- Either febrile neutropenia or neutropenia <500 cells/mm³ for >1 week despite the use of growth factors
- Any grade ≥2 non-skin, drug-related AE, except for fatigue and laboratory abnormalities and except for AEs that require study treatment discontinuation (as listed below)
- Any grade 3 drug-related laboratory abnormality (except for lymphopenia, AST, ALT, or total bilirubin or asymptomatic lipase or amylase)
  - Grade 3 lymphopenia will not require a dose delay
  - If the patient had a baseline AST, ALT, or total bilirubin level that was within normal limits, dosing should be delayed for a drug-related grade ≥2 toxicity
  - If the patient had a baseline AST, ALT, or total bilirubin level that was within the grade 1 toxicity range, dosing should be delayed for a drug-related grade ≥3 toxicity
  - Any grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis will not require a dose delay
- Any grade 3 skin drug-related AE
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study treatment

Resumption of treatment may be at the initial dose regimen or the dosing interval for ipilimumab could be increased from Q6W to Q12W, based upon the discretion of the investigator and the sponsor. Dose modification of cemiplimab will not be permitted.

A repeat occurrence of the same DLT after resumption of treatment will require permanent discontinuation of cemiplimab/chemo/ipi.

Criteria for Restarting Cemiplimab Plus Ipilimumab and Chemotherapy Dosing

Patients may resume treatment with cemiplimab/chemo/ipi when the drug-related AE(s) resolve to grade ≤1 or baseline value, with the following exceptions:

- Patients may resume study treatment in the presence of grade 2 fatigue.

- Patients who have not experienced a grade 3 drug-related skin AE may resume study treatment in the presence of grade 2 skin toxicity.
- Patients with baseline grade 1 AST, ALT, or total bilirubin level who require dose delays for reasons other than a 2-grade shift in AST, ALT, or total bilirubin may resume study treatment in the presence of grade 2 AST, ALT, OR total bilirubin.
- Patients with AST, ALT, and/or total bilirubin values meeting discontinuation criteria should have study treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must resolve to baseline before study treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume study treatment.
- Any AE that meets the discontinuation rules below requires that the patient discontinue study treatment.

Dosing Discontinuation Rules

The following categories require permanent discontinuation of cemiplimab/chemo/ipi:

- Any grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within the re-treatment period, or that requires systemic treatment, requires study treatment discontinuation.
- Any grade 3 non-skin, drug-related AE lasting >7 days require study treatment discontinuation, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, colitis, diarrhea, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, colitis, diarrhea, hypersensitivity reaction, or infusion reaction of any duration require study treatment discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require study treatment discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require study treatment discontinuation except for the following:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires study treatment discontinuation
    - Any drug-related liver function test abnormality that meets the following criteria requires study treatment discontinuation:
      - AST or ALT >5 to 10 × ULN for >2 weeks
      - AST or ALT >10 × ULN
      - Total bilirubin >5 × ULN

  - Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN
- Any grade 4 drug-related AE or laboratory abnormality requires study treatment discontinuation, except for the following events, which do not require study treatment discontinuation:
  - Grade 4 neutropenia ≤7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of onset
  - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, ACTH deficiency, hyperthyroidism, hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, as applicable, may not require study treatment discontinuation per approval from the Medical Monitor

- Any study treatment delay resulting in no dosing for >6 weeks (cemiplimab), >12 weeks (ipilimumab Q6W), or >18 weeks (ipilimumab Q12W, if dose was revised to Q12W due to a toxicity or another reason) requires study treatment discontinuation, with the exception of dosing delays to manage drug-related AEs, such as prolonged steroid tapers and with the exception of delays noted in the next bulleted item
- Study treatment delays resulting in no dosing for >6 weeks (cemiplimab), >12 weeks (ipilimumab Q6W), or >18 weeks (ipilimumab Q12W, if dose was revised to Q12W due to a toxicity or another reason) that occur for non-drug-related reasons are permitted and may not require study treatment discontinuation, if approved by the Medical Monitor
- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued cemiplimab or ipilimumab dosing, requires study treatment discontinuation.

If the investigator determines that an AE is definitely related to ipilimumab based on the Reference Safety Information in the Investigator's Brochure or based on local prescribing information and practice guidelines, the patient may discontinue treatment with ipilimumab and continue treatment with only cemiplimab.

Additional guidelines for discontinuation of ipilimumab are provided in Section 7.3.5.

7.3.3. Cemiplimab as Combination Therapy With Chemotherapy

The following cemiplimab treatment hold guidelines should be followed for patients in Treatment Arm C following completion of ipilimumab dosing (when cemiplimab will be monotherapy).

Cemiplimab treatment may be held upon occurrence of a drug-related AE at any time on the study. Resumption of cemiplimab 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 as 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.

Dose modification of cemiplimab will not be permitted.

Guidelines for cemiplimab temporary discontinuations, including delays and interruptions, criteria for restarting, and permanent discontinuations for toxicity are outlined in Table 2 and Appendix 3.

Table 2: Cemiplimab Guidelines for Temporary and Permanent Discontinuations for Toxicity

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological toxicity (other than grade 3 thrombocytopenia >7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to grades 0 to 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.*
Grade 3 thrombocytopenia >7 days or associated with bleeding	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. *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 lab 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 4 weeks*: Same dose and schedule *Clinical AE does not resolve within 4 weeks:* Discontinue	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 potential irAEs, see Table 3 and Appendix 3.

Appendix 3 includes recommendations on the management of specific treatment-related AEs and when to delay and/or discontinue cemiplimab. These guidelines are intended to be applied when the investigator determines the events to be treatment-related.

If the investigator determines that an AE is definitely related to chemotherapy based on the Reference Safety Information in the Investigator's Brochure or based on local prescribing information and practice guidelines, the patient may discontinue treatment with chemotherapy and continue treatment with only cemiplimab/ipi. Additional reasons for cemiplimab permanent discontinuation include the following:

- Cemiplimab dosing will be permanently discontinued in the event of pregnancy.
- In the event of an infusion reaction of grade 3 or greater severity during or directly following cemiplimab infusions, dosing should be stopped and the patient must be permanently discontinued from cemiplimab treatment. Infusion reactions are defined in Section 9.3.4.
- 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, patients in Treatment Arms B and C with confirmed CR may choose to stop cemiplimab 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 cemiplimab 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 cemiplimab treatment until RECIST 1.1-defined progressive disease, completion of all study assessments, or closure of the study (Section 6.3 and Section 8.1.2).

7.3.4. Immune-Related Adverse Events

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. Immune-related TEAEs have been reported with cemiplimab and with other anti-PD-1 antibodies; these are considered consistent with the mechanism of action of anti-PD-1 antibodies.

An irTEAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated for a possible immune etiology. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irTEAE. Suggested management guidelines are provided in Appendix 3 for certain anti-PD-1 irTEAEs including but not limited to:

- **Gastrointestinal events** (colitis, colitis microscopic, enterocolitis, enterocolitis hemorrhagic, gastrointestinal perforation, diarrhea, stomatitis)
- **Pneumonitis events** (pneumonitis, acute interstitial pneumonitis)
- **Hepatic events** (ALT/AST increased, autoimmune hepatitis, transaminases increased)

- **Endocrine events** (autoimmune thyroiditis, blood thyroid stimulating hormone [TSH] increased, diabetic ketoacidosis, diabetes mellitus, hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, thyroid disorder, thyroiditis, adrenal insufficiency, Type 1 diabetes mellitus)
- **Uveitis** (iritis, iridocyclitis, uveitis)
- **Renal events (**nephritis, autoimmune nephritis, tubulointerstitial nephritis)
- **Skin events** (dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalized, exfoliative rash, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash maculovesicular, rash morbilliform, rash papular, rash pruritic, rash rubelliform, rash scarlatiniform, rash vesicular, vitiligo)
- **Nervous system events** (encephalitis, paraneoplastic encephalomyelitis, myasthenia gravis)

Based on the emerging safety profile of cemiplimab and other antibodies targeting the PD-1/PD-L1 axis (Weber 2015, Naidoo 2015), the following working case definitions are provided to help investigators distinguish irTEAEs from non-immune AEs. These case definitions pertain to the more commonly reported irTEAEs associated with PD-1 inhibition (Weber 2015, Naidoo 2015) and are not exhaustive of all possible irAEs. Clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events (Zimmer 2016, Hofmann 2016), should be reviewed in patients with concerning presentations.

The investigator should refer to the latest version of the Investigator's Brochure for further details and guidance. The case definitions have not been validated and are intended only as guidance for investigators to help distinguish irTEAEs from non-immune AEs. Investigators' clinical judgment may include other factors when determining immune relatedness. The case definitions for irAEs may evolve as clinical experience increases with cemiplimab and other antibodies targeting the PD-1/PD-L1 axis.

Detailed guidance of management of irAEs is provided in Appendix 3. In the event of irAEs that are not addressed in Appendix 3, general guidance 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 Cemiplimab 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) irAE, 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, CTX, cyclosporine, and mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

Abbreviations: CTX=cyclophosphamide; irAE=immune-related adverse event

7.3.5. Ipilimumab

Ipilimumab-related toxicities should be managed in accordance with local prescribing information and practice guidelines.

Ipilimumab should also be discontinued for the following reasons:

- Ipilimumab combination dosing will be permanently discontinued in the event of pregnancy.
- In the event of an infusion reaction of grade 3 or greater severity during or directly following infusions, dosing should be stopped and the patient must be permanently discontinued from ipilimumab treatment. Infusion reactions are defined in Section 9.3.4.
- Ipilimumab 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 plus ipilimumab combination therapy or study participation at any time for any reason.
- Any reason listed in the local prescribing information and practice guidelines.

If a patient experiences a toxicity that is known to be associated only with ipilimumab therapy, ipilimumab will be discontinued but cemiplimab may be continued.

7.3.6. Pembrolizumab

Dose modification/reduction or temporary cessation of pembrolizumab should be managed in accordance with the regional guidelines.

Pembrolizumab dosing will be permanently discontinued in the event of pregnancy.

In addition, pembrolizumab 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 pembrolizumab or study participation at any time for any reason.

A patient who permanently discontinues pembrolizumab should continue follow-up in the study without additional pembrolizumab treatment until RECIST 1.1-defined progressive disease, completion of all study assessments, or closure of the study (Section 6.3 and Section 8.1.2).

In the event of an infusion reaction of grade 3 or greater severity during or directly following pembrolizumab, dosing should be stopped and the patient must be permanently discontinued from treatment.

For dose delay and discontinuation rules due to pembrolizumab toxicities, see local prescribing information and practice guidelines.

7.3.7. Platinum-Based Doublet Chemotherapy

Dose modification/reduction or temporary cessation of a given chemotherapy should be managed in accordance with the local prescribing guidelines for the specific chemotherapy agent.

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

If a patient experiences a toxicity that is known to be associated with chemotherapy, chemotherapy treatment will be discontinued but cemiplimab treatment may be continued.

A patient who permanently discontinues from chemotherapy should continue follow-up in the study without additional chemotherapy treatment until RECIST 1.1-defined progressive disease, completion of all study assessments, or closure of the study (see Section 6.3 and Section 8.1.2).

7.3.8. Permanent Study Treatment Discontinuation

Patients who permanently discontinue from study treatment 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.

Patients who permanently discontinue from study treatment and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

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. Vital signs should be closely monitored according to Table 4, Table 5, and Table 6. 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 current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale (Section 9.5.1).

In the event of an infusion reaction of grade 3 or greater severity during or directly following cemiplimab, ipilimumab, or pembrolizumab, dosing must be stopped and the patient must be permanently discontinued from treatment. Infusion reactions are defined in Section 9.3.4.

Acute infusion reactions may include cytokine release syndrome, angioedema, or anaphylaxis, and differ from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms may include the following:

- Allergic reaction/hypersensitivity (including drug fever)
- Arthralgia (joint pain)
- Bronchospasm
- Cough
- Dizziness
- Dyspnea (shortness of breath)
- Fatigue (asthenia, lethargy, malaise)
- Headache
- Hypertension
- Hypotension
- Myalgia (muscle pain)
- Nausea
- Pruritus/itching
- Rash/desquamation
- Rigors/chills
- Sweating (diaphoresis)
- Tachycardia
- Tumor pain (onset or exacerbation of tumor pain due to treatment)
- Urticaria (hives, welts, wheals)
- Vomiting

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 retreatment.

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.

See the local prescribing information for management of infusion interruptions for pembrolizumab and ipilimumab.

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

In the event of an infusion reaction of grade 3 or greater severity during or directly following cemiplimab, ipilimumab, or pembrolizumab, dosing should be stopped and the patient must be permanently discontinued from treatment.

See the local prescribing information for management of infusion termination for pembrolizumab and ipilimumab.

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 585 patients will be randomized in a 1:1:1 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).

Patients will be randomized 1:1:1 to receive pembrolizumab monotherapy, cemiplimab/ipi, or cemiplimab/chemo/ipi.

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

7.5.1. Blinding/Masking

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

Cemiplimab

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 withdrawable cemiplimab at a concentration of 50 mg/mL. Cemiplimab will be refrigerated at the site at a temperature of 2°C to 8°C. The temperature of the storage refrigerator should be checked and recorded at least daily as prescribed in the pharmacy manual. 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. Details on storage and preparation for drug product for IV administration will be provided in the pharmacy manual.

Ipilimumab

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

Ipilimumab will be refrigerated at the site at a temperature of 2°C to 8°C, and refrigerator temperature will be logged daily.

Platinum-Based Doublet Chemotherapy

Instructions on storage for chemotherapy agents will be provided in the pharmacy manual. A pharmacist or other qualified individual will be identified at each site to prepare platinum-based doublet chemotherapy for administration. Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

Pembrolizumab

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

Pembrolizumab will be refrigerated at the site at a temperature of 2°C to 8°C, and refrigerator temperature will be logged daily.

7.6.2. Supply and Disposition of Treatments

Cemiplimab

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.

Ipilimumab

Open-label ipilimumab will be supplied locally or may be provided by Regeneron.

Platinum-Based Doublet Chemotherapy

Open-label platinum-based doublet chemotherapy agents will be supplied locally or may be provided by Regeneron.

Pembrolizumab

Open-label pembrolizumab will be supplied locally or may be provided by Regeneron.

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; anonymized photocopies must be provided to the sponsor at the conclusion of the study.

7.6.4. Treatment Compliance

All treatments will be administered at the study site, and administration will be recorded on the electronic case report form (eCRF). 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

Any treatment administered from the time of informed consent until 90 days after the last study treatment 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 eCRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

7.7.1. Prohibited Medications and Procedures

While participating in this study, a patient may not receive any investigational drug or treatment for treatment of a tumor other than pembrolizumab monotherapy or cemiplimab plus study-specified chemotherapy regimens or ipilimumab combination therapy.

Treatment with idelalisib, bevacizumab, or necitumumab is not one of the protocol–defined treatment options. If the treating physician believes that treatment with one of these 3 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 study treatment 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 at doses >10 mg/day prednisone or equivalent. 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 and denosumab) are permitted.

Pemetrexed maintenance therapy should be given according to local prescribing information and practice guidelines.

7.8. Disease Progression While Receiving Cemiplimab or Pembrolizumab

It is recognized that some patients treated with immunotherapy or platinum-based chemotherapy may derive clinical benefit despite initial evidence of progressive disease. Patients treated with cemiplimab 350 mg and pembrolizumab will be permitted to continue treatment beyond initial RECIST 1.1-defined progressive disease if the investigator perceives the patient to be experiencing clinical benefit and the patient has not completed the 108-week treatment period and provided that he/she meets the following criteria:

- Investigator assessed no rapid disease progression.
- Patient continues to meet all other study eligibility criteria.
- Patient is tolerant of the cemiplimab containing regimen and has a stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression.

Patients may be required to sign a separate ICF per local regulatory requirements.

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. In these patients, further progression will be defined as an additional 10% increase in tumor burden from the time of initial progressive disease; this includes an increase in the sum of all target lesions and/or the development of new target lesions. If further progressive disease is confirmed, cemiplimab must be discontinued and other anti-cancer therapy considered, if appropriate.

If a patient continues treatment with cemiplimab or pembrolizumab beyond the initial determination of progressive disease, study assessments should continue as per Table 5.

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.

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 treatment period, and in Table 6 for the follow-up period.

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

Procedure	Screening Visit (within 28 days prior to randomization)	Notes
Eligibility Assessments		
Informed Consent	X	Informed consent must be obtained prior to any study-related procedures. Assessments performed as part of standard-of-care that fall within the screening window (28 days prior to randomization) but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility.
Inclusion/Exclusion Criteria	X	Eligibility of the patient must be confirmed prior to randomization. See Section 6.2.
Collection of Tumor Tissue Sample for PD-L1 Assessment	X	• Samples should be collected as described in the laboratory manual. See Section 8.2.5 • 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 • Samples will also be tested for EGFR mutations, ALK translocations, and ROS1 fusions by a central laboratory, unless this testing has been performed and the test results are available from other Regeneron NSCLC immunotherapy studies.
Medical/Oncology History	X	
Demographics	X	
Efficacy Assessments		
Baseline Radiographic Tumor Assessment	X	• CT or MRI (or PET) should be performed within 28 days of randomization. • CT or MRI of the brain with contrast (unless contraindicated) should be performed in patients with a known history of treated brain metastasis, if not 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. If PET is used at baseline, it should be used throughout the study
Baseline Tumor Burden Assessment	X	Tumor burden assessment using RECIST 1.1 criteria.
Safety Assessments		Assessments performed as part of standard-of-care that fall within the screening window (28 days prior to randomization) but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility
Complete Physical Exam	X	
ECOG Performance Status	X	

Procedure	Screening Visit (within 28 days prior to randomization)	Notes
Weight	X	
Height	X	
Vital Signs	X	• Vital signs include temperature, seated BP, RR, heart rate. • BP and heart rate should be measured prior to obtaining any blood samples.
12-Lead ECG	X	A 12-lead ECG should be acquired at screening and as clinically indicated thereafter, per the discretion of the investigator. See Section 8.2.3.5.
Chest X-ray	X	
Laboratory Tests: CBC w/ diff Serum Chemistry PT/PTT TSH Tuberculosis Amylase and lipase	X	• Measure free T4 if TSH is outside the normal range • TSH (and free T4 if TSH is abnormal) must be tested ≤72 hours prior to dosing ipilimumab, and the results must be reviewed prior to dosing ipilimumab • PPD/QuantiFERON testing for tuberculosis according to local guidelines in potential patients from tuberculosis-endemic areas
Serum Pregnancy Test	X	Women of childbearing potential must have a serum pregnancy test performed within 72 hours prior to administration of the first dose of study treatment.
Prior/Concomitant Medication Recording	X	
Adverse Event Recording	X	
Genomics Sub-study		
Genomics Sub-study Consent (optional)	X	DNA consent should be obtained during the screening period but may be obtained during the study as well.

Abbreviations: ALK=anaplastic lymphoma kinase; BP=blood pressure; CBC=complete blood count; CNS=central nervous system; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; MRI=magnetic resonance imaging; PD-L1=programmed death ligand 1; PET=positron emission tomography; PT/PTT=prothrombin time/partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; ROS1=C-ros oncogene 1 receptor tyrosine kinase; RR=respiratory rate; T4=thyroxine; TSH=thyroid stimulating hormone

Table 5: Schedule of Events: Treatment Period Assessments and Procedures

Study Procedure	Year 1				Year 2 (Starting at Cycle 19)			Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Day 1, Every Other Cycle (Every 42 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 [63 Days] ±5 Days)	Every 4 Cycles (12 Weeks ±5 Days)	
Randomization	X							
Study Treatment Administration								Treatment should be initiated within 3 days of randomization.
Treatment Arm A - Pembrolizumab monotherapy								
Pembrolizumab 200 mg	X	X			X			• Record start and stop infusion times.
Treatment Arm B - Cemiplimab/ipi								
Cemiplimab 350 mg	X	X			X			• Record start and stop infusion times. • Infuse cemiplimab after chemotherapy.
Ipilimumab 50 mg flat dose	X		X					• Record start and stop infusion times. • Administer Q6W for up to 4 doses. • Infuse after cemiplimab on the same day.
Treatment Arm C - Cemiplimab/chemo/ipi-								
Cemiplimab 350 mg	X	X			X			• Record start and stop infusion times. • Infuse chemotherapy first, then cemiplimab followed by ipilimumab on the same day.
Paclitaxel 200 mg/m^2 IV	X	X	• Record start and stop infusion times.					

Study Procedure	Year 1				Year 2 (Starting at Cycle 19)			Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Day 1, Every Other Cycle (Every 42 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 [63 Days] ±5 Days)	Every 4 Cycles (12 Weeks ±5 Days)	
plus carboplatin AUC of 5 or 6 mg/mL/min IV OR Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV OR Pemetrexed 500 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/min IV (non-squamous histology only) OR Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV (non-squamous histology only)			• Administer 2 cycles. • Administer on day 1 of each 21-day cycle (Q3W). • Calculate dose of carboplatin using the Calvert formula. • Note that patients with GFR <50 mL/min/1.73 m^2 may NOT receive cisplatin-containing regimens.					
Ipilimumab 50 mg flat dose	X		X					• Record start and stop infusion times. • Administer Q6W for up to 4 doses. • Infuse after cemiplimab on the same day.
Efficacy Assessments								
Radiographic Tumor Assessment				X			X	• For schedule, see Section 8.2.2.1. • Image with contrast (unless contraindicated) the chest/abdomen/pelvis and other areas being monitored. • For patients who have RECIST 1.1-defined progressive disease while receiving cemiplimab,

Study Procedure	Year 1				Year 2 (Starting at Cycle 19)			Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Day 1, Every Other Cycle (Every 42 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 [63 Days] ±5 Days)	Every 4 Cycles (12 Weeks ±5 Days)	
								imaging should be performed within 9 weeks of the original tumor progression.
Tumor Burden Assessment				X			X	Tumor burden assessment per RECIST 1.1 criteria
Quality of Life Questionnaires	X	X		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).
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.
ECOG Performance Status	X	X			X			
Vital Signs (Seated Blood Pressure, Heart Rate, Respiratory Rate, Temperature)	X	X			X			At cycle 1 day 1 and on all subsequent treatment days, vital signs will be collected prior to infusion of treatment. Vital signs must also be obtained approximately 15 minutes (±10 minutes) after completion of the infusion. See Section 8.2.3.4.
12-lead ECG	(X)	(X)			(X)			A 12-lead ECG should be

Study Procedure	Year 1				Year 2 (Starting at Cycle 19)			Notes
	Day 1, Cycle 1	**Day 1, Each Cycle (Every 21 Days ±3 Days)**	**Day 1, Every Other Cycle (Every 42 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 [63 Days] ±5 Days)**	**Every 4 Cycles (12 Weeks ±5 Days)**	
								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 (ACTH must be tested in Treatment Arm C; only prior to ipilimumab dosing)		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. • Screening laboratory examinations performed within 7 days of cycle 1 day 1 do not need to be repeated for this visit unless clinically indicated.
Amylase and lipase testing	X			X		X		
Coagulation Testing	(X)	(X)			(X)			As clinically indicated
TSH	X		X (Treatment Arm B and C;	X (after ipilimumab		X		• For Treatment Arm B and C, TSH (and free T4 if TSH

Study Procedure	Year 1				Year 2 (Starting at Cycle 19)			Notes
	Day 1, Cycle 1	**Day 1, Each Cycle (Every 21 Days ±3 Days)**	**Day 1, Every Other Cycle (Every 42 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 [63 Days] ±5 Days)**	**Every 4 Cycles (12 Weeks ±5 Days)**	
			prior to ipilimumab dosing)	dosing)				is abnormal) **must** be tested ≤72 hours prior to dosing ipilimumab, and the results must be reviewed prior to dosing ipilimumab. • For all treatment arms, TSH may be obtained again, as clinically indicated. • Measure free T4 if TSH is abnormal.
Pregnancy Testing	X	X			X			Women of childbearing potential must have a negative serum pregnancy test within 72 hours 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 and Q6W, or more frequently per local standard.
Concomitant Medication Recording	X	X			X			
Adverse Event Recording	X	X			X			Assess using current version of NCI-CTCAE
PK Drug Concentration/Cemiplimab Anti-Drug Antibody Procedures								For footnotes, see Section 8.1.1
Treatment Arms B and C Only: PK Drug Concentration Measurements and Samples	X	X					X	Collect samples as described in Appendix 4.
Treatment Arms B and C Only: Anti-Drug Antibody	X	X					X	Collect samples as described in Appendix 4.

Study Procedure	Year 1				Year 2 (Starting at Cycle 19)			Notes
	Day 1, Cycle 1	Day 1, Each Cycle (Every 21 Days ±3 Days)	Day 1, Every Other Cycle (Every 42 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 [63 Days] ±5 Days)	Every 4 Cycles (12 Weeks ±5 Days)	
Measurements and Samples								
Biomarker Procedures								
Serum Biomarker Sample	X	X						Collect samples as described in see Appendix 4.
Plasma Biomarker Sample	X	X						Collect samples as described in see Appendix 4.
Blood Sample for Germline DNA (Optional)	X							Collect the blood sample for DNA on day 1 of cycle 1. If consent is not obtained during screening, it can be obtained at any other visit prior to collection of the sample.
Tumor Biopsy								
Tumor Biopsy (Optional)		(X)			(X)			If possible, a tumor biopsy should be collected at the time of progressive disease (optional) as described in the laboratory manual.

Parentheses indicate assessments which are optional.
Abbreviations: cemiplimab/ipi = cemiplimab 350 mg in combination with ipilimumab; cemiplimab/chemo/ipi= cemiplimab 350 mg in combination with initial platinum-based doublet chemotherapy and ipilimumab; ACTH=adrenocorticotropic hormone; AUC=area under the curve; CBC=complete blood count; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; GFR=glomerular filtration rate; IV=intravenous; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PE=physical examination; PK=pharmacokinetic; Q3W=every 3 weeks; Q6W=every 6 weeks; Q18W=every 18 weeks; Q24W=every 24 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; T4=thyroxine; TSH=thyroid-stimulating hormone

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

Study Procedure	**Follow-up Visit 1/End of study visit for patients who discontinued treatment due to PD**	**Follow-up Visits 2 to 7**	**Notes**
	14 to 30 Days after the last study treatment if treatment is discontinued due to PD as an end of study visit OR Last Cycle Visit + 14 to 30 Days if treatment is discontinued for any other reason	**Prior Follow-up Visit + 28 days (±7 days)**	
Efficacy Assessments			
Radiographic Tumor Assessment	Radiographic assessments for patients who have not experienced RECIST 1.1-defined progressive disease or who discontinued study treatment early for reasons other than RECIST 1.1-defined progressive disease should be performed according to Section 8.2.2.1 regardless of when treatment is discontinued until RECIST-defined PD.		
Tumor Burden Assessment		X	Tumor burden assessment using RECIST 1.1 criteria.
Quality of Life Questionnaire	X		Complete prior to any study procedures.
Survival Data Collection	X	X	Every 3 months, until death, loss to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.
Safety Assessments			
Physical Examination	X	X	A limited PE should be performed but a complete PE should be performed when indicated.
ECOG Performance Status	X	X	
Weight	X		
Vital Signs	X	X	Vital signs including temperature, seated BP, RR, heart rate BP and heart rate should be measured prior to obtaining any blood samples.
Hematology (CBC with Differential)	X		Collect at follow-up visit 1 and then as clinically indicated.
Serum Chemistry	X		Collect at follow-up visit 1 and then as clinically indicated.
Coagulation Testing			Collect as clinically indicated.
Pregnancy Test (urine)	X		Women of childbearing potential.
Concomitant Medication Recording	X	X	

Study Procedure	Follow-up Visit 1/End of study visit for patients who discontinued treatment due to PD	Follow-up Visits 2 to 7	Notes
	14 to 30 Days (±7 days) after the last study treatment if treatment is discontinued due to PD as an end of study visit OR Last Cycle Visit + 14 to 30 Days (±7 Days) if treatment is discontinued for any other reason	**Prior Follow-up Visit + 28 days (±7 days)**	
Adverse Event Recording	X	X	Assess using current version of NCI-CTCAE. All AEs after initiation of study treatment and until 90 days after the last study treatment, regardless of relationship to study treatment, will be reported on the AE eCRF. See Section 9.4.1.
PK Drug Concentration/ Anti-Drug Antibody Samples			
Treatment Arms B and C Only: PK Drug Concentration Measurements and Samples	X	X	Samples will be collected at follow-up visits 1 and 3, as described in Appendix 4.
Treatment Arms B and C Only: Anti-Drug Antibody Measurements and Samples	X	X	Samples will be collected at follow-up visit 3 as described in Appendix 4.
Biomarker Samples			
Serum Biomarker Sample	X		Samples will be collected at follow-up visit 1 and at the time of progressive disease as described in Appendix 4.
Plasma Biomarker Sample	X		Samples will be collected at follow-up visit 1 and at the time of progressive disease as described in Appendix 4.
Tumor Biopsy			
Tumor Biopsy (Optional)			If possible a tumor biopsy should be collected at the time of progressive disease (optional) as described in the laboratory manual.

Abbreviations: CBC=complete blood count; ECOG=Eastern Cooperative Oncology Group; eCRF=Electronic Case Report Form; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PD=progressive disease; PE=physical examination; PK=pharmacokinetic; Q12W=every 12 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1

8.1.1. Footnotes for the Schedule of Events Table 5 and Table 6

1. Pre-dose is defined as before the start of the first cemiplimab infusion (specific to PK drug concentration and ADA samples in Table 5). Pre-dose samples may be collected ≤72 hours prior to day 1 dosing.
2. Pre-infusion is defined as 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 during the treatment period will be asked to return to the clinic to complete follow-up visit 1 study assessments (Table 6) as an early termination visit. Patients who withdraw from the study during the follow-up period will be asked to return to the clinic to complete visits of the follow-up period as indicated in Table 6.

Patients who discontinue study treatment due to progressive disease should return to the clinic 14 to 30 days after the last study treatment to complete the end of study assessments (follow-up visit 1).

Patients who discontinue study treatment for a reason other than progressive disease should return to the clinic 14 to 30 days (±7 days) after the last cycle visit for follow-up visit 1 and then continue with follow-up visit 2 through follow-up visit 7.

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. In response to adverse events of special interest (AESIs), such as anaphylaxis or hypersensitivity, ADA samples may be collected closer to the event, based on the judgment of the investigator and/or Medical Monitor.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

Informed consent must be obtained prior to any study-related procedures. Assessments performed as part of standard-of-care that fall within the screening window (28 days prior to randomization) but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility.

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

- Collection of tumor tissue sample for biomarker assessment by the central laboratory
  - A formalin-fixed, paraffin-embedded tissue block or unstained slide of a tumor tissue sample (archival tissue, if ≤5 months old, or recently obtained, on-study tumor biopsy collected during screening) 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 are provided in the laboratory manual.

  - Tumor tissue samples will also be tested for EGFR and ALK mutations as well as for ROS1 fusions by a central laboratory unless this testing has already been performed and the results are available from other Regeneron NSCLC immunotherapy studies.

- Medical/oncology history
- Demographics
- Baseline radiographic tumor assessment of the chest, abdomen, pelvis, and all other known or suspected sites of disease by CT or MRI (or positron emission tomography [PET]). The same imaging modality should be used throughout the study. If PET is used at baseline, it should be used throughout the study.
- Baseline tumor burden assessment
- Baseline safety assessments (see Table 4)
- Tuberculosis Testing
- Serum pregnancy test in women of childbearing potential within 72 hours prior to administration of the first study treatment
- Sample for a genomics sub-study (optional)

For the complete list of procedures performed at screening to determine eligibility, including those that are used throughout the study (ie, not only for determining eligibility), see Table 4.

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.

At screening, CT or MRI of the brain with contrast (unless contraindicated) should be performed in patients with a known history of treated brain metastasis, if not performed in the prior 60 days. Additional sites of known disease (including CNS) should be imaged at screening.

After the baseline tumor assessment, radiographic tumor assessments will be obtained in all patients Q9W beginning at week 9 (day 63 ± 5 days) during year 1 and Q12W beginning at week 55 (first radiographic tumor assessment in year 2 performed at end of week 54) during year 2, until RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment. Patients who discontinue for reasons other than progression who are not attending treatment visits may have radiographic tumor assessments between Q9W

and Q12W until RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment.

Radiographic tumor assessments will occur at the following time points:

End of week 9 ± 5 days (end of cycle 3)
End of week 18 ± 5 days (end of cycle 6)
End of week 27 ± 5 days (end of cycle 9)
End of week 36 ± 5 days (end of cycle 12)
End of week 45 ± 5 days (end of cycle 15)
End of week 54 ± 5 days (end of cycle 18)
End of week 66 ± 5 days (end of cycle 22)
End of week 78 ± 5 days (end of cycle 26)
End of week 90 ± 5 days (end of cycle 30)
End of week 102 ± 5 days (end of cycle 34)

In the follow-up period, radiographic assessments for patients who have not experienced progressive disease should be performed Q12W or until RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment.

Tumor assessments should be performed even if dosing is interrupted. Weeks are in reference to the calendar week and should not be adjusted due to dosing delays/interruptions.

For patients identified as having RECIST 1.1-defined progressive disease while receiving or after completion of study treatment, subsequent imaging should be performed within 9 weeks of the initial tumor assessment of progression.

8.2.2.2. Tumor Burden Assessments

Tumor measurements will be performed 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.

Investigators and the blinded IRC (Section 5.3.1) will assess response to therapy using RECIST 1.1 criteria. RECIST 1.1-defined progressive disease determined by the investigator will be used for clinical management of the patient. RECIST 1.1-based tumor burden assessments by the blinded IRC will be used for evaluation of efficacy endpoints.

8.2.2.3. Survival Data Collection

Every effort will be made to collect survival data on all patients, including patients who withdraw from the study for any reason but have not withdrawn consent to collect survival information, as indicated in Table 6. 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 alive.

8.2.2.4. Quality of Life Questionnaires

Patient-reported outcomes will be measured at the frequency indicated in Table 5 and Table 6 using the following validated patient self-administered questionnaires: EORTC QLQ-C30 and EORTC QLQ-LC13 (Berman 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 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 performed prior to the first dose on cycle 1 day 1, or at other visits if indicated, 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, at least, examination of the lungs, heart, abdomen, and skin.

8.2.3.2. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be measured at a frequency indicated in Table 4, Table 5, and Table 6.

8.2.3.3. Weight and Height

Body weight measurements will be obtained at screening according to Table 4 and at follow-up according to Table 6. 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 at screening; self-reported heights are not acceptable.

8.2.3.4. 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. Vital signs must also be obtained approximately 15 minutes (± 10 minutes) after completion of the infusion.

8.2.3.5. 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at screening and when clinically indicated during the active treatment period (Table 4 and Table 5). Electrocardiograms should be performed before blood is drawn during visits requiring blood draws.

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.

8.2.3.6. Laboratory Testing

Hematology, chemistry, coagulation, thyroid function, 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:

Hematology (Complete Blood Count with Differential)

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

For hematology, 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.

Serum Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Magnesium
Chloride	Blood urea nitrogen[a]	Phosphorus
Bicarbonate[b]	Aspartate aminotransferase	Uric acid
Calcium	Alanine aminotransferase	Adrenocorticotropic hormone[c]
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase	

[a] The urea test is acceptable instead of blood urea nitrogen at centers where this is commonly used instead of the blood urea nitrogen.

[b] The partial pressure of carbon dioxide (PCO_2) test is an acceptable test at centers where this is commonly used instead of the bicarbonate test.

[c] Adrenocorticotropic hormone (ACTH) will be included only for the 4 cycles when ipilimumab is administered and only in Treatment Arm C.

For chemistry, 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. For Treatment Arm C, ACTH should be tested during the 4 cycles in which ipilimumab is administered.

Other Laboratory Tests

Coagulation Tests: Prothrombin time/partial thromboplastin time will be analyzed by the investigative site's local laboratory. Testing will be performed at screening and then as clinically indicated.

Thyroid Function Tests:

Thyroid-stimulating hormone will be analyzed by the site's local laboratory.

For Treatment Arm B and C, TSH will be tested at screening, before the 4 ipilimumab doses every 6 weeks then Q9W, and as clinically indicated. If TSH is outside of normal range, a free thyroxine (T4) should be measured at the investigative site's local laboratory. Thyroid function test (and free T4 if TSH is abnormal) must be tested ≤72 hours prior to dosing ipilimumab, and the results must be reviewed prior to dosing ipilimumab, and on cycles when ipilimumab is not dosed.

For Treatment Arm A, TSH is tested at screening and as clinically indicated. If TSH is outside normal range, a free T4 should be measured at the investigative site's local laboratory.

Tuberculosis Testing: PPD/QuantiFERON testing according to local guidelines in tuberculosis-endemic areas.

Amylase and Lipase Testing: Testing will be performed at screening and every 9 weeks.

Pregnancy Testing: Women of childbearing potential must have a negative serum pregnancy test within 72 hours 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 and Q6W, 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.

8.2.3.7. Concomitant Medication Recording

Concomitant medication will be collected at time points according to Table 4, Table 5, and Table 6. See Section 7.7 for details on recording concomitant medications.

8.2.3.8. Adverse Event Recording

Adverse events will be collected at time points according to Table 4, Table 5, and Table 6. See Section 9.4 for details on recording and reporting AEs.

8.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

In addition to the procedures detailed below, blood samples will also be taken to measure drug concentrations/ADA, as appropriate, in case of AESIs.

8.2.4.1. Drug Concentration Measurements and Samples

Cemiplimab concentrations in serum of patients randomized to Treatment Arms B and C will be measured using a validated enzyme-linked immunosorbent assay method at visits and time points indicated in Table 5, Table 6, and Appendix 4. The actual time of each blood draw must be recorded. Pre-dose is defined as before the start of the first cemiplimab infusion. Pre-dose samples may be collected ≤72 hours prior to day 1 dosing. Pre-infusion is defined as before the start of subsequent infusions.

In addition, measurement of ipilimumab concentrations in serum may be considered in the future in the PK samples of patients randomized to Treatment Arm C.

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

Anti-drug antibody samples for cemiplimab immunogenicity assessments will be collected from patients randomized to Treatment Arms B and C prior to dosing at time points listed in Table 5 and during the follow-up period as shown in Table 6 (see Appendix 4). Any unused samples collected for immunogenicity assessments may be used for exploratory research or to investigate unexpected AEs. If necessary, these samples may also be used for ADA assessments of ipilimumab.

8.2.5. Biomarker Procedures

For biomarker assessments, a formalin-fixed, paraffin-embedded tissue block or unstained slides of a tumor tissue sample (archival tissue, if ≤5 months old, or recently obtained tumor biopsy collected during on-study) 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 sample, the following biomarker-based stratification strategies will be implemented in this study to determine study eligibility:

- A PD-L1 IHC 22C3 pharmDx assay will be utilized as the clinical trial assay to assess PD-L1 expression levels in recently obtained tumor tissue samples (on-study biopsy collected at screening visit or archival tissue, if ≤5 months old) in order to qualify patients for enrollment. The ≥50% PD-L1 positivity cut-off will be used as an inclusion criterion for this study.
- The PD-L1 IHC 22C3 pharmDx assay is a validated, automated, in vitro diagnostic assay that was developed as a companion diagnostic for pembrolizumab (Roach 2016). During development, the PD-L1 IHC 22C3 pharmDx assay was analytically validated for repeatability and reproducibility at 3 independent Clinical

Laboratory Improvement Amendments (CLIA)-certified laboratories and clinically validated in KEYNOTE-001, a clinical study of pembrolizumab in patients with NSCLC. Based on these studies, the PD-L1 IHC 22C3 pharmDx assay was demonstrated to be a robust PD-L1 assay and was approved by the FDA as a companion diagnostic for pembrolizumab. Further details on the assay are provided in the package insert (Dako, PD-L1 IHC 22C3 pharmDx Package Insert).

Tumor tissue biopsy samples will also be tested for EGFR mutations, ALK translocations, as well as 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. The results must indicate that the patient is negative for EGFR mutations, ALK translocations, and ROS1 fusions for enrollment in this study.

After completion of PD-L1 expression analysis, the remaining tumor tissue sample may be used to study the biomarkers associated with clinical response to cemiplimab, including but not limited to whole exome sequencing of tumor genome and tumor mutational load.

Biomarker serum and plasma samples will be collected from all patients enrolled in this study at multiple time points as indicated in Table 5, Table 6, and Appendix 4 to study the potential pharmacodynamics or predictive biomarkers of response to cemiplimab including, but not limited to, cytokines and circulating tumor nucleic acids (refer to the laboratory manual). Samples will be collected prior to drug administration.

If possible a tumor tissue biopsy sample should be obtained at the time of RECIST 1.1-defined progressive disease to obtain information on mechanism of resistance.

8.2.6. Future Biomedical Research

The biomarker samples unused for study-related research, as well as unused PK and ADA 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 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.

8.2.6.1. Genomics Sub-study - Optional

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 day 1/baseline (pre-dose), but may be collected at any study visit (Table 4).

Deoxyribonucleic acid 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 drug 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 variation 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.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

For the purposes of this section, study treatment refers to cemiplimab, platinum-based doublet chemotherapy agents, ipilimumab and pembrolizumab.

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients according to local regulations.

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 reactions) to the health authorities, ECs/IRBs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Reference Safety Information section of the cemiplimab Investigator's Brochure or in reference safety documents of the other study drugs will be considered as unexpected.

In addition, the sponsor will report all 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 study in the clinical study report to health authorities and ECs/IRB, 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 as an SAE.

Serious AEs must be reported as directed in Section 9.4.2.

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 study sponsor to other parties (eg, regulators) might also be warranted. All AESI, serious and non-serious, 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:

- Any AE that meets the DLT criteria (defined in Section 5.1.5)

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or greater irAEs
- irAEs of any grade in patients previously treated with PI3-K inhibitor

Note: An irAE can occur shortly after the first dose or several months after the last dose of study 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 is provided in Section 7.3.4 and Appendix 3. The recommendations in Section 7.3.4 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, endocrine, or pneumonitis) but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

9.3.3.1. Immune-Related Adverse Events

Detailed guidance of management of irAEs is provided in Section 7.3.4 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, endocrine, or pneumonitis) but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

9.3.4. Infusion Reactions

Infusion-related reactions are known to occur with protein therapeutic infusions and have been observed in cemiplimab studies. Acute infusion reactions are defined as any AEs that occur during the infusion or within 1 day after the infusion is completed. Signs and symptoms usually develop during, or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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 105 days after the end of study treatment. After informed consent has been obtained but prior to initiation of study treatment, only the following categories of AEs should be reported on the AE eCRF:

- 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 eCRF.

All AEs after initiation of study treatment and until 90 days after the last study treatment, regardless of relationship to study treatment, will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 90 days after last study treatment 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 of becoming aware of the event.

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 that the investigator is informed of an SAE that occurs more than 90 days after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of any treatment-related SAE until the event is considered 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 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.

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.

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 AE information will be collected until the event is considered 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 current version of the NCI-CTCAE 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 (ADLs)*.

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

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

5 (Death): Death related to AE

*Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADLs 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.

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.

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 study, as well as in any other clinical study 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

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

The primary statistical hypothesis is that cemiplimab/ipi or cemiplimab/chemo/ipi will prolong PFS as compared with standard-of -care pembrolizumab monotherapy in treatment-naïve patients with squamous and non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells. The secondary hypothesis is that cemiplimab/ipi or cemiplimab/chemo/ipi will improve OS in the study patients whose tumors express PD-L1 in ≥50% of tumor cells.

10.2. Justification of Sample Size

In KEYNOTE-024, the median PFS in the pembrolizumab group was 10.3 months (95% CI: 6.7 months to not reached) versus 6.0 months (95% CI: 4.2 to 6.2 months) in the chemotherapy group (Reck 2016).

This study assumes a median PFS of 10 months for patients treated with pembrolizumab monotherapy and a median PFS of 15 months for patients treated with each of the cemiplimab combination therapies. The assumptions correspond to a 50% increase in median PFS and an HR of 0.6667. Under these assumptions, and for each cemiplimab combination treatment arm versus the pembrolizumab comparison, 256 PFS events are needed to yield an approximately 90% power to detect statistical significance at a 2-sided 0.05 level.

Considering a uniform enrollment rate and a combined enrollment and PFS follow-up duration of approximately 36 months (24 months for enrollment and approximately 12 months follow-up for PFS) and a 10% dropout rate per year, enrollment of approximately 585 randomized patients (195 patients per arm) is needed to generate enough PFS events for each cemiplimab combination treatment arm versus the pembrolizumab comparison with 90% power. Under the enrollment assumption and the alternative hypothesis, it is estimated that at the time when 142 PFS events are observed in the pembrolizumab arm, each of the cemiplimab combination treatment arms plus the pembrolizumab arm will yield 256 PFS events in total. In order to harmonize the timing of the primary analysis for the 2 comparisons, the primary endpoint of PFS will be performed after 142 PFS events are observed in the pembrolizumab treatment arm.

Assuming a median OS of 18 months for patients treated with pembrolizumab monotherapy and a median OS of 24 months for patients treated with each of the cemiplimab combination therapies, a corresponding HR of 0.75 if OS is distributed exponentially in each treatment arm. If the final analysis of OS is performed 12 months after the analysis of PFS, enrollment of 585 patients will yield approximately a power of 59% for the analysis of OS at a 2-sided alpha level of 0.05.

For PFS, it is projected that an observed HR of 0 78 or lower, corresponding to an increase in median PFS of 2.8 months or more (10 versus 12.8 months), would result in a statistically significant improvement in PFS. For OS, it is also projected that an observed HR of 0.77 or lower, corresponding to an increase in median OS of 5.4 months or more (18 versus 23.4 months), would result in a statistically significant improvement in OS.

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.

10.3.2. Safety Analysis Set

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

10.3.3. Other Analysis Sets

The PK population includes all randomized patients (safety population) who received cemiplimab and who had at least 1 non-missing cemiplimab concentration assay result 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 drug and had at least 1 non-missing post-baseline ADA assay result following the first dose of study drug.

The DLT analysis set includes the first 10 patients treated with cemiplimab/ipi and the first 10 patients treated with cemiplimab/chemo/ipi who are DLT evaluable, defined as the patients who completed the DLT observation period and those patients who discontinued early due to the development of a DLT. This population will be used for the assessment of DLTs. The patients will be analyzed as treated.

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.

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: met the inclusion criteria regarding the target indication and signed the ICF
- 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, with the table sorted by decreasing frequency of SOC, followed by PT based on the overall incidence between treatment arms.

10.4.4. Prior Medications/Concomitant Medications

The number and proportion of patients taking prior/concomitant medication will be summarized by decreasing frequency of anatomical therapeutic chemical (ATC) level 2 and ATC level 4 according to the current version of the World Health Organization Drug Dictionary, based on the overall incidence between treatment arms.

Listings of pre-treatment medication and concomitant medications include generic name, ATC levels 2 and 4, indication, study day onset, the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, and route.

For medications started before treatment, the study day onset is defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset is defined as the date of medication start - date of the first dose + 1.

10.4.5. Efficacy Analyses

The primary and key secondary endpoints will be tested in the following order: PFS, OS, and ORR.

10.4.5.1. Primary Efficacy Analyses

The final analysis of PFS will be performed after observing 142 PFS events in the pembrolizumab treatment arm.

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

Two 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 will be performed based on investigator-determined progressive disease events.

10.4.5.2. Secondary Efficacy Analyses

If the final analysis of PFS is statistically significant for both cemiplimab combination therapy versus pembrolizumab treatment, the analysis of the secondary endpoint of OS for cemiplimab combinations-versus-pembrolizumab comparison will be performed at the time of PFS analysis and 12 months after analysis of PFS using the same method as used in the analysis of PFS. The family-wise type-I error will be controlled at the 2-sided 5% level and detailed in the SAP.

The ORR for each cemiplimab combination-versus-pembrolizumab comparison will be analyzed using the Cochran-Mantel-Haenszel test stratified by histological status (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 (Clopper 1934) for each treatment arm.

Overall survival at 12 and 18 months for each treatment arm will be summarized.

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

10.4.5.3. 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 performance status (0, 1)
- Histology (squamous, non-squamous)
- Geographic region of enrolling site
- Ethnicity

10.4.6. Safety Analyses

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.

Dose-limiting toxicities observed during the DLT evaluation period will be summarized by treatment arm and will be assessed using the DLT analysis set.

10.4.6.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pre-treatment 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 day from the first dose of study drug to the day of the last dose of study drug plus 90 days.
- The post-treatment period is defined as the time after follow-up visit 1.

Treatment-emergent AEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be to the lowest-level terms. The verbatim text, the PT, and the primary SOC will be listed.

Summaries of all 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 (graded according to the current version of the NCI-CTCAE or Section 9.5.1, if not listed in NCI-CTCAE), presented by SOC and PT
- TEAEs by outcome
- TEAEs by relationship to study drug (related, not related), presented by SOC and PT
- AESI

Deaths and other 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 AEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.6.2. Other Safety Analyses

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, including dose, number of doses, timing, and applicable study concomitant procedures, will be summarized by treatment arm. The analysis methods will be detailed in the SAP.

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.

Blood samples for analysis of ipilimumab concentrations will be stored for possible future analysis, the results of which may be reported in the same way as for cemiplimab concentrations.

10.4.8. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 4.4 will be summarized using descriptive statistics in the ADA analysis set of the cemiplimab treatment arms (Treatment Arms B and C). Frequency tables of the proportion of patients with treatment-emergent, treatment-boosted, persistent ADA response, and NAb status in the NAb assay will be presented as absolute occurrence (n) and percent of patients (%), presented by treatment arms.

Plots of cemiplimab concentrations will be examined, and the influence of ADAs on individual concentration-time profiles may be evaluated. Assessment of the impact of ADA 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. A detailed description of statistical methods that will be used for biomarker data analyses will be provided in a separate Biomarker Analytical Plan.

10.5. Multiplicity Considerations

For 2 cemiplimab combinations versus pembrolizumab comparisons, and for the tests of primary endpoint of PFS, secondary endpoint of OS and ORR, a familywise type-I error rate of 0.05 is controlled by the hierarchical gatekeeping approach with the order of tests listed below:

1. PFS for cemiplimab/chemo/ipi vs. pembrolizumab
2. PFS for cemiplimab/ipi vs. pembrolizumab
3. OS for cemiplimab/chemo/ipi vs. pembrolizumab
4. OS for cemiplimab/ipi vs. pembrolizumab
5. ORR for cemiplimab/chemo/ipi vs. pembrolizumab
6. ORR for cemiplimab/ipi vs. pembrolizumab

The alpha spending for analysis of OS at the time of PFS analysis and the final analysis will be controlled at the 2-sided 5% level and detailed in the SAP. All other statistical comparisons will be exploratory in nature and, therefore, not controlled for multiplicity and should be interpreted accordingly.

10.6. Interim Analysis

An interim analysis for secondary endpoint of OS will be performed at the time of primary analysis for PFS. There will be an early safety review conducted by the IDMC as detailed in Section 5.1.4.

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 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 eCRF 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

The study is expected to end after the last visit of the last patient.

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, 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, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The eCRF data for this study will be collected using 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 and analysis
- Pharmacovigilance safety database
- ARGUS safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization 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 eCRF. 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 eCRFs within the EDC system by trained site personnel. All required eCRFs 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 eCRF 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 eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including details regarding the 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, eCRFs, medical records, correspondence, ICFs, IRB/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 IRB/EC. A copy of the IRB/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 the 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.

A written informed consent should be obtained for treatment beyond radiologic disease progression, acknowledging that this practice is not considered standard in the treatment of cancer.

14.3. Patients' 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 patient identification number only on

eCRFs 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. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/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 patient, in which case the IRB/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 IRB/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 IRB/EC approval letter with a current list of the IRB/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 IRB/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 IRB/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 IRB/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 eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRFs 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. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the

protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, and Section 13)

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects/patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All subject/patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient/subject final CRF (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Phase 3, Open-Label Study of Combinations of REGN2810 (Cemiplimab, Anti-PD-1 Antibody), Platinum-based Doublet Chemotherapy, and Ipilimumab (Anti-CTLA-4 Antibody) Versus Pembrolizumab Monotherapy in First-Line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer with Tumors Expressing PD-L1 ≥50% and agree to abide by all the 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 IRB/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 STUDY DRUG AND STUDY CONDUCT

Is there a reasonable possibility that the event may have been caused by the study drug or study conduct?

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 study drug
- Do not reappear or worsen when dosing with study drug is resumed
- Are not a suspected response to the study drug based upon pre-clinical 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 study drug
- Resolve or improve after discontinuation of study drug
- Reappear or worsen when dosing with study drug is resumed
- Are known or suspected to be a response to the study drug based upon pre-clinical 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 a 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 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. Non-measurable disease

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

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 non-measurable) 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 non-cystic 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.

- **Clinical lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (eg, skin nodules).
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **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 5mm 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. Magnetic resonance imaging is also acceptable in certain situations (eg, for body scans).
- **PET-CT**. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately

measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

- **Ultrasound**. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- **Endoscopy, laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised.
- **Tumor markers**. Tumor markers alone cannot be used to assess response.
- **Cytology, histology**. These techniques can be used to differentiate between partial responses and complete responses in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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 5 lesions total (and a maximum of 2 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. (**Note:** the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** 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 CR 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 non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target 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 non-target 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 "non-target" 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 (eg, 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 PR or CR. 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 truly represents new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progressive disease based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease. If the positive FDG-PET at follow-up is not confirmed as a new

site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of progressive disease will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false-positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A "positive" FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

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 RECIST Version 1.1 (Eisenhauer 2009) is summarized in the table below.

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 Unevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluated 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

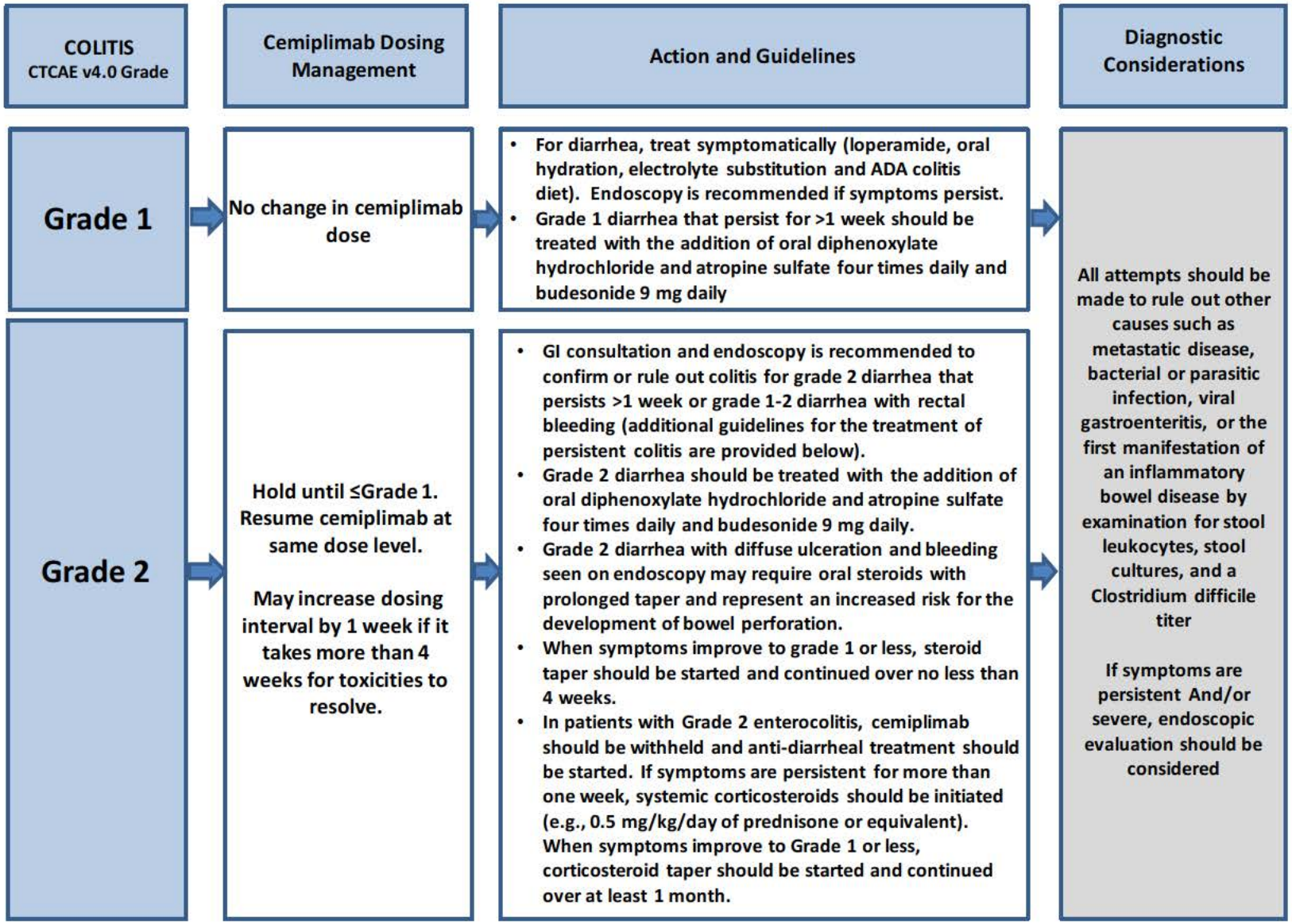
The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (eg, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a BOR 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 unevaluable.

2.0. Duration of overall response

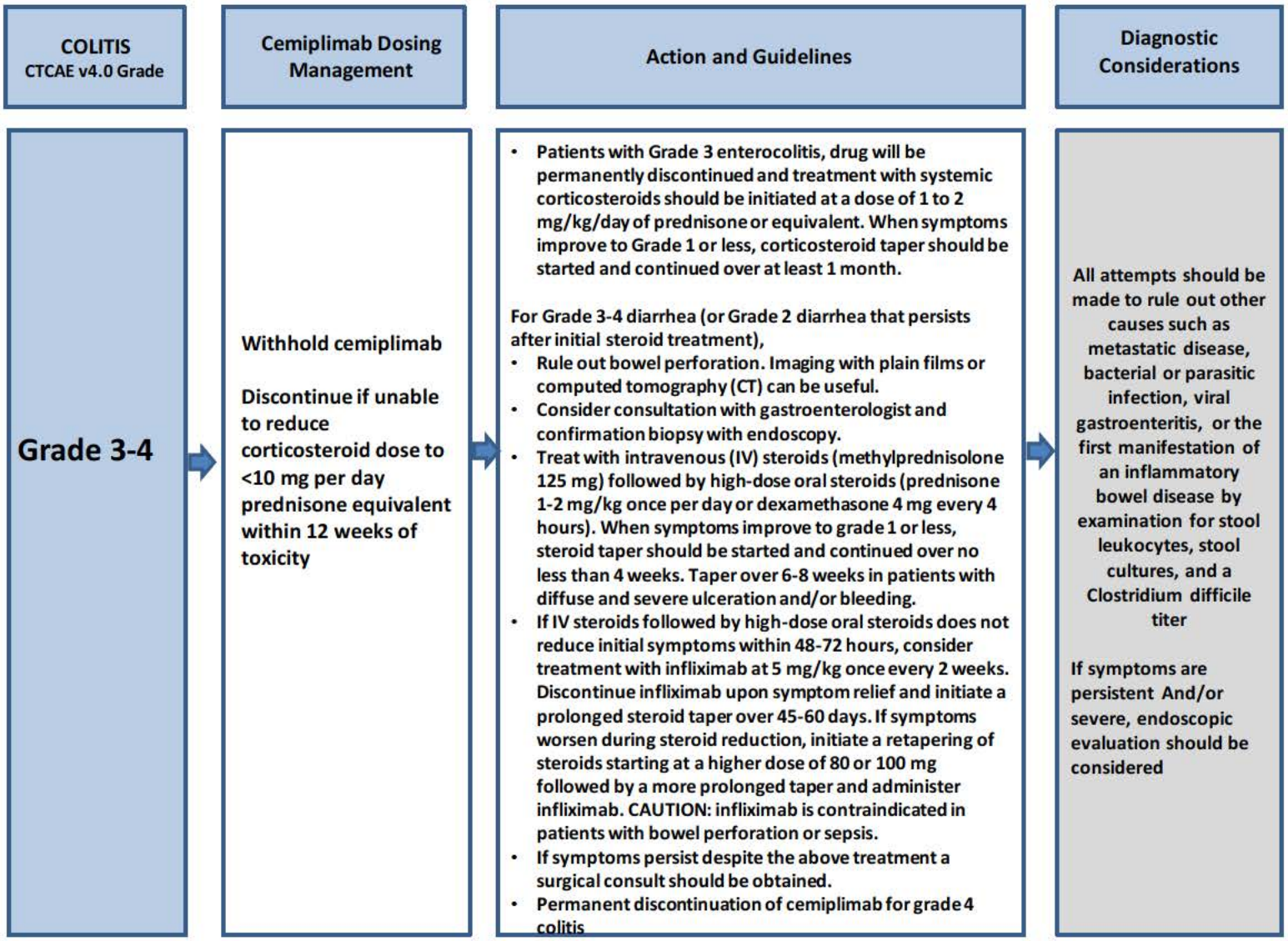
The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on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

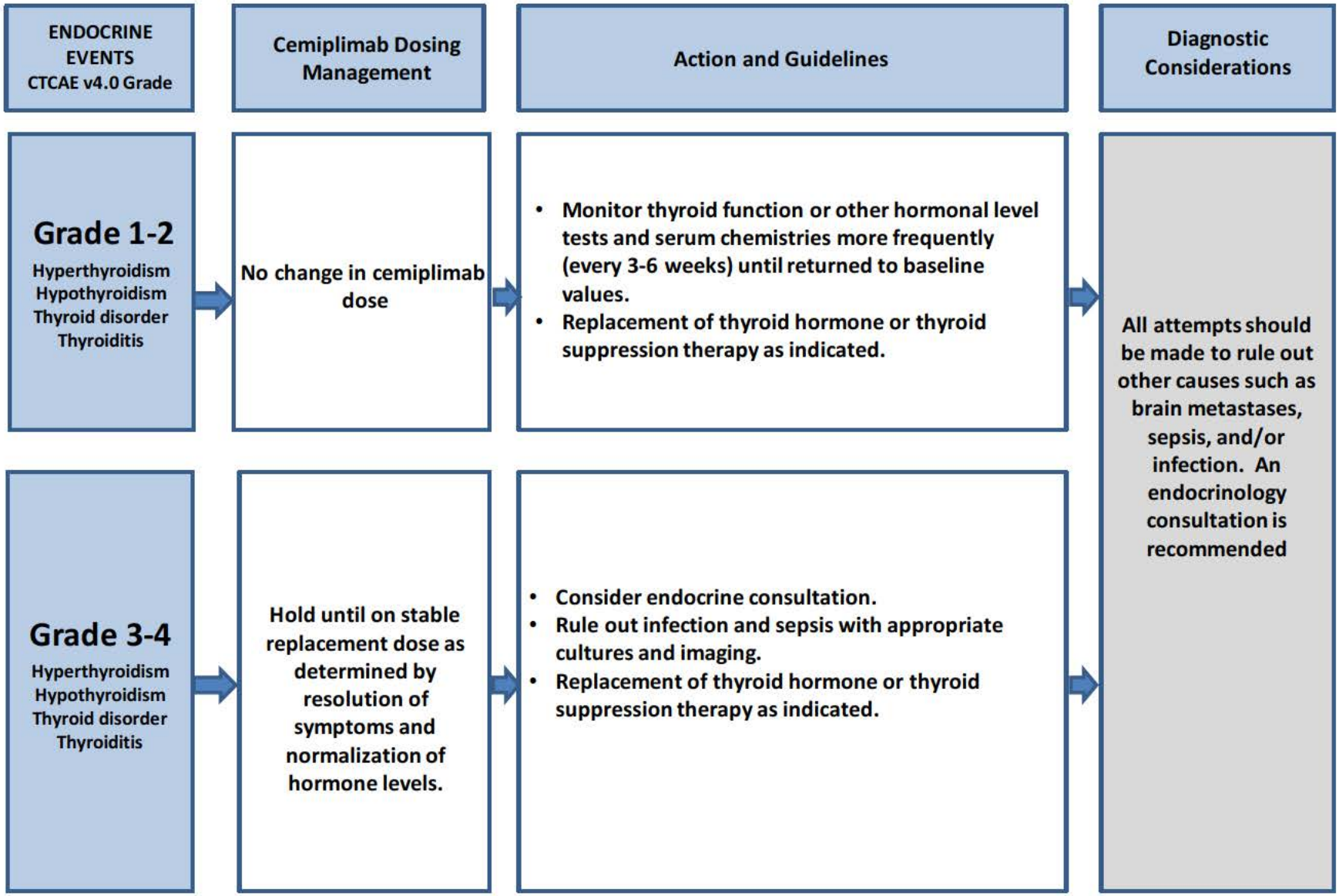
Colitis Adverse Event Management



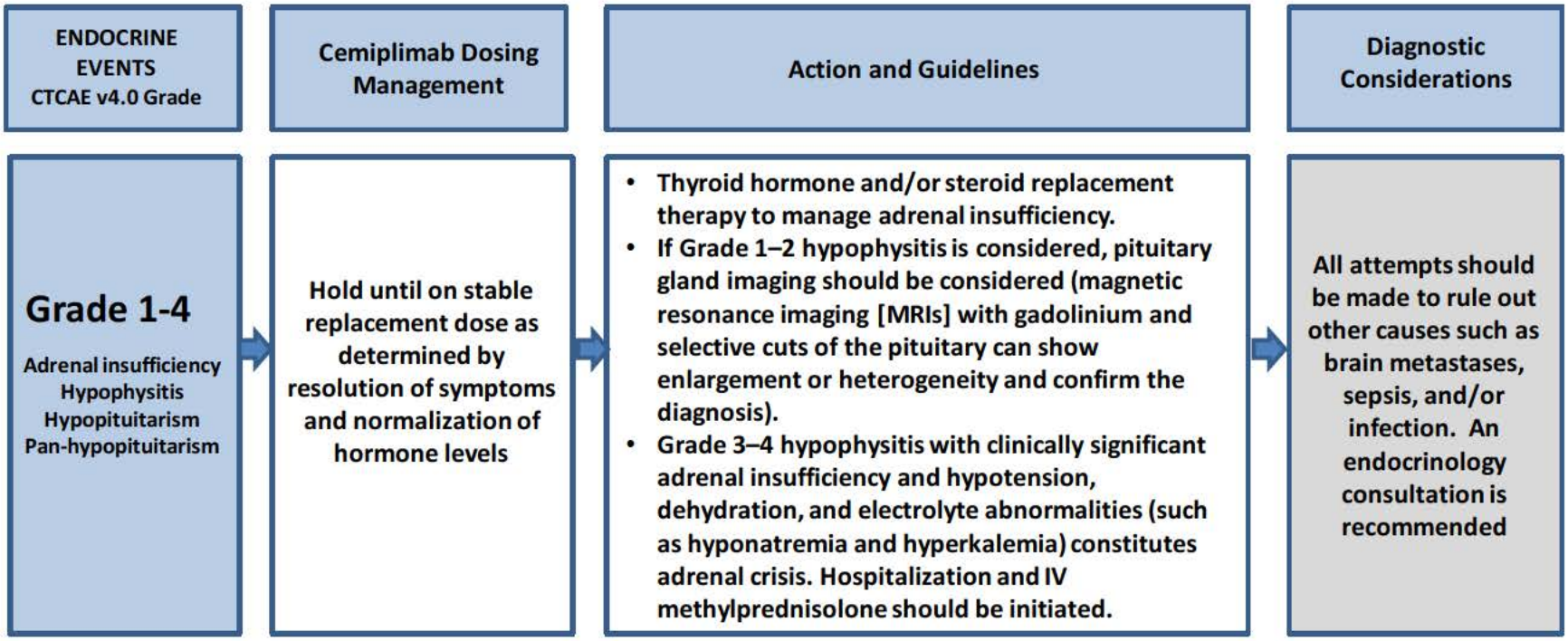
Colitis Adverse Event Management



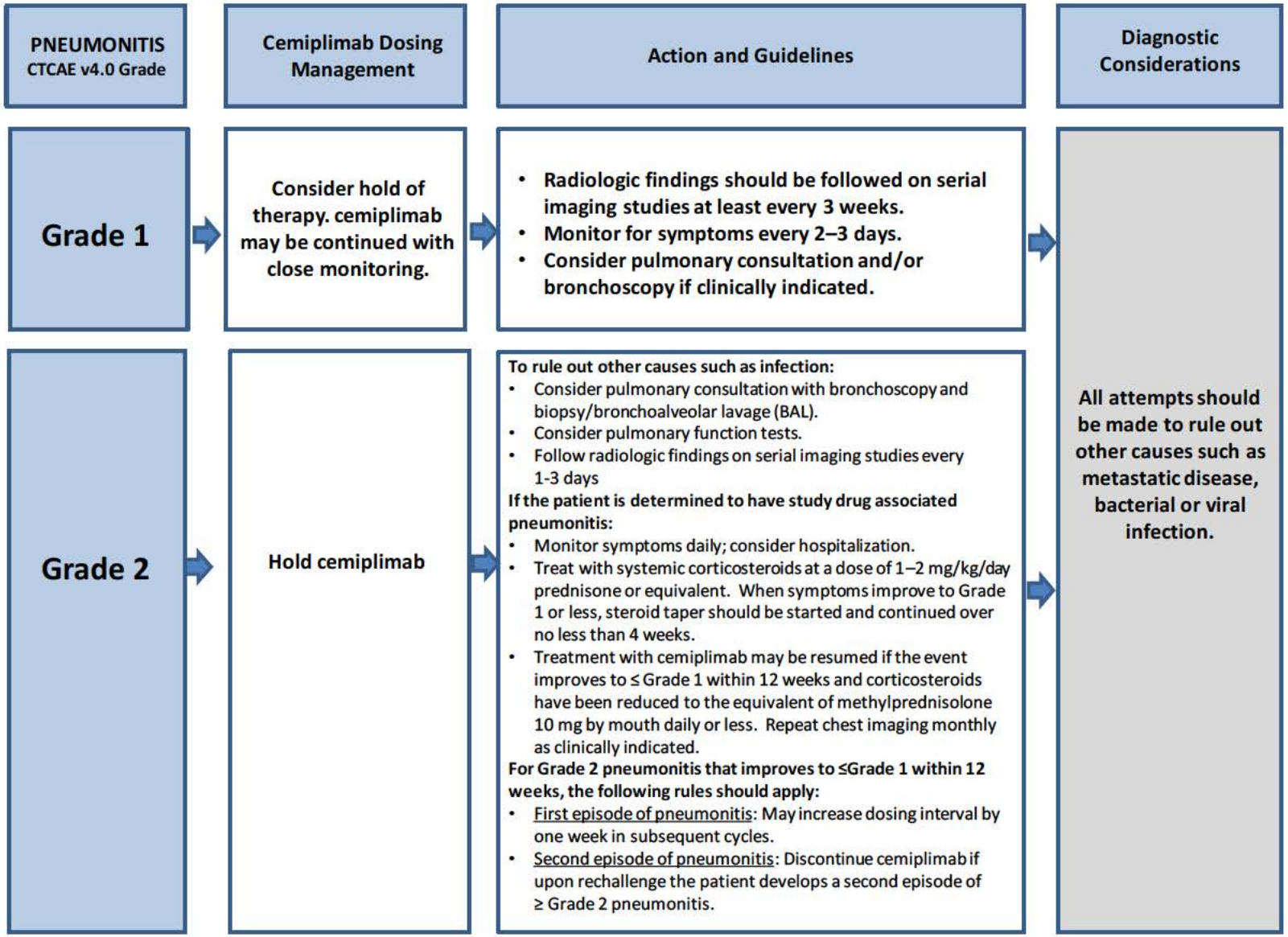
Endocrine Adverse Event Management



Endocrine Adverse Event Management (Cont)



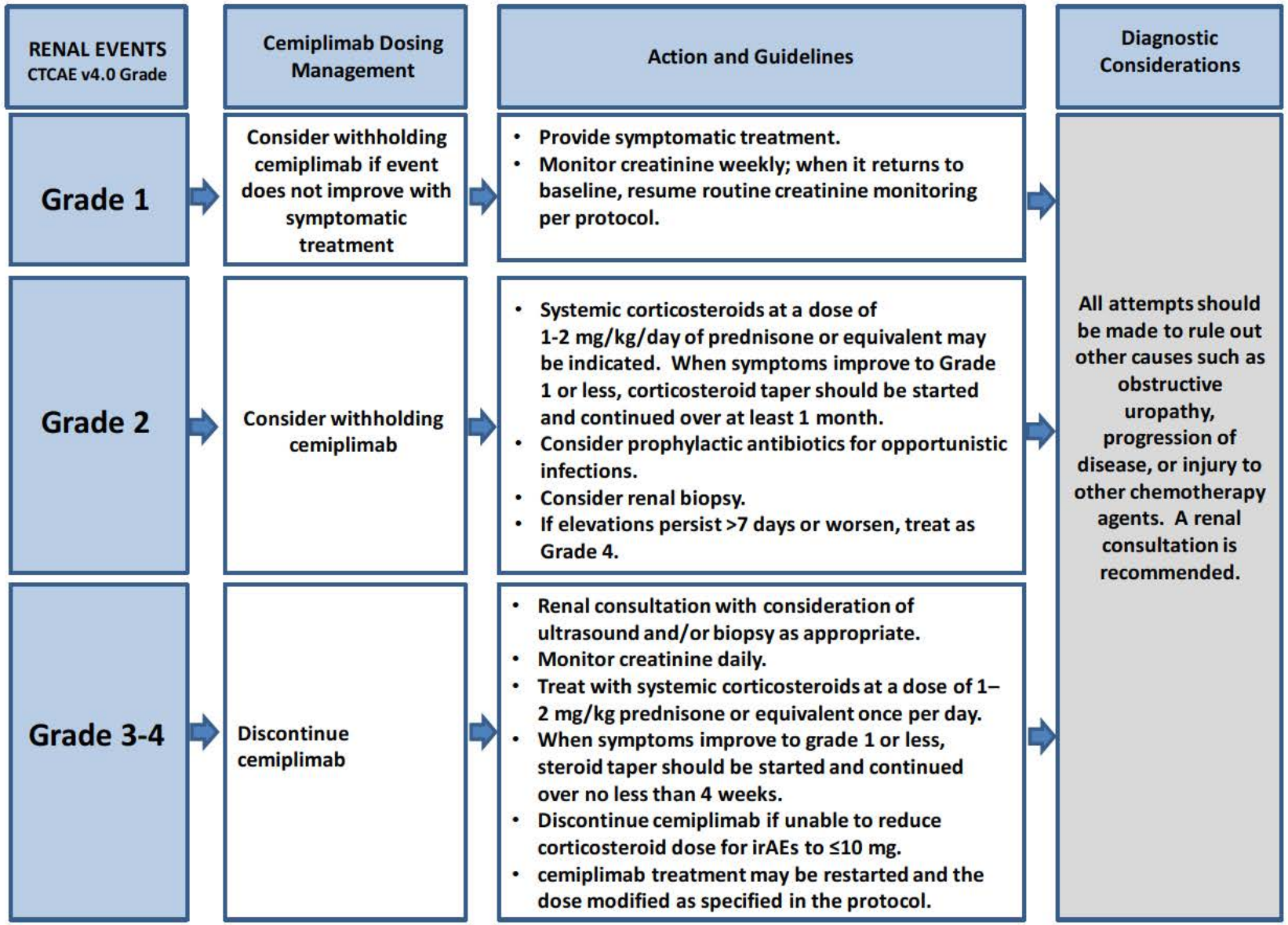
Pneumonitis Adverse Event Management



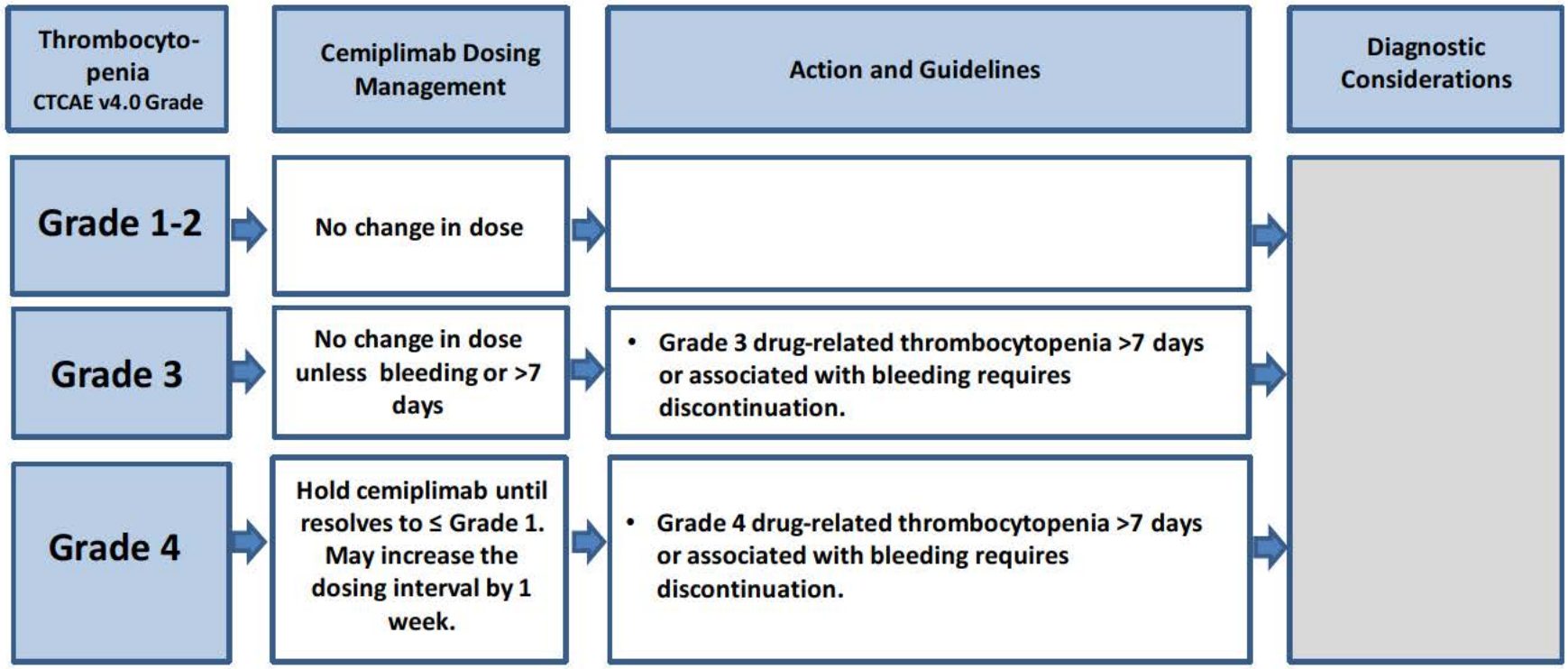
Pneumonitis Adverse Event Management (Cont)

PNEUMONITIS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3-4	Discontinue cemiplimab	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (methylprednisolone 125 mg). When symptoms improve to grade 1 or less, a high-dose oral steroid (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, treat 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.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Renal Adverse Event Management



Hematologic Adverse Event Management



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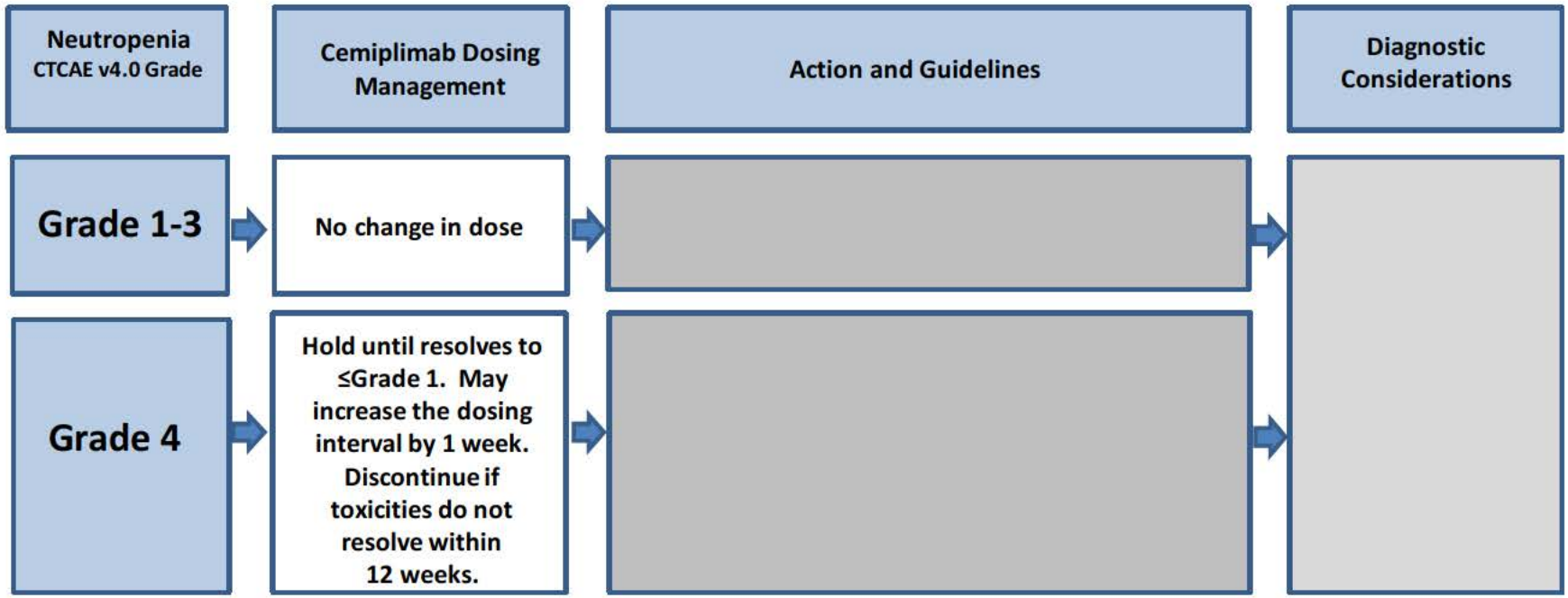
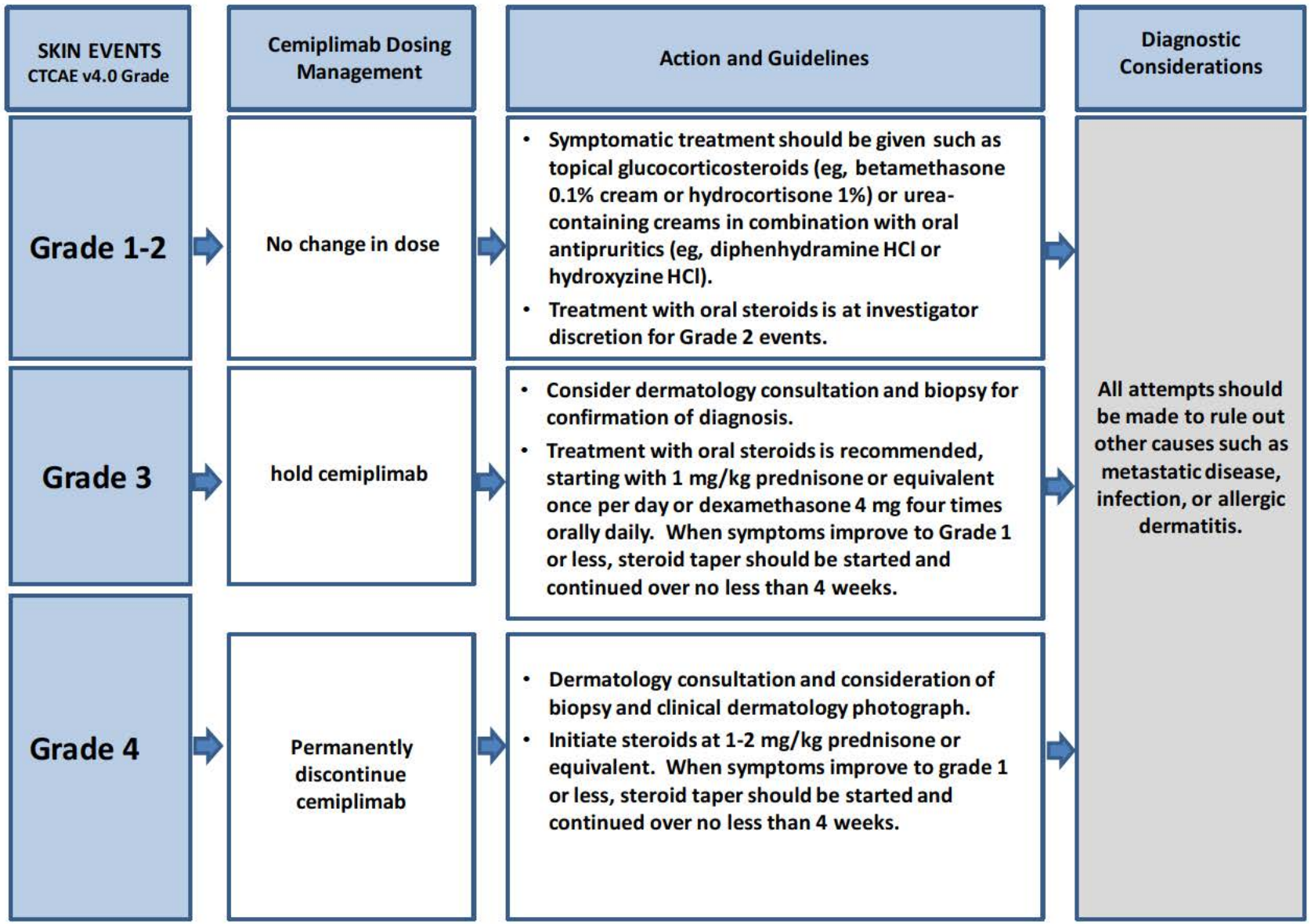
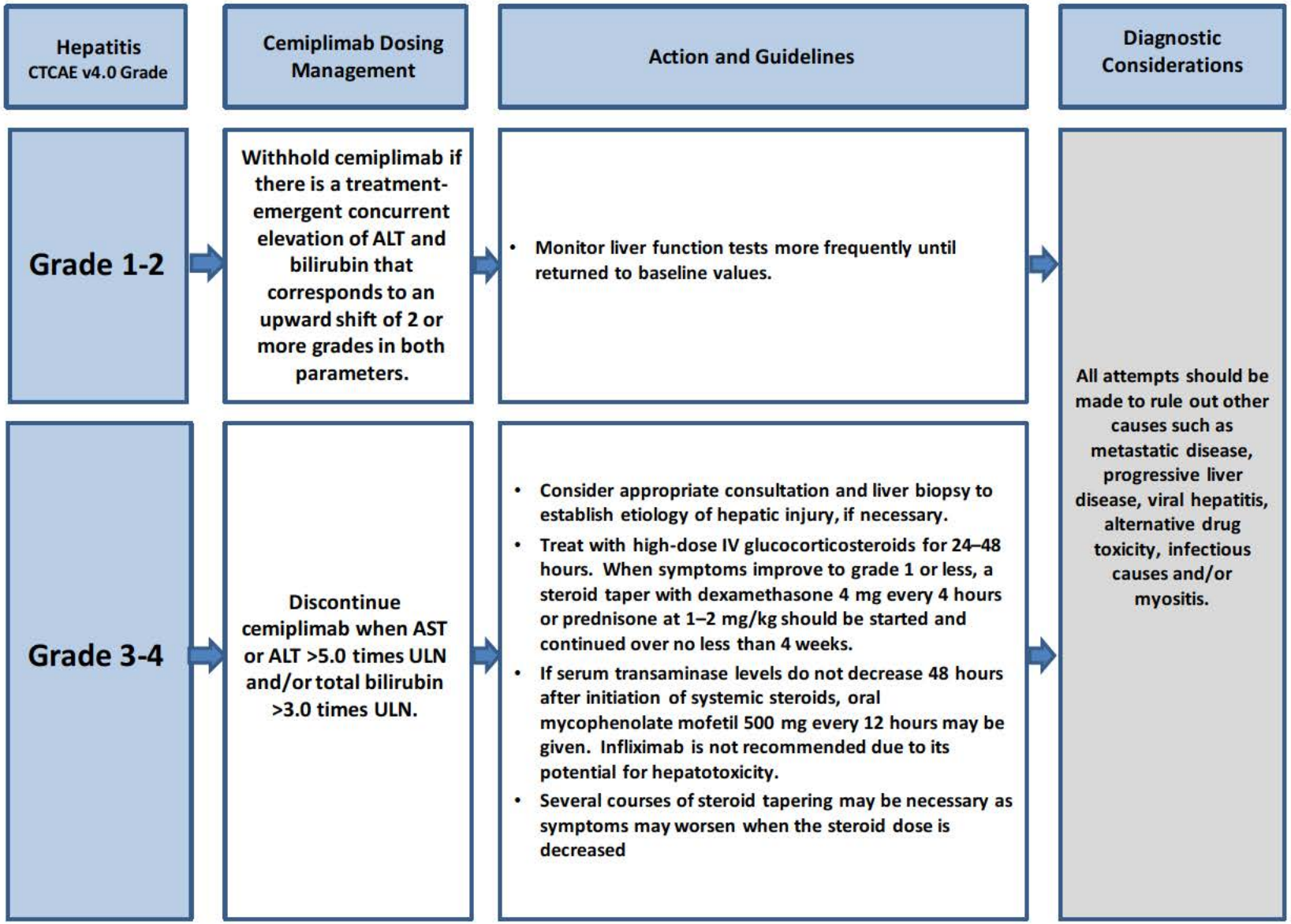


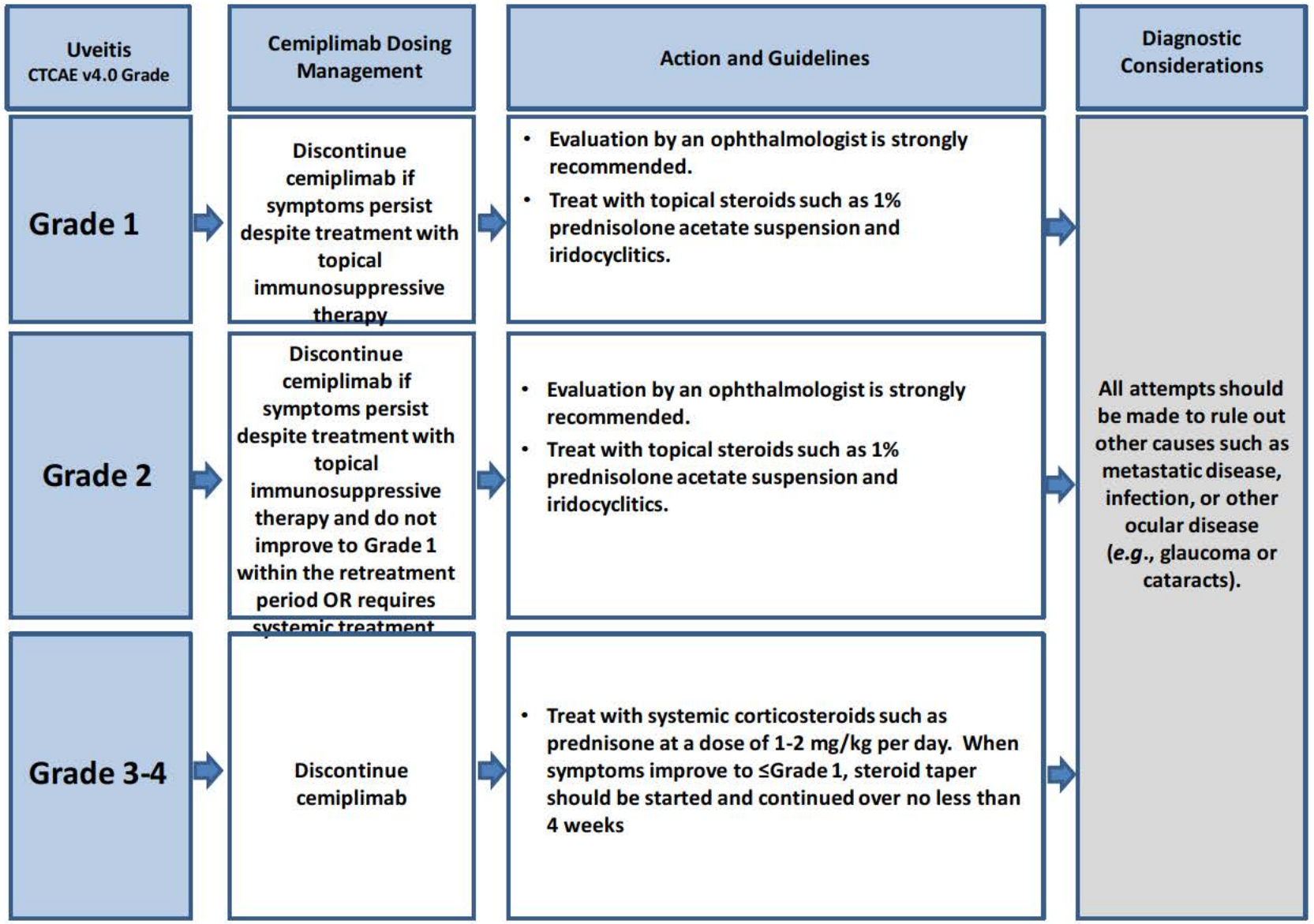
Dermatologic Adverse Event Management



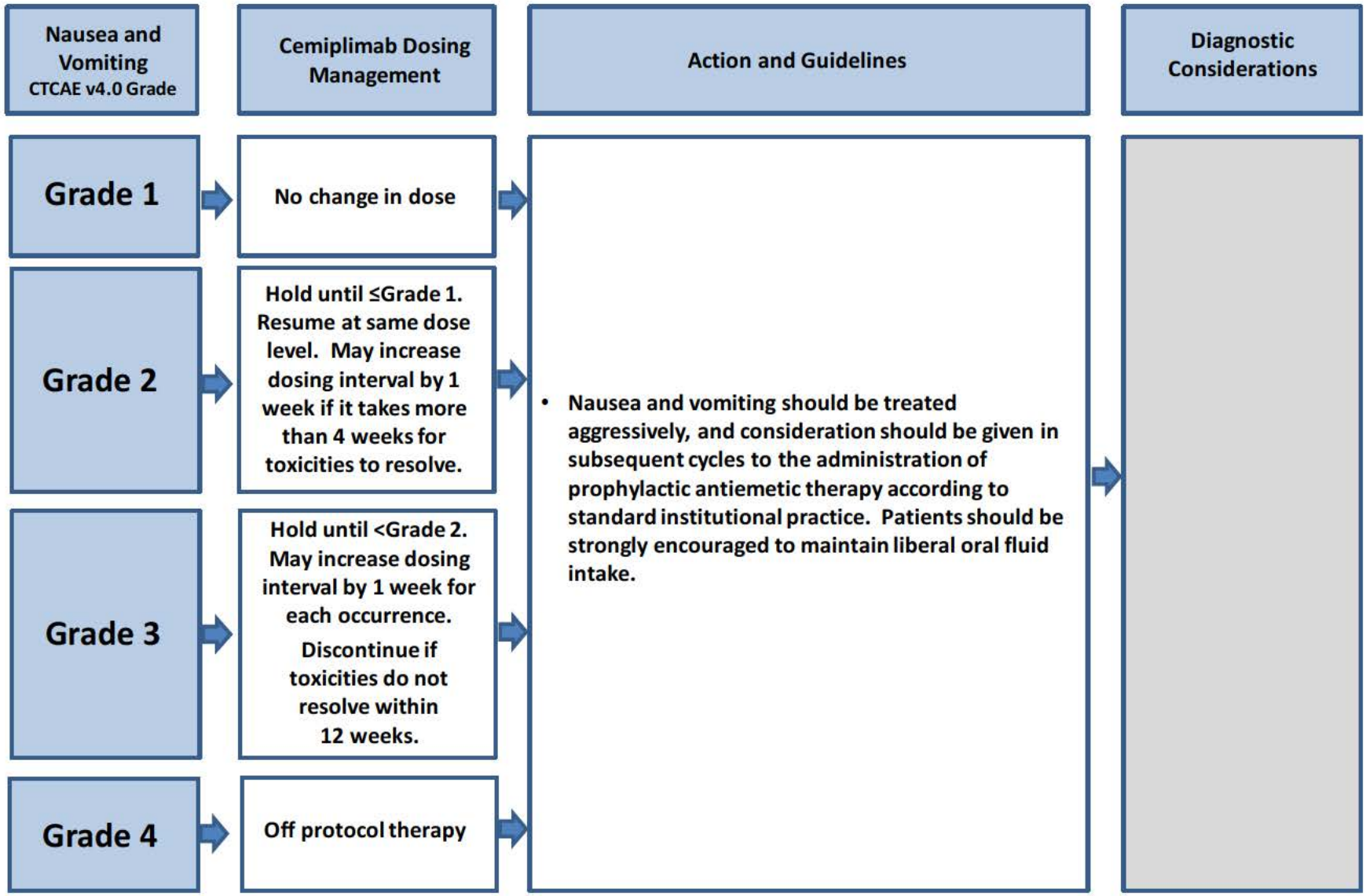
Hepatitis Adverse Event Management



Ophthalmologic (Uveitis) Adverse Event Management



Nausea and Vomiting Adverse Event Management



APPENDIX 4. CEMIPLIMAB PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLING SCHEDULE

Study Visit	PK Sampling Time[a]	Anti-Drug Antibody Sampling Time[a]	Serum and Plasma Biomarker Samples Sampling Time[a]
Screening			• Collect on-study or archival (≤5 months old) tumor tissue sample
Cycle 1, day 1	• Pre-dose • End of infusion[c]	• Pre-dose	• Pre-dose • Collect blood sample for DNA
Cycle 2, day 1	• Pre-infusion • End of infusion		• Pre-infusion
Cycle 3, day 1	• Pre-infusion • End of infusion		
Cycle 4, day 1	• Pre-infusion • End of infusion		• Pre-infusion
Cycle 9, day 1	• Pre-infusion	• Pre-infusion	
Cycle 18, day 1	• Pre-infusion • End of Infusion	• Pre-infusion	
Cycle 26, day 1	• Pre-infusion		
Cycle 30, day 1	• Pre-infusion • End of infusion		
Cycle 34, day 1	• Pre-infusion		
End of treatment	• Pre-infusion • End of infusion	• Pre-infusion	
Follow-up visit 1	• Collect at visit		• Collect at visit
Follow-up visit 2	• Collect at visit		
Follow-up visit 3	• Collect at visit	• Collect at visit	
At the time of RECIST 1.1-defined progressive disease			• Collect at visit[b]

Abbreviations: DNA=deoxyribonucleic acid; PK=pharmacokinetic; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1

[a] Pre-dose is defined as before the start of the first cemiplimab infusion. Pre-dose samples may be collected ≤72 hours prior to day 1 dosing. Pre-infusion is defined as before the start of subsequent cemiplimab infusions.

[b] If possible, a tumor biopsy should also be collected at this time point (optional)

[c] End of infusion is defined as ±10 minutes after the end of infusion

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 Randomized, Phase 3, Open-Label Study of Combinations of REGN2810 (Cemiplimab, Anti-PD-1 Antibody), Platinum-based Doublet Chemotherapy, and Ipilimumab (Anti-CTLA-4 Antibody) Versus Pembrolizumab Monotherapy in First-Line Treatment of Patients With Advanced or Metastatic Non-Small Cell Lung Cancer With Tumors Expressing PD-L1 ≥50%.

Protocol Number: R2810-ONC-16111

Protocol Version: R2810-ONC-16111 Amendment 3 Global

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-00043121 v1.0

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Signature Page for VV-RIM-00043121 v1.0 Approved